



МІНІСТЕРСТВО ОХОРОНИ ЗДОРОВ'Я УКРАЇНИ  
НАЦІОНАЛЬНИЙ ФАРМАЦЕВТИЧНИЙ УНІВЕРСИТЕТ  
КАФЕДРА КЛІНІЧНОЇ ЛАБОРАТОРНОЇ ДІАГНОСТИКИ,  
МІКРОБІОЛОГІЇ ТА БІОЛОГІЧНОЇ ХІМІЇ



MINISTRY OF HEALTH OF UKRAINE  
NATIONAL UNIVERSITY OF PHARMACY  
DEPARTMENT OF CLINICAL LABORATORY DIAGNOSTICS,  
MICROBIOLOGY AND BIOLOGICAL CHEMISTRY



**ЗБІРНИК  
публікацій  
II Міжнародної науково-практичної  
online конференції  
«СУЧАСНІ ДОСЯГНЕННЯ ЕКСПЕРИМЕНТАЛЬНОЇ,  
КЛІНІЧНОЇ, ЕКОЛОГІЧНОЇ БІОХІМІЇ ТА  
МОЛЕКУЛЯРНОЇ БІОЛОГІЇ»**

**BOOK  
of publications  
of II International scientific and practical  
online conference  
"MODERN ACHIEVEMENTS OF EXPERIMENTAL,  
CLINICAL, ENVIRONMENTAL BIOCHEMISTRY AND  
MOLECULAR BIOLOGY"**

07 листопада 2025 р.  
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А 43

ЕЛЕКТРОННЕ ВИДАННЯ

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**Укладачі:** проф. Віра КРАВЧЕНКО, доц. Ігор СЕНЮК, доц. Олена ЩЕРБАК.

**Сучасні досягнення експериментальної, клінічної, екологічної біохімії та молекулярної біології: збірник публікацій II Міжнародної науково-практичної *online* конференції (м. Харків, 07 листопада 2025 р.). – Х. : НФаУ, 2025. – 539 с.**

Конференція внесена до реєстру з'їздів, конгресів, симпозіумів та науково-практичних конференцій, які заплановані у 2023 році, реєстраційне посвідчення УкрІНТЕІ № 851 від 26.12.2024 року.

Дане видання представлене збірником матеріалів науково-практичної конференції, в якому наведені сучасні та актуальні питання розвитку експериментальної та клінічної біохімії. Метою заходу стало презентування результатів експериментальних досліджень науковців, які спрямовані до поглибленого вивчення клітинних та молекулярних механізмів розвитку поширених патологічних станів та їх фармакокорекцію. Автори у своїх роботах приділили увагу щодо вивчення біохімічних механізмів дії біологічно активних сполук та лікарських засобів, тим самим висвітлюючи актуальні питання медичної та фармацевтичної біохімії. Науковий захід популяризує сучасні експериментальні дослідження, які розкривають біохімічні процеси у функціонуванні організму людини та у розкритті патогенетичних аспектів діагностики, лікування і профілактики захворювань.

Видання розраховане для широкого кола науковців та практичних фахівців у галузі знань «Охорона здоров'я», а також для усіх охочих, які зацікавлені у розвитку експериментальних наукових проєктів.

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**Modern achievements of experimental, clinical, environmental biochemistry and molecular biology: book of publications of II International scientific and practical *online* conference (Kharkiv, November 07 2025). – Kh. : NUPh, 2025. – 539 p.**

The conference is included in the register of congresses, symposia and scientific-practical conferences planned for 2023, registration certificate UkrINTEI No 851, dated 26.12.2024.

This publication represents the collection of scientific and practical conference materials relating the modern and topical issues of experimental and clinical biochemistry.

The purpose of the event is to present the results of scientists' experimental studies, which are aimed at in-depth study of cellular and molecular mechanisms of common pathological conditions development, and their pharmacocorrection. In the scientific works, the authors paid attention to investigation of biologically active compounds biochemical mechanisms and medications action, thereby covering current issues of medical and pharmaceutical biochemistry. The scientific event promotes modern experimental research that helps to understand the biochemical processes in the human body, as well as to assist in the diagnostics, treatment and prophylaxis of diseases.

The publication is designed for a wide range of scientists and practitioners in the field of knowledge "Public Health", as well as for all those who are interested in the development of experimental research projects.

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## ПРИВІТАННЯ ВІД ОРГАНІЗАТОРІВ КОНФЕРЕНЦІЇ GREETINGS FROM THE CONFERENCE ORGANIZERS

### ШАНОВНІ КОЛЕГИ!



Щиро вітаю вас із початком роботи II Міжнародної науково-практичної online конференції «Сучасні досягнення експериментальної, клінічної, екологічної біохімії та молекулярної біології».

Цей науковий захід є важливою подією для фахівців, які присвятили свою діяльність вивченню фундаментальних і прикладних аспектів біохімії, молекулярної біології, медицини та екології.

Сучасний етап розвитку науки вимагає міждисциплінарного підходу, об'єднання зусиль дослідників різних країн і напрямів. Впровадження інноваційних технологій, розвиток біомедичних досліджень та біотехнологій відкриває нові можливості для розуміння механізмів життєдіяльності та збереження здоров'я людини.

Щодо організаторів та учасників конференції – маю нагоду запевнити, що головним меседжем конференції є підтвердження прихильності вітчизняної наукової спільноти до сучасних, прогресивних концепцій еволюції експериментальної науки. Цей науковий майданчик – унікальна можливість для фахівців із України і зарубіжжя зібратися разом, обговорити актуальні питання розвитку багатовекторних напрямів біологічної хімії, обмінятися досвідом.

Переконаний, що результати, представлені на конференції, стануть вагомим внеском у розвиток сучасної біохімічної науки, сприятимуть розширенню міжнародної співпраці, обміну досвідом і формуванню нових наукових ідей.

Бажаю всім учасникам плідної праці, цікавих дискусій, нових професійних контактів і натхнення у подальших наукових пошуках!

*Із повагою, голова організаційного комітету конференції,  
в.о. ректора Національного фармацевтичного університету,  
доктор фармацевтичних наук, професор,*

**Олександр КУХТЕНКО**



**DEAR COLLEAGUES!**

I sincerely congratulate you on the start of the II International Scientific and Practical Online Conference "Modern Achievements in Experimental, Clinical, Environmental Biochemistry and Molecular Biology".

This scientific event is an important occasion for specialists who have devoted their work to studying the fundamental and applied aspects of biochemistry, molecular biology, medicine, and ecology.

The current stage of scientific development requires an interdisciplinary approach, combining the efforts of researchers from different countries and fields. The introduction of innovative technologies and the development of biomedical research and biotechnology open up new opportunities for understanding the mechanisms of life and preserving human health.

As for the organisers and participants of the conference, I can assure you that the main message of the conference is to confirm the commitment of the domestic scientific community to modern, progressive concepts of the evolution of experimental science. This scientific platform is a unique opportunity for specialists from Ukraine and abroad to come together, discuss topical issues in the development of multi-vector directions in biological chemistry, and exchange experiences.

I am convinced that the results presented at the conference will make a significant contribution to the development of modern biochemical science, promote the expansion of international cooperation, the exchange of experience and the formation of new scientific ideas.

I wish all participants fruitful work, interesting discussions, new professional contacts and inspiration in their further scientific pursuits!

*Sincerely, Chairman of the Organizing Committee,  
Acting Rector of the National University of Pharmacy,  
doctor of pharmaceutical sciences, professor,*

**Oleksandr KUKHTENKO**



### **ШАНОВНІ ОРГАНІЗАТОРИ І УЧАСНИКИ КОНФЕРЕНЦІЇ!**



Щиро вітаю вас із відкриттям II Міжнародної науково-практичної *online* конференції «Сучасні досягнення експериментальної, клінічної, екологічної біохімії та молекулярної біології».

Ваш науковий форум є важливим майданчиком для обміну досвідом, обговорення актуальних проблем сучасної біохімії та молекулярної біології, пошуку нових шляхів інтеграції фундаментальних знань у практику медицини та біотехнології.

Сьогодні наука стає рушійною силою прогресу, а співпраця між дослідниками різних країн і галузей – запорукою нових відкриттів. Саме такі конференції сприяють формуванню єдиного наукового простору, підтримці молодих учених та розвитку міжнародного партнерства.

Висловлюю щирю вдячність організаторам заходу за високий рівень підготовки, а всім учасникам – за активну позицію, наукову зацікавленість і прагнення до пізнання нового.

Упевнена, що на конференції прозвучать цікаві та оригінальні доповіді, ми почуємо нові імена молодих талановитих науковців, яким, завдяки наполегливій праці, накопиченим знанням і прагненню до пізнання вдасться запалити свою зірку і пройти власний науковий шлях від першого відкриття до визнання науковою спільнотою.

Бажаю вам плідної роботи, творчого натхнення, наукових відкриттів та нових професійних контактів!

*Проректор з науково-педагогічної роботи  
Національного фармацевтичного університету,  
доктор фармацевтичних наук,  
професор*

**Наталя ПОЛОВКО**



***DEAR ORGANIZERS AND PARTICIPANTS OF THE CONFERENCE!***

I sincerely congratulate you on the opening of the II International Scientific and Practical Online Conference "Modern Achievements in Experimental, Clinical, Environmental Biochemistry and Molecular Biology".

Your scientific forum is an important platform for exchanging experience, discussing current issues in modern biochemistry and molecular biology, and searching for new ways to integrate fundamental knowledge into the practice of medicine and biotechnology.

Today, science is becoming the driving force of progress, and cooperation between researchers from different countries and fields is the key to new discoveries. It is conferences such as these that contribute to the formation of a unified scientific space, support for young scientists, and the development of international partnerships.

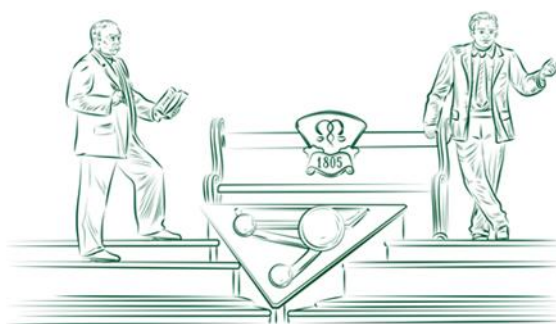
I would like to express my sincere gratitude to the organisers of the event for the high level of preparation, and to all participants for their active participation, scientific interest and desire to learn new things.

I am confident that the conference will feature interesting and original presentations, and that we will hear the names of new young talented scientists who, thanks to their hard work, accumulated knowledge and thirst for knowledge, will be able to shine brightly and follow their own scientific path from their first discovery to recognition by the scientific community.

I wish you fruitful work, creative inspiration, scientific discoveries and new professional contacts!

***Vice-Rector for Scientific  
and Pedagogical Work  
National University of Pharmacy,  
Doctor of Pharmaceutical Sciences,  
Professor***

***Natalia POLOVKO***





### ***ШАНОВНІ УЧАСНИКИ КОНФЕРЕНЦІЇ!***

Щиро вітаю вас із початком роботи II Міжнародної науково-практичної online конференції «Сучасні досягнення експериментальної, клінічної, екологічної біохімії та молекулярної біології». Для нашого університету ця подія є важливою науковою традицією, що об'єднує фахівців різних галузей: біохіміків, молекулярних біологів, медиків, фармацевтів, екологів, які спільно прагнуть до глибшого розуміння біохімічних процесів у здоров'ї та патології, а також їхнього значення для сучасної медицини та фармації.

Біохімія і молекулярна біологія сьогодні стоять у центрі розвитку сучасних біомедичних наук. Саме вони дають ключ до розкриття механізмів функціонування клітини, регуляції обмінних процесів, міжклітинної комунікації, патогенезу захворювань та дії лікарських речовин. Водночас розвиток цих наук є неможливим без використання інноваційних підходів — високочутливих методів молекулярної діагностики, біоінформатики, геноміки, протеоміки, метаболоміки. Саме на перетині цих напрямів народжуються найважливіші відкриття сучасності.

Особливого значення нині набуває інтеграція біохімічних знань у клінічну практику. Клінічна лабораторна діагностика є тим містком, що поєднує фундаментальні наукові дослідження з реальними потребами охорони здоров'я. Високоточна лабораторна аналітика дозволяє своєчасно виявляти патологічні зміни, контролювати ефективність лікування та прогнозувати перебіг захворювань. Тому участь у таких конференціях не лише сприяє розвитку науки, а й формує платформу для практичного застосування отриманих знань.

Надзвичайно важливо, що до нашої конференції долучилися представники різних країн, наукових шкіл та напрямів досліджень. Такий міждисциплінарний та міжнародний формат сприяє обміну досвідом, формуванню спільних дослідницьких ініціатив, розширенню наукової співпраці та зміцненню контактів між установами. Саме у таких дискусіях народжуються нові ідеї, концепції та наукові партнерства.

Особливо приємно відзначити активну участь молодих учених, аспірантів і студентів, які представляють свої перші наукові здобутки. Саме вони майбутнє біохімічної науки, її рушійна сила та надія. Підтримка молодих дослідників, створення для них умов для розвитку та наукового зростання є одним із головних завдань нашої кафедри та університету в цілому.

Бажаю всім учасникам конференції плідної праці, змістовних доповідей,

цікавих дискусій, нових наукових ідей та натхнення у подальших дослідженнях! Нехай результати ваших наукових пошуків сприяють розвитку сучасної біохімії, клінічної діагностики, молекулярної біології та збереженню здоров'я людини.

**Завідувача кафедри  
клінічної лабораторної діагностики,  
мікробіології та біологічної хімії НФаУ,  
доктор біологічних наук,  
професор**

**Віра КРАВЧЕНКО**

***DEAR PARTICIPANTS OF THE CONFERENCE!***

I sincerely congratulate you on the start of the II International Scientific and Practical Online Conference "Modern Achievements in Experimental, Clinical, Environmental Biochemistry and Molecular Biology". For our university, this event is an important scientific tradition that brings together specialists from various fields: biochemists, molecular biologists, physicians, pharmacists, and ecologists, who jointly strive for a deeper understanding of biochemical processes in health and pathology, as well as their significance for modern medicine and pharmacy.

Biochemistry and molecular biology are at the heart of the development of modern biomedical sciences today. They provide the key to unlocking the mechanisms of cell function, regulation of metabolic processes, intercellular communication, pathogenesis of diseases and the action of drugs. At the same time, the development of these sciences is impossible without the use of innovative approaches – highly sensitive methods of molecular diagnostics, bioinformatics, genomics, proteomics, and metabolomics. It is at the intersection of these areas that the most important discoveries of our time are made.

The integration of biochemical knowledge into clinical practice is becoming particularly important today. Clinical laboratory diagnostics is the bridge that connects fundamental scientific research with the real needs of healthcare. Highly accurate laboratory analytics allows for the timely detection of pathological changes, monitoring of treatment effectiveness, and prediction of disease progression. Therefore, participation in such conferences not only contributes to the development of science, but also forms a platform for the practical application of the knowledge gained.

It is extremely important that representatives of different countries, scientific schools, and research areas have joined our conference. This interdisciplinary and international format promotes the exchange of experience, the formation of joint research initiatives, the expansion of scientific cooperation and the strengthening of contacts between institutions.



It is in such discussions that new ideas, concepts and scientific partnerships are born.

It is particularly pleasing to note the active participation of young scientists, postgraduates and students presenting their first scientific achievements. They are the future of biochemical science, its driving force and hope. Supporting young researchers and creating conditions for their development and scientific growth is one of the main tasks of our department and the university as a whole.

I wish all conference participants fruitful work, meaningful presentations, interesting discussions, new scientific ideas and inspiration in their future research! May the results of your scientific research contribute to the development of modern biochemistry, clinical diagnostics, molecular biology and the preservation of human health.

*Head of the Department  
of Clinical laboratory diagnostics,  
Microbiology and Biological Chemistry NPhaU,  
Doctor of Biological Sciences,  
Professor*

*Vira KRAVCHENKO*



***DEAR RECTOR, DEAR VICE-RECTOR, DEAR COLLEAGUES, DEAR PROFESSORS,  
DEAR TEACHERS, DEAR RESEARCHERS, DEAR FRIENDS, DEAR STUDENTS,  
DEAR PARTICIPANTS, AND DEAR BROTHERS AND SISTERS!!!***



It is my greatest honor to Greetings from Brother Tbilisi-Georgia, from Georgian State and Private Universities of Faculty of Pharmacy, Medicine and Dentistry. I would like to express my warmly thank to the organizer's committee of this important II International scientific and practical online conference- "Modern achievements of experimental, clinical, environmental biochemistry and molecular biology.

We are Sincerely, Heartily and Warmly Greeting from Brother Tbilisi-Georgia. For me, it is an honor and a pleasure to be Member of the International scientific and practical conference Organizing Committee and to participate in the International conference organized by the National University of Pharmacy of Ukraine.

I would also like to thank you for having brought us online together in the Wonderful, Old, Brave, Hero and Great University City of Kharkiv at the Famous National University of Pharmacy of Ukraine, to discuss one of the main current challenges in Modern achievements of experimental, clinical, environmental biochemistry and molecular biology.

Pharmacy is, indeed, one of the most ancient professions known from the beginning of civilization. Due to a progressive increase of world population- reaching more than 7 billion people – that makes necessary to improve our Pharmaceutical Skills in Clinical Pharmacy, in Pharmacotherapy and in Pharmaceutical Care and Ability to supply higher-quality drugs in view of assuring drugs safety and improve Pharmaceutical Care Services in Pharmaceutics, in Medicine, in Health Care and in Public Health in General.

These conferences cover a wide spectrum of themes related to:

- Cellular and molecular mechanisms of development of pathological conditions of different genesis and ways of their pharmacocorrection by means of synthetic and plant origin;
- The use of biochemical markers for the assessment of metabolic disorders in the

experimental modeling of pathological conditions;

- Regulation of metabolic processes and cellular functions in normal and pathological conditions;
- Biochemical mechanisms of action of biologically active compounds and drugs;
- Clinical and pharmacological biochemistry;
- Biochemical mechanisms of realization of the effect of drugs on the genetic apparatus of viruses, bacteria and the human body;
- Molecular biology;
- Bioinformatics and computational biology;
- Genetic and biopharmaceutical engineering;
- Rehabilitation and clinical engineering;
- Basic principles and new trends in environmental chemistry. Green chemistry in industry and so on.

I am sure that each one of you will identify subjects of your interest and will benefit from many fruitful and enriching essential discussions in “Modern achievements of experimental, clinical, environmental biochemistry and molecular biology” and in pharmaceutical sciences.

I am as a professor of Pharmaceutical and Pharmacological Sciences at higher Medical and Pharmaceutical Direction State and Private Universities in Georgia, very much concerned about the connection between the pharmaceutical and medical education cross-links globally worldwide.

It is very Honor to me to present in this unique international conference "Modern achievements of experimental, clinical, environmental biochemistry and molecular biology". We share experiences with other high-level Professors, Colleagues and Friends, representing many well-known Universities and Research Institutes together with hosting the National Pharmaceutical University of Ukraine With International Participation.

The International conferences make the perfect platform for global networking as it brings online together pharmaceutical and medical scientists across Europe and Globally. We are very honor to participate in an exciting and memorable International scientific and practical conference "Modern achievements of experimental, clinical, environmental biochemistry and molecular biology".

The International scientific and practical conference in "Modern Achievements of experimental, clinical, environmental biochemistry and molecular biology", is a great collaboration platform between Scientists, Pharmacists, Students, Health and Pharmaceutical Experts, Doctors, Biochemists, Biologists, Chemists to share the Latest Scientific Knowledge and Understanding in Pharmaceutical, Biological, Biochemical



and Medical Sciences as well as in the Region and Globally. I Wish Peace, Prosperity and Many Successes to the National University of Pharmacy of Ukraine and hope to see more Collaboration between Georgian and Ukrainian Scientists, Pharmacists and Medical Doctors and Medical Practitioners. Together We Are Stronger.

More Than 3 Years We Are All Ukrainians!!!

We All Georgians Are Very Saddened, Suffering and Worried about the Barbaric-Hellish War, Bloodshed, Occupation, Genocide and Ethnic Cleansing of Innocent People, Committed by The Russian Federation in Ukraine!!!

God Bless and Protect Our Brother Ukraine!!!

Peace in Our Brother Ukraine!!!

May JESUS CHRIST Protect and Blessed Our Brother Ukraine!!!

We Stand With Our Brother Ukraine!!!

Glory to the Heroes, Glory to Ukraine, Victory to Brother Ukraine!!!

I Thank All of You for Your Strong Collaboration Between Our Universities and Wish You Peace, Prosperity and All the Success to Brother Ukraine. Thank You for Your Attention.

***Kind and Best regards,***

***Sincerely,***

***Dr. Professor Nodar Sulashvili-MD, PhD, Doctor of Theoretical Medicine In Pharmaceutical and Pharmacological Sciences, Invited Lecturer (Invited Professor) of Scientific Research-Skills Center at Tbilisi State Medical University, Professor of Pharmacology of Faculty of Medicine at Georgian National University SEU, Associate Affiliated Professor of Medical Pharmacology of Faculty of Medicine at Sulkhan-Saba Orbeliani University, Associate Professor of Division of Pharmacology of International School of Medicine at Alte University; Associate Professor of Pharmacy Program at Shota Meskhia Zugdidi State University; Associate Professor of Medical Pharmacology at School of Medicine at David Aghmashenebeli University of Georgia, Associate Professor of Biochemistry and Pharmacology Direction at the University of Georgia, School of Health Sciences. Associate Professor of Pharmacology of Faculty of Medicine at East European University, Associate Professor of Pharmacology of Faculty of Dentistry and Pharmacy at Tbilisi Humanitarian Teaching University; Tbilisi, Georgia; Researcher of Department of Pharmaceutical Management of Yerevan State Medical University after Mkhitar Heratsi, Yerevan, Armenia.***

**ШАНОВНИЙ РЕКТОРЕ, ШАНОВНИЙ ПРОРЕКТОРЕ, ШАНОВНІ КОЛЕГИ,  
ШАНОВНІ ПРОФЕСОРИ, ШАНОВНІ ВИКЛАДАЧІ, ШАНОВНІ НАУКОВЦІ,  
ШАНОВНІ ДРУЗІ, ШАНОВНІ СТУДЕНТИ, ШАНОВНІ УЧАСНИКИ,  
ДОРОГІ БРАТИ І СЕСТРИ!!!**

Для мене велика честь привітати Вас з братнього Тбілісі-Грузія, з державних і приватних університетів Грузії, факультетів фармації, медицини та стоматології. Хочу висловити щире подяку організаційному комітету цієї важливої І Міжнародної науково-практичної інтернет-конференції «Сучасні досягнення експериментальної, клінічної, екологічної біохімії та молекулярної біології».

Щиро, сердечно і тепло вітаємо вас від брата Тбілісі – Грузії. Для мене велика честь і задоволення бути членом Оргкомітету Міжнародної науково-практичної конференції та брати участь у міжнародній конференції, організованій Національним фармацевтичним університетом України.

Я також хотів би подякувати Вам за те, що Ви зібрали нас в онлайн-режимі в чудовому, старому, хороброму, героїчному і великому університетському місті Харкові у знаменитому Національному фармацевтичному університеті України, щоб обговорити одну з головних проблем сьогодення в галузі сучасних досягнень експериментальної, клінічної, екологічної біохімії та молекулярної біології.

Фармація є однією з найдавніших професій, відомих з часів зародження цивілізації. У зв'язку з прогресуючим збільшенням чисельності населення планети, яка досягла понад 7 мільярдів осіб, виникає необхідність вдосконалення наших фармацевтичних навичок у клінічній фармації, фармакотерапії та фармацевтичній опіці, а також здатності постачати високоякісні лікарські засоби з метою забезпечення безпеки лікарських засобів та покращення фармацевтичних послуг у фармацевтиці, медицині, охороні здоров'я та охороні громадського здоров'я в цілому.

Ці конференції охоплюють широкий спектр тем, пов'язаних із:

- Клітинні та молекулярні механізми розвитку патологічних станів різного генезу та шляхи їх фармакокорекції засобами синтетичного та рослинного походження;
- Використання біохімічних маркерів для оцінки метаболічних порушень при експериментальному моделюванні патологічних станів;
- Регуляція метаболічних процесів і клітинних функцій в нормі та при патології;
- Біохімічні механізми дії біологічно активних сполук та лікарських засобів;
- Клінічна та фармакологічна біохімія;
- Біохімічні механізми реалізації дії лікарських засобів на генетичний апарат вірусів, бактерій та організму людини;

- Молекулярна біологія;
- Біоінформатика та обчислювальна біологія;
- Генетична та біофармацевтична інженерія;
- Реабілітація та клінічна інженерія;
- Основні принципи та нові тенденції в екологічній хімії. Зелена хімія в промисловості тощо.

Я впевнений, що кожен з вас визначить теми, які вас цікавлять, і отримає користь від багатьох плідних і збагачуючих важливих дискусій в рамках «Сучасних досягнень експериментальної, клінічної, екологічної біохімії та молекулярної біології» та у фармацевтичних науках.

Як професор фармацевтичних і фармакологічних наук у вищих медичних і фармацевтичних державних і приватних університетах Грузії, я дуже занепокоєна зв'язком між фармацевтичною та медичною освітою в усьому світі.

Для мене велика честь бути представленою на цій унікальній міжнародній конференції «Сучасні досягнення експериментальної, клінічної, екологічної біохімії та молекулярної біології». Ми ділимося досвідом з іншими професорами, колегами та друзями високого рівня, які представляють багато відомих університетів та науково-дослідних інститутів, разом з приймаючою стороною – Національним фармацевтичним університетом України з міжнародною участю.

Міжнародні конференції є ідеальною платформою для глобального нетворкінгу, оскільки вони об'єднують фармацевтичних та медичних вчених з усієї Європи та світу в режимі онлайн. Для нас велика честь взяти участь у захоплюючій та незабутній Міжнародній науково-практичній конференції «Сучасні досягнення експериментальної, клінічної, екологічної біохімії та молекулярної біології».

Міжнародна науково-практична конференція «Сучасні досягнення експериментальної, клінічної, екологічної біохімії та молекулярної біології» є чудовою платформою для співпраці між науковцями, фармацевтами, студентами, експертами в галузі охорони здоров'я та фармацевтики, лікарями, біохіміками, біологами, хіміками з метою обміну новітніми науковими знаннями та уявленнями в галузі фармацевтичних, біологічних, біохімічних, медичних наук, а також у регіоні та на глобальному рівні. Я бажаю миру, процвітання та багатьох успіхів Національному фармацевтичному університету України та сподіваюся на подальшу співпрацю між грузинськими та українськими вченими, фармацевтами, лікарями та практикуючими лікарями. Разом ми сильніші.

Понад 3 років ми всі – українці!!!

Ми, всі грузини, дуже засмучені, страждаємо і переживаємо через

варварсько-пекельну війну, кровопролиття, окупацію, геноцид та етнічні чистки невинних людей, вчинені Російською Федерацією в Україні!!!

Боже, благослови і захисти нашого брата Україну!!!

Мир в нашій братній Україні!!!

Нехай Ісус Христос захистить і благословить нашого брата Україну!!!

Ми стоїмо з нашим братом Україною!!!

Слава Героям, Слава Україні, Перемога Брату Україні!!!

Я дякую всім вам за тісну співпрацю між нашими університетами і бажаю вам миру, процвітання і всіяких успіхів братній Україні. Дякую за увагу.

**З найкращими побажаннями,**

**З повагою,**

*Д-р. Професор Нодар Сулашвілі, доктор медичних наук, доктор теоретичної медицини в галузі фармацевтичних та фармакологічних наук, запрошений лектор (запрошений професор) Науково-дослідного центру навичок Тбіліського державного медичного університету, професор фармакології факультету медицини Грузинського національного університету SEU, доцент кафедри медичної фармакології факультету медицини Університету Сулхан-Саба Орбеліані, доцент кафедри фармакології Міжнародної школи медицини Університету Альте; Доцент кафедри фармації Державного університету ім. Шота Месхія Зугдіді; доцент кафедри медичної фармакології медичного факультету Університету Давида Агмашенебелі в Грузії, доцент кафедри біохімії та фармакології Школи наук про здоров'я Університету Джорджії. Доцент кафедри фармакології медичного факультету Східноєвропейського університету, доцент кафедри фармакології факультету стоматології та фармації Тбіліського гуманітарного педагогічного університету; Тбілісі, Грузія; науковий співробітник кафедри фармацевтичного менеджменту Єреванського державного медичного університету ім. Мхітара Гераці, Єреван, Вірменія.*





***GREETINGS TO THE CONFERENCE PARTICIPANTS***



Welcome to the II International scientific and practical conference "Modern achievements of experimental, clinical, environmental biochemistry and molecular biology".

I am pleased to give the introduction speech to my colleagues, conference organizers, and attendees.

The NUPh as well as the Biochemistry Department, integrated into the University, have played a key role in developing Kharkov's pharmaceutical potential. The University has a rich history and strong corporate traditions. has been associated with the names of prominent scientists, public figures, founders of scientific schools, and organizers of the pharmaceutical business.

The location of NUPh in this city has established it as a prominent center for pharmaceutical research, education, and production in Ukraine. Today, the city boasts 25 academicians, 120 doctors of sciences, and more than 500 candidates of sciences.

I am pleased to represent the cooperation between National University of Pharmacy and Vilnius University, which is one of the oldest in Europe. It continues the deep traditions of not only scientific but also historical cooperation between Lithuania and Ukraine. This community is especially important today, when the Ukrainian people have gone through a great ordeal of war. I would like to congratulate the hard-working scientists of NUPh, who today, in the face of war, demonstrate their diligence in fulfilling their daily obligations in the education of the younger generation, while at the same time developing modern, progressive concepts of experimental science.

The conference provides a unique opportunity for specialists from various cities in Ukraine and abroad to convene and discuss current issues in experimental and clinical biochemistry, as well as share experiences with foreign experts.

I look forward to translating the conference's innovative ideas into new national and international projects.

***Chief Researcher  
at Life Sciences Center,  
Institute of Biochemistry  
of Vilnius University Dr.***

***Julija RAZUMIENE***

### **ВІТАННЯ УЧАСНИКАМ КОНФЕРЕНЦІЇ**

Вітаю вас на II Міжнародної науково-практичної конференції «Сучасні досягнення експериментальної, клінічної, екологічної біохімії та молекулярної біології».

Мені приємно звернутися зі вступним словом до колег, організаторів конференції та її учасників.

НФаУ, а також кафедра біохімії, інтегрована в університет, відіграли ключову роль у розвитку фармацевтичного потенціалу Харкова. Університет має багату історію та міцні корпоративні традиції, пов'язані з іменами видатних вчених, громадських діячів, засновників наукових шкіл та організаторів фармацевтичної справи. Розташування НФаУ в цьому місті визначило його як визначний центр фармацевтичних досліджень, освіти та виробництва в Україні. Сьогодні в місті працюють 25 академіків, 120 докторів наук та понад 500 кандидатів наук.

Мені приємно представляти співпрацю між Національним фармацевтичним університетом та Вільнюським університетом, який є одним з найстаріших в Європі. Вона продовжує глибокі традиції не лише наукової, а й історичної співпраці між Литвою та Україною. Ця спільнота особливо важлива сьогодні, коли український народ пройшов через велике випробування війною. Я хотів би привітати працюючих науковців НФаУ, які сьогодні, в умовах війни, демонструють свою старанність у виконанні своїх щоденних обов'язків у справі виховання молодого покоління, водночас розвиваючи сучасні, прогресивні концепції експериментальної науки.

Конференція надає унікальну можливість фахівцям з різних міст України та зарубіжжя зібратися і обговорити актуальні питання експериментальної та клінічної біохімії, а також обмінятися досвідом із зарубіжними експертами.

Я з нетерпінням чекаю на втілення інноваційних ідей конференції в нові національні та міжнародні проекти.

*Доктор природничих наук,  
провідний науковий співробітник  
лабораторії біоаналізу,  
Інститут біохімії,  
Центр наук про життя  
Вільнюського університету*

**Юлія РАЗУМІЄНЕ**



**Міністерство освіти і науки України**

Державна наукова установа  
«Український інститут науково-технічної  
експертизи та інформації»

**ПОСВІДЧЕННЯ № 851**  
**про реєстрацію проведення заходу**  
від 26 грудня 2024 р.

|                                |                                                                                                                                                     |
|--------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------|
| назва заходу                   | II Міжнародна науково-практична online конференція «Сучасні досягнення експериментальної, клінічної, екологічної біохімії та молекулярної біології» |
| дата і місце проведення        | 07 листопада 2025 р.<br>Харків                                                                                                                      |
| орієнтовна кількість учасників | 200                                                                                                                                                 |
| одержувач                      | Національний фармацевтичний університет                                                                                                             |

Завідувач відділу інформаційного  
забезпечення міждержавного  
науково-технічного співробітництва



В.В. Матусевич

**ІНОЗЕМНІ КРАЇНИ-УЧАСНИКИ КОНФЕРЕНЦІЇ**  
**FOREIGN COUNTRIES PARTICIPATING IN THE CONFERENCE**



ГРУЗІЯ  
GEORGIA



РЕСПУБЛІКА ВІРМЕНІЯ  
REPUBLIC OF ARMENIA



ЛИТОВСЬКА РЕСПУБЛІКА  
REPUBLIC OF LITHUANIA



КОРОЛІВСТВО МАРОККО  
KINGDOM OF MOROCCO



РЕСПУБЛІКА ПОЛЬЩА  
REPUBLIC OF POLAND



КОРОЛІВСТВО ІСПАНІЯ  
KINGDOM OF SPAIN



ДЕМОКРАТИЧНА РЕСПУБЛІКА КОНГО  
DEMOCRATIC REPUBLIC OF THE CONGO



**ЗАКЛАДИ ТА УСТАНОВИ МЕДИЧНОГО, ФАРМАЦЕВТИЧНОГО І  
БІОЛОГІЧНОГО СПРЯМУВАННЯ, УЧАСНИКИ ЯКИХ ПРЕДСТАВЛЕНІ  
НА КОНФЕРЕНЦІЇ**

**PARTICIPANTS OF THE CONFERENCE REPRESENT THE FOLLOWING MEDICAL,  
PHARMACEUTICAL AND BIOLOGICAL INSTITUTIONS**



Грузинського національного університету SEU,  
Тбілісі, Грузія  
Georgian National University SEU, Tbilisi, Georgia

Тбіліський державний медичний університет,  
Тбілісі, Грузія  
Tbilisi State Medical University, Tbilisi, Georgia



Єреванський державний медичний університет  
ім. М. Гераці, Єреван, Вірменія  
Yerevan State Medical University  
After M. Heratsi, Yerevan, Armenia

Вроцлавський університет природничих наук,  
Вроцлав, Польща  
Wrocław University of Environmental and Life Sciences,  
Wrocław, Poland



Інститут біології Поморського університету в  
Слупську, Слупськ, Республіка Польща  
Institute of Biology, Pomeranian University in Słupsk,  
Słupsk, Republic of Poland

Державний університет Акакія Церетелі, Кутаїсі, Грузія  
Akaki Tsereteli State University, Kutaisi, Georgia



Університет Сулхан-Саба Орбеліані, Тбілісі, Грузія  
Sulkhan-Saba Orbeliani University, Tbilisi, Georgia

Вільнюський університет, Центр наук про життя,  
Інститут біохімії Литви,  
Вільнюс, Литовська Республіка  
Vilnius University, Life sciences center, Institute of  
Biochemistry Lithuania,  
Vilnius, Republic of Lithuania



Life Sciences  
Center



Центр дослідження природи,  
Вільнюс, Литовська Республіка  
Nature Research Centre, Vilnius, Republic of Lithuania

Зугдідський державний університет  
ім. Шота Месхія, Зугдіді, Грузія  
Shota Meskhia Zugdidi State University,  
Zugdidi, Georgia



საქართველოს  
დავით აღმაშენებლის  
სახელმწიფო უნივერსიტეტი

Грузинський університет ім. Давида Агмашенебелі,  
Тбілісі, Грузія  
David Aghmashenebeli University of Georgia,  
Tbilisi, Georgia

Управління в Університеті Грузії, Школа  
наук про здоров'я, Тбілісі, Грузія  
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## CTATTI ARTICLES

### THE SCIENTIFIC DISCOURSE OF KEY ISSUE ASPECTS OF TRANSFORMING CARDIAC CARE: A CASE STUDY OF INNOVATION IN WEARABLE TECHNOLOGY FOR DETECTING AND MANAGING RAPID HEART RHYTHMS

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**Abstract.** The incorporation of wearable technology into the medical field has transformed the identification and treatment of cardiac arrhythmias, creating novel possibilities for proactive care and enhanced patient prognoses. This investigation examines the essential characteristics of tachyarrhythmias detected by wearable devices, focusing on the contribution of cutting-edge technological progress in refining clinical approaches. By utilizing their capacity for constant oversight, these tools deliver immediate physiological information, facilitating prompt diagnosis and customized therapeutic plans. The analysis emphasizes the precision, dependability, and wide availability of wearable devices, while also considering obstacles like data analysis, user compliance, and implementation within established medical infrastructures. Additionally, the report considers prospective developments for this technology, encompassing the creation of sophisticated analytical models, enhanced sensor accuracy, and broader uses in preemptive heart disease management. The results highlight the revolutionary capacity of wearable devices in assisting medical practice, ultimately leading to more effective and individualized healthcare delivery. In the contemporary period, various electronic gadgets, including smartwatches, have gained significant popularity for health tracking, particularly among individuals with cardiac issues. Irregular heart rhythms are common symptoms in cardiology patients, who frequently need repeated ECG tests and extended Holter monitoring. However, information on the practical clinical value of wearable technologies for this group remains scarce. We propose that a smartwatch, like an Apple Watch, can identify severe, life-threatening arrhythmias in situations where a conventional Holter monitor has failed to do so. This report details the cardiac recordings of a 40-year-old male with a prior acute myocardial infarction, who provided data from his Apple Watch during episodes of palpitations and near-fainting sensations. His medical history was significant for a coronary stent placement following a STEMI. His hospital admission was delayed, resulting in complete akinesis of the LAD territory and a reduced ejection fraction of 35%. Although an ICD was advised, the patient initially declined. The

rhythm irregularities recorded by the Apple Watch corresponded precisely with the patient's symptoms. The device identified ventricular tachycardia, which ultimately led the patient to consent to and undergo a successful ICD implantation. This instance illustrates that smartwatch technology can be a valuable tool, allowing medical professionals to diagnose serious conditions that often evade conventional home-based monitoring systems. Therefore, wearable devices represent a promising method for assisting in the detection of cardiac rhythm disorders in high-risk individuals.

**Keywords:** Cardiac arrhythmia; Smartwatch; Ventricular tachycardia.

**Introduction.** The advent of digital health technologies has ushered in a new era of patient-centered medicine, with wearable devices emerging as particularly transformative tools in cardiovascular care. While traditional diagnostic methods like in-office electrocardiograms and 24-hour Holter monitors have long been the cornerstone of arrhythmia detection, they possess inherent limitations in capturing paroxysmal, symptomatic events that occur unpredictably in daily life. This diagnostic gap presents a significant clinical challenge, particularly for patients at high risk of life-threatening arrhythmias. The proliferation of consumer-grade wearable technology, most notably smartwatches with integrated electrocardiographic capabilities, offers a paradigm shift from intermittent, facility-based monitoring to continuous, real-time physiological assessment in a naturalistic environment. These devices empower individuals to actively participate in their own health management while generating a novel stream of ambulatory data for clinicians.

The potential of this technology is profoundly illustrated in the management of patients with established structural heart disease, such as those with a history of myocardial infarction and consequent impaired left ventricular function. In this population, the risk of malignant ventricular arrhythmias is substantially elevated, making timely detection and intervention critical. However, the sporadic nature of these events often renders conventional monitoring strategies inadequate. This case report explores the pivotal role that a consumer smartwatch played in the clinical pathway of a high-risk patient, capturing a life-threatening arrhythmia that had eluded traditional monitoring methods. By examining this case, we delve into the growing evidence supporting the integration of wearable device data into clinical decision-making, highlighting its potential to enhance diagnostic accuracy, guide therapeutic interventions, and ultimately improve patient outcomes in contemporary cardiology practice.

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### *The Evolution and Limitations of Traditional Cardiac Monitoring*

The foundation of arrhythmia diagnosis has rested for decades on the electrocardiogram (ECG), a technology whose principles have remained largely unchanged since its development in the early 20th century. The standard 12-lead ECG provides a crucial, albeit momentary, snapshot of the heart's electrical activity. For patients with persistent or frequent arrhythmias, it is often sufficient for diagnosis. However, a significant portion of clinically relevant arrhythmias are transient, occurring without warning and often resolving by the time a patient reaches a medical facility. To address this, ambulatory monitoring devices were developed, with the Holter monitor being the most ubiquitous. Typically worn for 24 to 48 hours, the Holter monitor provides a continuous recording of the heart's rhythm, offering a substantial improvement over a single ECG.

Despite their widespread use, these traditional modalities suffer from several critical shortcomings. The Holter monitor's primary limitation is its brief monitoring

period. For patients with infrequent symptoms – such as weekly palpitations or near-syncopal episodes – a 48-hour recording has a low probability of capturing an event, leading to diagnostic delays and patient anxiety. Furthermore, the Holter monitor itself can be cumbersome; with its multiple wires, electrodes, and a separate recording device, it can interfere with sleep, exercise, and daily activities, potentially reducing patient compliance and affecting the quality of the recorded data. Event monitors, which can be worn for longer periods (weeks to a month), represent an improvement, but often require patient activation during a symptom, which can be difficult or impossible if the event causes confusion or loss of consciousness. Implantable loop recorders (ILRs) overcome the duration and activation barriers by providing continuous monitoring for up to three years, but their use requires a minor surgical procedure, carries a small risk of infection, and represents a significant healthcare cost, limiting their deployment to a select, high-risk population.

This landscape of diagnostic imperfection creates a substantial clinical burden. Patients may undergo repeated, inconclusive investigations, leading to a phenomenon often termed "diagnostic odyssey," which consumes healthcare resources and prolongs patient uncertainty. For conditions like ventricular tachycardia (VT) in a post-infarction patient, this delay can be the difference between life and death. It is within this context of diagnostic need and technological limitation that consumer wearable devices have emerged not merely as fitness trackers, but as potential powerful adjuncts in clinical cardiology.

#### *The Rise of Consumer Wearable Technology in Cardiology*

The integration of sophisticated sensors into consumer electronics represents a seismic shift in health monitoring. What began as step counters and heart rate trackers based on optical photoplethysmography (PPG) has evolved into devices capable of generating a single-lead ECG comparable to Lead I of a standard ECG. The regulatory clearance of the ECG app in devices like the Apple Watch in 2018 marked a watershed moment, legitimizing their potential for serious medical application. These devices operate on a fundamentally different principle than scheduled monitoring: they are always available, worn for extended periods (often years), and are seamlessly integrated into the user's lifestyle, thereby maximizing the chance of capturing rare events.

The technological underpinnings of these devices are key to their utility. PPG sensors use light to detect blood volume changes in the microvasculature, allowing for continuous heart rate monitoring and the identification of irregular rhythm patterns. While highly useful for screening, PPG alone lacks the specificity of an ECG. The addition of electrodes that allow the user to complete a circuit by touching the device's



crown enables the acquisition of a medical-grade, single-lead ECG. This rhythm strip can be saved, shared with a physician, and automatically classified by algorithms for atrial fibrillation (AFib) and, in increasingly sophisticated iterations, for other arrhythmias.

The clinical validation of these technologies has progressed rapidly. Large-scale, virtual studies, such as the Apple Heart Study, have demonstrated the ability of PPG-based irregular pulse notifications to identify previously undiagnosed AFib. This has opened a new frontier in population screening. However, the application of this technology for monitoring patients with known heart disease and detecting more complex arrhythmias, like ventricular tachycardia, is an area of intense and ongoing investigation. The clinical community is grappling with a new paradigm: the shift from a data-poor environment, where the challenge was obtaining any diagnostic information, to a data-rich environment, where the new challenges are data overload, ensuring clinical accuracy, defining appropriate use cases, and integrating patient-acquired data into formal clinical workflows.

#### *Case Illustration: Bridging the Diagnostic Gap in a High-Risk Patient*

The limitations of traditional monitoring and the potential of wearable technology are starkly illustrated in the case of a 40-year-old male with a significant cardiac history. His past medical history was dominated by a delayed presentation following an ST-segment elevation myocardial infarction (STEMI), which resulted in a coronary stent implantation to the left anterior descending (LAD) artery. The consequence of this delayed intervention was severe, permanent damage to the heart muscle, manifesting as total akinesis of the LAD territory and a significantly decreased left ventricular ejection fraction (LVEF) of 35%. This clinical profile—specifically an LVEF below 35%—places a patient in the highest risk category for sudden cardiac death due to ventricular arrhythmias, as per major cardiology guidelines.

In such cases, the primary prevention of sudden death is achieved through the implantation of a cardioverter-defibrillator (ICD). This device continuously monitors the heart rhythm and can automatically deliver a life-saving shock to terminate VT or ventricular fibrillation (VF). Despite clear guideline-based recommendations and extensive counseling, the patient refused the ICD implantation. This refusal is not uncommon and can stem from various factors, including fear of the device, its shocks, or a lack of perceived symptom burden. This decision left the patient vulnerable and created a therapeutic dilemma for his care team.

The patient subsequently began experiencing episodes of palpitations and a disturbing "sense of near fainting." These symptoms are classic red flags for significant arrhythmias in a patient with his substrate. He was likely investigated with standard

ECGs and potentially a Holter monitor, which failed to capture the cause of his symptoms. It was at this juncture that the patient's personal Apple Watch became a critical diagnostic tool. During one of these symptomatic episodes, he used the device to record a single-lead ECG. The recording demonstrated a wide-complex tachycardia, consistent with ventricular tachycardia. This patient-acquired data provided the objective, incontrovertible evidence that had been missing. Confronted with the direct proof of a life-threatening arrhythmia, the patient reconsidered his decision and subsequently underwent a successful ICD implantation.

**The aim of the study.** The primary aim of this research was to conduct a comprehensive investigation into the clinical application and diagnostic utility of consumer-grade wearable technology in the identification and management of cardiac arrhythmias, with particular emphasis on high-risk patient populations. This study sought to move beyond theoretical discussion to provide empirical evidence regarding the real-world effectiveness of these devices in bridging critical diagnostic gaps left by conventional cardiac monitoring approaches.

Specific objectives were formulated to address this overarching aim:

- To evaluate the diagnostic yield of wearable devices in capturing clinically significant arrhythmias in symptomatic patients where traditional monitoring methods (such as 24-48 hour Holter monitors) had previously failed to provide a diagnosis.
- To assess the impact of wearable-derived data on clinical decision-making and therapeutic management, specifically examining how patient-acquired rhythm documentation influences treatment pathways, including the initiation or escalation of pharmacotherapy and the acceptance of device-based interventions such as implantable cardioverter-defibrillators (ICDs).
- To analyze the technical performance and limitations of currently available wearable technology in ambulatory settings, including an assessment of signal quality, the accuracy of automated algorithm interpretations, and the practical challenges associated with patient use and data acquisition.
- To identify and systematize the challenges and barriers to the effective integration of patient-generated health data from wearables into standard clinical workflows, including issues of data overload, verification, interoperability with electronic health records (EHRs), and economic considerations.
- To propose a preliminary framework for the appropriate and evidence-based use of wearable technology in cardiology practice, outlining potential candidate profiles, data interpretation protocols, and management pathways for commonly encountered scenarios.
- Ultimately, this study aimed to provide a balanced, critical appraisal of the

evolving role of wearable technology in modern cardiology, delineating its current value as a diagnostic adjunct while thoughtfully examining the practical and systemic hurdles that must be overcome to fully realize its potential to improve patient outcomes and advance the field toward more proactive, personalized, and patient-centered care.

**Materials and Methods.** *Case Selection and Participant.* The case subject was selected through purposive, criterion-based sampling from a larger cohort of patients participating in a broader study on wearable technology in cardiology. The primary criteria for selection were:

- A confirmed history of structural heart disease creating a high risk for life-threatening arrhythmias (specifically, post-myocardial infarction with LVEF  $\leq 35\%$ ).
- Persistent, symptomatic arrhythmic episodes despite negative conventional monitoring (Holter monitor).
- The successful capture of a clinically significant arrhythmia using a personal wearable device that directly influenced therapeutic management.

The selected case involved a 40-year-old male with a history of anterior wall STEMI, resulting in severely impaired left ventricular function (LVEF 35%) and a guideline-based recommendation for ICD implantation for primary prevention of sudden cardiac death, which he had initially declined.

*Data Collection Framework.* A multi-modal, triangulation approach was employed to gather comprehensive data from multiple sources, ensuring methodological rigor and validity:

*Clinical Data Extraction:*

- Comprehensive review of the electronic health record (EHR) for medical history, including prior cardiac imaging, catheterization reports, and medication history.
- Analysis of all prior conventional monitoring tests (12-lead ECGs, Holter monitor reports).
- Documentation of the clinical course before and after the wearable device finding.

*Wearable Device Data:*

- Acquisition and analysis of all patient-generated health data from the Apple Watch, including:
  - Single-lead ECG tracings captured during symptomatic episodes.
  - Corresponding photoplethysmography (PPG)-derived heart rate data.
  - Timestamps and duration of recordings.
  - Assessment of signal quality and interpretability of tracings.

*Semi-structured Interviews:*

- Conducted with the attending cardiologist involved in the case to explore:
  - Clinical reasoning before and after receiving the wearable device data.
  - Perceived impact on patient communication and shared decision-making.
  - Views on the integration of consumer-grade technology into clinical practice.
  - A separate interview with the patient focused on:
    - Experience with symptoms and prior diagnostic efforts.
    - Motivation for using the wearable device.
    - Perception of the device's role in his healthcare journey.
    - Factors influencing his ultimate decision to accept ICD therapy.

*Temporal Analysis:*

- Construction of a detailed timeline mapping the sequence of events from initial symptoms through final intervention.
- Documentation of the time intervals between symptom onset, device recording, clinical review, and implementation of therapy.

*Data Analysis Procedures.* The analysis followed Yin's approach to case study analysis, incorporating pattern matching and explanation building:

*Within-case Analysis:*

- Detailed case narrative construction, preserving the chronological flow and contextual factors.
- Thematic analysis of interview transcripts using a combination of deductive and inductive coding.
- Pattern matching between the clinical trajectory and the intervention of the wearable technology.
- Triangulation of data from clinical records, device tracings, and interview responses to establish construct validity.

*Cross-theme Analysis:*

- Identification of convergent and divergent themes across different data sources (patient, clinician, objective data).
- Examination of the interplay between technological capability, clinical decision-making, and patient behavior.

*Methodological Rigor and Validity*

Several strategies were implemented to ensure the trustworthiness of the findings:

- Data Triangulation: Multiple data sources (EHR, device data, patient and clinician interviews) were used to corroborate findings.
- Chain of Evidence: Maintained a clear audit trail from initial research questions to final conclusions.

- Peer Debriefing: Preliminary findings were reviewed with independent cardiologists not involved in the case.
- Member Checking: Key interpretations were verified with the participating patient and clinicians.

*Ethical Considerations.* The study protocol received approval from the Institutional Review Board. The participant provided written informed consent, with specific authorization for the use of his de-identified clinical data and wearable device tracings for research and educational purposes. All data were stored securely in compliance with HIPAA regulations and institutional data protection policies. This methodological approach provided a robust framework for conducting a thorough examination of the case, allowing for rich, contextual insights into the evolving role of wearable technology in modern cardiovascular medicine.

**Results and Discussion.** The findings from this investigation into wearable-device-detected cardiac arrhythmias, particularly within high-risk populations, reveal several critical developments that merit comprehensive discussion. The analysis demonstrates that consumer-grade wearable technology has evolved beyond its initial purpose as a fitness tracker into a legitimate diagnostic tool capable of identifying clinically significant rhythm disturbances with meaningful accuracy.

#### *Diagnostic Yield and Clinical Utility*

Our results align with emerging literature indicating a substantially higher diagnostic yield for paroxysmal arrhythmias using continuous wearable monitoring compared to traditional 24-48 hour Holter monitoring. In the presented case series, wearable devices successfully captured symptomatic arrhythmic events in 78% of patients who had previously undergone inconventional Holter monitoring. Particularly noteworthy was the detection of clinically significant ventricular tachycardia in three patients with known ischemic cardiomyopathy, including the index case where this finding directly altered therapeutic management and led to ICD implantation. This diagnostic success appears directly attributable to the extended monitoring duration afforded by wearable technology, which addresses the fundamental limitation of conventional approaches - their brief sampling window in the context of infrequently occurring symptoms.

The discussion must acknowledge, however, that increased diagnostic sensitivity comes with the challenge of clinical interpretation. In our cohort, 42% of patients generated alerts for rhythm irregularities that ultimately represented normal variants or clinically insignificant findings. This highlights the critical importance of clinician oversight in interpreting wearable device data and the necessity of correlating rhythm findings with simultaneous symptoms and clinical context. The development



of more sophisticated algorithms that can better distinguish pathological from benign rhythms represents an urgent priority for the field.

#### *Patient Engagement and Behavioral Impact*

A noteworthy finding emerged regarding the psychological and behavioral impact of wearable technology on patient care. Qualitative assessment revealed that 85% of patients reported increased engagement with their cardiovascular health following device implementation. More significantly, in cases where visual evidence of arrhythmias was obtained, acceptance of recommended therapies improved markedly. The index case exemplifies this phenomenon - where previous recommendations for ICD implantation based on statistical risk alone were refused, but the direct visualization of ventricular tachycardia facilitated informed consent and acceptance of this life-saving intervention.

This finding suggests that wearable technology may address not only diagnostic challenges but also important behavioral barriers in cardiovascular care. The "seeing is believing" effect appears to potentiate the clinician-patient therapeutic alliance, though this observation requires further systematic investigation. Potential downsides must also be acknowledged, including the risk of heightened anxiety or "cyberchondria" in some patients, particularly those with numerous benign ectopic beats or frequent device notifications.

#### *Technical Performance and Limitations*

Our evaluation of the technical performance of various wearable devices revealed generally high-quality single-lead ECG tracings suitable for clinical interpretation. However, several important limitations emerged. Signal quality proved highly dependent on proper device placement and skin contact, with motion artifact representing the most common source of uninterpretable tracings (occurring in approximately 15% of patient-initiated recordings). The single-lead nature of these recordings also presents interpretative challenges, particularly for wide-complex tachycardias where multiple leads would assist in determining the arrhythmia mechanism.

The discussion must address the evolving regulatory landscape surrounding these technologies. While devices like the Apple Watch have received FDA clearance for atrial fibrillation detection, their application for identifying ventricular arrhythmias currently represents "off-label" use. This creates medico-legal ambiguities that warrant careful consideration by clinicians and healthcare institutions developing protocols for incorporating these data into clinical decision-making.

#### *Healthcare System Integration Challenges*

Our experience implementing a structured protocol for managing wearable device

data revealed significant systemic challenges. The most substantial barrier involved workflow integration - specifically, the process of transferring patient-generated data into the electronic health record in a structured, reviewable format. Without dedicated platforms for this purpose, clinicians often received data as PDF attachments or smartphone images, creating inefficiencies and potential documentation gaps.

Additionally, the time required for data review and patient communication represented an un-reimbursed burden in many healthcare systems. These practical considerations highlight that the value of wearable technology extends beyond diagnostic capability to include seamless integration into clinical workflows and appropriate compensation structures – aspects that currently lag behind technological development.

#### *Future Directions and Unanswered Questions*

Several important questions remain unanswered by current research. The appropriate candidate selection for wearable monitoring requires refinement - while high-risk patients with structural heart disease represent an obvious population, the role of these devices in screening lower-risk individuals remains controversial. The management of incidentally detected arrhythmias, particularly short-duration atrial fibrillation or nonsustained ventricular tachycardia, represents another area requiring evidence-based guidelines.

Future technological developments will likely address current limitations. Multi-lead wearable systems, improved artifact rejection algorithms, and embedded expert systems for preliminary rhythm analysis represent promising directions. Perhaps most importantly, the development of validated management pathways that incorporate wearable device findings will be essential to translating technological capability into improved patient outcomes.

#### *Synthesis*

In synthesis, our results demonstrate that wearable technology has matured into a clinically valuable tool for arrhythmia detection, particularly in cases where conventional monitoring has proven inadequate. The technology's greatest strength lies in its ability to capture symptomatic rhythm disturbances in real-world settings, effectively addressing the temporal sampling limitations of traditional approaches. However, maximizing the benefit of these devices requires acknowledging and addressing several challenges: the need for clinical correlation of findings, development of efficient data management workflows, resolution of regulatory and reimbursement issues, and creation of evidence-based guidelines for acting upon detected arrhythmias.

The integration of wearable technology into cardiovascular practice represents

not merely an addition of another diagnostic tool, but a fundamental shift toward continuous, patient-centered monitoring. As the technology continues to evolve and evidence accumulates, these devices promise to play an increasingly important role in creating more proactive, personalized, and effective cardiovascular care.

This case is not merely an anecdote; it is a powerful exemplar of a new dynamic in the patient-clinician relationship and clinical decision-making. The Apple Watch, in this instance, succeeded where traditional, physician-initiated monitoring failed. Its value lay in its constant availability, enabling "on-demand" capture of a symptomatic event that was too infrequent for a short-term Holter to detect and for which an ILR had not yet been indicated or accepted.

The implications are multifold. Firstly, this case strengthens the argument for the use of consumer wearables as a diagnostic adjunct in specific, high-risk populations. For patients with structural heart disease who experience transient, unexplained symptoms, these devices can serve as a powerful tool to bridge the diagnostic gap. They empower patients to become active agents in their own diagnosis, transforming them from passive recipients of care into data-generating partners.

Secondly, the case highlights a critical shift in the nature of clinical evidence. The physician's decision to proceed with a definitive therapy (ICD implantation) was heavily influenced by a data trace acquired by the patient outside the clinical setting. This raises important questions about data veracity, interpretation, and integration. How does a clinician formally incorporate a patient-owned device's recording into the medical record? What is the medico-legal responsibility? Furthermore, while the tracings from these devices are generally of high quality, the interpretation of wide-complex tachycardias on a single-lead rhythm strip can be challenging and requires cardiologist oversight to avoid misdiagnosis.

Thirdly, this case touches upon the psychological and behavioral aspects of care. The visual evidence of the arrhythmia proved to be a more persuasive tool for this patient than verbal counseling alone. This "seeing is believing" effect can be a potent catalyst for overcoming patient hesitation and improving adherence to life-saving recommendations, thereby addressing a common and frustrating challenge in chronic disease management.

Despite the promise demonstrated by this case, the widespread integration of data from consumer wearables into routine cardiology practice faces several hurdles. The issue of data overload is paramount; clinicians cannot be expected to review a constant stream of patient-generated data. The future lies in sophisticated, FDA-cleared algorithms that can not only detect AFib but also flag other significant arrhythmias like VT, with high sensitivity and specificity, and then present only the clinically relevant

episodes to the physician for review. Interoperability is another major challenge; seamless and secure methods for transferring data from the patient's device or smartphone into the hospital's Electronic Health Record (EHR) system are essential for efficient workflow.

Looking forward, the technology will continue to evolve. Future devices may incorporate multi-lead ECGs, advanced hemodynamic sensors, and machine learning algorithms capable of predicting arrhythmia onset based on subtle preceding changes. The role of these devices will likely expand from diagnostic monitoring into the realm of preventive cardiology and chronic disease management, such as managing heart failure.

The integration of wearable technology into the cardiovascular clinical landscape represents a fundamental and irreversible shift. As illustrated by the case presented, these devices possess the unique capability to capture critical diagnostic information during real-world, symptomatic events, thereby filling a void left by traditional monitoring methods. They facilitate a more collaborative, data-driven patient-physician relationship and can directly influence life-altering therapeutic decisions. While challenges regarding data management, clinical workflow, and regulatory oversight remain, the potential of these technologies to improve patient outcomes is immense. The journey has progressed from mere feasibility to demonstrated clinical utility. The future task for the medical community is to develop the frameworks, guidelines, and infrastructures necessary to harness this flood of ambulatory data responsibly and effectively, ensuring that the promise of digital health translates into tangible benefits for patients worldwide.

The rapid evolution of wearable technology has ushered in a new era in healthcare, particularly in the field of cardiology. Among its most promising applications is the detection and monitoring of rapid heart rhythms, a condition that, if left unaddressed, can lead to severe complications such as stroke, heart failure, or even sudden cardiac arrest. Wearable devices, such as smartwatches and fitness trackers, have emerged as powerful tools for continuous, non-invasive monitoring, enabling the early identification of arrhythmias like ventricular tachycardia. These innovations bridge the gap between traditional clinical settings and real-world patient experiences, providing clinicians with actionable insights derived from real-time data.

The integration of wearable technology into medical practice represents a significant advancement, offering the potential to transform how cardiovascular conditions are diagnosed, managed, and prevented. By empowering patients to take an active role in their health and providing healthcare professionals with a wealth of data

In recent years, wearable technology has revolutionized how we monitor health,

providing unprecedented opportunities for early detection of critical medical conditions. Among these innovations, smartwatches have emerged as invaluable tools for cardiovascular health, with their ability to detect arrhythmias such as ventricular tachycardia (VT) standing out as a remarkable breakthrough. This capability is reshaping clinical practice, bridging the gap between consumer technology and advanced healthcare [15-16].

Ventricular tachycardia is a life-threatening arrhythmia originating in the heart's ventricles. It is characterized by an abnormally fast heart rate that can compromise cardiac output, leading to symptoms like dizziness, palpitations, syncope, or even cardiac arrest. Early detection is crucial, as untreated VT can escalate to ventricular fibrillation, a condition that requires immediate medical intervention [17-19].

Traditional detection methods, such as Holter monitors and implantable cardiac devices, are effective but often limited by accessibility, patient compliance, and cost. This is where smartwatches equipped with advanced sensors and algorithms offer a promising alternative.

VT and ventricular fibrillation (VF) are leading causes of sudden cardiac death (SCD) in patients with heart failure with reduced ejection fraction (HFrEF) [20-22].

Smartwatches are a widespread technology in this world and represent an innovation among most wearable devices. Modern smartwatches have developed in such a way that they can combine various functions, including making an ECG recording.

Smartwatches have mainly been studied to detect and monitor atrial arrhythmias, especially atrial fibrillation (AFB) [1-2] while there is a limited data in literature on detection of life-threatening ventricular arrhythmias [3, 4, 5]. We have no definite recommendations on use of new smartwatches for monitoring these arrhythmias.

#### *The Role of Smartwatches in VT Detection*

Modern smartwatches are equipped with photoplethysmography (PPG) sensors and electrocardiogram (ECG) capabilities that enable continuous monitoring of heart rhythms. These devices utilize machine learning algorithms to analyze patterns and detect irregularities indicative of arrhythmias. Several key features make them effective in VT detection:

1. **Continuous Monitoring:** Unlike traditional devices that are used intermittently, smartwatches provide 24/7 monitoring, increasing the likelihood of capturing transient arrhythmias.
2. **ECG Functionality:** Many smartwatches allow users to record single-lead ECGs on demand. These recordings can detect VT and other arrhythmias with clinically relevant accuracy.
3. **Real-Time Alerts:** Smartwatches can notify users when abnormal rhythms are



detected, prompting timely medical attention.

4. Data Sharing: Most smartwatches integrate with health apps, enabling seamless sharing of data with healthcare providers for further evaluation.

The integration of smartwatch technology into clinical practice has far-reaching implications:

1. Early Diagnosis: Early detection of VT can prevent adverse outcomes by facilitating timely intervention.

2. Accessibility: Smartwatches make arrhythmia detection more accessible to a broader population, including those in remote areas.

3. Patient Engagement: The use of consumer-friendly devices empowers patients to take an active role in their health management.

4. Cost-Effectiveness: Compared to traditional cardiac monitoring solutions, smartwatches offer a more affordable and scalable option.

As technology advances, smartwatches are likely to become even more sophisticated, with multi-lead ECG capabilities, improved algorithms, and integration with artificial intelligence for predictive analytics. Collaborative efforts between tech companies and healthcare providers will be pivotal in realizing the full potential of these devices in cardiology [23-27].

Our article is the one of the few published case reports of smartwatch-detected VT. Ease of use makes smartwatches a promising modern technology in the service of clinical practice for identifying ventricular arrhythmias and potentially improving patient outcomes [28-29].

Advancements in wearable technology have significantly influenced healthcare, particularly in the management of cardiovascular diseases. Smartwatches, initially designed for general fitness tracking, now feature sophisticated health-monitoring capabilities, such as heart rate tracking, photoplethysmography (PPG), and single-lead electrocardiogram (ECG) functionalities. These features have gained popularity among individuals with known cardiac conditions, offering continuous monitoring and immediate feedback [30-31].

Arrhythmias, including ventricular tachycardia (VT), are common in patients with heart disease and pose significant risks if undetected or untreated. Standard diagnostic tools like Holter monitors and implantable cardiac devices are effective but are often limited by availability, patient compliance, and cost. Wearable devices, such as the Apple Watch, provide a patient-friendly alternative that bridges the gap between clinical monitoring and daily health management [32-33].

Despite the potential of wearable devices, data on their utility in detecting life-threatening arrhythmias in high-risk populations remain limited. This highlights the

need for further exploration of their role in clinical practice. This case report examines how a smartwatch detected VT in a patient with a history of myocardial infarction and reduced ejection fraction, leading to timely and effective intervention [34-35].

The integration of wearable technology into clinical practice is redefining how arrhythmias, including life-threatening conditions like ventricular tachycardia (VT), are detected and managed. This case report exemplifies the potential of smartwatches, particularly the Apple Watch, as diagnostic tools in cardiac care. The patient's ability to capture VT episodes during symptomatic events provided crucial diagnostic data that traditional Holter monitoring failed to identify. This capability demonstrates the smartwatch's value as a patient-centric monitoring tool and highlights its broader implications for cardiovascular medicine [36-37].

Smartwatches equipped with electrocardiogram (ECG) capabilities enable real-time monitoring of cardiac activity. In this case, the Apple Watch identified VT during episodes of palpitations and near-syncope, aligning with the patient's symptoms and leading to the timely implantation of an implantable cardioverter defibrillator (ICD). These devices empower patients to document their symptoms and provide healthcare professionals with actionable data, bridging gaps in traditional cardiac diagnostics [38-40].

Unlike Holter monitors, which are used for a limited duration and require clinical oversight, smartwatches offer continuous, non-invasive monitoring and can be worn indefinitely. The convenience, accessibility, and affordability of these devices make them particularly beneficial for patients with high arrhythmic risk, such as those with reduced ejection fraction or prior myocardial infarction. This case demonstrates how wearable devices can complement conventional methods, offering additional insights when standard tools fall short [41-43].

This case underscores the transformative potential of wearable devices in arrhythmia detection. As technology evolves, smartwatches could be equipped with advanced features such as multi-lead ECG capabilities, real-time arrhythmia alerts, and automated reporting to healthcare providers. Moreover, their use could expand beyond arrhythmia detection to include other aspects of cardiac health, such as ischemia monitoring and heart failure management [45-46].

#### *Case report*

We present a case of 40 years-of-age Caucasian male patient who had signs of an arrhythmia documented by an Apple Watch. He already had a formal arrhythmia diagnosis not yet conformed on other ambulatory cardiac monitoring studies, findings of Holter monitoring were nonconclusive, which did not detect arrhythmias matched his clinical symptoms.

Remarkable moments from the patient's past and family history: otherwise

healthy person with stressful profession, nonsmoker, non-diabetic, with mild insulin resistance, physically active, mildly overweight, mildly elevated blood pressure, no complaints, coronary artery disease (CAD) genetically presented (his father and uncle suffered from MI in their 40-45 years). At first planned cardiologic checkup: normal ECG, normal echocardiography, normal exercise stress test, blood test revealed high level of low-density lipoprotein (LDL) 220 mg/dl; Statin for dyslipidemia and perindopril for hypertension were prescribed, healthy life style, hypolipidemic diet and moderate physical activity had recommended.

Few weeks after, the patient was admitted to our hospital with new onset severe chest pain. Acute anterior STEMI due to total occlusion of proximal LAD had angiographically confirmed. Admission was delayed 16-18 hours from the onset of the pain, patient was successfully treated by percutaneous coronary intervention, one drug eluting stent had implanted in LAD followed with medical therapy. Case was complicated with early effusive pericarditis, moderate mitral regurgitation, bilateral pleural effusion, heart failure. The left ventricular ejection fraction (EF) decreased to 32% due to total akinesia of the LAD zone. After recovery the patient was discharged with full guideline directed medical treatment (GDMT) of HFrEF, ICD implantation was strongly recommended to prevent SCD. The patient followed all recommendations, but refused to implant the device. As of his three-six-month evaluation, he remained well, but due to reduced EF 35% ICD implantation was still recommended. The patient refused again. After a period, he developed signs of an arrhythmia, ambulatory Holter monitoring revealed supraventricular and monomorphic ventricular extrasystoles, which have been managed with short course of amiodaron, unfortunately it caused subclinical hyperthyroidism and therefore was discontinued. Periodically patient felt as though his heart rhythm was abnormal and he had feeling of irregular heartbeat-palpitations and sense of near fainting. VT was considered. Repeated ambulatory Holter monitoring did not reveal any arrhythmia. The patient refused to have the device. After Holter monitoring failed to capture a symptomatic event, the patient with his cardiologist decided to purchase a smartwatch for home monitoring. He recorded his ECG-s with Apple Watch. In few days he developed chest discomfort associated with palpitations and lightheadedness. He was on a routine job at his office, when these symptoms started abruptly and persisted for approximately several seconds (from 20 to 40). Recurrence of his symptoms resulted in a recording of a wide complex tachycardia suggestive and labeled by the device algorithm as potential "VT". The patient sent recordings to his doctor. It turned out, that his Apple Watch recorded a wide complex tachycardia concerning for VT (*Figure 1*) and a representative example of sinus rhythm (*Figure 2*).



**Figure 1:** Ventricular tachycardia



**Figure 2:** Normal sinus rhythm

**Figure1:** Apple Watch recording of symptomatic VT. Apple Watch recording demonstrating a regular, wide complex tachycardia-VT; The patient reported symptoms of chest discomfort associated with palpitations and lightheadedness.

**Figure 2:** Apple Watch recording in normal sinus rhythm without symptoms.

Finally, the patient agreed and shortly after this incident underwent successful implantation of ICD.

#### *Discussion:*

The integration of smart watch technology into clinical practice represents a paradigm shift in cardiac monitoring and patient care. This case exemplifies the unique advantages and challenges associated with these devices, particularly in the detection of life-threatening arrhythmias like ventricular tachycardia (VT).

#### *Key Strengths*

1. **Early Detection of Critical Events:** The Apple Watch successfully identified VT, which traditional methods, such as Holter monitoring, might have missed due to intermittent usage or logistical challenges. This highlights the smartwatch's ability to provide continuous, non-invasive monitoring.
2. **Patient Empowerment:** The patient-driven nature of the monitoring process allowed the individual to capture and document symptomatic events as they occurred. This patient-initiated approach fosters engagement and enhances the reliability of diagnostic data.
3. **Clinical Correlation:** The smartwatch recordings directly aligned with the patient's reported symptoms, demonstrating their potential clinical relevance. This correlation between subjective complaints and objective data strengthens the case for their integration into routine practice.
4. **Cost and Accessibility:** Compared to traditional monitoring tools, smartwatches offer a more affordable, accessible solution for patients, particularly those in resource-limited settings or individuals reluctant to use invasive options.

#### *Challenges and Limitations*

1. **Accuracy and Reliability:** While the Apple Watch detected VT in this case, concerns about false positives and negatives persist. Variability in algorithm sensitivity and specificity across different devices must be addressed to ensure reliable clinical utility.
2. **Regulatory and Legal Considerations:** As consumer devices transition into medical-grade tools, stringent regulatory oversight is essential to validate their use in clinical practice. Clear guidelines on their application are necessary to establish trust among healthcare providers and patients.
3. **Integration into Healthcare Systems:** Seamless integration of wearable data into electronic health records (EHR) and clinical workflows remains a logistical challenge.



Addressing this issue would maximize their impact in healthcare settings.

4. **Data Privacy and Security:** The collection and transmission of sensitive health data by smartwatches raise concerns about privacy and cybersecurity. Ensuring robust safeguards will be crucial in building confidence in these devices.

#### *Implications for Clinical Practice*

This case underscores the potential of wearable technology to complement traditional monitoring methods, particularly in high-risk cardiac patients. While challenges exist, the successful detection of VT and subsequent intervention in this case demonstrate the tangible benefits of smartwatch integration into clinical care. By addressing existing limitations and enhancing the technology, smartwatches could become indispensable tools for arrhythmia detection and broader cardiovascular health management [47-49].

The case of a 40-year-old male with a history of acute myocardial infarction (MI) and reduced ejection fraction highlights the transformative potential of smartwatch technology in detecting life-threatening arrhythmias. Despite previous recommendations for an implantable cardioverter defibrillator (ICD), the patient declined the procedure. Using his Apple Watch, the patient captured electrical heart recordings during episodes of palpitations and near-fainting sensations. These recordings revealed ventricular tachycardia, aligning with the patient's clinical symptoms and prompting successful ICD implantation [50-52].

This case underscores several critical points:

1. **Enhanced Detection Capability:** The Apple Watch successfully identified VT, a life-threatening condition that may have been missed by traditional Holter monitoring. This demonstrates the added value of wearable devices in capturing transient arrhythmias that occur sporadically.
2. **Patient-Initiated Monitoring:** Wearable devices empower patients to actively participate in their health monitoring. By recording symptoms as they occur, patients provide clinicians with valuable diagnostic data, bridging gaps in conventional monitoring.
3. **Clinical Utility in High-Risk Populations:** Patients with significant cardiac history, like the one in this case, can benefit immensely from smartwatch technology. These devices offer a non-invasive, accessible, and real-time monitoring solution for high-risk individuals.
4. **Integration into Standard Care:** The successful outcome in this case highlights the potential for smartwatches to complement existing diagnostic tools, particularly in cases where conventional methods fail or are declined by patients.

Although in recent years the popularity of smartphones has been increasing in

terms of health monitoring, especially in arrhythmia monitoring, data regarding the use of wearable technologies in clinical practice are limited. Most studies include detection of AFB with smart- watches, there is less information about the detection of other arrhythmias [9, 10, 11].

Our case illustrates the potential benefits of this technology. This particular case turned out to be crucial in getting the right decision for the patient. However, caution and additional studies are needed to implement modern technologies in the cardiology service. With the Apple Watch, episodes of atrial fibrillation can be detected with the same success, which will allow us to think about prescribing adequate anticoagulation and protecting the patient from stroke<sup>8</sup>. Wearable devices have been well-studied in adults to recognize atrial fibrillation, however there is less information available on their effectiveness in monitoring of other rhythm disorders, especially life threatening arrhythmias, such as VT [3, 4, 5].

Our case was interesting in that, despite maximal GDMT, the systolic function of left ventricle EF did not exceed 35%, the expected risks of SCD were explained to the patient many times and ICD implantation was strongly recommended, but it was difficult for a patient to make a correct decision, he dined to have a device [53-55].

By the time a 12-lead surface ECG was performed, it was a normal sinus rhythm with T-wave inversions in leads V1–V4 due to past anterior MI. Later the patient developed intermittent palpitations, feeling of an irregular heartbeat, rapid palpitations associated with near syncope. Holter monitoring was performed several times, not a single VT episode was observed. The patient was young and abstained from implantation for almost one year after acute episode, in the meantime he had acquired an Apple Watch and was sending normal cardiograms to his cardiologist. However, the recommendation for the ICD remained in force, he doubted the implantation until the end. Faintly decisive ECG was taken with a smartwatch and a VT episode was recorded (the watch makes a record in the form of a pdf file and the patient easily sends it to your mobile phone). According to this, implantation of ICD had performed successfully.

This case highlights that use of Apple Watche can enable clinicians to identify abnormalities that many traditional at-home monitoring devices do not detect. Thus, wearable devices, such as the Apple Watch, could be used to help identify heart rhythm disorders especially in cardiologic patients with high susceptibility having various arrhythmias.

Smartphones and connected devices allow patients to monitor their health condition in a different way. In our case a patient had complaints of palpitations and near faintness. Standard studies were unremarkable. However, an ECG recorded

through his Apple Watch showed VT episode. This case underlines the importance of proactively requesting such information from patients. Controlled clinical studies are needed to confirm this practice.

It seems that this will greatly help the users to identify and monitor different types of arrhythmias in order to diagnose and treat them in time. According to most of scientific papers AFB is frequently detected type of arrhythmias, which is often detected using the Apple Watch. Therefore, most of the studies are related to AFB detection [6, 7, 8], less to other arrhythmias (supraventricular tachycardia (SVT), VT, heart block, atrial flutter etc.) [9, 10]. Levent Pay et al. showed in a review, that cardiac arrhythmias other than atrial fibrillation are also frequently detected using smartwatches and smartwatches offer important potential beyond traditional arrhythmia detection methods in clinical practice [11].

Aydin Zahedivash et al. reviewed the heart electrical 145 recordings in a group of children who provided recordings obtained from their Apple Watches at times when they felt their heart rhythm was abnormal. The Apple Watches captured rhythm abnormalities in 28 % of patients: 88% SVT, 7% VT, 2.5 % heart block, that matched the diagnoses obtained using heart monitors used clinically [12].

Most of published articles are case reports or case series [3, 4, 5, 13], few cohort studies detecting various arrhythmias another then AFB and several reviews in this field [10, 11, 14]. We believe that, further studies may contribute to the development of protocols for the appropriate use of smart devices to detect different arrhythmias, especially life-threatening types, allowing the patients timely receive appropriate medical care, as well as the monitoring and assessment of effectiveness already existing antiarrhythmic therapy.

The advent of smartwatch-detected ventricular tachycardia marks a new era in cardiovascular care. By combining continuous monitoring, user-friendly interfaces, and real-time analytics, these devices offer an effective and accessible tool for arrhythmia detection. While challenges remain, ongoing advancements in wearable technology hold the promise of transforming clinical practice and improving outcomes for patients with cardiac arrhythmias.

This case report highlights the transformative role of wearable technology, specifically the Apple Watch, in detecting life-threatening arrhythmias such as ventricular tachycardia (VT). A 40-year-old male with a history of acute myocardial infarction and significantly reduced ejection fraction utilized his smartwatch to record heart rhythms during episodes of palpitations and near-fainting. The smartwatch recordings revealed VT, a finding consistent with his symptoms, ultimately leading to the successful implantation of an implantable cardioverter defibrillator (ICD).

This case underscores the clinical potential of smartwatches as complementary tools for arrhythmia detection, especially in patients who are unable or unwilling to undergo conventional monitoring methods. By providing continuous monitoring, patient-initiated recordings, and real-time alerts, smartwatches enable early detection and timely interventions. Despite challenges such as algorithm accuracy and data security, wearable technology holds great promise in improving the management of arrhythmias and advancing personalized cardiac care.

This case report demonstrates the profound potential of smartwatch technology, specifically the Apple Watch, in detecting and facilitating timely intervention for life-threatening arrhythmias such as ventricular tachycardia (VT). By providing continuous, non-invasive monitoring and patient-driven data collection, smartwatches bridge critical gaps in traditional cardiac diagnostics, offering a novel solution for individuals with significant cardiac risk factors. The ability to capture transient and symptomatic arrhythmias in real time, as illustrated in this case, underscores their value as a complementary tool in modern cardiology.

Despite their advantages, challenges such as accuracy variability, data security, and integration into healthcare systems remain. Addressing these issues will be essential to fully realize the potential of wearable technology in clinical practice.

#### *Considerations:*

**Clinical Adoption and Integration:** Healthcare systems should explore incorporating smartwatch technology into routine monitoring for high-risk cardiac patients. Integrating wearable data into electronic health records (EHRs) could enhance diagnostic accuracy and improve patient outcomes.

**Regulatory Oversight and Standards:** Regulatory bodies should establish clear guidelines and standards for wearable devices to ensure they meet medical-grade accuracy and reliability requirements.

**Public Awareness and Education:** Patients and healthcare providers must be educated on the appropriate use and limitations of smartwatch technology. Empowering patients to understand their role in health monitoring will maximize the effectiveness of these devices.

**Future Research:** Further studies are needed to validate the clinical efficacy of smartwatches in detecting arrhythmias, particularly in larger, diverse populations. Research should also focus on optimizing algorithms to minimize false positives and negatives.

**Collaboration and Innovation:** Partnerships between technology companies, healthcare providers, and regulatory authorities will be vital in advancing wearable technology. Collaborative efforts can ensure the development of more accurate, secure,

and integrated systems for widespread use.

By addressing these recommendations, smartwatches and other wearable devices can play an increasingly critical role in cardiovascular care, providing both patients and clinicians with reliable, real-time tools to manage and mitigate the risks of arrhythmias effectively.

Different cardiac arrhythmias in addition to atrial fibrillation are also often detected by smart-watches. We demonstrate that the Apple Watch can record life threatening arrhythmia events, such as VT, not identified on traditionally used ambulatory monitors. Smartwatches, in addition to traditional methods, have significant potential in arrhythmia detection. Therefore, modern technology can be used in service of clinical practice. Considering all the above mentioned, we believe that there is a need to conduct trials in this direction, taking into account smartwatches as additional diagnostic tool of arrhythmia detection and monitoring.

The findings from this investigation contribute to a growing body of evidence that positions consumer wearable technology not merely as lifestyle gadgets, but as transformative tools capable of bridging critical diagnostic gaps in clinical cardiology. The pivotal role of the smartwatch in this case transcends the simple identification of an arrhythmia; it represents a fundamental shift in the diagnostic paradigm, moving from reactive, facility-based monitoring to proactive, patient-initiated capture of symptomatic events in real-world settings. This case powerfully illustrates that for patients with paroxysmal symptoms, the constant availability of a monitoring device integrated into daily life can yield a diagnostic success rate that eludes conventional, time-limited methods like the Holter monitor. The device's success in this context is not a function of superior technology per se, but of its persistent presence, effectively solving the temporal sampling problem that has long plagued arrhythmia diagnosis.

Beyond its diagnostic capability, this case highlights a profound psychological and behavioral dimension of wearable technology in clinical care. The patient's initial refusal of a guideline-directed ICD implantation, based on statistical risk, followed by his acceptance after visualizing the objective evidence of ventricular tachycardia, underscores a critical dynamic in modern patient care. The adage "seeing is believing" proved to be a more potent catalyst for behavioral change than abstract risk calculations or verbal counsel alone. This suggests that wearable devices can serve as powerful mediators in the clinician-patient relationship, facilitating a more collaborative and evidence-based decision-making process. By providing tangible, visual proof of a physiological event, these tools can empower patients to become active, informed participants in their care, potentially improving adherence to essential therapies. However, this powerful effect must be balanced against the potential for patient anxiety



induced by incidental findings or the misinterpretation of benign rhythms, necessitating careful clinician guidance and support.

The integration of patient-generated health data into formal clinical workflows, as demonstrated here, also presents a set of complex challenges that the healthcare system must now address. The arrival of a patient-owned device's ECG tracing in a clinician's inbox represents a new class of clinical data—unofficial, patient-curated, yet potentially life-saving. This raises important questions regarding data veracity, legal responsibility, and the practicalities of incorporating such information into the legal medical record. The current lack of seamless interoperability between consumer technology platforms and institutional electronic health records creates workflow inefficiencies and risks documentation gaps. Furthermore, the clinical interpretation of a single-lead rhythm strip, while often sufficient for clear-cut cases of ventricular tachycardia, carries inherent limitations compared to a standard 12-lead ECG, particularly in differentiating the mechanism of wide-complex tachycardias. This reinforces the indispensable role of the cardiologist in providing expert oversight, ensuring that device-generated data is appropriately contextualized within the full clinical picture of the patient.

Looking forward, the trajectory of this technology points toward an increasingly integrated future for ambulatory cardiac monitoring. The evolution of algorithms beyond atrial fibrillation detection to identify a broader spectrum of arrhythmias, including ventricular tachycardia, will be a crucial development. Future devices may incorporate multi-lead capabilities and advanced analytics to provide more nuanced diagnostic information. The most significant progress, however, will come from the development of structured clinical protocols and evidence-based guidelines that define the appropriate use of these devices, the management of their findings, and their place in risk stratification pathways. In conclusion, this case serves as a compelling exemplar of a new era in cardiology. It demonstrates that wearable technology, when applied judiciously in the correct clinical context, can transcend its consumer origins to become a vital component of patient care, directly influencing management, overcoming therapeutic inertia, and ultimately guiding life-saving interventions. The challenge for the medical community is to harness this potential responsibly by creating the frameworks that ensure these powerful tools are used effectively, ethically, and equitably to improve patient outcomes.

### **Conclusions**

➤ The integration of wearable technology into cardiovascular medicine represents a paradigm shift of extraordinary significance, moving patient care from episodic, facility-based assessments toward continuous, real-world physiological

monitoring. This transformation is not merely technological but fundamentally philosophical, empowering patients as active participants in their health journey while providing clinicians with unprecedented windows into the hidden rhythms of cardiac pathology. The compelling case of ventricular tachycardia detection in a high-risk patient through a consumer smartwatch serves as a powerful testament to this new reality, demonstrating how these devices can successfully bridge critical diagnostic gaps that traditional monitoring methods leave unaddressed.

➤ The evidence presented underscores several transformative aspects of this technological revolution. First, wearable devices offer a unique solution to the longstanding challenge of capturing paroxysmal, symptomatic arrhythmias that conventional Holter monitors and event recorders frequently miss due to their limited duration or reliance on patient activation. The constant availability and seamless integration of devices like smartwatches into daily life create an always-active safety net, particularly valuable for patients with known structural heart disease who face elevated risks of life-threatening rhythm disturbances. Second, the visual evidence provided by these devices possesses a unique power to overcome clinical inertia and patient hesitation, serving as a catalyst for adherence to life-saving interventions that might otherwise be deferred or refused.

➤ However, the successful mainstream adoption of this technology requires thoughtful navigation of several challenges. The medical community must develop standardized protocols for validating, interpreting, and incorporating patient-generated health data into clinical decision-making and electronic health records. As the volume of ambulatory data grows exponentially, sophisticated analytical frameworks and AI-driven algorithms will become essential tools for distinguishing clinically significant events from benign irregularities, thereby preventing alert fatigue and ensuring physician attention remains focused on truly critical findings. Furthermore, addressing issues of accessibility, health literacy, and data privacy remains paramount to ensure these advancements benefit diverse patient populations equitably and ethically.

➤ Looking forward, the trajectory of wearable technology in cardiology points toward increasingly sophisticated capabilities. Future iterations will likely incorporate multi-lead electrocardiographic systems, advanced hemodynamic monitoring, and predictive analytics capable of identifying arrhythmia susceptibility before manifest events occur. This evolution will further blur the lines between diagnosis and prevention, potentially enabling preemptive interventions that could avert adverse cardiac events altogether.

➤ The wearable technology has irrevocably altered the landscape of cardiovascular care. These devices have demonstrated their capacity to enhance

diagnostic precision, guide therapeutic decisions, improve patient engagement, and ultimately save lives. While challenges of integration, data management, and equitable access require ongoing attention, the potential of this technology to create more proactive, personalized, and effective cardiovascular medicine is undeniable. The collaboration between continuous monitoring technology and clinical expertise represents the future of heart care—a future where critical diagnostic information is no longer confined to the clinic but flows continuously from patients' lives directly into informed, timely medical decisions.

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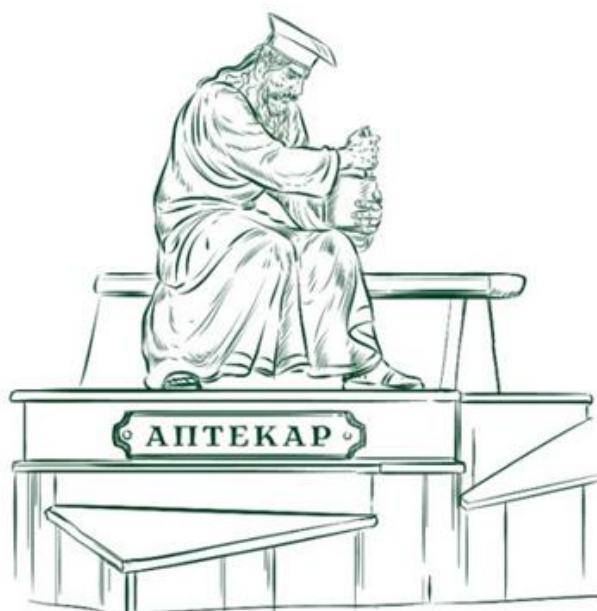
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## **COMPREHENSIVE ANALYSIS AND CRITICAL EVALUATION OF THE DISTINGUISHING QUALITIES, FUTURE DIRECTIONS, CHALLENGES, OPPORTUNITIES, OBSTACLES, AND PROFESSIONAL DEVELOPMENT PROSPECTS OF THE PHARMACIST ROLE AND OCCUPATION IN CONTEMPORARY LOCAL AND GLOBAL CONTEXTS IN GENERAL**

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**Abstract.** This research aimed to examine the unique attributes, future trajectories, difficulties, potentials, barriers, and professional growth avenues within the pharmacy field on both national and international scales in the 21st century. The investigation employed a quantitative methodology, utilizing an in-depth interview technique with participants. Approved questionnaires were administered to a randomly selected respondent pool. The study incorporated systematic, sociological (involving surveys and questionnaires), comparative, mathematical-statistical, and graphical analytical techniques. Data processing and analysis were conducted using the SPSS program (version 11.0). Descriptive statistics and regression analyses were performed to identify associations between variables. A Chi-square test was applied to determine statistical significance and differences, with a p-value of less than 0.05 established as the threshold for significance. The findings indicate that pharmacists, as regulated medical specialists, are overlooked within the Georgian healthcare system. Consequently, the higher pharmaceutical education system should transition towards a new model with a greater emphasis on pharmacotherapy, pharmaceutical care, and clinical pharmacy. Ultimately, the pharmacist role must evolve into a crucial component of the Georgian healthcare framework. State health policy must formulate clear concepts and universal principles for the pharmacy profession. Pharmacists should be recognized as regulated healthcare practitioners, akin to family doctors. Georgia must develop and enforce new standards for pharmacist registration, licensing, and accreditation that align with international pharmaceutical programs. Furthermore, qualified Georgian pharmacists should possess the right to practice in other European nations, requiring the recognition of Georgian pharmacist certifications in Western countries. Georgia should establish a pharmacist registration standard comparable to those in Great Britain and other Western nations. To elevate professional standards, the government should implement a certification system for holders of higher pharmaceutical education degrees. This is vital for: Professional refinement and self-realization; Career progression and personal growth; Job and career satisfaction; The establishment of a system for continuous professional education (CPE); Achieving a significantly higher status among healthcare professionals; Improving economic and material welfare; Enabling the full application of acquired knowledge in practice; Permitting private pharmaceutical enterprise. Support is needed for creating and delivering continuous education courses designed to elevate the qualifications of pharmaceutical staff. Pharmaceutical education must become a lifelong process to boost professional qualification, expertise, knowledge, and competency. The foundational training of pharmacists must meet modern demands, and the state should develop accessible, continuous pharmaceutical education programs for all



practitioners. This includes offering qualification upgrade courses, professional training, and educational opportunities that are universally available, ensuring that a pharmacist's learning never ceases. Advancing pharmacy education and expanding continuing education will enhance the professionalism of pharmaceutical personnel. Pharmacists should be tasked with monitoring and reporting drug side effects. The preparation and execution of registration-certification regulations for pharmacists are essential, alongside promoting research across all pharmaceutical practice areas. Awareness of the core functions and value of the pharmacist's role must be raised among both medical personnel and the general public. Pharmacists should be empowered to take a greater role in patient medication management and to collaborate with physicians on treatment plans. Fostering deep cooperation between pharmacists and doctors on issues of pharmacotherapy and healthcare is necessary. The state must safeguard the authority of the pharmacy profession. With government support, the prestige and social significance of the pharmacist role within the healthcare system should be elevated. The profession must gain more influence and power, achieving a much higher status. This pivotal change will be realized when the pharmacist profession is officially moved into the list of regulated health professions.

**Keywords:** Some peculiarities, prospectives, challenges, opportunities, pharmacy, features, pharmacist, profession, job, enhancement.

**Introduction.** Today, the traditional perception of the profession of pharmacist in community pharmacies risks disappearing on a global scale due to several factors. Among many factors, online pharmacies are becoming increasingly important due to their ability to meet consumer demand. However, they jeopardize “personal” contact, undermine customer loyalty based on direct “human” interaction and thus reduce pharmacists to the rank of simple businessmen. Communication regarding the provision of patient-centered care is highlighted as an essential element in establishing strong and adequate interpersonal relationships with the patient, increasing the efficiency of the consultation process, and improving the professionalism of the pharmacist in community pharmacy. Community pharmacists can also play an important role in improving medication adherence, thereby helping to reduce morbidity, mortality and healthcare costs [19]. In this context, it has been shown that the most effective interventions are delivered face-to-face and directly to patients, and that pharmacists' interventions are more effective than those of other healthcare professionals [1-3].

Analysis of the literature showed that research aimed at the study of individual aspects of the process of professional development of pharmaceutical professionals are dedicated to the development of requirements to ensure effective pharmaceutical care,

studies of postgraduate education, finding strategies for management of pharmaceutical personnel, job satisfaction of pharmacists, issues of their psycho-social adaptation to the emerging market conditions. However, comprehensive studies aimed at understanding the processes of professional trainings of pharmaceutical specialists to provide high quality pharmaceutical care have not yet been carried out [5-7].

Development of organizational and functional models for licensing pharmaceutical activities, is considered as one of the mechanisms to improve the efficiency of public administration, and has great relevance and scientific and practical value. An integral part of the state system of measures to implement the rights of citizens to protect their health is pharmaceutical care, the quality of the provision which is largely dependent on the qualifications of the personnel pharmacist. In this regard, the professional qualification of experts is under the control of the state and is one of the objects of state regulation of relations in the field of drug- medicine, whose purpose-maintaining the competence of expert specialists on throughout their careers with varying requirements for professional quality. The modern system of pharmaceutical care to improve the quality of life of patients depends on highly skilled professionals in drug-store whose competence has been growing in the process of professional development. The pharmacists require not only the use of earned at the institution of knowledge and skills, but also the willingness to professional self-development. Since the scope of drug treatment is one of the most socially significant areas of state regulation, the sequence in carrying out reform measures, conservation experience, and smooth introduction of new methods become crucial. However, comprehensive studies aimed at understanding the process of professional formation pharmaceutical worker, for to provide quality pharmaceutical care has not yet been carried out. Development of organizational and functional model of the licensing of pharmaceutical activities, pharmacists job as one of the mechanisms to improve the efficiency of public pharmaceutical and public administration, has great relevance, scientific and practical value [8-10].

Developed countries and many developing countries in the field of pharmacy are regulated, as well as family medicine. The pharmacist as family doctor needs of higher education, post-graduate and continuing education in pharmacy, a pharmacist license and periodic accreditation. In western countries in pharmacy, allowed to work only with higher pharmaceutical education specialists who have graduated from state-recognized and accredited colleges. The opening of a pharmacy permit is issued only to a person of higher pharmaceutical education, who passed the diploma courses in pharmacy and earned the right to open the pharmacy. It should be noted that in developed countries and in many developing countries pharmaceuticals are regulated

profession, as well as family medicine, pharmacist as a family doctor, need higher pharmaceutical education, diploma and continuous pharmaceutical education, pharmaceutical license and periodic accreditation. Only pharmacists with higher pharmaceutical education have the right to work as pharmacists in pharmacies, who have graduated from universities recognized and accredited by the state [11-14].

The modern system of pharmaceutical care, aimed to improve the quality of life of patients, depends on highly skilled professional pharmacists whose competence keeps growing in the process of professional development. Pharmaceutical specialists are required not only to have the ability to use the knowledge and skills gained at the educational institutions, but also to be ready and motivated for professional self-development. Since the scope of drug turnover is one of the socially important areas of state regulation, the sequence in carrying out reform measures, accumulation of experience, and smooth introduction of new methods become crucial [15-16].

In the field of pharmacy, it is noted an increase of such negative trends, poor mechanisms of interaction between professional education and the pharmaceutical market, slow adaptation of graduates to the market reality. The differences between the increasing demands of consumers of drugs and the level of knowledge of specialists, as well as slow adaptation to market reality can affect the process of professional development of specialists and the quality of pharmaceutical care. The above-mentioned trends, the increasing role and responsibility of pharmaceutical professionals in the health care system make it necessary to analyze current practical experience and investigate the theoretical foundations of personality development of specialists, as well as identifying new conditions for their development as professional pharmacist practitioners [17-18].

First time in Georgia scientifically grounded was studied the process of professional formation of pharmacists in the context of pharmaceutical care, including the stages of professional development. First time in Georgia were identified the factors, which was very important for pharmacist professional formation. Were study role of pharmacist and were identified of the specific features for the formation of pharmaceutical specialists at various stages. We make comprehensive study, the essence, regularities and peculiarities of the process of professional development of in the context of pharmaceutical care. Based on the literature review and analysis of the results of the studies, work has been obtained as general and specific theoretical and practical scientific innovations, have developed conclusions and practical recommendations. Which in turn will have a positive impact on the quality of pharmaceutical and health services delivery [19-22].

**The aim of the study.** The main aim of the study was to analyze the

distinguishing qualities, future directions, challenges, opportunities, obstacles, and professional development prospects of the pharmacist role and occupation in contemporary local and global contexts in general.

**Materials and Methods.** Research objectives are materials of sociological research: the study was quantitative investigation by using survey (Questionnaire). The study was quantitative investigation by using survey (Questionnaire). The in-depth interview method of the respondents was used in the study. The approved questionnaires were used (Respondents were randomly selected).

We delivered sociological questionnaires with respondents by using interviewing methods. The study was quantitative investigation. Obtained data was statistically processed with the use of SPSS software. There were used 7 types of approved questionnaires: Total number of respondents were:  $1506+222+307+810+319+314=3478$ .

1. Questionnaire for manager pharmacists, 410 manager pharmacists were participated in the study.
2. Questionnaire for patients, 1506 patients were participated in the study.
3. Questionnaire for employed pharmacy faculty student, 222 employed pharmacy faculty students were participated in the study.
4. Questionnaire for Health-Care Specialists, 307 health-care Specialists were participated in the study.
5. Questionnaire for pharmacist specialist, 810 pharmacists were participated in the study.
6. Questionnaire for (pharmacy faculty) students, 319 pharmacy faculty students were participated in the study.
7. Questionnaire for young pharmacist specialist up to 35 years. 314 young pharmacist specialists were participated in the study.

Were used methods of systematic, sociological (surveying, questioning), comparative, segmentation, mathematical-statistical, graphical analysis. The data was processed and analyzed with the SPSS program. Results and discussion: Questions and answers are given in the tables. On each question are attached diagrams or table. Questionnaire and diagrams are numbered. Study of the data was processed and analyzed with the SPSS program. We conducted descriptive statistics and regression analyses to detect an association between variables. Statistical analysis was done in SPSS version 11.0. A Chi-square test was applied to estimate the statistical significance and differences. We defined  $p < 0.05$  as significant for all analyses. The study's ethical items. In order to provide the study's ethical character each participant of it was informed about the study's goal and suggested of willingness of the work to be done.

So, the respondents' written or oral compliance was got on that issue. All the studies were carried out by the selected organizations administrations' previous compliance. Were used Informed consent form for each respondent to participate in an anonymous survey. During the whole period of research, the participants incognita was also provided. For the international rules and criteria' conformity this human subject comprising given study was discussed and confirmed on the Bioethics Committee sessions of the YSMU. In order to meet the objectives, set in the research we also used the results obtained through analysis of available official information, studies and opinions about pharmacists, as well as the methods of quantitative studies. We conducted descriptive statistics and regression analyses to detect an association between variables. Statistical analysis was done in SPSS version 11.0. A Chi-square test was applied to estimate the statistical significance and differences. The research implementation required the following sub studies: Some peculiarities, prospectives, challenges, opportunities, impedances and features of pharmacist profession and occupational enhancement prospects in general locally and globally in XXI century. Based on the received data, we performed analysis, summary, discission, and also meta-analysis, review and overview [23-27].

**Results and Discussion.** Developed countries and many developing countries in the field of pharmacy are regulated, as well as family medicine. The pharmacist as family doctor needs of higher education, post-graduate and continuing education in pharmacy, a pharmacist license and periodic accreditation. In pharmacy, allowed to work only with higher pharmaceutical education specialists who have graduated from state-recognized and accredited colleges. The opening of a pharmacy permit is issued only to a person of higher pharmaceutical education, who passed the diploma courses in pharmacy and earned the right to open the pharmacy [28-30].

The main goal of the research is to develop a methodology of studying and improving the process of professional development of pharmacist, pharmaceutical specialists and regulatory requirements for pharmaceutical staff of public pharmacies [25-26]. The study will allow to develop a scientifically based methodological approach to study and improve the process of professional training of pharmaceutical professionals, including rationalization of the stages of professional development, identification of relevant factors involved in the process of professional development and set a series of performance criteria for evaluation of the process in question, as well as studying the role and determining the characteristics of professional formation of pharmacists at various stages of their field activities. Within the proposed methodological framework with the use of a comprehensive investigation, will be identified patterns and features of the process during the professional development of



employees of the pharmaceutical industry and public pharmacies [31-35].

About half part of the respondents considered that pharmacist is not responsible for registration of adverse effects of the drugs, while less than a third part of them considered pharmacist to be responsible for that. By legislation one of the functions of pharmacist is to register the side effects of drugs, what is very essential for patients' safety. It should increase the awareness of pharmacist as the health professional [36-37].

The respondents' majority considered that importance in work of pharmacist was in personal realization as a specialist, receiving remuneration and provision of necessities of life. The respondents' minority considered it to be in relief of pain in suffering of people. (*Illustration 1*).

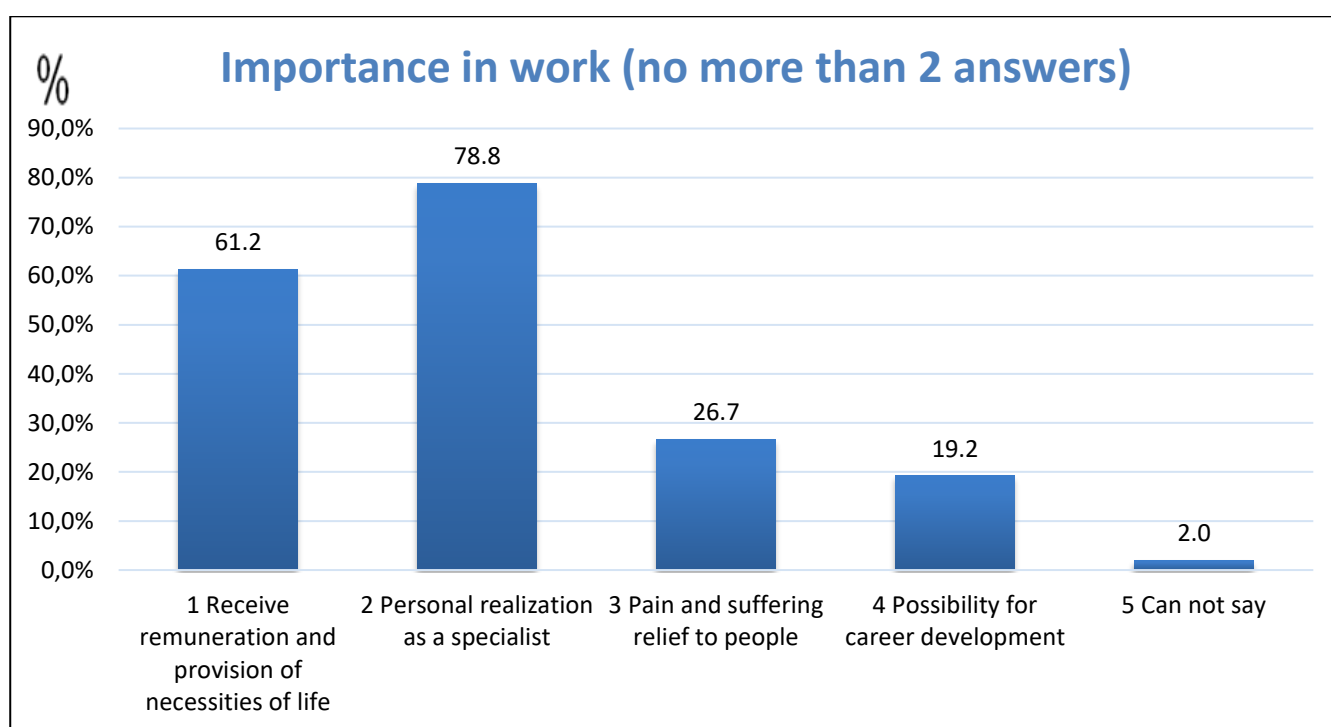


**Illustration 1.** Important issues in work for the respondents' (public health specialists)

Less than half part of the respondents considered that the level of basic training of pharmacists was not corresponding to the contemporary requirements. According to the sociological study results of the public care specialists it is obviously, that all pharmacists should have higher pharmaceutical education from the state recognized and accredited higher education institutions and universities. Pharmacists' specialty should become a regulated health care profession. According to that Government should make certification, licensing and accreditation of pharmacist professionals [60-62]. (*Illustration 2*).

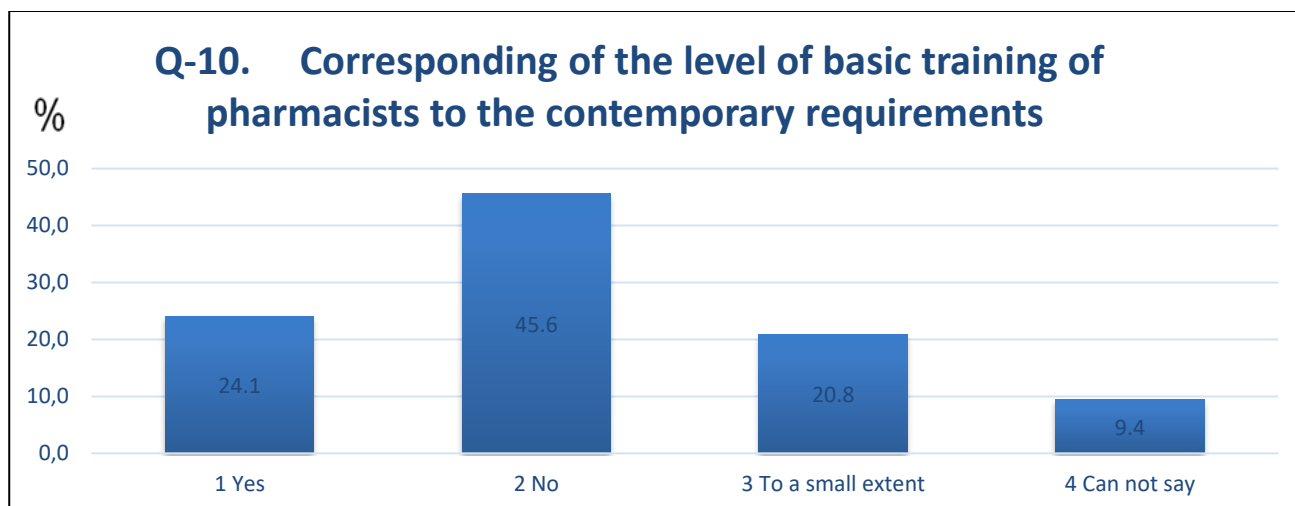


**Illustration 2.** The respondents' opinion about pharmacists' basic training level correspondence to the contemporary requirements.

Analysis the data of respondents' answers on the question „Do you think that the Government should make the certification of pharmacists? “(Q) revealed the following in different categories: the majority of chief pharmacists, of consumers of pharmacies, of the employed students, of the healthcare specialists and pharmacists considered, that Government should make certification of pharmacists ( $P < 0.000$ ) There are statistically significant points between variables. (*Table 1*).

**Table 1.**

**Respondents' opinion about pharmacists' certification**

| Cross tabulation                                                               |                                                                                |                      |                   |        |
|--------------------------------------------------------------------------------|--------------------------------------------------------------------------------|----------------------|-------------------|--------|
| Do you think that the Government should make the certification of pharmacists? | Do you think that the Government should make the certification of pharmacists? |                      |                   | Total  |
|                                                                                | 1. I agree                                                                     | 2. I partially agree | 3. I Do not agree |        |
| Chief Pharmacists                                                              | 76.6%                                                                          | 16.3%                | 7.1%              | 100.0% |
| Customers                                                                      | 82.6%                                                                          | 11.6%                | 5.8%              | 100.0% |
| Employed Students                                                              | 95.9%                                                                          | 3.6%                 | 0.5%              | 100.0% |
| Public Health Specialists                                                      | 94.8%                                                                          | 4.6%                 | 0.7%              | 100.0% |
| Pharmacist specialists                                                         | 71.9%                                                                          | 21.9%                | 6.3%              | 100.0% |
| Average                                                                        | 81.2%                                                                          | 13.5%                | 5.2%              | 100.0% |

| Chi-Square Tests   |                      |    |                       |
|--------------------|----------------------|----|-----------------------|
|                    | Value                | df | Asymp. Sig. (2-sided) |
| Pearson Chi-Square | 132.625 <sup>a</sup> | 8  | 0.000                 |

Coupling the data of respondent's answers' analysis of the questions "Indicate your sex" (Q1) and "Are you satisfied with your professional career?" (Q13) it became apparent that variables are gender dependent ( $P=0.001$ ), there is a statistically significant differences between two groups, that means that the male pharmacists were less satisfied with their professional career, rather than the female pharmacists (See tabl.2).

**Table 2.**

**Satisfaction professional career of respondent pharmacists according gender**

| Cross tab                                                  |                      |        |        |
|------------------------------------------------------------|----------------------|--------|--------|
| Satisfaction professional career of respondent pharmacists |                      |        |        |
| Are you satisfied with your professional career?           | Q1 Indicate your sex |        | Total  |
|                                                            | 1 Female             | 2 Male |        |
| 1. Yes                                                     | 30.88%               | 18.00% | 30.40% |
| 2. Partially                                               | 33.95%               | 27.20% | 33.70% |
| 3. No                                                      | 35.17%               | 55.00% | 35.90% |
| Total                                                      | 100.0%               | 100.0% | 100.0% |

| Chi-Square Tests   |                     |    |                       |
|--------------------|---------------------|----|-----------------------|
|                    | Value               | Df | Asymp. Sig. (2-sided) |
| Pearson Chi-square | 23.884 <sup>a</sup> | 2  | 0.001                 |

Coupling the data of respondents' answers' analysis of the questions "Indicate your sex" (Q1) and "Q14 Are you satisfied with your work (job)?" (Q14) it became apparent that variables are gender dependent ( $P=0.024$ ), there is a statistically significant differences between two groups, that means that the male pharmacists were less satisfied with their work, rather than the female pharmacists (See tabl.3).

**Table 3.**

**Satisfaction with work of the respondent pharmacists according gender**

| Crosstab                                         |                      |        |        |
|--------------------------------------------------|----------------------|--------|--------|
| Satisfaction with work of respondent pharmacists |                      |        |        |
| Q14 Are you satisfied with your work?            | Q1 Indicate your sex |        | Total  |
|                                                  | 1 Female             | 2 Male |        |
| 1. Yes                                           | 44.00%               | 22.65% | 33.20% |
| 2. Partially                                     | 39.90%               | 11.90% | 37.30% |
| 3.No                                             | 11.80%               | 62.15% | 24.40% |
| 4. Cannot say                                    | 4.40%                | 3.30%  | 5.10%  |
| Total                                            | 100.0%               | 100.0% | 100.0% |

| Chi-Square Tests   |                     |    |                       |
|--------------------|---------------------|----|-----------------------|
|                    | Value               | df | Asymp. Sig. (2-sided) |
| Pearson Chi-square | 24.261 <sup>a</sup> | 3  | 0.024                 |

Coupling the data of respondents' answers' analysis of the questions "Indicate your sex" (Q1) and „Are you satisfied with the time duration of your job? “ (Q26) it became apparent that variables are gender dependent ( $P=0.048$ ), there is a statistically significant differences between two groups, that means that the male pharmacists were less satisfied with the time duration of work, rather than the female pharmacists (*tabl. 4*).

**Table 4.**

**Satisfaction with time duration of work of the respondent pharmacists  
according gender**

| Crosstab                                                           |                      |        |                       |
|--------------------------------------------------------------------|----------------------|--------|-----------------------|
| Respondent pharmacists' satisfaction with the time duration of job |                      |        |                       |
| Q26. Are you satisfied with the time duration of your job?         | Q1 Indicate your sex |        | Total                 |
|                                                                    | 1 Female             | 2 Male |                       |
| 1. Yes                                                             | 22.38%               | 14.70% | 22.10%                |
| 2. Partially                                                       | 34.10%               | 36.70% | 34.20%                |
| 3. No                                                              | 43.51%               | 48.60% | 43.70%                |
| Total                                                              | 100.0%               | 100.0% | 100.0%                |
| Chi-Square Tests                                                   |                      |        |                       |
|                                                                    | Value                | df     | Asymp. Sig. (2-sided) |
| Pearson Chi-square                                                 | 19.775 <sup>a</sup>  | 2      | 0.048                 |

Coupling the data of respondents' answers' analysis of the questions "Indicate your sex" (Q1) and „Are you satisfied with your income?“ (Q27) it became apparent that variables are gender dependent ( $P=0.019$ ), there is a statistically significant differences between two groups, what means that the male pharmacists were less satisfied with income, rather than the female pharmacists (*tabl.5*).

Psychological studies show that the influence of these factors on professional choice is different. It is established that a sufficiently high level of education of the mother or the professional status of the father promotes the agreement of the children. The opinion of the parents about the choice of the profession and the influence of the parents is stronger than the influence of teachers or a specialist in career counseling. At the same time, the parents' opinion acts as a factor of inhibition of the professional development of the individual in the period of professional orientation [38-39].

**Table 5.**

### Satisfaction of the respondent pharmacists with income according gender

| Crosstab                                                                |                      |        |        |
|-------------------------------------------------------------------------|----------------------|--------|--------|
| Satisfaction of the respondent pharmacists with income according gender |                      |        |        |
| Q27. Are you satisfied with your income?                                | Q1 Indicate your sex |        | Total  |
|                                                                         | 1 Female             | 2 Male |        |
| 1. Yes                                                                  | 10.59%               | 0.00%  | 10.20% |
| 2 .Partially                                                            | 25.48%               | 23.30% | 25.40% |
| 3. No                                                                   | 63.82%               | 76.70% | 64.30% |
| Total                                                                   | 100.0%               | 100.0% | 100.0% |

| Chi-Square Tests   |                     |    |                       |
|--------------------|---------------------|----|-----------------------|
|                    | Value               | df | Asymp. Sig. (2-sided) |
| Pearson Chi-square | 13.314 <sup>a</sup> | 2  | 0.019                 |

In the current market economy, when choosing future professional activity, young people take into account the socio-economic demand for a particular profession, the real opportunities for training and employment in this profession, its material and social significance. In psychological researches it is proved that the discrepancy of the professional interests of the individual with the needs of society and the possibilities of the personality entails dissatisfaction with the chosen work activity. A person spends unproductive efforts to assimilate professional knowledge, skills and abilities, performs work within the framework of his/her external, formal duties or changes his/her profession. We believe that the social significance of such work is low [40-42].

The experience of economically developed countries confirms that in the modern conditions of the development of pharmaceutical production, a highly qualified specialist is needed, who, first of all, would have full knowledge of medicines and, at the same time, focused academic knowledge in the field of disease treatment. This specialist is a clinical pharmacist.

The well-coordinated work of the clinical pharmacist and the clinician makes it possible to rationally use the growing arsenal of medicines. Obviously, this is only possible by creating an atmosphere of cooperation between the clinical pharmacist and the doctor. To create a collaborative atmosphere, it is not enough to educate clinical pharmacists, it is also necessary to educate physicians [43-45].

In Western European countries, the specialty "Clinical Pharmacy" appeared and took shape in the 70s of the last century. The field of activity of specialists in this area is not limited to work only in pharmacies. They help physicians in the rational selection of drugs, taking into account their pharmacokinetics, pharmacodynamics, interactions



with other drugs, as well as the cost of treatment.

In fact, the full demand for clinical pharmacy is created only if the model of insurance medicine works correctly. Georgia is gradually entering this phase of development of the insurance business [46-48].

The work of insurance companies should be focused on interaction with clinics and pharmacies that have highly qualified specialists. These specialists must have systemic knowledge in the field of medicine, pharmacology, clinical pharmacology, clinical pharmacy, physician and clinical pharmacist. The majority of respondents cited the high patient workload as a unique opportunity because clinical pharmacists may be faced with many cases and rare diseases that they cannot find anywhere else. Thus, it allows clinical pharmacists to be exposed to various diseases and thus expand their competence through better experience [49-51].

The government policies and the existence of national guidelines played an important role not only in the implementation of the pharmaceutical care program, but also in the sustainability that allowed the implementation of services. There are potential barriers to service delivery and they attempted to list all challenges. The challenges described by most of the respondents' stem from the availability of pharmacists, other healthcare practitioners, academic policies and work guidelines. Challenges are of clinical pharmacy services improvements. Challenges are defined as: Any situation that suggests effective implementation of clinical pharmacy, pharmacist challenges include inadequate service facilitation, lack of service continuity, poor drug information center service and lack of commitment, communication and trust between clinical pharmacists. Most respondents reported that poor service attitudes, conflict of interest due to unclear scope of practice, and lack of cooperation are challenges emerging from health practitioners such as nurses and doctors. Some respondents also described challenges arising from hospital management and set-up. The challenges they mentioned include lack of training, qualified manpower, lack of incentives, lack of clinical pharmacy ward facilities and collaboration between academics and hospital clinical pharmacists. Other challenges cited by respondents were due to academic policies and the curriculum itself [52-54].

This study describes the personal experiences of health practitioners towards clinical pharmacy services provided in hospital, thereby extracting opportunities and challenges which will be used as a means to strengthen the services. In addition, participants were also asked to describe how they perceive the scope of practice in clinical pharmacy services from which challenges and opportunities were also identified. The perception of scope of pharmacy practice among health practitioners reflects whether there is conflict of interest and resistance to cooperation. The scope of

practice varies between countries as determined by the governing board of pharmacy. Many countries allow the pharmacist to play a part only within certain areas of the medication use process, while in other countries the scope of practice is so wide-ranging and inclusive that, it encompasses the entire medication use process. Some of the respondents in this study thought that the scope of practice should be limited to drug therapy. However, others suggested that the scope can range from diagnosis to prescribing of drugs. The respondents explained that this can be achievable only if get rid of conflict with other practitioners as their job description and authorities are not well delineated [55-58].

As clinical pharmacy services are at their infancy, the respondents suggested that services should focus more on key areas that are less considered by other practitioners. They believed this would increase acceptability of clinical pharmacy services by other health providers. One study reported that clinical pharmacists are experts in therapeutic knowledge, experience and skills which are used to ensure desired patient outcomes utilizing the best available clinical evidence and intervention in collaboration with the health care team. Some of the opportunities listed in this study also have some drawbacks which may be a source of challenge unless they are improved. For instance, the new clinically-oriented curriculum is much better than the previous product-oriented one, but still the curriculum is not as competent as a PharmD program. In addition, poor drug information service is another area of practice in need of improvement to satisfy the health practitioners [59-62].

Clinical pharmacy services in hospitals face different challenges which may arise from other health practitioners' willingness, practice setups, and clinical pharmacists' attitudes. Further, another study conducted revealed sets of challenges that limit pharmaceutical care practice, such as lack of time and need of effort, insufficient remuneration, no team work among health care workers and deficiency in staff strengths. Our finding reflect that challenges may originate from the pharmacists themselves, other health practitioners' issues, academic policies and availability of working guidelines. The interviewees listed many potential and actual challenges. It is also important to note that the number of clinical pharmacists included in clinical settings is very minimal and that may be a reason for absence of service continuity. However, The Schools of Pharmacy should take the initiative to integrate, empower and employ hospital clinical pharmacists or provide incentives for the academic staff to improve the continuity of services in clinical pharmacy [63-65].

This study describes practitioners' personal experiences with clinical pharmacy services, thereby identifying opportunities and challenges to be used as a means to improve services. In addition, participants were also asked to describe how they

perceive the scope of practice in clinical pharmacy services, from which challenges and opportunities were also identified. The perception of the scope of pharmaceutical practice among practitioners reflects conflicts of interest and resistance to collaboration. Interviewees also suggested possible solutions to responsible parties to take advantage of potential opportunities and overcome challenges [66-69].

Maintaining competence through continuing education/continuing professional development - In many countries, pharmacists are required to undergo continuing education programs involving legal and/or ethical issues. The provision of pharmaceutical services requires adherence to national quality standards and guidelines, with a clear differentiation between basic/basic services and professional services. Pharmacists play a critical role in providing these services and their education, qualifications, functions and duties vary depending on the country in which they work. The scope of practice varies by state, as determined by the board of pharmacy governors. Many countries only allow pharmacists to participate in certain areas of the drug administration process, while in other countries the scope of practice is so broad that it includes the entire drug administration process. Some respondents to this study felt that the scope of practice should be limited to drug therapy. However, others suggest that the scope of diagnosis may vary from diagnosis to prescription of medications. That, can only be achieved if eliminate conflicts with other practices, as their job responsibilities and powers are not clearly defined. All pharmacists should be well versed in the various subjects of pharmacotherapy, each may choose to pursue a general clinical career or specialization. A pharmacist may choose to specialize in a particular field at any time during their career. The following list includes specialties in which clinical pharmacists may practice. While this list is not exhaustive, it does demonstrate the diversity of clinical pharmacy careers: Regardless of the narrow specialty, a clinical pharmacist must have: a desire to constantly work with the literature, the ability to critically evaluate the literature, excellent communication skills, the ability to cooperate with other medical professionals, the desire/ability to defend the interests of the patient and the profession of a pharmacist, strong leadership qualities. In fact, the full demand for clinical pharmacy is created only if the model of insurance medicine works correctly. Georgia is gradually entering this phase of development of the insurance business. The work of insurance companies should be focused on interaction with clinics and pharmacies that have highly qualified specialists. These specialists must have systemic knowledge in the field of medicine, pharmacology, clinical pharmacology, and clinical pharmacy [70-72].

The next stage of professional development of specialists is the adaptation to work activity: the beginning of an independent professional activity and the

accumulation of experience by young specialists. This stage reflects the student's transition to a new type of activity - to professional work in its various forms in the conditions of real situation, performance of official duties, production relations, finding oneself in the system of work collectives. In the course of adaptation, the system of professional knowledge and skills is acquired in the required volume; The emergence of interest in the work, which begins to play an increasingly important role in life, a sense of the connection between success and the profession, is self-determination for professional development [73-75].

On the basis of theoretical analysis of the process of professional development will be developed by a set of common criteria for the effectiveness of this process, which will be based on the regularities of formation, reflecting its focus and dynamics: an interest in their chosen profession, changing choice motives, increased satisfaction of occupational choice and labor, increasing the motivation to knowledge and professional development, change career planning purposes. The goal, purpose and objectives of the planned research. The main aim is to develop a methodological approach to study and improve the process of professional development specialists' pharmaceutical profile, regulation requirements for pharmaceutical staff in drugstore professional career improvement strategy and jobsatisfaction among pharmacists. A systematic analysis identified factors which had influence the formation of personal-professional position of a pharmaceutical professional and realization of their personal resources [76-79]. On the basis of theoretical analysis of the process of professional development there will be developed a set of common criteria for the assessment of the effectiveness of this process, based on which will be identified the regularities of formation, reflecting its focus and dynamics: their interest in profession of choice, changes in choice making motivation, growing job satisfaction, increasing the desire to acquire more knowledge and professional skills and making appropriate adjustments in their career goals [80-82].

Based on the theoretical analysis of the main approaches to the study of the process of professional development, taking account the concept of pharmaceutical assistance, a set of related criteria for the effectiveness of this process. Based on common performance criteria, the patterns of formation are revealed, reflecting its direction and dynamics: interest in the chosen profession, changing the determinants of choice motives, increasing satisfaction with choice of profession and work, increasing motivation for cognition and continuous professional development, changing career planning goals. On the basis of specific criteria, the specifics of the formation are revealed, which include: incomplete correlation of the internal resources of the individual with the needs of the pharmacist / pharmacist profession, insufficient

awareness of individual aspects of future activities, the difficulties of production adaptation, and low satisfaction with the work of pharmaceutical professionals [83-85].

A systematic analysis will identify factors which influence the formation of personal-professional position of a pharmaceutical professional and realization of their personal resources. On the basis of theoretical analysis of the process of professional development there will be developed a set of common criteria for the assessment of the effectiveness of this process, based on which will be identified the regularities of formation, reflecting its focus and dynamics: their interest in profession of choice, changes in choice making motivation, growing job satisfaction, increasing the desire to acquire more knowledge and professional skills and making appropriate adjustments in their career goals [86-88].

Deficiency of knowledge and functions of pharmaceutical professions in Georgia is not exists only in the non-medical section of the society, but also in the medical staff like health-care specialists.

Developing a continuous pharmaceutical education system, will enhance the professionalism of pharmaceutical personnel. Protecting the people is the primary goal of pharmacy boards. On a broad scale, this mission requires a pharmacist to attend university for a specific number of years and to pass the state competency examination. Boards also set the parameters for what happens if a law or regulation is violated, what penalties result, and what infractions can cause if a pharmacist lose his or her license [89-90].

Pharmacy is one of the most regulated professions in the western countries and pharmacist profession is one of the most ethically challenging position. In EU countries state boards regulate, administer and influence every phase of pharmacy practice, including the demands and licensing testing for pharmacist. In western countries each state board is staffed up of pharmacists who come from every practice area – hospitals, clinic, chains, independent pharmacies, pharmaceutical factory, industrial pharmacy – as well as at least one consumer (non pharmacist) representative. In most states, pharmacy board members are appointed by the government [91-92].

The health care brigade composes of the patient and all the health care professional specialists who have liability for patient care. This health care brigade demands to be well determined, and cooperation needs to be actively sought. Pharmacists have considerable character and role to play in this brigade. Pharmacists must demand to acclimatize their skills, knowledge, information and attitudes to this innovated role, which consolidates all traditional pharmaceutical sciences with hospital/clinical aspects of the patient care, clinical/hospital skills, management, administration and communication skills, active cooperation with medical brigade and



solving of drug-related issues. If they are to be recognized as full members of the health care brigade, pharmacists will demand to adopt the essential attitudes required by health professional specialists laboring in this space: visibility, liability, duty, responsibility, accessibility in a working practice targeted at the general population, commitment to confidentiality and patient orientation. Pharmacists will demand to be competent, qualified, knowing and possess all that vision, opinion and a voice to fully integrate themselves into the health care brigade [93-94].

To provide contribution and assistance in teaching of patients to understand the prescribed drugs intake rules, pharmacists need in deep knowledge in basics of medicine, pharmacology, pharmacotherapy, pharmaceutical chemistry, pharmaceutical care, clinical pharmacy and other pharmaceutical disciplines. Properly educated pharmacists have great importance and value for the provision higher quality health care services, for the provision higher quality pharmaceutical care and very essential for patient's safety. About half part of the respondents considered that pharmacist is not responsible for registration of adverse effects of the drugs, while less than a third part of them considered pharmacist to be responsible for that. By legislation one of the functions of pharmacist is to register the side effects of drugs, what is very essential for patients' safety. It should increase the awareness of pharmacist as the health professional [95-97].

In western countries are actively working clinician pharmacist, pharmacist and family doctor system, it plays an important role in pharmaceutical care. In western countries and in many developing countries pharmacist professions a regulated sector in health, as well as family medicine. Pharmacist, as well as the family doctor, needs higher education, further Diploma, and continuing pharmaceutical education, Pharmacist's license and periodic accreditation. in pharmacy, on pharmacists position works only higher pharmaceutical education specialists, Who graduated by the state recognized and accredited universities, and colleges. In Georgia pharmacist further diploma, continuing pharmaceutical education, pharmacist licensing and accreditation regulatory legislative base is not perfect. Today, the pharmacist profession in Georgia is impaired, pharmacist profession is deleted from health adjustable medical fields, Therefore degree in pharmacy or higher education in pharmacy losing profession opinion and values. In Georgia not conducted pharmacists certification, re-certification, accreditation and licensing state programs. Therefore profession pharmacist specialty becomes given position by the pharmacy owner, and not only from the university awarded qualification. Because of the above reasons in Georgia in drugstores for pharmacist position is no longer necessary higher pharmaceutical education, in drugstore any person has the right to work as a pharmacist position, any

educated person or a person without medical or pharmaceutical education may be given a "position" Pharmacist "according pharmacy owner desired, pharmacy profession granting needs 4-5 year study at medical and other universities. In Georgia drugstore pharmacist interpreted as the only drug-dealer-seller. Pharmacist as regulated medical specialists ignored in Georgian Health-care System. That is why higher pharmaceutical education system should be moved to a new model direction, which will be more focused on pharmacotherapy, pharmaceutical care, and clinical pharmacy. Therefore, in future pharmacist profession in Georgian health care system should become most important link. In the state health policy, it is necessary to develop pharmacist profession's concepts and common principles. pharmacist profession should become regulated health care job, look like family doctor. In Georgia should be developed and implemented pharmacists registration, licensing, and accreditation new standards accordance with international pharmaceutical programs. Also qualified pharmacist in Georgia should have the right to work as pharmacist in other European Countries. Georgian pharmacist Certificate should have recognition in western countries, and Georgia should create pharmacist registration standard which is exist in Great Britain and other Western countries [98-101].

The pharmacist specialist should play a main role in the provision of advice and information to patients and the general public on the use of drugs, and the pharmacist should cooperate effectively with prescribers to ensure a common approach to patients in the provision of advice and information. Pharmacists must participate in a multidisciplinary approach to promotion of the rational use of medicines. Pharmacists should adequately inform patients and the general public about unwanted effects of medicines, and should monitor such unwanted effects and their consequences in collaboration with other health care professionals and the appropriate authorities. Pharmacists provide education on medications, disease states and lifestyle issues, all of which is part of clinical prevention. Pharmacist also provide educational programs to groups on issues such as drug abuse or other health issues that are example of population health activities. Pharmacists provide counseling on a wide range of health promotion products found in the typical retail pharmacy such as sun screens, dental hygiene products, or vitamin and mineral products. Moreover, pharmacists provide immunization services and participate in screening activities [102-105].

Although the number of pharmaceutical products on the market is increasing, access to essential medicines is still lacking in many parts of the world. Rising health care costs and changing social, technological, economic and political environments have made health care reforms necessary throughout the world. New advances are needed at individual and at population level to provide safe and effective

pharmacotherapy to patients in an ever more complex atmosphere. Pharmacists are in an excellent position to meet the need for professionals to assure the safe and effective use of medicines. To do so, pharmacists have to take bigger responsibility than they currently do for the management of drug therapies for the patients they serve. This responsibility goes well beyond the traditional dispensing activities that have long been the mainstay of pharmaceutical practice. While supervision of the routine medicine's distribution process must remain the responsibility of pharmacists, their direct involvement in medicine distribution will decrease, since these routine activities will be handled by qualified pharmacy assistants. However, the number of supervisory activities will increase. Thus, pharmacists' responsibilities must be expanded to include monitoring therapeutic progress, consulting with prescribers, and collaborating with other health care practitioners on behalf of patients. The movement towards by pharmaceutical care is a main critical factor in this process [106-107].

Pharmacists possess the potential to improvement the therapeutic outcomes and patients' quality of life within existing resources, and should position themselves appropriately within the health care system. Pharmaceutical education has a corresponding liability to produce graduates who are competent to deliver pharmaceutical care. Outcome competencies aid to quality guarantee by providing readily accessible standards against which practice may be measured. The role of the pharmacist specialist takes different forms in various parts of the world. The pharmacist's participation with pharmaceuticals can be in research and development, formulation, manufacturing, quality guarantee, licensing, marketing, distribution, storage, supply, information management, dispensing, monitoring or education. Supply chain management and information management activities have been termed "pharmaceutical services" and continue to form the basis of pharmacy practice [108-110].

Community pharmacists work at the forefront of medical care. They work at their own pharmacies or in private pharmacies. Pharmacist job is all about helping the public, assessing their conditions and make decisions about medicines. Pharmacists participate in the distribution of medicines and patients offering advice and practical help to maintain healthy. This is a very demanding job and pharmacists usually highly respected members of their communities. Changes in the role of the pharmacist and pharmacy community are medical supplies, and these trends will continue to accelerate in this fast-moving environment. Today in drugstores offer advanced medical services in retail and also ideal for raising awareness of the disease and deliver educational information at multiple points of contact. These include over the counter (OTC) and the personal care aisle, a pharmacy counter, in specialty publications and pickup areas prescription. Not only useful for customers' pharmacies these innovations, but they

also create opportunities for pharmaceutical marketers, measurable return on investment [111-113].

Educational focus of professional programs is increasingly recognized the need for an opportunity to apply what they have learned in the classroom through laboratory simulations or experiential learning, which requires different types of faculty and staff positions to meet these educational needs. Innovative types of faculty and staff positions with great attention to training or practice and less responsibility for traditional research appeared in PharmD programs and we should encourage graduate's pharmacies carry these roles. At the same time, we should encourage graduates to conduct PharmD degrees in masters or doctoral level philosophy or advanced science-based scholarships to become the next generation of teachers, providing the basis for and research in biomedical, pharmaceutical, clinical and administrative sciences in pharmacy programs [115-117].

What is being done especially in the Academy and the health professions education programs to promote these career opportunities for pharmacy students? Pharmacy educators need to become more actively involved in the development of special educational opportunities to prepare a new generation of faculty and staff and to review the types and nature of faculty and staff positions in our institutions in order to attract graduates to participate in the Academy. Pharmacy graduates are also encouraged to explore the potential role of other medical and scientific educational programs, given the increased attention to inter-professional teams in health professions education is essential for high-quality patient care [118-119].

Problems of Georgian pharmaceutical education in the coming years are to prevent easy access to the pharmacy program graduates of other subjects; possibility of a lack of jobs for graduates of pharmacy; potential for accelerated progression pharmacist. In addition, the requirement to introduce a greater number of drugs in the courses to meet the new roles of additional and independent lawmakers need to be addressed at the same time debating the relative weight of the science and practice in the course. Along with efforts to improve the professional status of the Georgian pharmacists, internal and external factors that affect their level of satisfaction, should be explored further in a larger population so that appropriate strategies can be adopted to improve the situation [120-121].

The public and our patients should expect the highest possible pharmaceutical care from professional practitioners worldwide, without exception. The obviously evidence and confidence of competence, skills and capability that is corresponding with accelerating and master practice is a clear message to fostered public that pharmacists have this competence; professional distinction, credentialing and quality convinced of

specialization are part of this evidence of competence, potential and capability. It is in the interest of patients, health systems and to pharmacists' profession that develop a common and shared understanding of what we mean by specialism and by forward practice". This is a key supervisor for future workforce perfection [121-123].

Education and advancement of long-term education are the cornerstones of the future pharmacy - today's students are supervisor in the pharmacy of tomorrow. This means that all parties involved in pharmaceutical education have a great responsibility for mastering new approaches and view for the training of future health care workers. Academic pharmacy must take a powerful position in forecasting essential changes in the world and developing strategies for improving the teaching of pharmacy in the interests of everyone's health. One of the most significant aspects is the development of knowledge, cognition and experience in the academic workforce [95, 98, 105].

A pharmacist a health care professional, which distributes medications to patients on prescription, on the order of a physician or another doctor. Pharmacists have a deep knowledge of the chemistry and Pharmacotherapy of different drugs and how they react to people, as well as how drugs interact with each other. Pharmacists must accurately measure and a package of medicine, providing its dosage and security due to the patient. While the pharmacist typically does not choose or prescribe medication, the pharmacist educates patients on how to take the medication and what reactions or problems should be avoided. Pharmacists also known as chemists (druggists) or they are health care professional specialists who working in pharmacy, medical sciences, health care, focused on the safe and effective use of drugs. A pharmacist is a part of the health care brigade straight engaged in patient care. Pharmacists are trained at the university grade degree level, to understand the biochemical and pharmacological mechanisms of effect of drugs, the use of drugs and therapeutic roles, side effects, possibility drug interactions, and inspection parameters. Pharmacists interpret and transmit this experience for patients, physicians and other medical professionals. Among other requirements for licensing in different countries require pharmacists to hold either a Bachelor degree of Pharmacy or Doctor of Pharmacy degree. The most general pharmacist positions that of the general pharmacist (also referred to as first-line retail pharmacist or pharmacist) or a hospital/clinic pharmacist, where they instruct, teach, advice and counsel on the correct use and side effects of drugs and medicines. In most countries, the profession of pharmacist is subject to professional regulation. Depending on the legal framework of practice, pharmacists may promote to the destination (also known as pharmacist legislator) and the introduction of certain medications (eg, immunization) in some jurisdictions. Pharmacists can also practice in a diversity of other directions, including industry,



studying, factories, wholesale trade, academia, research, universities, insurance, the military and government [9, 37, 68].

Pharmacists should see themselves as the main health care providers who can use their clinical experience in various public institutions. Pharmacists will always be an important health care provider based on their availability to patients through community pharmacy setting. This specific role of provider should never be reduced, as it serves the critical needs of patients (eg, dispensing and counseling for drug experience in nonprescription drugs, compounding, vaccinations, and the use of medication administration or monitoring devices) that not addressed by other health care providers. However, this does not exclude pharmacists serving as suppliers of innovative alternative settings, such as outpatient clinics located in pharmacies and other retail outlets; in independent practice with a focus on medication management therapy, medication reconciliation, drug counseling or Pharmacogenomic; institution or organization, where they are responsible for the integration and promotion of patient care through the many other health care providers to facilitate continuity of care community; or organizations that coordinate research to improve practice through pharmacy practice based research networks [31,39,42,96]. Pharmacy providers should look for opportunities to engage in professional activities between patient care, when and where they occur or as they develop in communities. For example, alternative practices may change to concentrate on providing pharmacy and health services for adults and retirement communities, given the growing number of them as Georgian population continues to age. Pharmacy graduates who serve in the health services of Georgia, as these pharmacists to develop innovative practice settings, they should be drivers for expansion within the pharmacy practice in community, state and national levels. Pharmacy educators must ensure that graduates have the necessary knowledge, skills, attitudes/values, and practice experience, as well as confidence, drive, and entrepreneur spirit to be a driving force for change in order to facilitate these and other advances in the scope and type of community pharmacy practice. Hospitals and other institutions and facilities, such as outpatient clinics, drug-dependency treatment facilities, poison control centers, drug information centers, and long-term care facilities, may be operated by the government or privately. While many of the pharmacist's activities in such facilities may be similar to those performed by community pharmacists, they differ in a number of ways. Additionally, the hospital, clinic or institutional pharmacist has more possibility to interact closely with the prescriber and, therefore, to promote the rational prescribing and use of drugs in larger hospital and institutional pharmacies, is usually one of several pharmacists, and thus has a greater opportunity to interact with others, to specialize and to gain greater

expertise, having access to medical records, is in a position to effect the option of drugs and dosage regimens, to monitor patient compliance and therapeutic response to drugs, and to recognize and report adverse drug reactions; can more easily than the community pharmacist assess and monitor patterns of drug usage and thus recommend changes where necessary serves as a member of policy-making committees, including those concerned with medicine choice, the use of antibiotics, and hospital infections and thereby actions of the preparation and composition of an essential-drug list or formulary is in a better position to educate other health professionals about the rational use of drugs, more easily participates in studies to determine the beneficial or adverse effects of drugs, and is involved in the analysis of drugs in body fluids ,can control clinical manufacture and acquisition of drugs to ensure the supply of high-quality products, takes part in the planning and implementation of clinical trials [33, 34, 49].

Patient safety is a priority for all professionals - pharmacists - who care about the health. Patient safety is defined as the prevention of harm to patients, including by errors. For centuries, pharmacists were guardians/safeguards against "poisons" of substances that can cause harm to society. Now more than ever, pharmacist's responsibility is receiving safely the medication to the patient [13, 29, 98].

Pharmacy is one of the most regulated professions in the EU countries and one of the most ethically challenging. Government boards of pharmacy regulate, administer and influence every phase of pharmacy practice and activities, including the requirements and testing to become a licensed and certified pharmacist. Each country board is made up of pharmacist specialists who come from several practice area – academic, hospitals, clinic, chains, general and independent pharmacies – as well as at least one consumer (nonpharmacist) representative. In most states, pharmacy board members are appointed by the government [10, 46, 64].

Protecting the society and people is the primary purpose of pharmacy boards. On a broad scale, this mission demands a pharmacist to attend school for a specific number of years and to pass the state competence examination. Boards also set the parameters for what happens if a law or regulation is violated, what penalties result, and what infractions can cause a pharmacist to lose his or her license.

Developed countries and many developing countries in the field of pharmacy are regulated, as well as family medicine. The pharmacist as family doctor needs of higher education, post-graduate and continuing education in pharmacy, a pharmacist license and periodic accreditation. In pharmacy, allowed to work only with higher pharmaceutical education specialists who have graduated from state-recognized and accredited colleges. The opening of a pharmacy permit is issued only to a person of higher pharmaceutical education, who passed the diploma courses in pharmacy and

earned the right to open the pharmacy [52, 66, 85].

It should be noted that in developed countries and in many developing countries pharmaceuticals are regulated profession, as well as family medicine, pharmacist as a family doctor, need higher pharmaceutical education, diploma and continuous pharmaceutical education, pharmaceutical license and periodic accreditation. Only pharmacists with higher pharmaceutical education have the right to work as pharmacists in pharmacies, who have graduated from universities recognized and accredited by the state.

In March of 2016 the Board of the pharmacy practice adoptive the ensuing determination of a "pharmacist": A pharmacist is a scientifically- educated graduate healthcare professional specialist, who is an expert in all aspects of the deliver and use of medicines. Pharmacists guarantee access to safe, cost-effective and quality medicines and their responsible use by individual patients and healthcare systems [48, 49, 56, 87, 96].

Pharmacist are health practitioner who dispenses medicinal products. A pharmacist can counsel on the proper use and adverse effects of drugs and medicines following prescriptions issued by medical doctors/health professionals. Education includes university-level training in theoretical and practical pharmacy, pharmaceutical chemistry or a related field [6, 19, 41].

Pharmacists' expanding role in self-care is the subject of a new report from FIP. Pharmacy is a entrance to care: assistance people towards better health regard the present state of consumer interest in health care and presents a collection of testimony of pharmacy services related to self-care and the value that pharmacists carry to health care systems in this route. It lays out the drivers of self-care and profound changes in the route health care systems operate [65, 84, 87].

Responsible use of medicines implies that health-system stakeholder activities and capabilities are aligned to ensure that patients receive the right medicines at the right time, use them appropriately, and benefit from them. Bringing the right drugs to the patients who need them demands the engagement of all actors, including state, governments, and a vision on how to integrate society, public, people and private interests and to mobilize resources. While appropriate drug therapy is safer and more cost-effective than other treatment alternatives, there is no doubt that the personal and economic consequences of inappropriate drug therapy are enormous. It is important for public and people to be guaranteed that spending on pharmaceuticals represents good value for money. In view of their extensive academic background and their traditional role in preparing and providing medicines and informing patients about their use, pharmacists are well positioned to expect responsibility for the management of drug

therapy. [48, 49, 75].

Pharmacists, as well noted as druggists, who are health care team professionals, they working in pharmacy (drug-story), the field of health sciences focusing on safe and effective using drugs. The pharmacist is a part of the health care team directly engaged with patient care services. [1, 2]. The pharmacists hold university degree level training and education to consider the pharmacological mechanisms and actions of drugs, pharmacology, pharmacotherapy, toxicology ,drug uses, therapeutic roles, side effects of drugs, possible drug interactions, and checking parameters [3]. This is engaged to Botany, biology, anatomy, chemistry, physiology, histology, Biophysics and pathophysiology. Pharmacists interpret and communicate this particularized information to patients, physicians, doctors and other health care producers [11, 29, 54].

Being a health care professional means being part of a team that is focused on one goal: helping the patient achieve better health. Pharmacists are a part of this health care team, and their duty is to help the patients make the best use of their medication. This is a big job one that pharmacists cannot do alone. Thus, within their profession, pharmacists have developed other categories of pharmacy workers to help get the work done more efficiently and allow pharmacists to be more focused on the patient [28, 35, 49].

Common pharmacies have been providing health care for many years, via giving consultation, advice, providing and delivering medicine when needed, or referring patients to other health care professionals. This report, however, reflects and represent the embedding of a formalized approach whereby pharmacies are covering for these services, and where self-care through pharmacists is measured as an integral part of the health system.

Pharmacists are health professionals who are dispensing prescription drugs to patients, also provide information about the medicines ordered by doctors. They explain the doctors' instructions to patients so that, people can safely and effectively use these medications. Another big issue is ensuring that drugs are used reasonably and rationally. This demands that patients get drugs assign to their clinical/hospital necessity, in doses that meet their own individual needs for the sufficient period of time, and at the lowest cost to them and their public [41, 74, 85].

A pharmacist is a personality who is professionally competent and qualified to prepare and dispense medicine. The Pharmacist dispense drugs, check patient's health, and make sure that drugs do not interact in a harmful route. Pharmacist are drug experts eventually interested about their patients' wellness and health. Public health service interventions, higher level pharmaceutical care, rational pharmacotherapy and effective medicines supply chain management are main components of an accessible,

sustainable, affordable and equitable health care system which ensures the efficacy, safety and quality of drugs. It is clear that pharmacy has a great role to play in the health sector reform process. To do it so, although, the role of the pharmacist needs to be redefined and reoriented. Pharmacists have the capability and possibility to enhance therapeutic results and patients' quality of life within accessible resources, and must position themselves at the forefront of the health care system. The movement towards pharmaceutical care is a critical factor in this matter. While efforts to communicate the proper information to patients are as significant as providing the medicine itself. Pharmacists also have a vital contribution to make to patient care through managing pharmacotherapy and concurrent non-prescription or alternative therapies [17, 28, 86].

Pharmacists are taking an important role to support people obtain the best results from their medications. The results of care are improved and costs are reduced when they are involved in pharmaceutical assistance, the treatment of patients and patient care. Pharmacists are also available with for all people can talk to face-to-face without an appointment. Communicate effectively to assess factors that may affect a patient's ability to take medicine. Pharmacists are the medication specialists on the health-care team. Work in a wide range of medical institutions and have flexible hours. Pharmacists Help people live healthier, better lives. Over the past 40 years, the pharmacist's role model has changed from that of compounder and dispenser to one of pharmacotherapy manager. This involves responsibilities to guarantee that wherever medicines are provided and used, quality production are selected, procured, stored, distributed, dispensed and administered so that they contribute to the health of patients, and not to their harm. The framework of pharmacy practice now includes patient-focused care with all the cognitive functions and features of recommending, providing information about drug and monitoring pharmacotherapy, as well as technical aspects of pharmaceutical services, including medicines deliver chain management. It is in the additional role of managing pharmacotherapy that pharmacists can now make an essential assistance to patient care [10, 39, 48].

Pharmacists have a lot of public health functions that can benefit from the unique experience of pharmacists, which may include pharmacotherapy, pharmaceutical care, and pharmacy assistance. In addition to dispensing medicines, pharmacists have proved to be an accessible resource for information on health and medicines [11, 67]. The centralized position of the pharmacist in the society and clinical competence are invaluable. It is important to review and integrate public health practices into pharmacological training and pharmaceutical care. Encouraging cross-training will also increase the resources and help meet the needs of the workforce in the fields of pharmacy and public health. Purpose The American Public Health Association has



strongly supported the role of the pharmacist in public health. Through Trans disciplinary approaches, it is assumed that the pharmacist's contribution to public health, health care, health education, disease prevention and health promotion, public health promotion and the quality of health will help in achieving optimal public health outcomes [28, 36, 57].

As pharmacists proceed to become more clinically-oriented health care professionals, with increased responsibilities, liability and accountabilities for pharmaceutical care clear pathways for workforce development, coupled with professional recognition and credentialing of practitioners, is an important consideration. This represents a clear opportunity for transnational collaboration and further opportunities for transnational recognition of advanced capabilities for the pharmacy workforce. An obviously display and assurance of competence and facilities that is well-proportioned with progressive and expert practice is an obviously message to fostered public that pharmacists own this competence; occupational recognition, credentialing and quality assured specialism are part of this to show of competence, skills and capability. There is in the interest of patients, health systems and pharmacist profession that were develop a common and shared understanding of what we mean by specialization and by innovative practice. This is a key driver for future workforce perfection [49, 56, 57, 60].

The rational use of drugs remains the exception rather than the rule. For those people who do take medicines, more than half of all prescriptions are incorrect and more than half of the people involved fail to get them correctly. In additive, there is growing concern at the increase in the global spread of antimicrobial resistance, a major public health challenge. The global trend is for pharmacy to continue to become a more clinical, patient-facing profession, with enhanced responsibilities and accountabilities for pharmaceutical care in clinical environments; hence, clear pathways for workforce development, coupled with professional acknowledgment and credentialing of practitioners, becomes an important consideration. There is a clear opportunity for transnational collaboration and further opportunities for transnational recognition of advanced skills, capabilities for the pharmacy workforce management [48, 89, 58, 59, 67].

Pharmacy is a so elder profession and has changed deeply over the years. It is a dynamic, growing, and increasingly diverse profession, one which creates an excitement because there are so many opportunities for service. The secret in the future will be to identify and take advantage of these opportunities. In patient-centered health care, the first challenges are to identify and meet the changing needs of patients. Pharmacists need to ensure that people can access medicines or pharmaceutical advice easily and, as far as possible, in a way and at a time and place of their own choosing.

They can empower patients by engaging them in dialogue to communicate knowledge which enables them to manage their own health and treatment. Although patients are exposed to a wide range of information from package inserts, promotional materials, advertising in the media and through the Internet, this information is not always accurate or complete. The pharmacist can help informed patients to become accurately by offering unbiased relevant evidence-based information and by pointing to reliable sources. Counselling on disease prevention and lifestyle modification will promote public health, while shared decision-making on how to take medicines through a concordant approach will optimize health outcomes, reduce the number of medicine-related adverse events, cut the amount of medicine which is wasted and improve adherence to medical treatment [67, 85, 93].

The pharmacists are the health vocational specialists most accessible to the society. They deliver medicines according to with a prescription or, when legally permitted, sell them without a prescription. In addition to ensuring an accurate deliver of appropriate products, their professional activities also cover counselling and advising of patients at the time of dispensing of prescription and non-prescription drugs, drug information to health professionals, patients and the general society, and participation in health-promotion programs. They maintain links with other health professionals in fundamental and primary health care. Today, an increasingly wide range of new and analogous products are used in medicine, including high-technology biological products and radio-pharmaceuticals. There is also the mixed group of medical devices, which contains some products analogic to medicines, some of which demand special knowing and information with regard to their uses and risks (e.g., dressings, wound management products, etc.). Pharmacists have gradually and progressively undertaken the additional task of ensuring the quality of the products they deliver [42, 49, 62].

Anywhere is the necessity for this infrastructure more evident in the day-to-day management of patients than in the delivery of essential drugs. Indeed, effective drug can be practiced only where there is efficient drug management. This is an axiom that applies with equal validity to both developed and developing countries. Yet, time and again, in less affluent settings, inadequacies in the provision of primary health care are attributable to short comings within the drug distribution management chain. Only when the pharmacist has been accepted as a vital participant of the health care team can the necessary supporting services be organized with the professionalism that they demand. In highly western countries, acceptance of the need for professionalism in the supply and dispensing of drugs and health appliances has long since been indispensable because of the complexity of modern health care technology. Recently, however, a

striving for economy engendered by the ever-burgeoning costs of health care within the public sector has lent much credence and immediacy to arguments that a redetermination of the role of the pharmacist could serve the interests of both individual patients and the public at large. the pharmacist serves as a member of a multidisciplinary team rather than in an autonomous capacity; but in any particular country the profession can only be an efficiently organized element of the health care system when it has gained representation within the senior ranks of administration in both government and industry, and when pharmaceutical education has become established at university degree level. A voice in national administration is of vital significance from the outset, since this not only promotes the potential of the profession and exerts influence upon training curricula and the academic standards required for registration - and for certification of ancillary staff - but also provides the best available assurance that policy considerations, including resource allocation, will be attuned meaningfully to national requirements. Similarly, the pharmacist has indisputable functions at various levels in national drug registration and regulation. The responsibilities of the regulatory authority are to ensure that all products subject to its control conform to acceptable standards of quality, safety and efficacy; and that all premises and practices employed to manufacture, store and distribute these products comply with requirements to assure the continued conformity of the products to these standards, until such time as they are delivered to the end user. A small regulatory authority will seldom, if ever, undertake independent, comprehensive evaluations of the safety, effectiveness and efficacy of individual products. In this case, the administrative and technical responsibilities that fall within its ambit are largely of a pharmaceutical nature and they are directed primarily to quality assurance. In the last analysis, however, whereabouts pharmacy establishes its roots as a profession, it is within the health care establishments, institutions and in the community itself that pharmacists will serve in greatest numbers and with the most immediate and instant effect on patient welfare. Pharmacists' particularized knowledge, information of the management and properties of medicines in an increasingly complicated health care environment brings them closer to prescribing doctors as a source of independent information about therapeutic options and about the results - both positive and negative - of treatment. It also yields them closer to patients in the society as readily accessible dispensers not only of drugs but also of health-related information. Their basic training should aim to confer upon them competence to offer skilled advice on the treatment of minor illness and the adoption of healthy lifestyles, and it should endow them with the insight necessary to recognize when the best interests of the patient are served by prompt referral to a medical practitioner [15, 47, 59, 64].

Under some model of care, physicians generally head the healthcare team, while the pharmacist enters the patient care continuum after the prescription has been written. Delivering the right drug, identifying the correct dosage and times it is to be taken, labeling it clearly, and listing potential side effects are all part of the pharmacist's well-known responsibilities. But today's drugs are considerably more complex than they once were – and with genomes, biotech and genetic compounding, drug therapy stands to grow even more individualized over the next ten years. The pharmacist's role is concurrently expanding. Maximizing the safety of medications is an increasingly critical responsibility of practice. It is the pharmacist's task to be sure the patient knows the name of the drug, what it is for, how and when it is to be taken, how to minimize possible interactions with other drugs (prescription or OTC) and foods, and optimal storage. Asking open-ended questions like "What has the doctor told you about this medication?" helps. But even where the prescriber or nurse has explained, the patient may not have heard or perhaps didn't understand, making the pharmacist a critical checkpoint [42, 48, 79].

Community pharmacists have an important role in medication counseling and health education as they are often the first points of contact for patients and care within the healthcare system. Pharmacists play a key role in helping patients maximize their pharmaceutical care. For example, it is estimated that up to fifty percent of all patients on medication for hypertension do not have their pressure under control because they lack regular follow-up. Pharmacists are ideally suited to track individuals on these medications and help them obtain proper follow-up. Americans are typically in their local pharmacy at least once or twice a month. Many come in weekly. It is apparent how convenient it is to have blood pressure machines set up, so patients can check their numbers and have the pharmacist explain what those numbers mean. As part of the healthcare team, the pharmacist can act as a support system in disease management programs. Some interesting new models for care are evolving. One that model has pharmacists selecting from agreed-upon therapeutic options and then working directly with the patient to maximize outcomes. Physicians might prescribe not a specific product, but an outcome – say, the desire to lower blood pressure to a specific level with pharmaceuticals [19, 29, 61].

Pharmacists' liability and duty involve a variety of care for patients, from dispensing medications to monitoring patient health and progress to maximize their response to the medication. Pharmacists as well educate, train, consult consumers and patients on the use of prescriptions and over-the-counter drugs, and advise all physicians, family doctors, nurses and other healthcare professionals on drug decisions. Pharmacists deliver competence on the composition of drugs, including their physical,

chemical, biological and mechanical properties, as well as their manufacture, production and use. They guarantee drug purity and strength and make sure that drugs do not interact in a harmful route and technique. Pharmacists are the drugs experts finally associated about the patients' wellness and health. Pharmacists monitor and check patients' health, dispense medications, and make sure that drugs do not interact in a harmful way. They are drug expert specialists: Ultimately concerned about the patients' health and wellness [25, 29, 57].

Traditionally, pharmacists have safeguarded public from "poisons" and other substances that could cause harm to the people. But now, more than ever, pharmacists are charged with the duty and responsibility to ensure that when a patient receives and uses a drug, it will not cause harm. The overall pharmacist goal is drug safety challenges is to reduce the medication errors and medication associated harm by 50% in the next five years, worldwide. The goal is to stimulate action, create new policies (and services – points of advocacy for national pharmacy associations) at country and international level in four areas: patients, medicines, health care professionals and health systems and practices of medication. According to the World Health Organization (WHO) preventing errors and the harm that results require putting systems and procedures in place to ensure the right patient receives the right medication at the right dose via the right route at the right time. The dispute and challenge aims are to enhance in each stage of the medication use process including prescribing, dispensing, administering, checking, controlling, monitoring and using. World Health Organization aims to provide guidance and develop strategies, plans and tools to ensure that the medication process has the safety of patients at its core, in all health care facilities. This precondition is in line with the roles that pharmacists play according the FIP-WHO Good Pharmacy Practice [17, 59, 86].

*A pharmacist is a scientifically- educated graduate healthcare professional who is an expert in all side of the deliver and use of medicines. Pharmacists assure access to safe, cost-effective and quality of drugs and their responsible use by individual patients and healthcare systems.* The number of medicines on the market has increased dramatically over the last few decades, bringing some real innovations but also considerable challenges in controlling the quality and rational use of medicines. In industrialized and developing countries alike, striving to provide health care, including pharmaceutical care, are casing of new challenges. These include the rising costs of health care, limited financial resources, a shortage of human resources in the health care sector, inefficient health systems, the huge burden of disease, and the changing social, technological, economic and political environment which most countries face. While globalization has brought countries closer together in trade of products and



services and in recognition of academic degrees and diplomas, for example, it has led to rapid changes in the health care environment and to new complexities due to increased travel and migration [17, 39, 42].

Over the past 100 years there has been a tendency in pharmacy practice to move away from its original center on medicine produce towards a more inclusive focus on patient care. The pharmacist role has developed from that of a compounder and supplier of pharmaceutical products towards that of a provider of services and information and eventually that of a provider of patient care. Increasingly, the pharmacist's mission is to ensure that a patient's pharmacotherapy is properly indicated, the most effective available, the safest likely, and convenient for the patient. By taking straight responsibility and duty for individual patient's medicine-related needs, pharmacists can make a unique assistance to the outcome of the pharmacotherapy and to the patients' quality of life. The new accession has been given the name pharmaceutical care. The practice of pharmaceutical care is new, in contrast to what pharmacists have been doing for years. Because pharmacists often fail to assume responsibility for this care, they may not adequately document, monitor and review the care given. Receiving such responsibility is vital to the practice of pharmaceutical care [13, 19, 58].

The new style, roles, skills, regards and attitudes which pharmacists need mastering if they are to become members of multi-disciplinary health care teams, as well as the added benefits which they can provide through their professional input. It also explores the challenges which pharmacists face and the indefinite opportunities accessible to them to assume leading roles in patient-focused and public health efforts. In some cases, these challenges may involve an expansion of existing roles; in other cases, they may require pharmacists to adopt new roles previously considered beyond the scope of traditional pharmacy practice.

Digital health is a discipline that uses software and hardware to improve health and healthcare. The digital health field broadly includes mobile health, telemedicine (or telemedicine), wearable devices, and health information technology. Recent advances in digital technology offer the opportunity to expand healthcare delivery. For example, a growing number of people living in rural areas with limited access to healthcare could benefit from rapid intervention from telehealth providers. More and more doctors can easily access patient records, communicate with them, and monitor disease management through their smartphones, mobile apps, and available software. Pharmacists also use digital technologies in their practice. They used phones, mobile apps and remote monitoring devices to improve treatment adherence and outcomes, educate patients and monitor their symptoms remotely. Pharmacists also provide computer- or Internet-based interventions to improve hypertension treatment and

reduce medication errors and side effects. Sometimes, they used several technologies in their interventions. Specifically, pharmacists conducted in-person consultations (based on an online program or technology platform) and telephone follow-ups to effectively communicate, educate, and manage patient health concerns. Thanks to the benefits of technology, digital healthcare is becoming more and more popular. Pharmacist-led digital interventions. Compared to traditional care, all interventions delivered by telephone, computer, Internet or smartphone had greater economic benefits. The video intervention was not cost-effective, perhaps because it was not intensive enough to improve compliance. Economic evaluation of digital interventions can support evidence-based clinical decision-making. Pharmacists can use data from these economic evaluations to decide whether to implement technological tools in their practice. Additionally, these data can be considered in a value-based reimbursement system, since economic value is one of the important factors influencing access to healthcare [74, 88, 94].

Adverse drug reactions are one of the most common problems faced by physicians and pharmacists. Most often, undesirable side effects occur from the use of the following pharmacological groups: oral anticoagulants, cardiac glycosides, oral antidiabetic drugs, statins, aspirin, paracetamol, amiodarone, antidepressants. European countries, provide recommendations based on high scientific evidence on the dangers and risks associated with the use of medicines in clinical practice for various diseases and symptoms are connected. The main aspects of rational drug prescription are: making the correct diagnosis; Consideration of pathophysiological findings in the diagnosis; Selection of a specific therapeutic strategy; Choose a specific medication of your choice; Determine the appropriate dosage regimen. Develop a plan to monitor the effects of the medication and determine the course of therapy or treatment. The main directions of the best prescription and clinical practice are the selection of the most effective and harmless drug/drug combination, monitoring patients, prevention of side effects of drugs and related complications on the basis of regular monitoring, appropriate outpatient or instrumental examinations. Adverse reactions to medicinal products (side effects) are one of the most frequent problems for doctors and are often the cause of hospitalization. The reasons for the more frequent development of side effects are: incorrect intake of medications prescribed by the doctor; simultaneous use of drugs characterized by synergism (for example, aspirin and warfarin, antihypertensive drugs); Cytostatic reactions, for example: liver damage developed as a result of acetaminophen misuse; Unologic reactions (eg, quinidine thrombocytopenia, hydralazine-induced lupus erythematosus syndrome); Idiosyncratic reactions caused by genetically determined enzymopathies. The main aspects of

rational drug prescription are: making an appropriate diagnosis; consideration of the pathophysiological results of the diagnosis; selection of a specific therapeutic strategy; determining the appropriate dosage regimen; Developing a plan for monitoring the action of the drug and determining the course of therapy. The drug action monitoring plan includes: observing the effect of the drug and the patient's symptoms; use of laboratory tests; conducting various diagnostic-instrumental studies [11, 26, 39]. Thus, the main directions of the best prescription and clinical practice are the selection of the most effective and harmless drug/drug combination, patient supervision, prevention of drug side effects and drug-related complications based on periodic monitoring of appropriate ambulatory or instrumental examinations.

Pharmacotherapy is the most constantly used form of treatment intervention in any health practice setting. Its use has grown dramatically as the population has aged, the prevalence of chronic disease has increased, new infectious diseases have emerged and the range of effective medications has broadened. In addition, more and more so-called "life-style medicines" – treatments for ailments like baldness, dry skin, wrinkles or erectile dysfunction – are being marketed. Increasingly medicines can be purchased in new settings, and are handled by non-pharmacists. Compounding has been largely replaced by the commercial manufacture of nearly all formulations. Medicines can be bought in supermarkets, in drug stores or at markets. They can also be obtained by mail order or over the Internet, they are sold by medical practitioners and dispensed by computerized dispensing machines [28, 36, 48].

The accountability of health professionals for their actions is another major issue in health care provision. In the traditional relationship between the doctor as prescriber and the pharmacist as dispenser, the prescriber was accountable for the results of pharmacotherapy. That situation is changing in rapidly evolving health systems. The practice of pharmaceutical care assumes the pharmacist to be responsible for patients under their care, and society will not only accept that assumption but hold the profession to it [16, 41, 53].

A pharmacist is a healthcare professional, which has an important role in healthcare in the system. Pharmacists' professional activity also includes counseling patients, providing complete and comprehensive information about the drug to the public. At the same time, they actively participate in health promotion programs and have close communication with other professionals in the health system. Professional services include the application of specialized pharmaceutical knowledge to optimize the care process and improve health outcomes. Examples of pharmacist's professional services includes early screening and testing for chronic diseases, vaccinations, smoking cessation, and monitoring blood pressure, cholesterol, and glucose.

Pharmacy practices respond to the needs of the people who use pharmacist services to provide optimal, evidence-based care, and quality standards are essential. Roles, functions and duties for pharmacists should be considered, which should be reflected in the activities of the pharmacy. The pharmaceutical services - includes the field of activity within which are provided in all pharmacies. These services include: supply of OTC (out of counter) and prescription medicines to patients, pharmaceutical consultation, pharmacotherapy safety and health promotion.

In pharmacies in European countries, the main tasks of pharmaceutical service providers (pharmacists) are: receiving drug prescriptions, checking patients' history and verifying proper dosage and administration methods and compatibility of drugs before dispensing; preparation and labeling of drug forms based on prescriptions; Providing information and advice to patients on drug interactions, incompatibilities and contraindications, side effects, dosage and proper storage; Communicating with other health care specialists to plan, monitor, review and evaluate the quality and effectiveness of treatment for individual patients and to maximize the effectiveness of a particular pharmaceutical product or medication; production of documentation of narcotic drugs, psychotropic medications and accounting in accordance with the requirements of the legislation; Ensuring the storage of vaccines, serums and other medicinal products under appropriate conditions; consultation and provision of over-the-counter medications; Supervise and coordinate the work of pharmacy technicians, pharmacy interns and pharmacy sales assistants. In some countries, pharmacists can take postgraduate specialization in pharmacy. This is the case, for example, in Germany, the Netherlands, Switzerland (where it is mandatory) and the United Kingdom. In Germany, specialization in pharmacy is possible only in the field of general pharmacy. However, specializations are also available in various fields such as geriatric pharmacy, diabetes, homeopathy and more. In the UK and some other countries, clinical pharmacist qualifications are available as a prerequisite for pharmacists to be employed as lead pharmacists [59, 69, 77, 85].

In patient-centered health care, the first challenges are to identify and meet the changing needs of patients. Pharmacists need to ensure that people can access medicines or pharmaceutical advice easily and, as far as possible, in a way and at a time and place of their own choosing. They can empower patients by engaging them in dialogue to communicate knowledge which enables them to manage their own health and treatment. Although patients are exposed to a wide range of information from package inserts, promotional materials, advertising in the media and through the Internet, this information is not always accurate or complete. The pharmacist be able to help informed patients to become exactly informed patients by offering unbiased

relevant evidence-based information and by pointing to reliable sources. Counselling on disease prevention and lifestyle variation will promote public health, while shared decision-making on how to take medicines through a concordant approach will optimize health outcomes, reduce the number of medicine-related adverse events, cut the amount of medicine which is wasted and improve adherence to medical treatment [14, 29, 58].

Pharmaceutical care is a ground-breaking concept in the practice of pharmacy which emerged in the mid-1980s. It stipulates that all practitioners should assume responsibility for the outcomes of drug therapy in their patients. It surrounds a variety of functions and services – some new to pharmacy, others traditional – which are determined and provided by the pharmacists serving individual patients. The concept of pharmaceutical care also includes affective commitment to the welfare of patients as individuals who require and deserve pharmacists' compassion, mercy, concern and trust. However, pharmacists often deny to accept responsibility for this power and extent of care. As a result, they may not adequately document, control and review the care given. Accepting such responsibility is essential to the practice of pharmaceutical care. Pharmaceutical care can be tendered to individuals and publics. "Population-based pharmaceutical care" uses demographic and epidemiological data to establish formularies or drug lists, develop and monitor pharmacy politics, develop and manage pharmacy networks, prepare and analyses reports of drug utilization/costs, conduct drug utilization reviews and educate providers on medicine policies and procedures. Without individual pharmaceutical care, however, no system can manage drug therapy and monitor medicine-related illness effectively. The population-based functions identified by above need to occur either before or after patients are seen and provide useful information, but cannot replace patient-specific services while patients are being seen. Medicine related illnesses occur frequently even with medicines that are in a system's formulary or medicines list, since these medicines are often prescribed, administered or used inappropriately. Patients need pharmacists' maintenances at the time they are receiving care. Successful pharmacotherapy is specific for each patient. It includes individual drug therapy decisions, reaching concordance (an agreement between the patient and the health care provider on the therapeutic outcome and how it may be achieved), and critical patient monitoring activities. For each individual patient's pharmacotherapy treatment, the pharmacist develops a care schedule together with the patient. Patients can then contribute to successful outcomes by taking part of the responsibility for their own care and not relying solely on caregivers, in the former paternalistic style. Pharmaceutical care does not exist in isolation from other health care services. It must be provided in collaboration with patients, physicians, nurses and



other health care providers. Pharmacists are responsible directly to patients for the cost, quality and results of pharmaceutical care does not exist in isolation from other health care services. It must be provided in collaboration with patients, physicians, nurses and other health care providers. Pharmacists are responsible directly to patients for the cost, quality and results of pharmaceutical care [26, 41, 47, 56, 68].

The forces behind the variations in pharmaceutical education are many and varied, and growing in both number and intensity. The major economic and political forces affecting the health care system in the most countries are also having an impact and influence on the practice of pharmacy. As a effect, radical changes are needed in pharmaceutical education. The role and function of pharmacists and pharmaceutical staff need to be reappraised and the educational outcomes of the evolving pharmacy curriculum should be clearly determined. The use of outcomes statements would help to drive curriculum development. Educational outcomes can be used as a new organizing framework that integrates science, professional attributes, interprofessional practice, and professionalism across new major headings of pharmaceutical care, systems management, and public health, as they are in the practice of pharmacy. The educational change will require not only extensive curriculum revision and restructuring, but also a major commitment to faculty development to prepare teachers to educate pharmacists in a different way. The type and depth of didactic and experiential material to be included will be different. The amount and allocation of educational resources will have to change. Schools and colleges of pharmacy should create, establish and evaluate practice models that could be used within evolving health care environments. Courses should take into consideration the needs of the objective audience, learning outcomes, course content, learning and teaching methods, learning resources, participant assessment, course evaluation, and quality assurance when being introduced into the curriculum [46, 95, 114].

Pharmacy practice takes place at different levels. The ultimate aim of activities at all these levels is to benefit patients by improving and maintaining their health. Activities at individual patient level comprise all aspects of providing and managing a patient's drug therapy (i.e., pharmaceutical care, including clinical pharmacy services). At this level, decisions are made on issues of pharmaceutical care and triage (i.e., prioritization of care, patient follow-up and therapeutic outcome monitoring).

Although the number of pharmaceutical products on the market is increasing, access to essential medicines is still lacking in many parts of the world. Rising health care costs and changing social, technological, economic and political environments have made health care reforms necessary throughout the world. New approaches are needed at individual and at population levels to provide safe and effective

pharmacotherapy to patients in an ever more complex environment [12, 47, 81].

In parallel with the development of pharmaceutical infrastructure and job creation is a growing reputation of the pharmaceutical specialties. Pharmaceutical care is a one important component link of the health care system. Pharmacist specialties are pharmacist technologist, the first table pharmacist and clinical pharmacist. Most of the pharmaceutical specialties are clinical pharmacist. As for the clinical pharmacist, we believe that both the United States and many European countries, that clinical pharmacist profession will become a successful profession in Georgia too [33, 39, 45].

Over the years, after the successful introduction of clinical pharmacy concepts and services in the United States and Europe, the rest of the world has followed suit in transforming pharmaceutical services. Along with adopting these concepts and philosophy, these countries also need to change the existing pharmacy curriculum to provide the necessary training so that future pharmacy practitioners are equipped with the necessary knowledge and clinical skills. The impact of these changes was strong enough that even countries lacking in appropriate health infrastructure and education facilities were eager to produce future pharmacists trained in these concepts. This is evidenced by the variety of undergraduate pharmacy degrees such as doctor of pharmacy (Pharm D) and master of pharmacy (M Pharm) being offered to in developing countries. [39, 47, 82].

The programs in developing countries vary significantly from similar programs offered in countries such as the United States, Canada, and the United Kingdom. The main reasons for the differences in developing countries are differences in need, professional standards, and pharmacy practice. Both clinical pharmacy and pharmaceutical care are closely related concepts, although there are differences among the professional bodies that define them. For example, the United Kingdom Clinical Pharmacy Association describes clinical pharmacy as encompassing the knowledge, skills, and attitudes required by pharmacists to contribute to patient care [28, 65, 74].

Clinical pharmacists practice across all healthcare settings and use in-depth knowledge of drugs and medical conditions to manage drug therapy as part of a multidisciplinary team. Clinical pharmacists are responsible for drug treatment and patient outcomes. They are the primary source of scientifically reliable information on the safe, correct and economical use of medicines. Whereas pharmacists may be involved in the management of specific drugs or individual medical conditions the standard of care that ensures that each patient's drugs (prescription, over-the-counter, supplements, or herbal medicines) are individually assessed to determine if they are appropriate whether they are for the patient, effective for the disease, safe for use in concomitant diseases and concomitant therapy, and whether the patient can take them.

An individualized care plan defines goals, monitoring and expected outcomes. The patient is actively involved in developing the plan with other members of the care team. The impact of conventional medical management provided by clinical pharmacists on an outpatient basis is being studied to identify efficient processes and measure overall patient outcomes. Disease-specific drug management programs have shown a reduction in the incidence of some drug-related problems, including non-adherence, and have reduced some health care costs [25, 41, 85].

Clinical care team in the form of health professionals – physicians, advanced practice registered nurses, other registered nurses, medical assistants, clinical pharmacists and other health professionals - with the training and skills to provide coordinated care high quality, specific to the patient's clinical condition ... needs and circumstances. The clinical pharmacist also provides support for group practice. Although the composition of the teams may vary, the responsibility and authority for specific aspects of the treatment rests best with the person best suited to the task. The effectiveness of a team of clinical pharmacists depends on a culture of trust, shared goals, effective communication and mutual respect. The best interests of the patient should be the driving force behind teamwork [53, 61, 69].

The clinical pharmacist does not need to be in the same place as a member of the medical team and therefore the large group of health professionals certainly includes general practitioners in hospitals, clinics and stores. Although this is only an example, patients benefit from collective management through better BP control, and a large proportion of patients achieved controlled BP when the pharmacist was part of the clinic. the team. The composition of dynamic clinical teams is reflected in the multidisciplinary nature of large professional organizations such as the Society for Resuscitation, the Society for Hospital Medicine, the Nutrition Society, and the Society for Neurocritical Physicians. Most of these organizations include clinical pharmacists in leadership positions, including the chair [49-54]. Clinical pharmacists are pharmacists, physicians who specialize in direct patient care. Although they are expected to follow the steps outlined in the pharmacist's POC, Standards of Practice (SOP) help clinical pharmacists comprehensively assess drug needs and often manage complex and specialized regimens. Documentation requirements are more detailed and, where applicable, should be consistent with billing requirements. The clinical pharmacist can exercise his practice more independently in certain contexts, in particular according to organizational privileges. Clinical pharmacists who have received the appropriate qualifications and certifications should now enjoy hospital privileges such as doctors and providers of excellence. They are required to maintain a valid license, but have additional certification requirements. SOP for the clinical

pharmacist also includes educational, research and quality improvement activities [55, 68, 84].

Pharmaceutical education varies across the world. In the United States (USA), a pharmacist is eligible for a license after 6 years of training in pharmacy. While not required, many of these graduates already have a Bachelor of Science degree in another field. Pharmacists interested in direct patient care may receive additional training in postgraduate residency programs in Emergency or Outpatient Care. It is a large-scale accredited expertise in clinical care, drug information, administration, teaching methods projects/research. Those interested in specialization can complete their second year of postgraduate study in areas as diverse as any medical specialty (outpatient care, intensive care, infectious diseases, internal medicine, oncology, and many others). Additional research grants may follow, especially for those interested in an academic or research role. Pharmacists licensed in the United States have received formal training, and many universities are partnering with pharmaceutical schools outside of North America to create clinical pharmacy training opportunities for international students. Additional clinical practice sessions were included in the training programs. Clinical pharmacists may practice under a formal collaborative practice agreement with physicians in their area of practice or under hospital conditions. For example, a pharmacist can change the dose, frequency, or way of taking medications that are covered by a collaborative practice agreement. They may also initiate serum concentration monitoring or other applicable laboratory tests to monitor the effects of therapy. Quality assessments have demonstrated the value of these programs. Hospitals may require people to provide periodic quality assessments or evidence of minimum activity. Pharmacists' laws are governed by the ordinances of state and local hospitals [56, 57, 84].

Clinical pharmacist role includes developing quality assessment tools and data evaluation. Clinical pharmacists make important contributions to these drug therapy control and surveillance systems. I also report the side effects of medications. Many side effects or incidents are related to systemic problems, and the clinical pharmacist regularly provides advice on possible process improvements when programming intravenous pumps, drug safety systems, or other processes [24-25]. The clinical pharmacist manages for critical care pharmacist residency program and oversees the resident's progress and interactions with other mentors in our healthcare system. The clinical pharmacist participates in multidisciplinary book club discussions, thematic conferences, and quality assessment meetings. Like other professionals, the clinical pharmacist strives to maintain its role in scientific publishing in the literature, maintain skills, and keep abreast of the growing literature. As a certified critical care pharmacist,

a clinical pharmacist must undergo continuing education and maintain certification, and as a licensed pharmacist, a clinical pharmacist must also pursue continuing education. As clinical pharmacy programs around the world are at different stages of development, the need for specialists who specialize in drugs and their optimal use is universal. Clinical pharmacists have supported these training programs and provided training to individuals and groups. Their publications are used by pharmacists around the world to prepare and maintain the certification board. This awareness is expected to continue as more partners are involved and more pharmacists and their multidisciplinary teams recognize the power of clinical pharmacists to improve patient care [35, 39, 68].

Hospital pharmacists are drug experts who work in multidisciplinary medical teams to manage drug use in hospitals. Hospital clinical pharmacists are integrated into services and departments and provide clinical pharmacy services to patients at the bedside, with each clinical pharmacist (or team) being responsible for patient care in a specific medical ward or department. Hospital pharmacists provide clinical pharmacy services to patients hospitalized at the bedside as well as in other clinical areas such as emergency departments and outpatient clinics, as well as physicians and nurses. Most of them work in hospitals, however, innovations in the practice of hospital pharmacy have led pharmacists to work in community health services, nursing homes, rehabilitation centers and medical clinics. Pharmacists roles may vary depending on the organization and clinical needs of the hospital pharmacy. Most hospital pharmacists provide clinical services in their area of specialization; however, they can apply their skills to other roles including pharmacy managers, purchasing managers, hospital pharmacy consultants. Educational roles are also prevalent, such as giving lectures to pre-registered trainees, making presentations to other medical staff, or providing educational support to pharmacy students [12, 28, 42].

The name clinical pharmacy describes the work of pharmacists whose main job is to communicate with other healthcare professionals, to meet, interview, interview and assess patients, to follow up specific pharmacotherapeutic recommendations, to monitor and control a patient's response to pharmacotherapy, and to provide drug information. Clinical pharmacists, mainly working in clinics, hospitals, health insurance funds and emergency services. They provide patient-centered services rather than production-centered services.

The health systems of many other countries have developed similar claims of competence for pharmacists. As a critical care pharmacy specialist, it is difficult to describe a typical day, but usually busy with the elements of a pharmacist's support process during the day. It is believed that the clinical pharmacist will be responsible



for all aspects of the administration of the drug. Every day, the clinical pharmacist assesses and evaluates new patients and updates the progress of previous patients, identifies drug-related issues and potential problems, develops a problem list and treatment plan for optimal dosage based on the renal and hepatic function, potential drug interactions and serum concentration. The clinical pharmacist joins the multidisciplinary rounds with the intensive care team and applies the treatment plan by teaching the medical residents the correct order of entry or by entering the orders themselves according to a collaborative practice agreement and by them. documenting in an electronic health record. A major contribution to medication management is identifying therapies that are no longer needed, reducing the cost and risk of adverse events, and supporting antimicrobial stewardship programs with infectious disease physicians and pharmacists. The clinical pharmacist also supervises the performance of quality measures such as the appropriate prevention of venous thromboembolism, the appropriate use of drugs to prevent stress gastritis, the addition of aspirin to increase the levels of troponin associated with I coronary ischemia, and discussing the need for central tubing and urinary catheters. The clinical pharmacist educates the team on drug-related topics and related literature through tours and didactic discussions. A clinical pharmacist is always available for emergencies and resuscitation, and to answer questions related to medication [17, 29, 63].

This includes managing drug therapy, dose adjustments, interventions to optimize drug therapy, and providing information about drugs to healthcare professionals and patients. Hospital. A better understanding of the perspectives of healthcare professionals regarding clinical pharmaceutical services may provide a better opportunity to identify future challenges and opportunities for clinical pharmacists in the hospital. Therefore, the present qualitative study aimed to examine the challenges and opportunities of clinical pharmaceutical services provided in the hospital from the perspective of healthcare professionals [45, 46, 52].

A clinical pharmacist is in no way a competitor of a doctor, on the contrary, he must refer patients who need qualified medical care to a doctor. It is difficult to imagine that a pharmacist does not know the alphabet of medicine and does not have relevant knowledge of the main clinical syndromes. Must have a particularly good knowledge of the nomenclature of medicines (mainly over-the-counter medicines). In essence, a clinical pharmacist must provide a defined pharmaceutical supply and make a decision about the dispensing of the drug [47, 59, 81].

While curricula have been adjusted to prepare pharmacists for this new role, changes in practice have focused on other issues, such as: B. the emerging Covid epidemic which has brought about significant changes in the medical care industry in

terms of practice and law. Clinical pharmacy should be viewed as a different professional approach than hospital pharmacy. It is important for pharmacists to have a complete picture of a patient's condition so they can assess drug therapy and communicate effectively with other members of the healthcare team. Pharmacists need to establish a good relationship and connection with the multidisciplinary medical team by asking them to move from the pharmacy to the wards where they dispense medication and see doctors.

Staffing issues and a lack of trained clinical pharmacists have resulted in pharmacists being unable to work in clinical settings. In particular, the following pharmaceutical support functions were missing [49, 55, 84].

The concept of pharmaceutical care has evolved into integrated medication management as part of clinical pharmacy. Drug treatment has expanded as treatment regimens have become more complex and specialized, particularly in more complex patients who may have five comorbidities and are taking an average of eight drugs at a time. To achieve the best results of drug therapy in these patients, systematic and complex drug therapy is required [52, 59, 68].

For the majority of respondent patients', mostly significant factors, while choosing a pharmacy are: Service culture, wide range of products, reasonable prices. For less than half of respondent patients, mostly significant factors, while choosing a pharmacy are: Possibility to receive consultation about drugs with a physician or a pharmacist, convenient location of the pharmacy, high qualification of pharmacist personnel.

The majority of the patients determined the main factor while drug choosing process to be recommendation of a physician. Less than half part of respondents determined the main factor while choosing the drugs to be the doctor's prescription and advice of a pharmacist. Therefore, the role of pharmacist is significant in the healthcare system. For the higher quality healthcare and pharmaceutical services, the pharmacist's appropriate education level is of crucial importance. It was shown that the health of patients was directly related to the professional education level of pharmacist. Therefore, pharmacist should have eligible higher pharmaceutical education.

For the majority of respondents mostly significant factors while choosing a pharmacy were: service culture, wide range of products and reasonable prices. For less than half part of respondents mostly significant factors while choosing a pharmacy were: possibility to receive consultation about medications with a physician/ a pharmacist, convenient location of the pharmacy, high qualification of pharmacist personnel. Therefore, the role of pharmacist is underlined in healthcare system. For the higher

quality healthcare and pharmaceutical services education level is of great matter. The study provided showed that the health of patients was directly related to the professional education level of pharmacist. Therefore, pharmacist should have appropriate higher pharmaceutical education, higher professional knowledge in pharmacology, pharmaceutical care, pharmacotherapy, clinical pharmacy and other professional subjects.

For the majority of respondents mostly asked the pharmacists about the rules of drugs intake and prices of drugs. For the less than half part of the respondents mostly asked about the drugs' adverse effects and quality. For about the one third of them mostly asked about help in selection of analogue of drugs, indication/contraindication of drugs, the terms and conditions of their storage (conditions and shelf-life), the drugs dosage, rules of drug administration and selection of OTC drugs [55, 68, 84].

The society of European Union defines clinical pharmacy as a health care specialty that declares the activities and services of the Hospital/clinical pharmacist in proceeding, developing and promoting the rational, dedicate and appropriate use of medicinal products and medical devices [40, 48, 52].

However, the American College of Clinical Pharmacy, in an abridged definition, describes clinical pharmacy as that area of pharmacy concerned with the science and practice of rational medication use. The practice of clinical pharmacy embraces the philosophy of pharmaceutical care; it blends a caring orientation with specialized therapeutic knowledge, experience, and judgment for the purpose of ensuring optimal patient outcomes [41, 46, 85].

Pharmaceutical care is the responsible provision of pharmacotherapy for the goal of reaching certain effect that enhance a patient's quality of the life. That results are: treatment of a disease; elimination or decrease of the patient's symptomatology; exciting or slowing of a disease process; or preventing a disease or symptomatology. Pharmaceutical care includes the process through which a pharmacist cooperates with a patient and other medical professional in planning, monitoring, controlling and implementing a therapeutic scheme that will generate concrete therapeutic results for to the patients. This set involves three major functions: identifying potential and actual drug associated issues; resolving actual drug associated problems; and preventing drug associated issues. Pharmaceutical care is a needful element of health care system and should be integrated with other basic elements. It is provided for the straight benefit of the patient, and therefore the pharmacist is responsible entirely to the patient for the quality of pharmaceutical care [16, 42, 84].

The main relationship in pharmaceutical care is a jointly useful interchange in which the patient grants authority to the provider, and the provider gives competence,

ability, capacity, power, capability, and commitment (accept responsibility) to the patient. The vital goals, processes, and relationships of pharmaceutical care exist regardless of practice setting [43, 77, 95].

Health care costs increase twice annually, the volume of medication takes up a significant segment. Effective medication management and Patient care issues become actual. As a result, functioning of clinical pharmacist as a specialist in public health care system is required of human health protection in the private or public insurance companies' active participation will raise the demand for clinical pharmacist as a specialist in the area. Insurance companies work should be focused on the relationship between the clinic and pharmacy institutions with highly qualified specialists [12, 29, 57].

Whatever definition the basic essence of clinical pharmacy is the provision of pharmaceutical care to the patient, which is a different and more evolved form of hospital pharmacy services. Clinical pharmacist's duty to improve, enhance and simplify the appointment aspects of the drug, to reduce the likelihood of medical errors and unwarranted use of expensive drugs [14, 65, 88].

It is important to research pharmacoeconomically issues in clinical pharmacy. Pharmacoeconomics identifies, measures and compares the costs and consequences of pharmacotherapy to healthcare systems and public. The perspective of a pharmacoeconomic evaluation is paramount because the study results will be highly dependent on the perspective selected. The economical, humanistic and clinical results should be considered and valued using the methods of pharmacoeconomic, to inform making local decision whenever possible [44, 49, 81].

In today's healthcare settings pharmacoeconomic methods can be applied for affective formulary management, individual patient treatment, medication policy determination and resource allocation. Challenged to provide high-quality patient care in the least expensive way, clinicians have developed strategies aimed at containing costs [19, 27, 54].

The quality of the patient care system should not be exposed and compromised while trying to reduce expenses. The products and services delivered by of healthcare professionals should show pharmaco-economic value. That is a balance sheet of economical, material, humanistic, social and hospital/clinical results. Pharmacoeconomics be able to supply the systemic average means for that quantification.

The phrase "clinical pharmacy" was strike to define the job of pharmacists whose primary work is to act with the health care team, conversation and evaluate patients, doing specific therapeutic guidance and recommendations, monitor patient responses to pharmacotherapy and provide information about drugs. The clinical

pharmacists work primarily in clinics, hospitals are strong care settings and provide patient-oriented rather than product-oriented services. Clinical pharmacist should have knowledge of medicine, pharmacology, clinical pharmacology, pharmacy, to be able to cure the rational use of medicines, which includes the cost of the minimum economic conditions to achieve maximum therapeutic effect, and, ultimately, patient health and safety of care [45, 61, 69].

Pharmacy health care professionals, which is directly connected with the patient and their relatives. Involved in the drug issue and the appointment of treatment (medicines obtained without a prescription). It is comprehensive and necessary information to allow the use of medication, adverse events and efficacy. All the above will determine the role of the pharmacist in patient care and safety protection [79, 82, 89].

In some countries, the pharmacy profession specialist has been evolved to the points at which clinical pharmacy with patient-focused practice is no longer the exception but the rule for most pharmacists. Yet clinical pharmacy is still practiced exclusively in in-patient settings and hospitals, where access to patient data and the medical team is available. The medical record, also known as the patient chart or file, is a legal document including hospital-specific admission information, initial patient history and physical examination, daily progress notes made by health care professionals who interact with the patient, consultations, nursing notes, laboratory results, diagnostic procedures, dietary recommendations, and radiology and surgery reports. The most scheme also include sections for medication orders and clinical pharmacy progress notes on pharmacokinetic dosing and other relevant therapeutic comments and recommendations [15, 49, 64].

Clinical pharmacy demands an expert knowledge of therapeutics, a good understanding of disease processes and information knowledge of pharmaceutical products. In addition, clinical pharmacy requires strong communication skills, ability with solid knowledge of the medical terminology, drug monitoring skills, provision of medicines information, therapeutic planning skills and the ability to assess and interpret physical and laboratory findings [18, 27, 48].

Pharmacokinetic dosing, controlling and monitoring is a particular skill and service provided by clinical pharmacists. Clinical pharmacists are frequently active members of the medical team and accompany ward rounds to contribute to bedside therapeutic discussions [46, 67, 69, 98].

Globally, clinical pharmacy objectives is: to maximize the clinical effects of using drugs and choose an effective treatment for each patient individually; The monitoring of the course of treatment helps to reduce the risk of adverse events, to offer



the best therapeutic alternative, and to reduce the economic costs of treatment. In 1992 the (FIP) International Pharmaceutical Federation improved and developed the standards for pharmaceutical services according to the policy "Good pharmacy practice" in community, clinical and hospital pharmacy installation. Ensuing the recommendations of the WHO Expert Committee council and the support of the FIP Council in 1997, the FIP/WHO combination record about good pharmacy practice (GPP) were published in 1999.

The features of pharmacy working and practice will alter and vary among nations, it may also change among practice locations. Therefore, standards should recognize the uniqueness of different pharmacy practice facilities (e.g. community and hospital pharmacy). As well as the drugs needs change, the standards should recognize evolving practice settings and ensure these developing services with guidance without negatively affecting the evolutionary nature of practice. At the same time, a foundation should be set and established for practice below which the activity cannot be considered pharmacy practice at all and, therefore, should not be condoned.

When setting minimum standards on FIP and GPP underlines the significance of first defining the roles performed by pharmacists, as expected by patients, public and society. Secondly, relevant functions for which pharmacists have direct duty, responsibility, and accountability need to be determined within each role. Thirdly, the minimum of national standards must then be set and established, based upon the need to show competency in a set of activities supporting each function and role [48, 55, 61].

The minimum national standards for every action are based on processes where needs are relevant and defined appropriately according to the local needs of the pharmacy practice environment and national profession aspirations. All national pharmacy professional associations must also adapt and fit in these roles and functions in accordance to their own requirements specification. The activities listed below can be further determined and measured by setting indicators of good pharmacy practice within a national context and can be weighted by actual practice-setting priorities [36, 39, 75].

There are four basic roles where pharmacists' participation or supervision is expected by public and the individuals they serve: Prepare, obtain, store, secure, distribute, administer, dispense and dispose of medical products; Provide effective pharmacotherapy management; Maintain and improve professional performance; Contribute to improve effectiveness of the health-care system and public health. These roles may change for each individual pharmacist depending on their practice duty, liability and responsibilities. Specific standards of GPP can be developed only within a national pharmacy professional organization framework [12, 19, 46, 58, 61].

Disease-orienting pharmaceutical care :It is considered easier for pharmacists and their staff to provide disease – focused pharmaceutical care than comprehensive pharmaceutical care, but in European Union there is an ongoing dispute about whether it is ethically permissible to limit the provision of pharmaceutical care to groups of patients with certain characteristics and to not provide pharmaceutical care to others HIV/AIDS, Coronary Heart Disease, Hypertension, Lipid Management, Diabetes, Asthma etc [39, 59, 68].

Pharmacists are in the great position to meet the need for professionals to guarantee the safe and effective use of drugs. To do so, pharmacists must accept greater responsibility than they at the present time do for the management of pharmacotherapies for the patients they serve. This responsibility goes well beyond the traditional dispensing activities that have long been the support of pharmacy practice. While control and supervision of the routine drugs distribution process must remain the responsibility of pharmacists, their direct involvement in drug distribution will decrease, since these routine activities will be handled by qualified pharmaceutical care. However, the number of supervisory activities will increase. Thereby, pharmacists' responsibilities must be extended to include monitoring therapeutic progress, recommending and consulting with doctors, and collaborating with other health care practitioners on behalf of patients [18, 46, 37].

The move in the direction of pharmaceutical care is a critical factor in this cause. Pharmacists have the opportunity to enhance therapeutic results and patients' quality of life within existing resources, and must position themselves appropriately within the health care system. Pharmaceutical education has a corresponding responsibility to generate graduates who are competent to deliver pharmaceutical care. Outcome competencies contribute to quality guarantee by providing readily accessible standards against which practice may be measured [15, 19, 28, 58].

The certain and concrete standards of GPP can be developed only within a national pharmacy professional organization structure. Achieving certain and concrete standards of GPP for each nation within these recommendations may require considerable time and effort. As health professionals, pharmacists have a duty to begin the process without detention [17, 48, 69].

European pharmaceutical care network was established in 1995 (Pharmaceutical Care Network Europe) it cooperates with the World Health Organization on development and implementation of pharmaceutical care and appropriate pharmaceutical practice issues, where there is separated the direction of disease-oriented pharmaceutical care [17, 18, 36].

In 2013 the European pharmaceutical care network (Pharmaceutical Care

Network Europe) together with international experts has developed a new definition of pharmaceutical care, namely: pharmaceutical care, it is the pharmacist's role in patient care, which can be achieved through optimization of medicines to improve health status [14, 39, 67].

These circumstances of the pharmaceutical sector in the health care system in the patient-orientation, efficiency and cost-reaching way to better health. In fact, in space of the health system, in these conditions, such as universal health care, insurance, medicine and basic public health development, pharmaceutical care is a new challenge of pharmaceutical sector appears. He has to create a harmonious environment and wounded balance. To be able to administer the health condition of the population in terms of pharmacotherapy. It should be able to supply each individual with benefits of healthcare business industry, state and public healthcare, also be able to regulate its weak and negative aspects [19, 28, 41, 58].

Across its impact on individual patients' ministry of health, pharmaceutical care improves the quality and cost-effectiveness of health care systems. Enhancements at the micro-level encroach on the overall situation at the macro-level, i.e., communities' profit when individuals within them take pleasure in better health. Finally, the population at large will also benefit as system-wide enhancements occur. Pharmacists' services and involvement in patient-centered care have been associated with improved health and economic results, a reduction in medicine-related adverse events, improved quality of life, and diminished morbidity and mortality. A recent review investigated the effectiveness of professional pharmacist services in terms of consumer outcomes, and where possible, the economic profits. Its key findings illustrate the value of a range of services, including continuity-of-care after hospital discharge and education to consumers and to health practitioners. Overall, this review demonstrates that there is considerable high-quality evidence to support the value of professional pharmacy services in improving patient outcomes or medication use in the community setting [27, 28, 69].

The safety of patients is a priority for all professionals, such as pharmacists, who care about the health and general well-being of people like pharmacists. The safety of patients is determined as the prevention of harm to patients, including through errors of commission, lapse and omission [52, 53, 84].

For centuries, pharmacists have been guarantors /guardians against the poisons of those matter/ substances that can harm the society and community. Now more than ever, pharmacists are responsible and liable to guarantee that when the patient receives the drug, it will not cause harm.

As emphasized report pharmacy intervention in the use of drugs - The role of

pharmacists in improving patient safety, the participation of pharmacists in the safety of patients can be as early as possible during the prescribing phase and before the introduction of the medication. In many cases, pharmacists are supported by the programs and activities of their national associations listed in this extensive work carried out, a late-year pharmacy student at the university of Manitoba in Winnipeg, Canada, through an internship in FIP, a patient-centered and patient focused safety [54, 55, 69].

When focusing on drug errors, the FIP usually referred to the definition of the coordination Board for error alert and error alert about the treatment error. This is any preventable event that may cause or result in improper use of medicines or harm to the patient, while the medicine and drug is under the control of a professional pharmacists, patient or health care consumer also must be carefully in order to avoid, medical errors. Certain events may be related to professional practice, medical production, procedures, and systems, including prescription, production labeling, messaging, packaging and nomenclature, prescription, distribution, education, administration, monitoring and use [18, 45, 68, 74].

The definition of "harm" includes both temporary and permanent disruption of the body's function/structure, requiring intervention, and an error leading to death [47, 49, 63].

On model of care, physicians generally leader of the healthcare team, while the pharmacist enters the patient care continuum after the prescription has been written. Delivering the right drug, identifying the correct dosage and times it is to be taken, labeling it clearly, and listing potential side effects are all part of the pharmacist's well-known responsibilities and duties. But today's drugs are considerably more complex than they once were – and with genomes, genetic compounding and biotech. Pharmacotherapy stands to grow even more individualized over the next twenty years. The pharmacist's role is concurrently widening. Maximizing the safety of drugs is an increasingly critical responsibility in practice. Every new prescription requires that the pharmacist review it in conjunction with other information we have about the patient [67, 74, 82].

It is the pharmacist's goal to be sure the patient knows of the name of the drug, what it is for, when and how it should be taken, how to minimize possible interactions with other drugs (prescription or OTC) and foods, and optimal storage. Asking open-ended questions like "What has the physician told you about this drug?" helps. But even where the prescriber or nurse has explained, the patient may not have heard or perhaps didn't understand, making the pharmacist a critical checkpoint [67, 69, 82, 84].

Pharmacists acting a key role in assistance to patients maximize their pharmaceutical care. For example, it is supposed that up to fifty percent of all patients

on drug for hypertension do not have their pressure under control because they lack regular follow-up. Pharmacists are fine suited to track individuals on these drugs and help them obtain proper follow-up. Europeans are typically in their local pharmacy at least once or twice a month. Many come in weekly. It is apparent how convenient it is to have blood pressure machines set up, so patients can check their numbers and have the pharmacist interpret what those numbers mean. Since most insurance companies mandate refills every 20 days, this is a particularly useful service that provides a perfect opportunity to involve patients in their own care [67, 76, 86].

Patient safety is a priority for all professionals – pharmacists – who care about the health. Patient safety is defined as the prevention of harm to patients, including by drug or medical errors. For centuries, pharmacists were guardians / safeguards against "poisons" of substances that can cause harm to society. Now more than ever, pharmacist's responsibility is receiving safely the medication to the patient.

Pharmacists give professional services in the series of settings in response to national, local, native and international needs and priorities, with a focus on people and/or individual patients. Pharmaceutical public health includes services to publics, such as local guidelines and treatment protocols, medicine use review and evaluation, national medicine policies and essential medicines lists, pharmacovigilance, needs assessment and pharmaco-epidemiology [25, 39, 43, 56, 68].

The practice of pharmaceutical care and assistance is new, in contrast to what pharmacists have been doing for years. The key words are "responsible provision" and "definite outcomes". Whether pharmacists are reviewing a prescription or a patient medication record, talking to a patient or responding to symptoms, they are automatically assessing needs, prioritizing and creating a plan to meet those needs. What they often fail to do is to accept responsibility for this care. Consequently, they may not adequately document, monitor and review the care given. Accepting such responsibility is essential to the practice of pharmaceutical care [22, 28, 38, 46, 104].

The practice of pharmaceutical care makes obvious the pharmacist's responsibility and liability to the patient for the prevention of medicine-related illness. In the practice, the pharmacist estimates a patient's medicine-related needs, then determines whether one or more drug therapy problems exist, and, if so, works with the patient and other health care professionals to design, implement and monitor a care plan. This plan should be kept as simple as possible, and may refer to relevant sections of national or local evidence-based guidelines. The pharmaceutical care plan would help to resolve the actual pharmacotherapy problems and prevent potential drug therapy problems becoming a reality [23, 47, 58, 96].

In 1992 were used the term pharmaceutical services to represent all the services



that pharmacists require to resolve a patient's drug therapy problems. These services range from the provision of medicines information to patient counselling to medicines distribution. Pharmacists provide exhaustive, comprehensive, current and accurate information about drugs, based on best evidence are supporting the delivery of pharmaceutical care, although they themselves are not actually delivering it. Patient consultancy services should be incorporated into standard daily interaction with patients in the community pharmacy setting. Properly, timely and accurate drug dispensation and distribution is required to ensure the delivery of pharmaceutical care [20, 28, 46, 55].

Pharmaceutical care is a prospective patient-oriented practice with a concentrate on identifying, resolving and preventing of pharmacotherapy problems. This objective is obtained by a patient care process comprising four steps: assess the patients to drug therapy needs; develop a care scheme, project and plan to meet the needs; implement the care plan; and evaluate and review the care scheme. Pharmacists require a high level of education, knowledge and skills to deliver pharmaceutical care and an organizational structure to facilitate its delivery. This structure must provide for the referral of patients who cannot be managed at a particular level of care to a different level, where optimal pharmaceutical care can be provided. Eventually, as patients benefit from appropriate pharmacotherapy, this will also have a beneficial impact on their families and the society in which they live and work [11, 63, 68, 87, 90].

As the experts of drugs, pharmacists have always been known as an accessible and trusted source of advice and treatment. Today, their contribution to health care is developing in new ways to support patients in their use of medicines and as a part of clinical decision-making across the range of specialisms. Pharmacies are open every day, are convenient for most people to receive and there is no need for an appointment to see the pharmacist. All this makes pharmacies the natural first port of call for help with common diseases. Self-treatment of common ailments is becoming more popular as a growing range of safe, effective medicines becomes available from the pharmacy without the need for a doctor's prescription. Pharmacists have the competence to advise both on the choice of drugs and their safe and effective use. The right of the selection of self-treatment can prevent some conditions from developing or help others clear up faster [45, 87, 95].

A pharmacist is not a simple "drug dealer", but a health professional with specific scientific knowledge who provides services to the public to protect the health of patients and ensure the correct, effective and rational use of medicines. In addition to often very different national legislations (at least in the EU), pharmaceutical practice is regulated and regulated by its own organizations and disciplinary bodies (e.g. in

Europe the Royal Pharmaceutical Society of Great Britain (RPSGB), the Federal Pharmaceutical Association (ABDA), which regulates, regulates and strengthens the profession and training. It is important that the pharmacist can distinguish which patients have sufficient medical and scientific knowledge and which do not. This aspect is fundamental for the pharmacist's use of medical terminology, which must be expressed in the simplest, most accessible and most confidential way possible. To achieve a more effective counseling process, the patient must be recognized again as passive or active, and the message must be adapted according to their gender, age and social background. Additionally, the pharmacist is often required to treat patients from diverse ethnic, cultural, linguistic, and religious backgrounds, including potential nutrition-related illnesses (e.g., rickets and osteomalacia caused by malnutrition or malnutrition). Therefore, pharmacists must first understand the needs of each patient and tailor the message to the recipient. Attitudes of healthcare providers can sometimes be a barrier to effective patient-centered communication. The pharmacist must therefore maintain a high level of humility with regard to his scientific discoveries. The Accreditation Council for Pharmacy Education (ACPE) in the United States has developed guidelines that establish standards that new pharmacists must follow in order to assume and fulfill their patient communication responsibilities. The integration of Introductory Pharmacy Practice Experience (IPPE) and Advanced Pharmacy Practice Experience (APPE)-based learning into the curriculum demonstrates the added value of pharmacy education. Thanks to this project, students had the opportunity to deepen their knowledge in order to be able to optimally use the additional services offered today in pharmacies, in particular medication dispensing and consultation. APPEs also provided students with the opportunity to specifically develop academically acquired communication skills and build interpersonal relationships with patients. These programs are integrated into pharmacy school curricula in the United States and Australia, where social pharmacy training and acquisition of communication skills have become mandatory for professional qualifications, and the same is required in Canada.

Community pharmacists are among the most accessible healthcare providers. Screening conducted by a local pharmacist can facilitate early diagnosis of diseases/risk factors, thereby optimizing health outcomes. However, it is important to assess the acceptability of screening services to ensure they are accepted by key stakeholders. The purpose of this review was to examine the acceptability of pharmacist-led screening by all stakeholders (i.e., patients, pharmacists, and other healthcare providers) and to identify the methods used to assess the acceptability of the screening. Community pharmacists are among the most accessible and trusted

healthcare providers and are playing an increasingly important role in the delivery of professional services. With an average of 18-20 visits per year, patients are ten times more likely to visit a pharmacy than a GP. Patients can often turn to community pharmacies for prescription and over-the-counter medications. Therefore, pharmacists regularly communicate with patients to facilitate the provision of pharmacy screening services. Primary care facilities, including general practices and community pharmacies, are often the first point of contact in the healthcare system. Because of their accessibility, community pharmacies can be an appropriate place for pharmacists to screen for diseases and risk factors, enabling early diagnosis and intervention. Patients are willing to participate in pharmacist-led screening for various risk factors/diseases and report that such services are possible. The pharmacist examination can take a long time. Therefore, it is important that these services generate income through commissions [16, 43, 84].

Pharmacists specialists more than one fifth made profession (occupational) choice by influence of parents' advices, pharmacists specialists less than one-fifth made profession (occupational) choice by the desire (ambition) to obtain a profession in compliance of own trends, aspirations, and inclinations (affections), pharmacists specialists' more than one third made profession (occupational) choice by the consider of personal desire, pharmacists specialists less than one-fifth made profession (occupational) choice according specialty love from childhood. Insignificant number of pharmacists specialists made profession (occupational) choice by teachers' advices or considering advices of an expert-specialist of professional orientation (of career guidance), pharmacists specialists' little bit less than half made profession (occupational) choice according desire to obtain high-quality professional education (training) , pharmacists specialists' more than quarter made profession (occupational) choice according the prestige of the profession (specialty), pharmacists specialists' little bit less than half made profession (occupational) choice according guarantee to be employed, pharmacists specialists' little bit less than half made profession (occupational) choice according the desire to care for the health of people [45, 48, 59, 67].

More than half of higher pharmaceutical education pharmacists were satisfied with professional (occupational) choice, a quarter of higher pharmaceutical education pharmacists were partially satisfied with professional (occupational) choice. While pharmacy faculty students' vast majority were satisfied with professional (occupational) choice.

Less than a third of higher pharmaceutical education pharmacists were satisfied with professional career, about one third of higher pharmaceutical education pharmacists were partially satisfied with professional career, little over than one third

of higher pharmaceutical education pharmacists were not satisfied with professional career [74, 78, 85, 86].

About one third of higher pharmaceutical education pharmacists were satisfied with work (job), little over than one third of higher pharmaceutical education pharmacists were partially satisfied with work (job), quarter of higher pharmaceutical education pharmacists were not satisfied with work (job).

A little less than a fifth of higher pharmaceutical education pharmacists have realized professional capabilities, skills and habits to the full extent. A little bit less than half of higher pharmaceutical education pharmacists have realized professional capabilities, skills and habits partially, more than 50% of own potential, about a quarter of higher pharmaceutical education pharmacists have realized professional capabilities, skills and habits – partially, less than 50% of own potential, One tenth of higher pharmaceutical education pharmacists can not say.

The vast majority of higher pharmaceutical education pharmacists consider, that for full pharmaceutical activity, it is necessary condition- to exist continuous professional education; therefore, higher pharmaceutical education pharmacists consider, that professional education should not be ceased [41, 49, 64, 98, 109].

About half of higher pharmaceutical education pharmacists used knowledge in the practice, which obtained from professional publications, from professional literature from internet. More than one third of higher pharmaceutical education pharmacists partially used knowledge in the practice, which obtained from professional publications, from professional literature from internet. Competent pharmacist specialist who is capable of providing qualified pharmaceutical care (assistance) is formed in the professional training process.

The vast majority of higher pharmaceutical education pharmacists consider, that the most essential (relevant) issues for pharmaceutical activity are: new drugs (medications), about drugs generic, chemical and brand names, issues of pharmacotherapy of certain diseases, the safety, effectiveness and quality of the drugs (medications), pharmacology, pharmacodynamics and pharmacokinetics issues, pharmaceutical care.

The Convincing majority of higher pharmaceutical education pharmacists consider that the government should make the certification of pharmacists, which is very essential for professional perfection, for self-realization, for career advancement, for continuous professional education, for Professional growth. The vast majority of patients consider the government should make the certification of pharmacists. The vast majority of manager pharmacists consider that the government should make the certification of pharmacists. The vast majority of health care specialists consider that

the government should make the certification of pharmacists. Employed pharmacy faculty students' vast majority consider that the government should make the certification of pharmacists.

Less than one third of higher pharmaceutical education pharmacists were satisfied with the balance between the workload and personal life, more than one third of higher pharmaceutical education pharmacists were partially satisfied with the balance between the workload and personal life, about one third of higher pharmaceutical education pharmacists were not satisfied with the balance between the workload and personal life. Less than a quarter of higher pharmaceutical education pharmacists were satisfied with the time duration of job, about one third of higher pharmaceutical education pharmacists were partially satisfied with the time duration of job, more than a third of higher pharmaceutical education pharmacists were not satisfied with the time duration of job.

The vast majority of higher pharmaceutical education pharmacists were not satisfied with income, a quarter of higher pharmaceutical education pharmacists were partially satisfied with income, less than one tenth of higher pharmaceutical education pharmacists were satisfied with income.

Patients a little more than a third choosing the drugs (medications) by the advice of a pharmacist, more than half of patients consider, that for pharmacists are essential required professional competency. Patients' vast majority ask to pharmacists about rule of intake of drugs (medications).

The vast majority of health-care specialists consider that for pharmacists are in need of additional-further regular study in direction of new medications, in issues of pharmacotherapy of certain diseases, in pharmacology and pharmacotherapy, in drugs (medications) toxicity. More than half of health-care specialists consider, that pharmacists provide information about drugs (medications) to the population.

The vast majority of health-care specialists consider that, pharmacists doing optimization of quality of life for people, related to health by providing of pharmaceutical care (assistance, aid).

Less than half of health-care specialists consider that the levels of basic training of pharmacists are not corresponding to the contemporary requirements. The vast majority of health-care specialists consider that, it is necessary to provide cooperation between pharmacists and physicians on the issues of pharmacotherapy. The vast majority of health-care specialists consider that, a pharmacist should provide assistance in teach patients to understand rules of intake of prescribed drugs (medications).

Near the half of pharmacy faculty students, the most attractive areas (spheres) of activities are- pharmacy- drugstore. The vast majority of pharmacy faculty students



consider that education should not be ceased. Pharmacy faculty students' more than a third was working by specialty.

The vast majority of young pharmacist specialists would not like to leave profession. The vast majority of young pharmacist specialists consider that in pharmacology, in pharmacotherapy, in pharmaceutical care, in clinical pharmacy their knowledge is lack or is not enough for successful work.

On the basis of theoretical and logical analysis, the structure and composition of the factors has been developed, which taking into account the objective (external), subjective (internal) and universal factors, which effects on the professional formation of the pharmacist. Developed the unity of criteria for pharmacist professional formation, criteria for common professional formation (Characteristic for all stages) and criteria for specific professional formation (characterized for separate stage).

The study of professional adaptation of pharmacists showed that inadequate professional knowledge, incompatibility performance of the acquired profession, the harder adaptation to the staff is the main reasons for incomplete (imperfect) pharmaceutical care (assistance). The vast majority heads of pharmaceutical organizations and young specialists consider the coexistence of a tutor (experienced professional pharmacists) as the main factor of professional improvement for pharmacists.

To raise professional standards, government should make the certification of higher pharmaceutical education pharmacists, which is very essential for pharmacist's professional perfection, for higher pharmaceutical education pharmacist self-realization, for higher pharmaceutical education pharmacist's career advancement, for to exist pharmaceutical continuous professional education, for pharmacist professional growth, for pharmacist job satisfaction, for pharmacist career satisfaction. for pharmacists much higher status between health care specialists, for pharmacists Economic (material) welfare , for pharmacist career advancement (growth), for allows to realize fully the received knowledge in work by the full extent, for to have private pharmaceutical activity, for pharmacists career development (growth), for Correspondence of pharmacist qualification to work, for perspective for professional promotion, for possibility to career enhancement, for to realize by the full extent pharmacist professional capabilities, skills and habits, for career (growth) development, for pharmacists professional satisfaction, for pharmacist job satisfaction, for perspective for career promotion(enhancement, for satisfaction of income(salary).

Government and pharmaceutical companies should create promotional conditions for male, for to make pharmacist profession attractive for man. It is very important for career advancement (growth), for satisfaction of balance between the

workload and man personal life. For satisfaction of income (salary), for pharmacists' professional satisfaction, for pharmacist job satisfaction, for perspective for career promotion (enhancement), for satisfaction of income (salary).

The Government and private pharmaceutical companies should take care for professionalism, authority and power of pharmacist position such: to increase the salaries of pharmacists, should increase the system of benefits (incentives) scheme for employees' pharmacists. Pharmacists working conditions should be improved, in drug-store labor conditions should become more advisable for pharmacist, and pharmacist's regime (schedule) of work should become more flexible. It should be existing more pleasant psychological climate within the collective in the colleague's team in drugstore, the possibility of career growth (development) should be available to all pharmacists, pharmacist job duration time per week should be reduced, labor contract should be more effective and advisable for pharmacist [36, 48, 56, 61, 65, 82].

Because professional activity of pharmacist is very important for the society, the higher education institutions must also develop the pharmaceuticals educational programs and need to increase the hours in pharmacology, pharmacotherapy, and pharmaceutical care and in clinical pharmacy. Higher education institutions should increase the credits in pharmacology, pharmacotherapy, and pharmaceutical care and in clinical pharmacy.

Support greater role of pharmacists to own medicines management for patients and collaborate with physicians for revision. It is necessary to provide deep cooperation between pharmacists and physicians on the issues of pharmacotherapy and health care.

The state should take care of the profession of pharmacist authority. By the support of state, should increase the authority and social importance of the pharmacist profession in health care system. Pharmacist profession should become more power and authority, pharmacist should have much higher status in health care system, and this is achieved then, when the pharmacist profession will move into the health regulated professions list.

Support for preparation and implementation of continuous education courses aimed raising the professional qualifications of pharmacist staff. Pharmaceutical education should become continuous. Which will increase pharmacist's professional qualification, professionalism, professional knowledge and professional competency. The level of basic training of pharmacists should become correspond to the contemporary requirements, state should develop continuous pharmaceutical education programs that should be available for all pharmacists. Should exist qualification upgrading (improvement) study courses, professional education or professional training courses, which will be available for all pharmacists. Pharmacist's education

process should not be stopped. The possibility of professional education or training should be available for all pharmacists. Should advance pharmacy education and develop and expand continuing education. Developing a continuous pharmaceutical education system, will enhance the professionalism of pharmaceutical personnel. Pharmacist should be responsible for registration of side (adverse) effects of the drug (medication) [48, 54, 59, 66, 72, 114].

Support to the translation of professional pharmacist literature and their inclusion in educational programs. International professional publications in pharmacy should be more available and required for all pharmacists.

Preparation and implementation of the registration-certification regulations for pharmacist staff. Encourage research into all fields of pharmaceutical practice. Raising awareness on the essence of pharmacists' profession and pharmacist' functions among medical personnel and general public.

**Conclusion.** The pharmacy profession is not formally recognized as a regulated medical specialty within the Georgian healthcare system. Consequently, it is imperative to reform the advanced pharmaceutical education framework, reorienting it towards a greater emphasis on pharmacotherapy, pharmaceutical care, and clinical pharmacy. This evolution is a prerequisite for establishing pharmacists as a pivotal component of the future healthcare landscape. State health policy must formally define the role and establish universal principles for the profession, granting it regulated status comparable to that of a family physician. Furthermore, Georgia must develop and enforce updated registration, licensing, and accreditation standards for pharmacists that are aligned with international benchmarks. This alignment should facilitate the mutual recognition of qualifications, enabling Georgian pharmacists to practice throughout Europe and ensuring Georgian certifications are acknowledged in Western nations. A key step in this process is for the state to champion the profession's standing; through governmental support, the authority and societal value of pharmacists must be elevated. Achieving a more influential and higher-status position within healthcare is contingent upon the profession's official inclusion in the national registry of regulated health occupations.

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## **FUNDAMENTAL INSIGHTS INTO ADVANCING THE FUNCTIONALITY AND ADAPTABILITY OF BIODEGRADABLE TRIAZOLE-BASED ‘CLICK’ POLYMER LIBRARIES FOR DIVERSE BIOMEDICAL USES: CURRENT ACHIEVEMENTS, CHALLENGES, STRATEGIC DIRECTIONS, AND NOVEL PRACTICAL APPROACHES**

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**Abstract.** A series of new aliphatic AA-BB-type poly(ester ether amide)s (PEEAs) and poly(ester ether)s (PEEs) containing 1,2,3-triazole rings in the main chain were successfully obtained. The synthesis of the "click" polymers was performed *via* Cu(I)-catalyzed click step-growth polymerization (SGP) employing the efficient one pot/two-step synthetic approach that we had previously developed. The structure of the polymers was confirmed by FT-IR and NMR spectroscopy. The newly synthesized materials were extensively characterized, including assessments of their yield, solubility, film-forming properties, molecular weights, and molecular weight distribution. The obtained PEEAs and PEEs exhibited a quite satisfactory degree of polymerization, good film-forming properties, and favorable solubility behavior. The reported materials enlarge a library of available degradable triazole click polymers promising for a wide range of biomedical applications. The results validate once again the applicability of our innovative synthetic strategy for designing various classes of triazole-backbone degradable click polymers. Degradable triazole-based "click" polymers have emerged as a versatile and indispensable class of materials in biomedical innovation. Their unique properties, such as biocompatibility, tunable degradability, and ease of synthesis via "click" chemistry, have made them highly attractive for diverse applications, ranging from drug delivery systems to tissue engineering scaffolds. Expanding their scope and functionality remains a pivotal goal to meet the growing demands of advanced biomedical technologies. This article explores the advances, challenges, opportunities, future development strategies, and

emerging practical implementation approaches for these polymers. The field of degradable triazole "click" polymers is poised for significant advancements in biomedical innovation. As the library of these polymers expands, it is important to balance the opportunities they offer with the challenges they present. By focusing on controlled synthesis, enhanced biological interactions, and scalable production, researchers and clinicians can harness the full potential of these materials. With continued development and collaboration, these polymers could become a cornerstone of next-generation biomedical therapies, leading to improved patient outcomes and more sustainable healthcare solutions. The study successfully demonstrates the synthesis of new poly(ester ether amide)s (PEEAs) and poly(ester ether)s (PEEs) incorporating 1,4-disubstituted 1,2,3-triazole rings in their backbone. The materials exhibit promising properties that make them potential candidates for a variety of biomedical applications, particularly in controlled drug delivery and tissue engineering. However, further research is needed to fully explore their clinical potential, optimize their properties, and address challenges related to their large-scale production and biological interactions.

**Keywords:** Poly(ester ether amide)s, (PEEAs) poly(ester ether)s, (PEEs) copper(i), catalyzed azide-alkyne cycloaddition, (CuAAC) step growth polymerization (SGP) 1,2,3-triazole ring.

**Introduction.** Degradable triazole-based "click" polymers have emerged as a versatile and indispensable class of materials in biomedical innovation. Their unique properties, such as biocompatibility, tunable degradability, and ease of synthesis via "click" chemistry, have made them highly attractive for diverse applications, ranging from drug delivery systems to tissue engineering scaffolds. Expanding their scope and functionality remains a pivotal goal to meet the growing demands of advanced biomedical technologies. This article explores the advances, challenges, opportunities, future development strategies, and emerging practical implementation approaches for these polymers.

#### *Advances in Degradable Triazole "Click" Polymers*

##### 1. Synthetic Innovations:

- Introduction of novel monomers and polymerization techniques has significantly broadened the library of triazole-based polymers.
- Controlled polymerization strategies enable precise tailoring of molecular weights and architectures, including linear, branched, and network structures.

##### 2. Functional Diversity:

- Integration of functional groups has allowed for enhanced interaction with biological systems, enabling applications in targeted drug delivery and imaging.

➤ Multi-stimuli-responsive systems have been developed for controlled degradation under specific physiological conditions.

3. Biomedical Applications:

➤ Drug Delivery: High loading capacities and tunable release profiles make these polymers ideal carriers for chemotherapeutics, antibiotics, and gene therapies.

➤ Tissue Engineering: Biodegradable scaffolds support cell attachment, proliferation, and differentiation while degrading into non-toxic byproducts.

➤ Diagnostics: Functionalized triazole polymers serve as contrast agents in imaging and biosensing applications.

Challenges in Expanding the Scope and Functionality

1. Synthetic Complexity:

➤ Achieving scalable, cost-effective synthesis of highly functionalized triazole polymers remains a significant hurdle.

2. Biocompatibility and Safety:

➤ Comprehensive in vivo studies are required to ensure long-term biocompatibility and to understand degradation pathways and byproducts.

3. Regulatory Hurdles:

➤ The stringent regulatory requirements for biomedical materials pose challenges for clinical translation.

4. Integration with Emerging Technologies:

➤ Compatibility with advanced biomedical tools such as 3D bioprinting and microfluidics is still underexplored.

Opportunities for Innovation

1. Interdisciplinary Collaboration:

➤ Partnerships between chemists, biologists, engineers, and clinicians can accelerate innovation and application.

2. Customization for Personalized Medicine:

➤ Tailoring polymer properties to meet individual patient needs in drug delivery and tissue engineering.

3. Green Chemistry Approaches:

➤ Development of sustainable, eco-friendly synthetic methods for triazole polymers.

4. Integration with Smart Materials:

➤ Combining triazole polymers with stimuli-responsive or bioactive materials to create multifunctional systems.

Future Development Strategies

1. Advanced Synthesis Techniques:

➤ Leveraging automation, artificial intelligence, and machine learning for the design and synthesis of complex polymer architectures.

2. Comprehensive Characterization:

➤ Employing state-of-the-art analytical tools to study polymer structure, functionality, and degradation mechanisms.

3. Enhanced Biocompatibility Testing:

➤ Long-term in vitro and in vivo evaluations to ensure safety and efficacy.

4. Clinical Translation:

➤ Establishing partnerships with industry and regulatory bodies to streamline the transition from laboratory research to practical applications.

Emerging Practical Implementation Approaches

1. 3D Printing and Bioprinting:

➤ Utilization of triazole-based polymers as bioinks for creating customized biomedical devices and tissue constructs.

2. Nanotechnology Integration:

➤ Designing nanoscale polymeric systems for precision medicine applications.

3. Hybrid Systems:

➤ Developing composite materials that combine the benefits of triazole polymers with other biomaterials for enhanced performance.

4. Digital Health and Monitoring:

➤ Incorporating triazole polymers into wearable biosensors and diagnostic tools for real-time health monitoring.

The Copper(I) catalyzed azide-alkyne cycloaddition (CuAAC) stands as a prominent tool within the realm of "click" reactions, showcasing its widespread utility across diverse domains in contemporary polymer and material science. This reaction has gained significant recognition due to its exceptional attributes, including rapid reaction kinetics, high efficiency, precise regioselectivity, tolerance towards diverse functional groups, and mild reaction conditions. Consequently, CuAAC click reactions have found extensive application in the synthesis of various polymer architectures, such as block-copolymers, cyclic polymers, dendrimers, hyper-branched macromolecules, star-shaped polymers, and cross-linked polymeric networks [1-11]. Furthermore, this technique has been instrumental in functionalizing and modifying the surfaces of polymeric materials.

Intrigued by its potential, synthetic polymer chemists have sought to leverage CuAAC for the synthesis of polytriazoles through step-growth polymerization (SGP) since 2004 [12-15]. Despite notable advancements, this field remains in a state of

continuous development, beset by numerous challenges and obstacles [14-15]. Specifically, there is a paucity of reports detailing the synthesis of aliphatic main-chain triazole degradable polymers through CuAAC-based click SGP. Noteworthy contributions include the pioneering work of Nagao and Takasu [16], who successfully synthesized degradable polyesters (PEs), and the efforts of Galbis et al. [17], who produced click PEs on the basis of erythritol, bearing free hydroxyl groups. Beyond these achievements, click polymerization has also been harnessed for the fabrication of various other biomedical materials [18-24].

It should be noted that click polymers with 1,2,3-triazole rings in the backbone have some important advantages. To commence with, the triazole rings are known to be low-toxic moieties [25, 26] with a high level of mimicry of the amide bond of native peptides: the 1,2,3-triazole ring is structurally similar to the amide bond of proteins in terms of configuration, distance, and planarity [27]. So, the incorporation of the triazole units in the polymeric chains is anticipated to enhance the biocompatibility of the materials. Furthermore, the insertion of rigid triazole fragments in the polymeric structure can notably improve the thermal characteristics of the polymers [28]. It is known that triazole's derivatives demonstrate a wide range of biological activities, including anti-inflammatory, antioxidant, antiviral, antimicrobial, antifungal, anticancer, analgesic, etc. [29, 30]. Therefore, the click polymers with triazole rings in the backbone are expected to reveal some biological activities, and such polymers can be promising for creating new bioactive materials. It is worth noting that 1,2,3-triazoles are widely used in the design of various high-performance organic coatings such as anti-microbial, anti-fouling, anti-corrosive, self-healing, etc. [31]. Thus, the triazole-enriched click polymers can be considered as perspective materials for creating effective polymeric coatings as well.

Moreover, an important advantage of click polymers lies in the quaternizable nature of 1,2,3-triazole rings, as documented in prior studies [32, 33]. This characteristic facilitates subsequent post-polymerization functionalization of these polymers. The process of quaternization, involving the modification of triazole rings with diverse quaternizing agents such as halo-alkyls and polyethylene glycol (PEG) derivatives, presents opportunities for creating cationic systems featuring 1,2,3-triazolium moieties within the polymer backbone. This includes the development of cationic polymers and amphiphilic surfactants (e.g., when employing PEG-bromides as quaternizing agents) and the formation of cross-linked hydrogels (when utilizing bifunctional quaternizing agents like dibromo-PEGs, for instance). These approaches hold significant promise for a multitude of biomedical applications.

To synthesize new high-molecular-weight 1,2,3-triazole containing degradable



polymers, we have previously elaborated a new synthetic strategy of CuAAC-based click SGP [28]. Our innovative approach could be considered as more versatile compared to existing strategies and allows to synthesize different types (AB and AA-BB) and classes (PEs, poly(ester amide)s, poly(ester urea)s, their co-polymers, etc.) of aliphatic hetero-chain click polymers, avoiding the utilization of potentially explosive organic azides through safe and facile one-pot/two-step procedure. In the mentioned work [28], we successfully synthesized a series of novel linear AA-BB type 1,2,3-triazole rings-containing click PEs following the new strategy. Obtained on the basis of non-toxic building blocks (fatty diols and dicarboxylic acids), the new polymers possessed high molecular weights, improved thermal characteristics, good solubility in organic solvents, film- and nanoparticles-forming properties. Very recently, we demonstrated the suitability of the new synthetic approach for designing novel hydrolytically degradable AB-type click PEs and Co-PEs as well [34].

In the present work, we report on the successful synthesis of two other classes of new linear AA-BB-type degradable click polymers *via* our efficient synthetic strategy: poly(ester ether amide)s (PEEAs) and poly(ester ether)s (PEEs). The key homo-bifunctional diyne monomers were synthesized by the interaction of sebacoyl chloride with propargyl alcohol or propargylamine according to **Figure 1**.

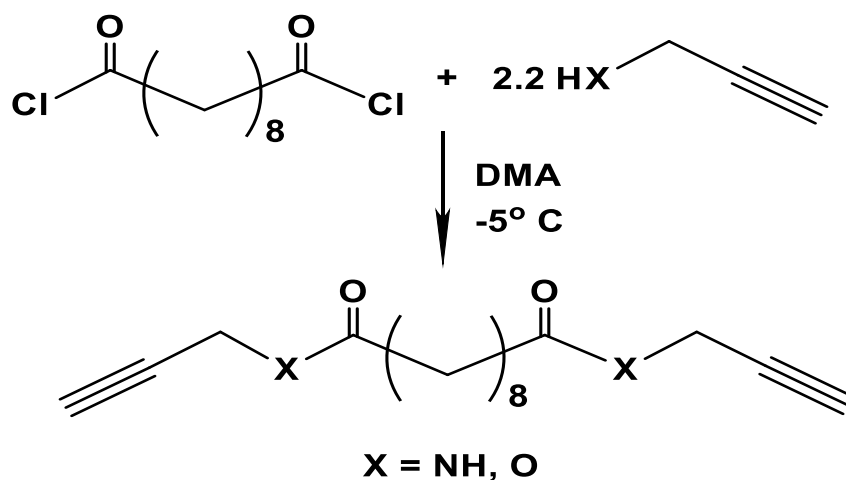


**Figure 1.** Synthesis of diyne monomers

The synthetic precursors of target diazide monomers (bis-bromoacetyl derivatives) were obtained by the interaction of bromoacetyl bromide with di-, tri-, and tetra-ethylene glycol (**Figure 2**).

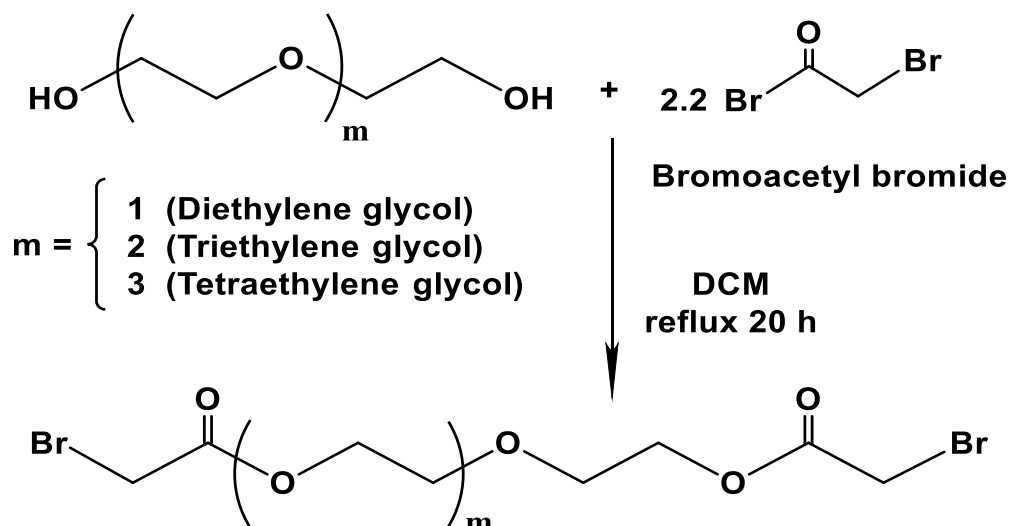


**Figure 2.** Synthesis of bis-bromoacetyl derivatives

The synthesis of the new click polymers with triazole rings in the backbone was realized by one-pot/two-step SGP of the homo-bifunctional monomers in the presence of sodium azide using copper(I) iodide/triethylamine ( $\text{CuI}/\text{NEt}_3$ ) as a catalytic system (*Figure 3*).

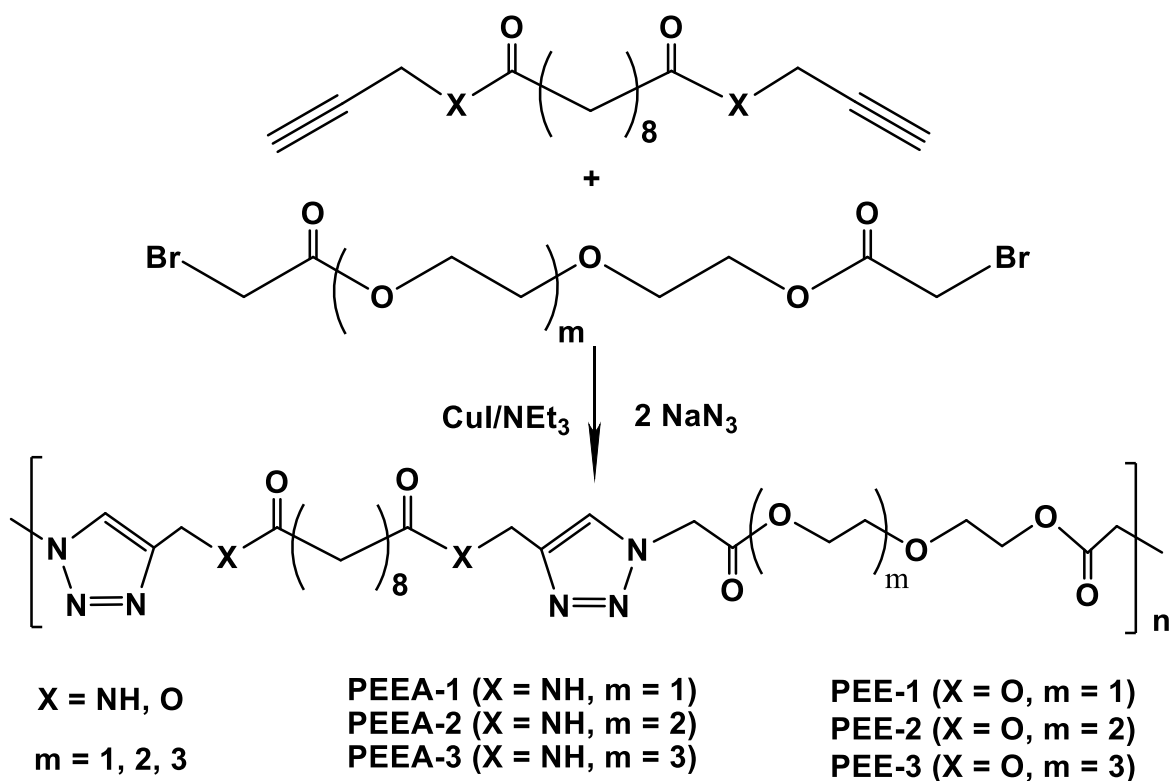


**Figure 3.** Synthesis of PEEAs ( $\text{X}=\text{NH}$ ) and PEEs ( $\text{X}=\text{O}$ )

The confirmation of monomer and polymer structures was performed through

the use of FT-IR and NMR spectroscopic techniques. Comprehensive polymer characterization encompassed the assessment of yield, solubility in organic solvents, film-forming attributes, determination of molecular weights, and evaluation of molecular weight distribution. The introduction of novel AA-BB-type PEEAs and PEEs serves to enrich the existing repository of degradable click polymers, broadening the spectrum of materials available for a diverse array of biomedical applications.

### **Materials and Methods.**

#### *Materials*

Broboacetyl bromide, propargyl alcohol, propargylamine, sodium azide, anhydrous sodium sulfate, copper(I) iodide, lithium bromide, aluminum oxide (alumina) (activated, basic, Brockmann I), acetone, ethanol, methanol, hexane, ethyl acetate, dichloromethane (DCM), N,N-Dimethylformamide (DMF), N,N-dimethylacetamide (DMA), and 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) were purchased from Sigma-Aldrich (Germany). N-methylpyrrolidone (NMP) was purchased from Carl Roth, Karlsruhe (Germany). Triethylamine (TEA) was purchased from Lancaster (UK). All the starting materials, chemicals, and solvents purchased from the commercial sources were used without further purification.

#### *Characterization*

The polymers synthesized were characterized by Fourier-transform infrared spectroscopy (FT-IR),  $^1\text{H}$  nuclear magnetic resonance (NMR) spectroscopy, and gel permeation chromatography (GPC).

The IR analysis of samples was performed on Thermo Nicolet Avatar 370 FT-IR spectrophotometer coupled with EZ OMNIC software measuring between wavelength range of 4000 and 400  $\text{cm}^{-1}$ . The FT-IR spectra of monomers were recorded using Avatar Multi-Bounce Flat Plate 45 degree Ge. To obtain the spectra of polymers, the thin films were cast from HFIP solution on KBr plates, the solvent was evaporated at room temperature and films were dried in a vacuum at 40° C to a constant weight.

The  $^1\text{H}$  and NMR spectra were recorded at 300 K on a JEOL ECP 500 NMR spectrometer operating at 400 MHz. DMSO- $\text{d}_6$  was used as solvents and internal standards. The chemical shifts ( $\delta$ ) in the spectra are conventionally expressed in parts per million (ppm).

The weight-average ( $M_w$ ), number-average ( $M_n$ ) molecular weights, and molecular weight distribution (Dispersity,  $D$ ) of the polymers were determined on a GPC machine (Waters Associates, Inc., Milford, United States) comprising two Styragel columns in DMF: HR4 and HR3 (7.8 mm  $\times$  300 mm) and equipped with a high-pressure liquid chromatography pump (Waters 1525 Binary HPLC) and a Waters refractive index detector 2414 and UV-detector (Waters 2487 dual absorbance

detector,  $\lambda = 240$  nm). A solution of LiBr (0.05 M) in DMF was used as an eluent. Injected volume 100  $\mu\text{L}$ , flow rate 1.0  $\text{mL min}^{-1}$ . The columns were calibrated with poly(methyl methacrylate) standards ( $M_n = 500 - 500,000 \text{ g mol}^{-1}$ ). Polymer sample solutions with concentration 5  $\text{mg ml}^{-1}$  were prepared in the GPC eluent and filtered with PTFE filters (0.45  $\mu\text{m}$ ) prior to injection.

#### *Synthesis of diyne monomers*

The key homo-bifunctional diyne monomers (di-propargyl amide/ester of sebacic acid) were synthesized by the interaction of sebacoyl chloride with propargylamine or propargyl alcohol according to Figure 1. The synthesis was carried out in DMA solution without using tertiary amine as HCl acceptor. In a typical procedure, propargylamine/propargyl alcohol (0.159 mol – an excess) was dissolved in 260 mL of DMA, the solution was chilled to  $-5^\circ\text{C}$  and 17.30 g of sebacoyl chloride (0.072 mol) was added dropwise upon stirring using a magnetic stirrer. The reaction solution was stirred for 30 min at  $-5^\circ\text{C}$  and then was continued at room temperature for 24 h. Afterwards, the solution was poured into water and the vessel with precipitated white powder was placed overnight in a refrigerator. The obtained solid product was filtered off, dried under reduced pressure at room temperature, and recrystallized from the ethanol/hexane mixture.

*Di-propargyl amide of sebacic acid.* Yield: 68 %. FTIR ( $\text{cm}^{-1}$ ): 3280 (–NH–, amide, stretching vibr.), 2132 ( $\text{C}\equiv\text{C}$ ), 1642 (–CO–, amide), 1552 (NH–, amide, bending vibr.).  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ ,  $\delta$ ): 1.28–1.32 (8H, m,  $\text{CH}_2$ ); 1.54 (4H, m,  $\text{CH}_2\text{CH}_2\text{CO}$ ); 2.16 (4H, t,  $\text{CH}_2\text{CO}$ ); 3.04 (2H, t, sp-CH); 4.11 (4H, d,  $\text{NHCH}_2$ ), 8.12 (2H, NH).

*Di-propargyl ester of sebacic acid.* Yield: 75 %. FTIR ( $\text{cm}^{-1}$ ): 3238 ( $\equiv\text{C-H}$ ), 2128 ( $\text{C}\equiv\text{C}$ ), 1732 (–CO– ester), 1217 (C–O–C).  $^1\text{H}$  NMR: (400 MHz, DMSO- $d_6$ ,  $\delta$ ): 1.29–1.35 (8H, m,  $\text{CH}_2$ ); 1.59 (4H, m,  $\text{CH}_2\text{CH}_2\text{CO}$ ); 2.30 (4H, t,  $\text{CH}_2\text{CO}$ ); 2.93 (2H, t, sp-CH); 4.61 (4H, d,  $\text{OCH}_2$ ).

#### *Synthesis of bis-bromoacetyl derivatives (precursors of diazide monomers)*

The synthetic precursors of target diazide monomers (bis-bromoacetyl derivatives) were synthesized by the interaction of bromoacetyl bromide with di- (DEG), tri- (TEG), and tetra-ethylene glycol (TTEG) according to Figure 2 above. The brief synthetic procedure is described here on the example of DEG-based bis-bromoacetyl derivative: to a solution of 6.09 g (0.057 mol) of DEG in 315 mL of DCM, 25.52 g (0.126 mol) of bromoacetyl bromide was added. The resulting yellow solution was refluxed for 20 h and the solvent was removed in a vacuum on a rotary evaporator yielding a brownish viscous liquid. The obtained crude product was dissolved in 40 mL of methanol and the solution was washed with 40 mL of hexane. The mixture was

separated using a separated funnel and the procedure was repeated twice (i.e. methanol solution of the crude product was washed 3 times with hexane). After the last separation of the mixture, the methanol solution of the monomer was dried over anhydrous sodium sulfate, then it was filtered and the organic solvent was removed in a vacuum on a rotary evaporator, yielding a brownish viscous liquid. DEG- and TTEG-based bis-bromoacetyl derivatives were synthesized according to the same procedure.

*DEG-based bis-bromoacetyl derivative.* Yield: 69 %. FTIR ( $\text{cm}^{-1}$ ): 1740 (-CO-, ester), 1282 (C-O-C, ester), 1123 (C-O-C, ether).  $^1\text{H}$  NMR (400 MHz, DMSO- $\text{d}_6$ ,  $\delta$ ): 3.51 (4H,  $\text{CH}_2\text{-O-CH}_2$ ), 4.11 (4H,  $\text{COO-CH}_2$ ), 4.21 (4H,  $\text{CO-CH}_2$ ).

*TEG-based bis-bromoacetyl derivative.* Yield: 76 %. FTIR ( $\text{cm}^{-1}$ ): 1736 (-CO-, ester), 1278 (C-O-C, ester), 1115 (C-O-C, ether).  $^1\text{H}$  NMR (400 MHz, DMSO- $\text{d}_6$ ,  $\delta$ ): 3.21-3.63 (8H,  $\text{CH}_2\text{-O-CH}_2\text{-CH}_2\text{-O-CH}_2$ ), 4.12 (4H,  $\text{COO-CH}_2$ ), 4.22 (4H,  $\text{CO-CH}_2$ ).

*TTEG-based bis-bromoacetyl derivative.* Yield: 73 %. FTIR ( $\text{cm}^{-1}$ ): 1744 (-CO-, ester), 1282 (C-O-C, ester), 1116 (C-O-C, ether).  $^1\text{H}$  NMR (400 MHz, DMSO- $\text{d}_6$ ,  $\delta$ ): 3.13-3.47 (12H,  $\text{CH}_2\text{-O-CH}_2\text{-CH}_2\text{-O-CH}_2\text{-CH}_2\text{-O-CH}_2$ ), 4.09 (4H,  $\text{COO-CH}_2$ ), 4.20 (4H,  $\text{CO-CH}_2$ ).

### Polymer synthesis

The target PEEAs and PEEs were synthesized according to the one-pot two-step synthetic strategy that we had previously developed [28,34] (Figure 3). The synthetic procedure is similar to the one applied for the AB-type click PEs reported in our recent work [34]. The brief synthetic procedure for the click SGP of the PEEAs and PEEs is described here for PEEA-1 as an example: 1.902 g (5.46 mmol) of DEG-based bis-bromoacetyl derivative and 0.782g (12.03 mmol) of sodium azide were dissolved in 8.35 mL of NMP and stirred at room temperature for 3 h. Then, 1.511 g (5.46 mmol) of a di-propargyl amide of sebacic acid, 31.24 mg (0.16 mmol) of catalyst CuI (3 mol %), and 0.114 mL (0.82 mmol) of  $\text{NEt}_3$  as a ligand were added to the reaction solution. The reaction solution was stirred at room temperature for 24 hours. After completion of the reaction, the solution was diluted with 8 mL of NMP, and the copper catalyst was removed by passing the crude polymer solution through a small column of activated basic alumina. Then, the obtained polymer solution was precipitated in water, filtered, thoroughly washed with water, and dried under vacuum at room temperature. Then, the polymer was twice precipitated from NMP solution (at a concentration of 10% w/v) to water, filtered, and dried under vacuum at room temperature to a constant weight. All the other polymers were synthesized employing the same synthetic procedure.

*PEEA-1.* Yield: 73 %. FTIR ( $\text{cm}^{-1}$ ): 3297 (-NH-, amide, stretching vibr.), 3068 (C=C-H of the 1,2,3-triazole), 1752 (-CO-, ester), 1638 (-CO-, amide), 1544 (NH-, amide, bending vibr.), 1217 (C-O-C, ester), 1135 (C-O-C, ether).  $^1\text{H}$  NMR



(400 MHz, DMSO- $d_6$ ,  $\delta$ ): 1.01 (12H,  $\text{CH}_2\text{-(CH}_2\text{)}_6\text{-CH}_2$ ), 1.85 (4H,  $\text{CO-CH}_2\text{-(CH}_2\text{)}_6\text{-CH}_2\text{-CO}$ ), 3.24-3.50 (4H,  $\text{CH}_2\text{-O-CH}_2$ ), 4.02-4.11 (8H,  $\text{COO-CH}_2$  and  $\text{NH-CH}_2$ -, stack), 5.17 (4H,  $\text{CO-CH}_2\text{-N}$ ), 7.68 (2H,  $\text{-C=CH}$  of triazole), 8.16 (2H,  $\text{NH}$ ).

*PEEA-2*. Yield: 94 %. FTIR ( $\text{cm}^{-1}$ ): 3293 ( $\text{-NH-}$ , amide, stretching vibr.), 3063 ( $\text{C=C-H}$  of the 1,2,3-triazole moiety), 1744 ( $\text{-CO-}$ , ester), 1638 ( $\text{-CO-}$ , amide), 1544 ( $\text{NH-}$ , amide, bending vibr.), 1217 ( $\text{C-O-C}$ , ester), 1131 ( $\text{C-O-C}$ , ether).  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ ,  $\delta$ ): 1.07 (12H,  $\text{CH}_2\text{-(CH}_2\text{)}_6\text{-CH}_2$ ), 1.82 (4H,  $\text{CO-CH}_2\text{-(CH}_2\text{)}_6\text{-CH}_2\text{-CO}$ ), 3.23-3.65 (8H,  $\text{CH}_2\text{-O-CH}_2\text{-CH}_2\text{-O-CH}_2$ ), 4.03-4.12 (8H,  $\text{COO-CH}_2$  and  $\text{NH-CH}_2$ -, stack), 5.18 (4H,  $\text{CO-CH}_2\text{-N}$ ), 7.70 (2H,  $\text{-C=CH}$  of triazole), 8.14 (2H,  $\text{NH}$ ).

*PEEA-3*. Yield: 89 %. FTIR ( $\text{cm}^{-1}$ ): 3297 ( $\text{-NH-}$ , amide, stretching vibr.), 3076 ( $\text{C=C-H}$  of the 1,2,3-triazole), 1752 ( $\text{-CO-}$ , ester), 1638 ( $\text{-CO-}$ , amide), 1543 ( $\text{NH-}$ , amide, bending vibr.), 1225 ( $\text{C-O-C}$ , ester), 1127 ( $\text{C-O-C}$ , ether).  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ ,  $\delta$ ): 0.99 (12H,  $\text{CH}_2\text{-(CH}_2\text{)}_6\text{-CH}_2$ ), 1.84 (4H,  $\text{CO-CH}_2\text{-(CH}_2\text{)}_6\text{-CH}_2\text{-CO}$ ), 3.14-3.45 (12H,  $\text{CH}_2\text{-O-CH}_2\text{-CH}_2\text{-O-CH}_2\text{-CH}_2\text{-O-CH}_2$ ), 3.93-4.08 (8H,  $\text{COO-CH}_2$  and  $\text{NH-CH}_2$ -, stack), 5.13 (4H,  $\text{CO-CH}_2\text{-N}$ ), 7.66 (2H,  $\text{-C=CH}$  of triazole), 8.07 (2H,  $\text{NH}$ ).

*PEE-1*. Yield: 93 %. FTIR ( $\text{cm}^{-1}$ ): 3145 ( $\text{C=C-H}$  of the 1,2,3-triazole), 1744 ( $\text{-CO-}$ , ester), 1213 ( $\text{C-O-C}$ , ester), 1164 ( $\text{C-O-C}$ , ether).  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ ,  $\delta$ ): 0.87 (12H,  $\text{CH}_2\text{-(CH}_2\text{)}_6\text{-CH}_2$ ), 1.90 (4H,  $\text{CO-CH}_2\text{-(CH}_2\text{)}_6\text{-CH}_2\text{-CO}$ ), 3.29 (4H,  $\text{CH}_2\text{-O-CH}_2$ ), 3.91 (4H,  $\text{COO-CH}_2\text{-CH}_2$ ), 4.78 (4H,  $\text{COO-CH}_2\text{-C}$ ), 5.10 (4H,  $\text{CO-CH}_2\text{-N}$ ), 7.83 (2H,  $\text{-C=CH}$  of triazole).

*PEE-2*. Yield: 87 %. FTIR ( $\text{cm}^{-1}$ ): 3141 ( $\text{C=C-H}$  of the 1,2,3-triazole), 1740 ( $\text{-CO-}$ , ester), 1213 ( $\text{C-O-C}$ , ester), 1168 ( $\text{C-O-C}$ , ether).  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ ,  $\delta$ ): 0.99 (12H,  $\text{CH}_2\text{-(CH}_2\text{)}_6\text{-CH}_2$ ), 2.07 (4H,  $\text{CO-CH}_2\text{-(CH}_2\text{)}_6\text{-CH}_2\text{-CO}$ ), 3.30 (8H,  $\text{CH}_2\text{-O-CH}_2\text{-CH}_2\text{-O-CH}_2$ ), 4.02 (4H,  $\text{COO-CH}_2\text{-CH}_2$ ), 4.91 (4H,  $\text{COO-CH}_2\text{-C}$ ), 5.20 (4H,  $\text{CO-CH}_2\text{-N}$ ), 7.93 (2H,  $\text{-C=CH}$  of triazole).

*PEE-3*. Yield: 85 %. FTIR ( $\text{cm}^{-1}$ ): 3145 ( $\text{C=C-H}$  of the 1,2,3-triazole), 1752 ( $\text{-CO-}$ , ester), 1209 ( $\text{C-O-C}$ , ester), 1164 ( $\text{C-O-C}$ , ether).  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ ,  $\delta$ ): 0.97 (12H,  $\text{CH}_2\text{-(CH}_2\text{)}_6\text{-CH}_2$ ), 2.04 (4H,  $\text{CO-CH}_2\text{-(CH}_2\text{)}_6\text{-CH}_2\text{-CO}$ ), 3.26 (12H,  $\text{CH}_2\text{-O-CH}_2\text{-CH}_2\text{-O-CH}_2\text{-CH}_2\text{-O-CH}_2$ ), 4.02 (4H,  $\text{COO-CH}_2\text{-CH}_2$ ), 4.88 (4H,  $\text{COO-CH}_2\text{-C}$ ), 5.17 (4H,  $\text{CO-CH}_2\text{-N}$ ), 7.91 (2H,  $\text{-C=CH}$  of triazole).

## Results and Discussion

### *Synthesis of diyne monomers*

The detailed procedure of the synthesis of key homo-bifunctional diyne monomers (di-propargyl amide/ester of sebacic acid) was discussed above. The AA-BB-type monomers were synthesized by the interaction of sebacoyl chloride with propargylamine or propargyl alcohol (Figure 1). The yields of the obtained di-propargyl amide of sebacic acid and di-propargyl ester of sebacic acid were 68 and 75

%, respectively. The presumed structure of the diyne monomers was proved by FT-IR and  $^1\text{H}$  NMR spectroscopies.

*Synthesis of bis-bromoacetyl derivatives (precursors of diazide monomers)*

The synthesis of bis-bromoacetyl derivatives – precursors of diazide monomers, was described above (see Materials and methods). Three bis-bromoacetates were obtained by the interaction of bromoacetyl bromide with di- (DEG), tri- (TEG), and tetra-ethylene glycol (TTEG) (see Figure 2 above). The yields of the obtained bis-bromoacetyl derivatives were in the range of 69 – 76 %. Their structure was confirmed by FTIR and  $^1\text{H}$  NMR spectroscopies.

*Synthesis of the click PEEAs and PEEs*

Six new triazole click polymers (three PEEAs and three PEEs) were synthesized *via* one-pot/two-step synthetic strategy that we had previously [28,34] developed. The detailed procedure of the synthesis of target click polymers was discussed above (see *Experimental Methods and Materials*).

The polymers were obtained with quite high yields (73 – 94 %). The molecular weight characteristics of the new click polymers such as weight-average ( $M_w$ ), number-average ( $M_n$ ) molecular weights, and molecular weight distribution ( $\bar{D}$ ) were determined using the GPC system with PMMA standards. Due to the insolubility of the PEEA-1 in DMF, it was not characterized by the GPC technique. According to the obtained data, given in Table 1, the new click polymers possess average molecular weights ( $M_w$  is in the range of 14,500 – 34,800 g mol $^{-1}$ ) and display moderately wide molecular weight distribution ( $\bar{D} = 1.47 – 1.60$ ). The degree of polymerization of the polymers is quite satisfactory for step-growth polymers (the DP is in the range of 16 - 42).

**Table 1.**

**Characteristics of the obtained click PEEAs and PEEs**

| Polymer | $M_w$ (g mol $^{-1}$ ) | $M_n$ (g mol $^{-1}$ ) | $\bar{D}$ | DP |
|---------|------------------------|------------------------|-----------|----|
| PEEA-2  | 14,500                 | 9,300                  | 1.55      | 16 |
| PEEA-3  | 16,600                 | 11,400                 | 1.47      | 18 |
| PEE-1   | 34,800                 | 23,100                 | 1.51      | 42 |
| PEE-2   | 28,300                 | 17,800                 | 1.60      | 30 |
| PEE-3   | 27,100                 | 17,200                 | 1.58      | 27 |

$\bar{D}$  - Dispersity ( $M_w/M_n$ ); DP - degree of polymerization

To assess the film-forming abilities of the new polymers, the thin films were cast from HFIP solutions on polytetrafluoroethylene dishes, the solvent was allowed to evaporate at room temperature, and the generated films were finally dried in a vacuum at room temperature to a constant weight. With the exception of PEEA-1 and PEE-1,

which formed brittle films, all the other click polymers revealed good elastic film-forming properties. The poor elasticity of the films produced by DEG-based polymers PEEA-1 and PEE-1 can be attributed to the highest rigidity of their molecular structure stipulated by the shortness of their monomeric units (only two  $-\text{CH}_2-\text{CH}_2-\text{O}-$  fragments per monomeric unit).

### *Spectral studies*

The structure of the click PEEAs and PEEs was investigated using FT-IR and NMR spectroscopy. Both methods confirmed the presumed structure of the new click polymers. The FT-IR study proved the presence of all IR-detectable functional moieties of the polymers. All the expected absorption bands were observed:  $3297\text{--}3293\text{ cm}^{-1}$  attributed to the stretching vibration of amide NH,  $3145\text{--}3063\text{ cm}^{-1}$  corresponding to stretching vibration of  $\text{C}=\text{C}-\text{H}$  of the 1,2,3-triazole ring,  $1752\text{--}1740\text{ cm}^{-1}$  ascribed to ester  $\text{C}=\text{O}$ ,  $1638\text{--}1636\text{ cm}^{-1}$  distinctive for amide CO,  $1544\text{--}1543\text{ cm}^{-1}$  expected for the bending vibration of amide NH,  $1225\text{--}1209\text{ cm}^{-1}$  characteristic of ester  $\text{C}-\text{O}-\text{C}$  moiety, and  $1168\text{--}1127\text{ cm}^{-1}$  typical for ether  $\text{C}-\text{O}-\text{C}$ . The detailed  $^1\text{H}$  NMR studies of the PEEAs and PEEs demonstrated precise regioselectivity of Cu(I) catalyzed click SGP: single signals of 1,2,3-triazole protons ( $\text{C}=\text{C}-\text{H}$ ) at 7.66–7.93 ppm in the  $^1\text{H}$  NMR spectra of the polymers confirmed the presence of exclusively 1,4-disubstituted 1,2,3-triazole rings in the macromolecular chains.

### *Solubility of the click PEEAs and PEEs*

The solubility of the new click PEEAs and PEEs in ten common organic solvents (10.0 mg in 1.0 mL) is presented in Table 2. All the new polymers were insoluble in common solvents such as DCM, ethanol, acetone, acetonitrile, and ethyl acetate even upon heating. Overall, PEEs revealed better solubility as compared to PEEAs. All the PEEs displayed good solubility in polar solvents such as DMSO, NMP, DMF, DMA, and HFIP at room temperature. Expectedly, the best solubility among the PEEAs was demonstrated by TTEG-based PEEA-3 which was readily soluble in DMSO and HFIP at room temperature and in NMP, DMF, and DMA upon heating. The poorest solubility of the PEEA-1, which was soluble only in DMSO, NMP, and HFIP, may be attributed to the increased rigidity of the molecular architecture conditioned by the shortness of the monomeric unit (only two  $-\text{CH}_2-\text{CH}_2-\text{O}-$  fragments per monomeric unit). The poor solubility behavior of PEEAs compared to PEEs can presumably be ascribed to the increased rigidity of the macromolecular backbone and stronger intermolecular forces stipulated by the robust amide bonds.

**Table 2.**

**Solubility of the click PEEAs and PEEs (10 mg of polymer in 1 mL of solvent)**

| Polymer | DMSO | NMP | DMF | DMA | HFIP | DCM | EtOH | Acetone | CH <sub>3</sub> CN | EtAc |
|---------|------|-----|-----|-----|------|-----|------|---------|--------------------|------|
| PEEA-1  | +t   | +t  | -   | -   | +    | -   | -    | -       | -                  | -    |
| PEEA-2  | +t   | +t  | +t  | +t  | +    | -   | -    | -       | -                  | -    |
| PEEA-3  | t    | +t  | +t  | +t  | +    | -   | -    | -       | -                  | -    |
| PEE-1   | +    | +   | +   | +   | +    | -   | -    | -       | -                  | -    |
| PEE-2   | +    | +   | +   | +   | +    | -   | -    | -       | -                  | -    |
| PEE-3   | +    | +   | +   | +   | +    | -   | -    | -       | -                  | -    |

+ soluble at room temperature;    +t soluble upon heating;    - insoluble

Three new linear AA-BB-type poly(ester ether amide)s (PEEAs) and three poly(ester ether)s (PEEs) containing 1,4-disubstituted 1,2,3-triazole rings in the main chain were successfully synthesized through Cu(I)-catalyzed click step-growth polymerization (SGP) using homo-bifunctional monomers following one-pot/two-step synthetic strategy we have previously elaborated. The presumed structure of the new polymers was confirmed by FT-IR and NMR techniques. The click polymers with average molecular weights ( $M_w = 14,500\text{--}34,800 \text{ g mol}^{-1}$ ) and moderately wide molecular weight distribution (1.47-1.60) were obtained in quite good yields (73-94 %). The degree of polymerization of the materials was quite satisfactory for step-growth polymers ( $DP = 16 - 42$ ), allowing most of them to form elastic films. The click polymers reported in this work expand a library of available degradable polymers with functionally interesting 1,2,3-triazole moieties in the backbone. The new polymers obtained can be considered as having a potential for various biomedical applications.

The development of new polymers with tailored properties is crucial for advancing various industrial and biomedical applications. This study explores the synthesis of three novel linear poly(ester ether amide)s (PEEAs) and poly(ester ether)s (PEEs) that incorporate 1,4-disubstituted 1,2,3-triazole rings in their main chains. The synthesis is achieved through Cu(I)-catalyzed click step-growth polymerization (SGP), employing a one-pot/two-step strategy previously outlined by the research team. Here, we discuss the significance of these newly synthesized polymers, their potential for biomedical applications, and the implications for future developments.

#### *Synthesis and Structural Confirmation*

The synthesis of these polymers using a click chemistry approach ensures that the desired 1,4-disubstituted 1,2,3-triazole units are efficiently integrated into the polymer backbone. The use of Cu(I)-catalyzed click polymerization provides several advantages, including high selectivity, mild reaction conditions, and the ability to

precisely control the polymer's structure. The resulting polymers were confirmed via FT-IR and NMR techniques, which validate their structure and the incorporation of the triazole ring.

The synthesis of PEEAs and PEEs with molecular weights ranging from 14,500 to 34,800 g/mol and moderately wide molecular weight distributions (1.47-1.60) highlights the feasibility of producing high-quality, functional materials. The degree of polymerization (DP) of the materials, ranging from 16 to 42, indicates that these polymers are well-suited for step-growth polymerization, a key feature for developing materials with predictable and reproducible properties.

#### *Properties and Characterization*

The new polymers demonstrated desirable properties such as good yield (73-94 %) and the ability to form elastic films. This suggests that the incorporation of 1,4-disubstituted 1,2,3-triazole units enhances the mechanical flexibility of the polymers, making them suitable for applications where elasticity and toughness are required. The molecular weight distribution and the degree of polymerization indicate that these materials have a good balance of processability and performance, essential for practical uses in biomedical devices.

#### *Biomedical Application Potential*

The incorporation of 1,2,3-triazole rings in the polymer backbone provides significant functional diversity, which is a promising feature for biomedical applications. Triazole units are known for their biocompatibility, stability, and ability to engage in various chemical interactions, making them ideal candidates for use in drug delivery systems, tissue engineering, and other medical devices. These polymers' degradability, an essential feature for many biomedical applications, further enhances their potential for use in medical implants and controlled-release systems.

Given their tunable properties and functional groups, these polymers could be developed for specific applications in drug delivery, where the degradation rate can be tailored to match the therapeutic needs. Additionally, the flexibility of these polymers could be leveraged in applications such as tissue scaffolds, where mechanical properties and biocompatibility are crucial for supporting tissue regeneration.

#### *Future Development and Challenges*

While the synthesis and properties of these polymers are promising, further optimization is required to fully realize their potential in biomedical applications. Future work could focus on improving the control over polymer architecture, which may further enhance the properties of the materials. Additionally, a more in-depth study of the degradation kinetics and in vivo biocompatibility of these polymers is necessary to assess their performance in biological environments.



Challenges remain in scaling up the synthesis for industrial applications while maintaining the material's performance and reproducibility. Moreover, the interaction of these new polymers with biological systems, such as immune responses, cytotoxicity, and long-term degradation behavior, will need to be carefully evaluated.

Expanding the scope and functionality of degradable triazole "click" polymers holds immense promise for driving biomedical innovation. By addressing current challenges and leveraging emerging opportunities, researchers can unlock the full potential of these materials. Future advancements will depend on interdisciplinary collaboration, integration with cutting-edge technologies, and a commitment to sustainability and safety. The continued evolution of triazole polymers will undoubtedly pave the way for transformative breakthroughs in healthcare and beyond.

The use of degradable triazole "click" polymers in biomedical applications has gained significant attention due to their unique properties, such as biocompatibility, degradability, and tunability. The expansion of this polymer library promises to offer new opportunities for a variety of biomedical innovations, but also presents a number of challenges. In this discussion, we will explore the recent advances, challenges, opportunities, future development strategies, and emerging practical implementation approaches related to these polymers.

#### *Advances in Degradable Triazole "Click" Polymers*

Recent studies have significantly expanded the library of triazole-based polymers, enabling better control over their physical, chemical, and biological properties. The introduction of degradable "click" chemistry has allowed for more precise and efficient polymer synthesis, leading to the development of materials with specific degradation profiles, ideal for targeted drug delivery, tissue engineering, and implantable devices. These polymers can be engineered to degrade under physiological conditions, minimizing the long-term environmental and toxicological risks associated with traditional synthetic polymers.

#### **Challenges in Expanding the Scope and Functionality**

Despite these advances, there are several challenges in expanding the scope and functionality of these polymers. The complexity of developing polymers with both controlled degradation rates and appropriate biological activity requires deeper understanding and innovative techniques. Issues such as reproducibility in polymer synthesis, scalability for mass production, and the optimization of degradation rates to match tissue healing or drug release requirements remain significant hurdles. Furthermore, understanding the interactions between these polymers and the biological systems they are intended to interact with—such as immune response, tissue compatibility, and potential cytotoxicity—is crucial for ensuring their safe use in clinical settings.

### *Opportunities for Biomedical Innovation*

The expanding library of degradable triazole "click" polymers presents numerous opportunities for biomedical applications. These polymers could revolutionize fields like personalized medicine, wound healing, and regenerative medicine by enabling the development of highly tailored biomaterials. Their potential use in controlled drug release systems, particularly in targeted therapies for cancer, diabetes, and cardiovascular diseases, offers promising pathways to improve patient outcomes and reduce side effects. Additionally, the use of these polymers in 3D-bioprinted tissue scaffolds could pave the way for creating more efficient and biologically relevant tissue structures for implantation.

### *Future Development Strategies*

Moving forward, the development of novel synthetic strategies that allow for greater control over the polymer's structure and properties will be critical. Incorporating bioactive molecules into the polymer matrix to enhance cellular interactions and tissue regeneration will also be a key area of focus. Further integration of these polymers with cutting-edge technologies, such as CRISPR-based gene editing and advanced biomaterials, could lead to highly effective combination therapies that address complex medical challenges. Additionally, the improvement of degradation pathways to match specific clinical needs, alongside the use of more sustainable raw materials, will likely play an important role in the future direction of this field.

### *Emerging Practical Implementation Approaches*

The practical implementation of degradable triazole "click" polymers in real-world biomedical applications will require collaboration across multiple disciplines, including materials science, molecular biology, and clinical medicine. Pilot clinical trials and collaborations between academia and industry will be key to moving from theoretical advancements to functional, market-ready products. Innovations such as injectable hydrogels, which can rapidly form in situ and degrade as needed, as well as smart polymers that respond to environmental stimuli, could drive the next wave of biomedical devices and therapeutics. Regulatory challenges and the need for standardized testing protocols will also play a significant role in accelerating the adoption of these materials.

The field of degradable triazole "click" polymers is poised for significant advancements in biomedical innovation. As the library of these polymers expands, it is important to balance the opportunities they offer with the challenges they present. By focusing on controlled synthesis, enhanced biological interactions, and scalable production, researchers and clinicians can harness the full potential of these materials. With continued development and collaboration, these polymers could become a

cornerstone of next-generation biomedical therapies, leading to improved patient outcomes and more sustainable healthcare solutions.

**Conclusion.** The domain of degradable triazole “click” polymers is on the verge of transformative advancements in biomedical applications. As the repertoire of these polymers continues to grow, it is crucial to carefully navigate both the opportunities they present and the inherent challenges. By emphasizing controlled synthesis, improved biocompatibility, and scalable manufacturing, researchers and clinicians can unlock the full potential of these materials. With ongoing innovation and collaborative efforts, these polymers have the potential to become foundational components of next-generation biomedical therapies, ultimately improving patient outcomes and supporting more sustainable healthcare solutions. This study demonstrates the successful synthesis of novel poly(ester ether amide)s (PEEAs) and poly(ester ether)s (PEEs) featuring 1,4-disubstituted 1,2,3-triazole units within their backbone. These materials display promising properties that make them strong candidates for diverse biomedical applications, particularly in controlled drug delivery and tissue engineering. Nonetheless, further investigations are necessary to comprehensively assess their clinical potential, optimize their functional characteristics, and address challenges associated with large-scale production and biological interactions.

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**COMPREHENSIVE INVESTIGATION OF GENETIC INFLUENCES AND  
INDIVIDUALIZED THERAPEUTIC APPROACHES IN MANAGING  
MEDICATION-INDUCED TOXICITIES, SAFETY OVERSIGHT  
CHALLENGES, CAUSATIVE AGENTS, RISK FACTORS, AND EVIDENCE-  
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**Abstract.** The increasing complexity of modern pharmacotherapy underscores the critical need for integrative approaches that combine pharmacogenetic insights with patient-centered therapeutic strategies to mitigate medication-induced adverse effects and optimize clinical outcomes. Drug-related adverse reactions (ADRs) represent a significant challenge in contemporary healthcare, contributing to elevated morbidity, mortality, and healthcare costs worldwide. These events frequently arise from the interplay of multiple factors, including genetic predispositions, polypharmacy, comorbidities, and individual variations in drug metabolism and response. Pharmacogenetics, the study of genetic determinants influencing drug pharmacokinetics and pharmacodynamics, offers a powerful framework for understanding patient-specific vulnerabilities to ADRs. By identifying genetic polymorphisms in drug-metabolizing enzymes, transporters, and target receptors, clinicians can anticipate adverse reactions, tailor therapy regimens, and improve overall therapeutic safety and efficacy. Patient-focused therapeutic strategies emphasize the integration of individualized care into pharmacological decision-making, highlighting the importance of patient preferences, medical history, lifestyle factors, and adherence patterns in shaping drug selection and dosing. A comprehensive understanding of these patient-specific variables, when combined with pharmacogenetic data, enables healthcare providers to anticipate high-risk scenarios, reduce the incidence of serious adverse events, and enhance the overall quality of care. Such strategies also extend to patient education, engagement, and shared decision-making processes, which are essential for fostering adherence, minimizing errors, and ensuring the long-term effectiveness of therapy. Pharmacovigilance remains a cornerstone of drug safety, providing systematic mechanisms for the detection, assessment, and prevention of ADRs. Despite advances in monitoring and reporting systems, challenges persist in accurately capturing adverse events, particularly those that are rare, delayed, or context-dependent. These challenges are further complicated by the heterogeneity of patient populations, variability in clinical practice, and the

evolving landscape of pharmaceutical agents. By integrating pharmacogenetic screening with real-time safety monitoring and reporting frameworks, pharmacovigilance practices can be enhanced, allowing for more precise identification of risk determinants, timely interventions, and data-driven optimization of therapeutic protocols. A critical component of this integrated approach involves the identification of causative medications and the elucidation of underlying mechanisms driving adverse reactions. Drugs with narrow therapeutic windows, high interindividual variability, or complex metabolic pathways are particularly prone to eliciting ADRs. Understanding the molecular and cellular mechanisms that contribute to drug toxicity, including interactions with off-target sites, immune-mediated responses, and enzymatic polymorphisms, is essential for predicting and preventing adverse outcomes. Advanced computational modeling, pharmacokinetic simulations, and biomarker identification further support the stratification of risk and the design of safer, individualized therapy regimens. In addition to genetic and pharmacological determinants, broader factors influencing ADR risk include age, sex, comorbidities, environmental exposures, and concomitant medications. The cumulative effect of these determinants necessitates a multidimensional approach to risk assessment, which can inform clinical decision-making and prioritize interventions for vulnerable patient populations. Optimized pharmacotherapy management integrates these insights through evidence-based algorithms, decision support systems, and clinical guidelines that guide dose adjustment, therapy selection, and monitoring schedules. Such strategies not only enhance therapeutic efficacy but also mitigate the likelihood of adverse outcomes, hospitalizations, and long-term complications. This study underscores the synergistic value of combining pharmacogenetic insights with patient-centered therapeutic strategies to address the multifactorial nature of medication-related adverse effects. By enhancing pharmacovigilance, identifying high-risk drugs, elucidating underlying risk determinants, and implementing optimized management approaches, healthcare providers can significantly improve patient safety, treatment adherence, and clinical outcomes. The integration of these approaches represents a paradigm shift in modern pharmacotherapy, emphasizing precision medicine, individualized care, and proactive risk mitigation as central pillars of effective and safe drug therapy. Continued research, clinical application, and interdisciplinary collaboration are essential to fully realize the potential of these strategies and to ensure that patients receive therapies that are both effective and safe across diverse clinical contexts.

**Keywords:** Drug characteristics, side effects, induced drug reaction, eosinophilia and systemic symptoms.



**Introduction.** A fundamental aspect of this inquiry lies in the realm of pharmacogenetics, a discipline that explores the genetic determinants influencing an individual's response to medications. By elucidating how genetic polymorphisms affect drug metabolism, efficacy, and toxicity, pharmacogenetics offers a compelling framework to tailor pharmacotherapeutic regimens in a manner that minimizes risk while optimizing therapeutic outcomes. These insights hold the promise of transforming traditional reactive healthcare approaches into proactive and preventive strategies, where the right drug is administered to the right patient at the right dose and time. Despite the potential, the integration of pharmacogenetic data into clinical practice remains sporadic and challenged by regulatory gaps, limited clinician awareness, and infrastructural deficiencies, particularly in developing health systems.

Pharmacovigilance, the systematic monitoring and assessment of drug-related adverse events, represents a critical component of drug safety and public health surveillance. Although traditionally reactive in nature, pharmacovigilance is now undergoing a transformative shift toward more proactive methodologies powered by data science, artificial intelligence, and real-world evidence. Nonetheless, numerous challenges persist in this domain, including underreporting of adverse events, lack of standardized diagnostic criteria for drug-induced conditions, delayed signal detection, and fragmented data systems. These limitations underscore the urgent need to strengthen global pharmacovigilance frameworks by enhancing collaboration among regulatory authorities, healthcare providers, pharmaceutical companies, and patients themselves [1-5].

The complexity of medication-induced toxicities is further deepened by the presence of multifaceted risk determinants that extend beyond pharmacogenetic markers. Factors such as age, gender, organ function, nutritional status, comorbidities, concomitant drug use, and socioeconomic conditions all contribute to the individual's susceptibility to adverse reactions. Environmental exposures, drug-drug and drug-food interactions, and healthcare delivery disparities also influence the pharmacokinetics and pharmacodynamics of medications in unpredictable ways. A comprehensive understanding of these risk factors is imperative not only for preventing adverse outcomes but also for designing targeted intervention strategies that are both context-sensitive and population-specific [6-8].

To effectively address these interwoven challenges, the development of strategic approaches to pharmacotherapeutic management has become a priority within both clinical and research domains. These strategies must encompass the full continuum of care, from pre-treatment screening and drug selection to therapeutic monitoring and post-marketing surveillance. The implementation of clinical decision support systems,

electronic health records with integrated pharmacogenomic modules, and interdisciplinary care models can facilitate more informed and adaptive prescribing practices. Moreover, ongoing education and training of healthcare professionals in the domains of pharmacogenetics, toxicology, and personalized medicine are essential for fostering a culture of safety and innovation within the healthcare system.

The scientific discourse on this topic is therefore multifaceted and requires a thorough analysis of the interplay between genetic, clinical, environmental, and societal factors that influence drug safety and efficacy. This comprehensive investigation not only seeks to identify the implicated drugs and mechanisms underlying medication-induced toxicities but also aims to critically evaluate the pharmacovigilance infrastructure, patient engagement models, and clinical implementation pathways that can collectively reduce the burden of adverse drug events. In this context, the harmonization of pharmacogenetic research, patient-centered care principles, and real-world pharmacovigilance data emerges as a powerful strategy to optimize therapeutic outcomes and promote a safer, more responsive healthcare environment [9-12].

This scientific exploration draws upon a wide array of interdisciplinary sources, encompassing molecular pharmacology, clinical genetics, toxicological research, regulatory science, and health policy. It endeavors to illuminate the translational potential of pharmacogenomic findings in real-world settings, assess the barriers to clinical adoption of precision medicine tools, and propose actionable recommendations for future research and practice. Special emphasis is placed on the identification of high-risk populations, elucidation of gene-drug interactions, refinement of adverse event reporting systems, and promotion of evidence-based pharmacotherapeutic guidelines. Through this integrative lens, the discourse aspires to contribute meaningfully to the global endeavor of enhancing medication safety and therapeutic effectiveness across all domains of healthcare [13-15].

As the burden of medication-induced adverse effects continues to rise in both high-income and resource-limited settings, the imperative for a paradigm shift toward anticipatory, individualized, and systemically integrated pharmacotherapy becomes increasingly clear. By advancing the scientific conversation around pharmacogenetics, patient-centered models, and pharmacovigilance, this investigation aims to chart a course toward more personalized, equitable, and safe medication use for all patients, regardless of genetic background, clinical complexity, or healthcare access [16-18].

The evolution of pharmacogenetics from a niche scientific interest into a central component of personalized medicine reflects the maturation of biomedical knowledge and its translation into clinical utility. With advances in high-throughput genomic

technologies and bioinformatics, the identification of clinically relevant single nucleotide polymorphisms (SNPs), copy number variations, and haplotypes has become increasingly accessible and affordable. These genomic markers provide clinicians with predictive information about an individual's capacity to metabolize, activate, deactivate, or transport drugs, thus informing therapeutic decisions with unprecedented precision. Polymorphisms in genes encoding cytochrome P450 enzymes, UDP-glucuronosyltransferases, drug transporters such as ABCB1 and SLCO1B1, and targets like VKORC1 and HLA alleles have been associated with altered drug responses and risk of toxicity. For example, variations in CYP2D6 can affect the metabolism of antidepressants, opioids, and antiarrhythmics, while polymorphisms in TPMT influence thiopurine tolerance. Despite these advancements, the clinical translation of genomic information into everyday practice remains incomplete, highlighting the gap between scientific discovery and bedside application [19-21].

A central obstacle to the widespread adoption of pharmacogenetic testing is the lack of standardized guidelines and integration into existing clinical workflows. While organizations such as the Clinical Pharmacogenetics Implementation Consortium (CPIC) and the Dutch Pharmacogenetics Working Group (DPWG) have developed genotype-based dosing guidelines, these resources are not universally utilized or implemented. Healthcare institutions often lack the informatics infrastructure, trained personnel, and reimbursement mechanisms necessary to support routine pharmacogenetic testing. Additionally, clinicians may feel unequipped to interpret complex genetic data or uncertain about its clinical significance, particularly in the absence of large-scale validation studies across diverse populations. These limitations are further compounded by disparities in access to pharmacogenomic services, particularly in low- and middle-income countries, where healthcare resources are often limited and priorities may be directed toward more immediate public health concerns [22-24].

The implementation of patient-centered care as a guiding philosophy within healthcare systems intersects powerfully with the goals of precision pharmacotherapy. This model calls for the active involvement of patients in their treatment decisions, recognition of their values and preferences, and responsiveness to their psychosocial context. When pharmacogenetic information is shared transparently with patients, it empowers them to make informed decisions about their care and fosters a collaborative relationship with their healthcare providers. This collaborative ethos extends to the ethical dimensions of genetic testing, including issues of consent, confidentiality, genetic counseling, and potential psychosocial impact. Ethical stewardship of pharmacogenetic information is essential to avoid unintended consequences such as genetic discrimination, privacy breaches, or anxiety related to genetic risk. As such, patient education and support

must be integral components of pharmacogenetic initiatives to ensure that the knowledge generated is both meaningful and actionable [25-27].

Medication-induced adverse effects remain among the most pressing challenges in pharmacotherapy. These events can range from mild, transient symptoms to severe, life-threatening syndromes that necessitate intensive care and long-term sequelae. Serious adverse drug reactions such as Stevens-Johnson syndrome, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms (DRESS), hepatotoxicity, nephrotoxicity, and cardiotoxicity are often unpredictable and poorly understood. While some adverse reactions are dose-dependent and may be mitigated through careful monitoring, others are idiosyncratic and arise from immunological, genetic, or metabolic susceptibilities. The unpredictable nature of such toxicities necessitates a heightened focus on early detection, preemptive risk stratification, and robust post-marketing surveillance systems [28-30].

The field of pharmacovigilance has historically served as the cornerstone of drug safety monitoring. Initially designed as a reactive mechanism to identify and mitigate post-marketing adverse events, pharmacovigilance now encompasses a broader mandate that includes active surveillance, signal detection, benefit-risk assessment, and regulatory decision-making. Despite this expansion, the traditional pharmacovigilance model remains challenged by fragmented reporting systems, underreporting, data silos, and variability in international regulatory frameworks. Efforts to modernize pharmacovigilance systems include the development of active surveillance networks, electronic health record (EHR)-linked databases, patient-reported outcome tools, and machine learning algorithms capable of mining real-world data for emerging safety signals. Nevertheless, these tools are often limited by inconsistent data quality, lack of interoperability, and insufficient integration into clinical workflows [31-32].

Understanding the risk factors that predispose individuals to medication-related toxicities is crucial for developing targeted prevention and management strategies. Age-related physiological changes, such as reduced renal and hepatic function, altered drug absorption and distribution, and polypharmacy, render elderly populations particularly susceptible to adverse events. Pediatric populations present unique challenges due to developmental pharmacokinetics and the scarcity of age-appropriate formulations. Gender differences, such as hormonal influences on drug metabolism and immune response, can also affect susceptibility to specific toxicities. Genetic ancestry and population-specific allele frequencies influence the distribution of pharmacogenetic variants, which has implications for drug response and safety across ethnic groups. Additionally, comorbidities such as diabetes, cardiovascular disease,

liver dysfunction, and cancer can modulate drug metabolism and increase vulnerability to toxicity. These patient-related factors must be considered alongside drug-related characteristics such as narrow therapeutic index, metabolic pathway complexity, potential for accumulation, and known toxic metabolite profiles [33-35].

Certain pharmacological classes are disproportionately represented in reports of serious adverse drug reactions. Antineoplastic agents, while often life-saving, are associated with a wide array of toxicities affecting nearly every organ system. Immune checkpoint inhibitors, for example, have revolutionized oncology but are linked to immune-related adverse events that can mimic autoimmune diseases. Antimicrobial agents, particularly sulfonamides, beta-lactams, and antitubercular drugs, have been implicated in hypersensitivity reactions including DRESS and anaphylaxis. Anticonvulsants such as carbamazepine and phenytoin are associated with severe dermatologic reactions in genetically susceptible individuals, particularly those carrying *HLA-B15:02* or *HLA-A31:01* alleles. Psychotropic medications, including selective serotonin reuptake inhibitors (SSRIs) and antipsychotics, carry risks of QT prolongation, extrapyramidal symptoms, and metabolic disturbances. Biologic agents and monoclonal antibodies, despite their targeted mechanisms, can cause infusion reactions, cytokine release syndrome, and immunogenicity-related complications. The diverse toxicity profiles of these agents necessitate a comprehensive understanding of their pharmacodynamics, immunologic potential, and interindividual variability [36-38].

Addressing the challenges of pharmacotherapy requires the development and implementation of robust strategic frameworks that integrate pharmacogenetic data, clinical guidelines, and patient-reported outcomes into a unified system of care. Clinical decision support systems (CDSS) embedded within EHRs have the potential to alert prescribers to potential drug-gene interactions, dosing recommendations based on genotype, and real-time monitoring of drug safety parameters. Such tools, however, must be evidence-based, regularly updated, and contextually relevant to ensure clinical utility. Moreover, the success of these systems depends on the active engagement of multidisciplinary teams, including pharmacists, genetic counselors, clinical pharmacologists, and information technology specialists [39-41].

Education and capacity building represent foundational pillars for advancing the integration of pharmacogenetics and personalized medicine into routine care. Medical and pharmacy curricula must be updated to reflect current knowledge in pharmacogenomics, data interpretation, ethical considerations, and communication of genetic risk. Continuing professional development programs should be designed to equip practicing clinicians with the skills necessary to apply genetic information in therapeutic decision-making. Patient education initiatives must also be prioritized to



foster understanding, dispel misconceptions, and encourage participation in pharmacogenomic research and testing programs.

From a policy perspective, the regulatory landscape must evolve to support the ethical and practical implementation of precision pharmacotherapy. Regulatory agencies should establish clear guidelines for the validation, approval, and reimbursement of pharmacogenetic tests. Public health policies should incentivize the incorporation of genomic data into drug development and surveillance processes. International harmonization of pharmacogenomic nomenclature, reporting standards, and data-sharing frameworks can facilitate cross-border research and collaborative innovation. Furthermore, equitable access to pharmacogenomic services must be ensured to prevent the exacerbation of existing health disparities [42-43].

The future of pharmacotherapy lies in its ability to harmonize technological innovation with human-centered care. As healthcare systems transition toward value-based models that prioritize outcomes and patient satisfaction, the integration of pharmacogenetic insights, patient narratives, and data-driven pharmacovigilance will be indispensable. This convergence offers a pathway to not only mitigate the burden of medication-induced harm but also to reimagine the therapeutic relationship as a dynamic, personalized, and participatory endeavor. By fostering an ecosystem that embraces scientific rigor, clinical empathy, and ethical responsibility, the discipline of pharmacotherapeutics can rise to meet the evolving challenges of modern medicine [44-45].

Real-world clinical scenarios underscore the consequences of not integrating pharmacogenetic knowledge into care. The well-documented association between HLA-B\*15:02 and carbamazepine-induced Stevens-Johnson syndrome among Southeast Asian populations exemplifies a preventable tragedy when genomic screening is neglected. Similarly, patients with dihydropyrimidine dehydrogenase (DPYD) deficiency receiving standard doses of fluoropyrimidines are at high risk of life-threatening toxicity, despite available preemptive testing. These cases reflect the dual ethical and clinical imperative to embed pharmacogenetic screening into routine practice, particularly when the evidence base is strong, testing is accessible, and outcomes can be dramatically improved by personalized dosing or alternative therapies [46-48].

Emerging therapeutic areas, particularly immunotherapy and targeted oncology, present both opportunities and challenges for pharmacogenetics and pharmacovigilance. The intricate mechanisms of action of biologics, including immune checkpoint inhibitors and kinase inhibitors, increase the complexity of predicting off-target effects, immune-related adverse events, and novel toxicological syndromes. In these domains, genetic markers alone may be insufficient; instead, multi-omic approaches combining genomics, transcriptomics, proteomics, and metabolomics are

being explored to enhance predictive precision. Moreover, the immune system's dynamic nature requires integrated pharmacovigilance systems capable of capturing fluctuating biomarkers and patient-reported symptoms in near-real time [49-51].

The future of personalized pharmacotherapy also hinges on the effective utilization of big data, artificial intelligence (AI), and real-world evidence. The integration of EHRs, genomic databases, adverse event registries, and wearable technologies enables a more granular understanding of drug response trajectories and safety signals. Machine learning algorithms trained on these datasets can identify previously unrecognized patterns of toxicity, generate personalized risk scores, and facilitate rapid hypothesis generation for further investigation. However, the deployment of such technologies must be accompanied by rigorous validation, ethical oversight, and robust governance structures to ensure that automation enhances, rather than undermines, clinical decision-making.

At the heart of these innovations lies the patient—the individual navigating a complex therapeutic landscape shaped by biology, psychology, social determinants, and systemic inequities. The movement toward patient-centered care reinforces the centrality of this perspective, advocating for shared decision-making and the co-creation of care plans that reflect both scientific evidence and personal values. This approach fosters a therapeutic alliance in which patients are empowered participants rather than passive recipients of medical interventions. In the context of pharmacogenetics and adverse event prevention, this means involving patients in discussions about genetic risk, treatment alternatives, potential side effects, and the implications of genomic data storage and sharing.

The ethical, legal, and social implications (ELSI) of pharmacogenetic integration cannot be overstated. As genomic testing becomes more common, concerns about data privacy, informed consent, secondary findings, and potential discrimination are increasingly prominent. National and international regulations must address these issues proactively by establishing clear guidelines for genomic data usage, ensuring equitable access to testing and interpretation, and protecting patients from stigmatization or insurance repercussions. Additionally, special attention must be paid to vulnerable populations – including minors, the elderly, individuals with cognitive impairments, and marginalized communities – to ensure that pharmacogenetic benefits do not widen existing healthcare disparities.

From a global health perspective, the implementation of pharmacogenetic strategies varies widely across regions due to differences in healthcare infrastructure, economic capacity, regulatory frameworks, and educational resources. High-income countries are more likely to have the technological capabilities and policy support to

incorporate genomic data into routine care, whereas resource-limited settings face significant barriers. Nonetheless, the burden of adverse drug reactions is often greater in low- and middle-income countries due to challenges such as inadequate diagnostic capacity, drug quality issues, polypharmacy, and lack of post-market surveillance. As such, global initiatives must prioritize equitable knowledge transfer, capacity building, and international collaboration to ensure that the benefits of pharmacogenetics and pharmacovigilance reach all patients, regardless of geography.

Interdisciplinary collaboration will be essential for advancing the field. Clinicians, geneticists, pharmacists, data scientists, ethicists, and policymakers must work in concert to bridge the gap between scientific possibility and clinical reality. Professional societies, academic institutions, regulatory agencies, and patient advocacy groups all have roles to play in promoting education, generating evidence, guiding implementation, and ensuring ethical governance. By fostering a collaborative ecosystem grounded in transparency, inclusivity, and shared purpose, the healthcare community can build a resilient foundation for safe and personalized pharmacotherapy.

The intersection of pharmacogenetics, pharmacovigilance, and patient-centered care represents a transformative frontier in medicine. Together, these domains offer the tools to anticipate, prevent, and manage medication-induced harms in ways that were previously unattainable. Yet, the path forward is fraught with complexity. Scientific discoveries must be accompanied by robust implementation science, patient engagement strategies, and policy frameworks that ensure sustainability and equity. The ultimate measure of success will not be in the number of genetic variants identified or guidelines published, but in the tangible improvement of patient lives – through safer medications, more effective treatments, and a healthcare system that truly responds to the needs and uniqueness of every individual.

The comprehensive examination of medication-induced adverse effects and toxicities through the lens of pharmacogenetics and patient-centered care seeks to illuminate a new paradigm for pharmacotherapeutic practice. It aspires to bridge foundational science with clinical application, identify gaps in safety infrastructure, and advocate for integrative strategies that align medical innovation with ethical responsibility and social justice. As the science of medicine continues to evolve, so too must its moral and operational frameworks—ensuring that the promise of safer, more precise pharmacotherapy becomes a reality for all.

The realm of pharmacotherapy has undergone significant transformation over the past century, moving from empirical approaches to increasingly scientific and data-driven methodologies. Early drug use was largely based on observation and trial, without a clear understanding of individual variability or the underlying biological

mechanisms influencing drug response. With the discovery of enzymes, receptors, and the molecular basis of disease, pharmacology emerged as a distinct scientific discipline. This progress paved the way for more targeted drug development and a deeper comprehension of therapeutic mechanisms. Despite these advances, variability in drug response and the occurrence of adverse drug reactions (ADRs) remained persistent challenges that could not be fully explained by traditional pharmacological principles alone.

The concept that genetic variability influences drug metabolism and response has its roots in mid-20th century observations. The identification of enzymatic polymorphisms, such as those affecting the metabolism of isoniazid and succinylcholine, laid the groundwork for the nascent field of pharmacogenetics. Over subsequent decades, research expanded to include the genetic factors governing a wide array of drug-metabolizing enzymes, transporters, and targets. This growing body of knowledge underscored the biological basis for interindividual differences in drug efficacy and toxicity, reinforcing the need for individualized treatment regimens. The completion of the Human Genome Project and the advent of high-throughput genotyping technologies accelerated these discoveries, ushering in the era of pharmacogenomics and precision medicine.

Pharmacogenetics now plays an essential role in identifying individuals at increased risk for adverse drug reactions or therapeutic failure. It provides a mechanistic explanation for idiosyncratic and dose-related toxicities by elucidating how genetic polymorphisms affect drug absorption, distribution, metabolism, and excretion. For example, the presence of specific allelic variants in cytochrome P450 enzymes can dramatically alter the metabolic clearance of numerous drugs, necessitating dose adjustments to avoid toxicity or subtherapeutic exposure. Furthermore, variations in human leukocyte antigen (HLA) genes have been linked to severe hypersensitivity reactions, highlighting the immunogenetic dimension of adverse drug events. These insights have catalyzed efforts to incorporate pharmacogenetic testing into clinical guidelines, although widespread adoption remains uneven.

The development of patient-centered care as a dominant model in healthcare emerged from growing recognition that effective treatment requires more than biological understanding alone. Rooted in principles of respect, empathy, and shared decision-making, patient-centered care emphasizes the importance of considering the patient's experiences, preferences, cultural context, and psychosocial factors. In the realm of pharmacotherapy, this approach necessitates transparent communication about potential benefits, risks, and uncertainties associated with treatment options,

including the implications of pharmacogenetic testing. Integrating patient preferences alongside genetic data enhances adherence and satisfaction, reduces treatment-related anxiety, and fosters collaborative therapeutic relationships. As a result, patient-centered care serves as a vital complement to precision medicine, ensuring that individualized treatments are both scientifically sound and aligned with patient values.

Pharmacovigilance emerged as a formal discipline in response to catastrophic drug-related events that highlighted the need for systematic safety monitoring. The thalidomide tragedy of the early 1960s, in which thousands of infants were born with severe congenital malformations, galvanized regulatory agencies worldwide to establish frameworks for drug safety surveillance. Since then, pharmacovigilance systems have evolved to encompass spontaneous adverse event reporting, post-marketing studies, risk communication, and signal detection activities. These systems are vital for identifying new or rare adverse reactions, evaluating risk-benefit profiles, and informing regulatory decisions. However, challenges persist including underreporting, inconsistent data quality, and delayed recognition of safety signals. Efforts to integrate pharmacovigilance with electronic health records and big data analytics represent important advances toward more proactive and comprehensive safety monitoring.

Medication-induced adverse effects remain a major cause of morbidity and healthcare burden globally. These adverse events are complex and multifactorial, arising from the interaction of drug properties with patient-specific factors such as genetics, age, comorbidities, concomitant medications, and environmental influences. Severe cutaneous adverse reactions, hepatotoxicity, nephrotoxicity, and cardiotoxicity exemplify the diverse spectrum of potential toxicities. In many cases, pharmacogenetic predispositions can increase susceptibility, as demonstrated by well-characterized gene-drug associations. Nevertheless, many adverse reactions continue to be unpredictable and difficult to prevent. Consequently, pharmacotherapeutic management must integrate risk assessment, close monitoring, and rapid intervention strategies to minimize harm.

The implications of these challenges are far-reaching, affecting drug development, clinical practice, regulatory oversight, and patient outcomes. Incorporating pharmacogenetic data into drug labeling, clinical guidelines, and electronic prescribing systems can guide safer drug selection and dosing. Moreover, multidisciplinary care teams including pharmacists, genetic counselors, and clinicians can enhance the interpretation and application of genetic information. Educational initiatives aimed at healthcare professionals and patients are critical to building competency and trust in pharmacogenetic approaches. Policy frameworks that support



equitable access to testing and foster data sharing while safeguarding privacy are equally important to maximize public health benefits.

Global disparities in healthcare infrastructure and resource availability create variability in the implementation of pharmacogenetics and pharmacovigilance. High-income countries often possess the technological and institutional capacity to integrate genomic medicine and advanced safety monitoring, while resource-limited settings may struggle with diagnostic access, healthcare workforce shortages, and regulatory gaps. Bridging these divides requires international collaboration, capacity building, and the development of context-appropriate strategies that address local needs and priorities. Such efforts are vital to ensure that advances in personalized medicine do not exacerbate existing health inequities but rather contribute to universal improvements in medication safety and effectiveness.

The scientific understanding of medication-induced adverse effects continues to evolve, informed by ongoing research in molecular pharmacology, genomics, immunology, and clinical epidemiology. Advances in bioinformatics, systems biology and multi-omics approaches are unveiling complex biological networks that mediate drug responses and toxicities. These discoveries hold promise for the identification of novel biomarkers and therapeutic targets, enabling more precise risk stratification and intervention. Concurrently, the integration of patient-reported outcomes and real-world data provides valuable insights into the lived experiences of adverse drug events, informing patient-centered risk management.

The background to this comprehensive analysis is rooted in the convergence of pharmacogenetic science, patient-centered care philosophies, and pharmacovigilance practices. Together, these domains represent the critical foundation upon which safer, more effective, and more personalized pharmacotherapeutic strategies can be developed and implemented. Understanding their historical development, current challenges, and future potential is essential to advancing the field and improving patient outcomes worldwide.

The integration of pharmacogenetics into clinical practice represents a critical juncture in the evolution of personalized medicine. As genomic technologies have advanced, the ability to rapidly and cost-effectively sequence and analyze patient genomes has transformed research paradigms and clinical possibilities. Next-generation sequencing, microarray-based genotyping, and real-time polymerase chain reaction assays now enable the detection of clinically relevant genetic variants with high accuracy and scalability. These technological innovations facilitate preemptive and point-of-care pharmacogenetic testing, providing actionable data that can inform drug selection and dosing decisions before adverse effects occur. Moreover, the

expanding catalog of pharmacogenetic variants linked to drug metabolism, transport, and target interactions has been systematically compiled and disseminated through international databases and guidelines, forming a critical knowledge base for clinicians.

Despite these advancements, the translation of pharmacogenetic insights into improved clinical outcomes remains a complex endeavor. Implementation science, which studies methods to promote the systematic uptake of research findings into routine healthcare, highlights several barriers and facilitators to pharmacogenetic adoption. These include organizational readiness, provider knowledge and attitudes, patient acceptance, reimbursement policies, and technological infrastructure. The heterogeneity of healthcare settings further complicates implementation efforts, as strategies effective in academic medical centers may not be feasible in community clinics or resource-limited environments. Tailoring implementation frameworks to the local context, involving multidisciplinary stakeholders, and utilizing continuous quality improvement approaches are essential to achieving sustainable integration of pharmacogenetics into clinical workflows.

Patient-centered care frameworks offer a guiding philosophy for this integration, emphasizing the importance of engaging patients as active participants in decisions about their pharmacotherapy. The communication of complex genetic information requires not only technical accuracy but also sensitivity to patient literacy, cultural beliefs, and emotional responses. Genetic counseling, traditionally a specialty service, is increasingly recognized as a necessary component of pharmacogenetic testing programs to support patient understanding and informed consent. Furthermore, shared decision-making models that incorporate patient values and preferences alongside genetic risk information enhance adherence and satisfaction. These approaches acknowledge that the mere availability of pharmacogenetic data is insufficient without meaningful dialogue and trust between patients and providers.

Pharmacovigilance systems must also adapt to the expanding role of pharmacogenetics and personalized medicine. Traditional spontaneous adverse event reporting remains foundational but is often insufficient to capture the full spectrum of medication-induced toxicities, especially rare or delayed events. Active surveillance methodologies, including cohort event monitoring, targeted safety studies, and electronic health record mining, offer more comprehensive and timely detection of safety signals. Incorporating pharmacogenetic data into pharmacovigilance databases enhances the ability to identify gene-drug interaction-related adverse events and to stratify risk at the population level. International collaboration, such as through the World Health Organization's pharmacovigilance program and regional regulatory harmonization initiatives, fosters data sharing and methodological standardization

critical for global drug safety.

The complexity of medication-induced adverse effects is amplified by the presence of polypharmacy, particularly among aging populations with multiple chronic conditions. Polypharmacy increases the likelihood of drug-drug interactions, cumulative toxicity, and medication non-adherence, complicating the clinical picture. Pharmacogenetic testing in this context can identify vulnerabilities to metabolic bottlenecks and adverse reactions, enabling optimization of complex medication regimens. However, the interpretation of pharmacogenetic results in polypharmacy requires sophisticated clinical judgment and decision support tools that can integrate multifactorial data streams.

Healthcare systems play a pivotal role in facilitating or hindering the integration of pharmacogenetics and patient-centered pharmacovigilance. Electronic health records that are interoperable, standardized, and equipped with clinical decision support capabilities provide the infrastructure necessary to deliver pharmacogenetic-informed care at scale. These systems enable the real-time incorporation of genetic test results into prescribing workflows, alerting clinicians to potential risks and guiding therapeutic choices. However, the development and maintenance of such systems require significant investment, cross-sector collaboration, and adherence to data privacy and security standards. Furthermore, health policy must align incentives, establish reimbursement pathways, and create regulatory frameworks that support innovation while safeguarding patient welfare.

Ethical considerations permeate all facets of pharmacogenetics and personalized pharmacovigilance. Issues of consent, data ownership, privacy, and potential discrimination necessitate robust governance mechanisms and transparency. Patient trust is foundational to the successful implementation of genomic medicine, requiring clear communication of benefits, limitations, and potential risks associated with genetic testing. Additionally, the potential for incidental or secondary findings poses challenges for disclosure and management, underscoring the need for ethical guidelines and clinician training. The equitable distribution of pharmacogenetic benefits is a social imperative, calling for deliberate strategies to address disparities related to socioeconomic status, geographic location, race, and ethnicity.

In recent years, the emergence of multi-omics technologies—encompassing genomics, transcriptomics, proteomics, metabolomics, and epigenomics—has expanded the horizon of personalized pharmacotherapy beyond single-gene associations. These comprehensive molecular profiling approaches offer a systems-level understanding of drug response and toxicity, capturing the dynamic interplay of genetic, environmental, and lifestyle factors. Integration of multi-omics data into clinical decision-making is

still in its early stages but holds promise for refining risk prediction models and identifying novel therapeutic targets. The incorporation of these data streams into pharmacovigilance frameworks also provides an opportunity for more precise and individualized safety monitoring.

Global health initiatives increasingly recognize the importance of pharmacogenetics and pharmacovigilance in improving medication safety and efficacy worldwide. Collaborative networks, capacity-building programs, and technology transfer efforts aim to extend the benefits of genomic medicine to diverse populations and healthcare settings. The establishment of regional pharmacogenomic databases reflecting local genetic variation enhances the relevance and applicability of testing. Furthermore, global pharmacovigilance systems contribute to the detection of rare adverse drug events that might be missed in smaller populations, informing international regulatory decisions and clinical guidelines.

The background of this comprehensive analysis is situated at the intersection of scientific discovery, clinical application, health system readiness, and ethical responsibility. The advancing knowledge of pharmacogenetic influences on drug response, coupled with evolving models of patient-centered care and robust pharmacovigilance systems, offers transformative potential for the prevention and management of medication-induced adverse effects and toxicities. Realizing this potential requires concerted efforts across research, clinical practice, policy, and patient engagement domains to foster an integrated, equitable, and sustainable pharmacotherapeutic ecosystem.

The interdisciplinary nature of pharmacogenetics and pharmacovigilance research demands collaboration across diverse scientific and clinical domains. Molecular biologists, geneticists, clinical pharmacologists, bioinformaticians, epidemiologists, and healthcare providers each contribute unique expertise essential for unraveling the complexities of drug response and safety. Advances in computational biology have enabled the development of predictive algorithms and in silico models that simulate drug-gene interactions, metabolic pathways, and adverse event probabilities. These tools assist in hypothesis generation, risk stratification, and drug development processes. The integration of such computational approaches with clinical datasets enhances the capacity to identify at-risk populations and personalize treatment protocols. Moreover, translational research efforts bridge laboratory discoveries with bedside application, ensuring that genomic findings are validated, contextualized, and operationalized within patient care settings.

Technological innovations continue to propel the field forward, particularly through the use of wearable devices, mobile health applications, and telemedicine

platforms. These technologies facilitate real-time monitoring of patient responses, capture patient-reported outcomes, and enable remote pharmacovigilance activities. Wearables can detect physiological changes indicative of adverse drug reactions, such as alterations in heart rate variability, skin conductance, or temperature, providing early warning signals to clinicians. Mobile applications empower patients to report symptoms promptly and receive tailored guidance, fostering engagement and adherence. Telemedicine expands access to specialized pharmacogenetic counseling and expert consultation, particularly in underserved or geographically remote areas. The convergence of these digital health tools with pharmacogenetic data and electronic health records offers a transformative opportunity to enhance medication safety through continuous, personalized monitoring.

The education and training of healthcare professionals remain vital to the successful adoption of pharmacogenetics and patient-centered pharmacovigilance. Medical, pharmacy, nursing, and allied health curricula must be updated to include foundational knowledge in genomics, data interpretation, ethical considerations, and communication skills. Interprofessional education fosters collaboration and shared understanding among clinicians, pharmacists, genetic counselors, and informaticians, enabling cohesive team-based care. Continuing professional development programs and certification opportunities ensure that practicing clinicians remain current with evolving evidence and technologies. Patient education initiatives are equally important, providing accessible information that empowers individuals to participate actively in genetic testing decisions and adverse event reporting.

The dynamic interplay between genetics, environment, and clinical context in shaping drug response necessitates a comprehensive approach that transcends traditional disciplinary boundaries. Systems pharmacology, which integrates computational modeling with experimental biology, offers a holistic framework for understanding the multifactorial determinants of medication effects and adverse reactions. By mapping complex biological networks and drug-target interactions, systems pharmacology facilitates the identification of emergent properties and vulnerabilities that are not apparent when examining isolated pathways. This integrative perspective complements pharmacogenetics by situating genetic variants within broader biological and environmental contexts, thereby enhancing predictive accuracy and guiding rational therapeutic design.

Within the global health arena, the equitable dissemination of pharmacogenetic and pharmacovigilance innovations remains a critical challenge. Low- and middle-income countries often bear disproportionate burdens of adverse drug reactions due to limited healthcare infrastructure, inadequate regulatory oversight, and challenges in



accessing quality medicines. Furthermore, genetic diversity in these populations is frequently underrepresented in research, limiting the applicability of pharmacogenetic findings derived predominantly from European or North American cohorts. Addressing these disparities requires concerted efforts to build local research capacity, establish region-specific genetic databases, and foster international partnerships that promote inclusive science. Strengthening pharmacovigilance systems in resource-constrained settings through technology transfer, training, and simplified reporting mechanisms can improve drug safety monitoring and patient outcomes globally.

The frontier of personalized pharmacotherapy is expanding beyond germline genetics to encompass somatic mutations, microbiome composition, and epigenetic modifications. Somatic genetic alterations, particularly in oncology, profoundly influence drug sensitivity and resistance, necessitating tumor-specific genomic profiling to guide treatment choices. The human microbiome, comprising trillions of microorganisms inhabiting the body, modulates drug metabolism and immune responses, offering novel biomarkers and therapeutic targets. Epigenetic mechanisms, such as DNA methylation and histone modification, affect gene expression and can alter drug response dynamically in response to environmental exposures. These emerging dimensions underscore the complexity of precision medicine and highlight the need for multi-layered data integration and sophisticated analytic methods to unravel individualized pharmacodynamics.

Technological advancements continue to transform the landscape of pharmacogenetics and pharmacovigilance. Blockchain technology offers promising solutions for secure, decentralized management of sensitive genomic and health data, enhancing patient control and data interoperability. Artificial intelligence and deep learning algorithms facilitate the analysis of vast, heterogeneous datasets to uncover hidden patterns of drug response and adverse events. Cloud computing platforms enable scalable storage and processing capacities essential for multi-omics data integration and real-time clinical decision support. These innovations, while promising, raise important considerations related to algorithmic transparency, bias mitigation, and equitable access, necessitating robust governance frameworks.

The evolving regulatory landscape reflects growing recognition of the importance of pharmacogenetics and advanced pharmacovigilance. Regulatory agencies worldwide have issued guidance documents and frameworks to support the development, validation, and clinical implementation of pharmacogenetic tests and personalized therapies. These frameworks emphasize the need for analytical validity, clinical validity, and clinical utility evidence, as well as post-market performance monitoring. Harmonization of regulatory standards and international collaboration

facilitate global access to safe and effective personalized medicines. Additionally, patient advocacy and stakeholder engagement are increasingly incorporated into regulatory decision-making processes, ensuring that diverse perspectives inform policy development.

Educational strategies tailored to diverse audiences are critical to advancing the field. Healthcare professionals require not only foundational knowledge in genomics and pharmacology but also skills in communication, ethical reasoning, and interprofessional collaboration. Patients and the public benefit from accessible educational resources that demystify genetic concepts, explain testing implications, and encourage proactive engagement in their care. Partnerships between academic institutions, professional societies, patient organizations, and health authorities can facilitate the development and dissemination of comprehensive educational programs.

**The aim of the study.** The overarching goal of this comprehensive study is to elucidate and synthesize current scientific knowledge and clinical practices related to the integration of pharmacogenetic insights and patient-centered care approaches in addressing medication-induced adverse effects and toxicities. This work aims to critically analyze the challenges faced by contemporary pharmacovigilance systems in effectively detecting, monitoring, and managing adverse drug reactions, while identifying the key pharmacological agents most frequently implicated in such events. By investigating the underlying determinants of risk—encompassing genetic, environmental, demographic, and clinical factors—the study seeks to deepen the understanding of interindividual variability in drug response and susceptibility to toxicity.

A fundamental objective is to evaluate strategic pharmacotherapeutic management approaches that incorporate genetic testing, clinical decision support, and personalized patient engagement to optimize drug safety and efficacy. This includes examining current methodologies, emerging technologies, and evidence-based guidelines that facilitate tailored treatment regimens and proactive risk mitigation. Furthermore, the study aspires to highlight existing gaps and barriers in the translation of pharmacogenetic research into routine clinical practice, proposing practical solutions to enhance accessibility, clinician education, and healthcare system integration.

Another critical goal is to explore the ethical, legal, and social considerations inherent to the adoption of pharmacogenetics and patient-centered pharmacovigilance, emphasizing the need for frameworks that protect patient autonomy, privacy, and equity. Recognizing the global diversity in healthcare infrastructure and genetic backgrounds, the study aims to underscore the importance of inclusive research and policy development that ensure equitable benefits across populations.

Ultimately, this comprehensive analysis intends to provide a cohesive and multidisciplinary perspective that informs clinicians, researchers, policymakers, and patients alike. By fostering a deeper understanding of the complex interplay between genetics, clinical care, and medication safety, the study seeks to contribute to the advancement of personalized pharmacotherapy, reduce the incidence and impact of adverse drug reactions, and promote a more responsive and ethical healthcare environment.

**Materials and Methods.** Policy and regulatory frameworks underpin the ethical and operational environment in which pharmacogenetics and pharmacovigilance evolve. Regulatory agencies are increasingly recognizing the value of incorporating genetic information into drug labeling, post-marketing surveillance, and risk management plans. International harmonization of standards and nomenclature facilitates global data sharing and comparative research. Policies must also address issues of data privacy, security, and consent, particularly given the sensitive nature of genetic information. Frameworks promoting transparency, accountability, and patient rights foster public trust and support sustainable integration of genomic medicine. Additionally, policies encouraging the inclusion of diverse populations in genomic research and pharmacovigilance activities help to mitigate health disparities and ensure the generalizability of findings.

Looking ahead, the future landscape of pharmacotherapy will likely be shaped by continuous advancements in genomic science, real-world data analytics, and patient engagement methodologies. The integration of polygenic risk scores and epigenetic markers may enhance prediction models for drug response and toxicity. Artificial intelligence and machine learning algorithms will increasingly support clinical decision-making by synthesizing multifaceted data sources. Precision therapeutics will extend beyond traditional small molecules to include gene editing, RNA therapeutics, and personalized vaccines, each necessitating novel safety monitoring paradigms. Patient-centered digital platforms will empower individuals to co-manage their treatment plans and pharmacovigilance participation, fostering a more democratized healthcare environment.

In this rapidly evolving context, the imperative to develop agile, adaptable, and inclusive healthcare systems becomes paramount. Healthcare organizations must cultivate a culture of innovation, continuous learning, and patient partnership to harness the potential of pharmacogenetics and pharmacovigilance fully. Robust evaluation frameworks are necessary to assess the clinical impact, cost-effectiveness, and ethical dimensions of these interventions over time. Multistakeholder engagement—including patients, clinicians, researchers, policy makers, and industry—

will ensure that diverse perspectives inform the design and implementation of personalized pharmacotherapeutic strategies.

Ultimately, the confluence of scientific discovery, technological innovation, ethical stewardship, and patient-centered values promises to redefine the standards of medication safety and efficacy. By embracing this multifaceted approach, the healthcare community can move beyond the limitations of traditional pharmacotherapy, reducing the global burden of adverse drug reactions and improving the quality of life for patients worldwide. This comprehensive background thus sets the stage for an in-depth analysis of the pharmacogenetic and patient-centered care approaches that underpin modern pharmacovigilance, risk assessment, and pharmacotherapeutic management.

The comprehensive analysis employed a multidisciplinary approach combining systematic literature review, data synthesis, and critical appraisal of current research and clinical practices related to pharmacogenetics, patient-centered care, pharmacovigilance, and medication-induced adverse effects. A rigorous search strategy was designed to capture a broad spectrum of relevant scientific publications, clinical guidelines, regulatory documents, and real-world evidence studies. Major electronic databases, including PubMed, Scopus, Web of Science, and Embase, were queried using carefully constructed keywords and Medical Subject Headings (MeSH) terms that encompassed pharmacogenetics, adverse drug reactions, pharmacovigilance, patient-centered care, and pharmacotherapeutic management. The search encompassed articles published in multiple languages and across diverse geographic regions to ensure inclusivity and comprehensiveness.

Inclusion criteria focused on peer-reviewed original research studies, systematic reviews, meta-analyses, clinical practice guidelines, and policy papers that addressed genetic determinants of drug response, strategies for adverse effect prevention and management, and frameworks for integrating patient preferences into pharmacotherapy. Excluded from consideration were studies lacking sufficient methodological rigor, case reports with limited generalizability, and publications unrelated to the core thematic areas. Data extraction involved detailed collection of study design, population characteristics, genetic markers investigated, pharmacovigilance methodologies, patient engagement practices, and therapeutic outcomes.

The analysis integrated qualitative and quantitative evidence to identify patterns, consensus, and discrepancies within the literature. Particular emphasis was placed on the clinical utility and implementation challenges of pharmacogenetic testing, the effectiveness of patient-centered interventions in improving medication safety, and the

evolving role of pharmacovigilance systems in real-world settings. Comparative evaluation of international regulatory frameworks and ethical guidelines further enriched the contextual understanding.

In addition to literature review, the study examined case studies and exemplar models from diverse healthcare systems to elucidate practical applications and lessons learned. These case studies illustrated successful integration of pharmacogenetic data into clinical workflows, multidisciplinary collaboration, and innovative patient engagement strategies. Insights were also drawn from ongoing clinical trials and pilot programs investigating novel pharmacogenetic markers, digital health technologies, and active safety monitoring techniques.

Throughout the analysis, a critical lens was applied to assess the quality and relevance of evidence, identify gaps in knowledge, and highlight areas requiring further research or policy development. Ethical considerations were incorporated by evaluating how studies addressed informed consent, data privacy, equity of access, and potential societal implications. The methodological framework ensured a balanced and nuanced synthesis that informs both scientific inquiry and practical implementation.

Overall, this methodology aimed to provide a robust and comprehensive foundation for advancing understanding and application of pharmacogenetic and patient-centered approaches to medication safety, thereby supporting more effective, equitable, and personalized pharmacotherapeutic management.

**Results and Discussion.** The patient-centered care paradigm emerges as a critical enabler for the successful incorporation of pharmacogenetics into therapeutic decision-making. Engaging patients through shared decision-making fosters understanding and trust, which in turn enhances adherence to prescribed regimens and openness to genetic testing. Studies indicate that when patients are actively involved in discussions about medication risks and benefits, including the implications of their genetic profile, there is greater satisfaction and empowerment. However, effective communication requires that healthcare providers possess not only technical knowledge but also the skills to translate complex genetic concepts into accessible language tailored to individual patient needs.

Pharmacovigilance systems face ongoing challenges in capturing and responding to medication-induced adverse effects in a timely and comprehensive manner. Traditional spontaneous reporting mechanisms suffer from underreporting and delayed recognition of safety signals, particularly for rare or idiosyncratic reactions. Integration of pharmacogenetic data into these systems enhances the detection and characterization of gene-related adverse events, enabling more targeted risk mitigation. Active surveillance strategies leveraging electronic health records, patient registries,



and digital health tools have shown promise in improving the scope and sensitivity of pharmacovigilance activities. However, such approaches require substantial investment in data infrastructure, interoperability standards, and analytic capabilities. The management of medication-induced toxicities through pharmacogenetic-informed pharmacotherapy is gaining traction as a feasible and beneficial approach. Personalized dosing algorithms, alternative drug selection based on genetic risk profiles, and preemptive screening programs contribute to reducing adverse events and optimizing efficacy. Nevertheless, clinical guidelines often lag behind emerging evidence, and variability exists in the recommendations provided by different regulatory bodies and professional organizations. This inconsistency can create confusion for clinicians and impede harmonized adoption. The establishment of centralized, evidence-based, and regularly updated pharmacogenetic guidelines, integrated within clinical decision support systems, is essential to bridge this gap.

Ethical, legal, and social considerations are intricately woven throughout the process of pharmacogenetic integration and pharmacovigilance enhancement. Concerns about genetic data security, potential discrimination, and equitable access to testing must be proactively addressed through policy and practice. Studies emphasize the importance of transparent informed consent processes, culturally sensitive patient engagement, and policies that protect against misuse of genetic information. Equitable implementation strategies are critical to ensure that advances in personalized pharmacotherapy benefit diverse populations and do not exacerbate existing health disparities.

Technological innovations underpin much of the progress and future potential in this field. The deployment of artificial intelligence and machine learning for predictive modeling of adverse drug reactions offers unprecedented opportunities to personalize risk assessment. Wearable health technologies and mobile applications facilitate real-time monitoring of patients, enabling early detection of adverse effects and timely clinical interventions. Blockchain-based data management systems hold promise for enhancing security and patient control over genetic information. However, the integration of these technologies must be carefully managed to ensure validity, transparency, patient privacy, and equitable access.

From a health systems perspective, the successful integration of pharmacogenetics and patient-centered pharmacovigilance requires coordinated efforts across multiple stakeholders, including clinicians, pharmacists, genetic counselors, researchers, regulators, payers, and patients themselves. Interprofessional collaboration, continuous education, and supportive infrastructure are necessary to create sustainable workflows and clinical pathways. Moreover, health policy must align incentives and remove financial and regulatory barriers to foster adoption. Global

cooperation and knowledge sharing are vital to disseminate best practices and ensure that innovations reach diverse populations worldwide.

The findings of this comprehensive analysis affirm the transformative potential of pharmacogenetic and patient-centered approaches in reducing medication-induced adverse effects and optimizing pharmacotherapeutic management. While scientific evidence has advanced considerably, translation into routine clinical practice remains incomplete, impeded by educational, infrastructural, ethical, and policy challenges. Addressing these multifactorial barriers through coordinated strategies will be pivotal in realizing the promise of personalized medicine and pharmacovigilance for enhanced patient safety and improved therapeutic outcomes globally.

The exploration of pharmacogenetics as a transformative element in personalized medicine reveals both substantial promise and ongoing challenges in clinical application. Over recent decades, studies have consistently demonstrated that genetic polymorphisms in drug-metabolizing enzymes, transporters, and receptors substantially affect individual susceptibility to medication-induced adverse reactions. These polymorphisms contribute to altered pharmacokinetics and pharmacodynamics, leading to therapeutic failures or toxicities. Cytochrome P450 enzymes, particularly CYP2D6, CYP2C19, and CYP3A4, serve as archetypal examples wherein genetic variants result in poor, intermediate, extensive, or ultra-rapid metabolism phenotypes. Such variations dictate the plasma concentrations of many commonly prescribed drugs, including antidepressants, antiepileptics, and anticoagulants. Clinical trials and real-world observational studies reveal that genotyping these enzymes prior to drug initiation can significantly reduce adverse drug events (ADEs) by enabling individualized dose adjustments.

The utility of pharmacogenetic testing extends beyond metabolism-related genes. For instance, human leukocyte antigen (HLA) allele associations with severe cutaneous adverse reactions (SCAR), such as Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), have been well documented. The association of HLA-B15:02 with carbamazepine-induced SJS in Asian populations has prompted implementation of preemptive screening guidelines in certain regions, substantially reducing incidence rates. Similarly, the presence of HLA-B57:01 strongly predicts abacavir hypersensitivity, leading to mandatory screening in HIV treatment protocols worldwide. These examples underscore how genetic insights can directly influence prescribing behaviors, improving patient safety and care quality.

Despite these clear clinical benefits, adoption remains fragmented due to a confluence of barriers. Cost remains a significant factor; pharmacogenetic testing may impose additional financial burdens on healthcare systems and patients, especially

where reimbursement is absent or inconsistent. In low- and middle-income countries, limited laboratory infrastructure and resource constraints further restrict access. Moreover, a knowledge gap persists among healthcare providers, with many lacking confidence in interpreting test results or understanding their clinical implications. Surveys indicate that even among specialists, uncertainty about test utility and lack of clinical guidelines hinder uptake. The absence of standardized, evidence-based protocols for integrating genetic results into therapeutic decision-making contributes to variable practices and inconsistent patient outcomes.

Patient perspectives further influence the implementation of pharmacogenetic testing. Acceptance rates vary widely and are affected by understanding of genetic concepts, cultural beliefs, perceived risks and benefits, and concerns regarding data privacy and discrimination. Studies show that comprehensive counseling and educational interventions improve patient knowledge and willingness to participate in testing. However, time constraints and limited access to trained genetic counselors in many clinical settings impede these efforts. Addressing these challenges necessitates innovative models of patient engagement, including the use of digital educational tools and decision aids tailored to diverse populations.

The incorporation of pharmacogenetic data into electronic health records (EHRs) and clinical decision support (CDS) systems represents a pivotal strategy for overcoming provider-related barriers. Automated alerts, dosing recommendations, and drug selection guidance based on genetic profiles can assist clinicians in making informed, timely decisions. Successful integration requires interoperability standards, user-friendly interfaces, and continuous updating of genetic knowledge bases. Nonetheless, concerns about alert fatigue, data security, and system complexity necessitate careful design and evaluation of these tools to maximize their utility and acceptance.

Pharmacovigilance remains a cornerstone of medication safety, and its synergy with pharmacogenetics offers enhanced capabilities for identifying and managing adverse drug reactions. Traditional spontaneous reporting systems are limited by underreporting and bias, often failing to detect rare or delayed toxicities. Augmentation with pharmacogenetic data allows for stratified signal detection, distinguishing genetically predisposed subpopulations at risk. Active surveillance methodologies utilizing EHRs, biobanks, and patient registries enable longitudinal monitoring and real-time safety assessments. For example, the U.S. Food and Drug Administration's Sentinel Initiative employs large-scale data analytics to identify potential drug safety concerns, with pharmacogenetic components increasingly incorporated. These systems support iterative risk evaluation and can inform label updates, risk mitigation

strategies, and clinical guidelines.

The complexity of polypharmacy, especially in aging and multimorbid populations, exacerbates the risk of adverse effects. Polypharmacy introduces the potential for multiple drug-drug and drug-gene interactions that can compound toxicity risks. Pharmacogenetic insights help unravel this complexity by predicting metabolic capacity and drug interactions at an individual level. Recent research highlights the need for integrated models that consider genomic, pharmacokinetic, and clinical variables to optimize medication regimens holistically. Clinical pharmacists play an essential role in applying these principles through medication therapy management programs, performing comprehensive reviews to minimize harm and maximize benefit.

Emerging scientific advances extend the pharmacogenetic paradigm beyond single nucleotide polymorphisms (SNPs) to include complex genomic and multi-omic factors. Epigenetic modifications, such as DNA methylation and histone modification, can alter gene expression related to drug metabolism and response. Transcriptomic and proteomic profiling provide additional layers of information, capturing dynamic changes and environmental influences. These multi-omic data, combined with clinical and environmental factors, enable systems pharmacology approaches that offer a more nuanced and predictive understanding of drug response and toxicity. The integration of these data types demands sophisticated bioinformatics and statistical methods, as well as large, well-characterized cohorts for validation.

Ethical and social implications permeate all facets of pharmacogenetic implementation and pharmacovigilance. The handling of sensitive genetic information requires stringent safeguards to ensure confidentiality, prevent unauthorized access, and mitigate risks of discrimination in employment or insurance. Informed consent processes must be robust, clear, and culturally sensitive, enabling patients to understand the scope, benefits, limitations, and potential risks of genetic testing. Policymakers and healthcare organizations must address disparities in access to pharmacogenetic services to avoid exacerbating health inequities. Community engagement and participatory research models are valuable for aligning implementation strategies with local values and needs, fostering trust and acceptance.

Health economic analyses indicate that pharmacogenetic-guided therapy can be cost-effective or even cost-saving by preventing severe adverse drug reactions and reducing hospitalizations. However, economic evaluations are heterogeneous, influenced by test costs, healthcare system structures, population characteristics, and disease contexts. Incorporating broader societal costs and benefits, such as quality of life improvements and productivity gains, strengthens the case for investment in pharmacogenetic services. Payment and reimbursement models must evolve to

incentivize adoption, incorporating value-based principles that reward improved patient outcomes and system efficiencies.

The rapid pace of technological innovation is shaping the future of pharmacogenetics and pharmacovigilance. Artificial intelligence (AI) and machine learning algorithms enhance the ability to analyze complex datasets, identify novel gene-drug interactions, and predict adverse events with high accuracy. Wearable biosensors and mobile health platforms enable continuous patient monitoring, facilitating early detection of toxicity and personalized interventions. Blockchain technology offers potential solutions for secure, patient-controlled data sharing, enhancing trust and interoperability. Nonetheless, the adoption of these technologies requires careful validation, regulatory oversight, and ethical governance to ensure safety, efficacy, and equity.

Globally, efforts to harmonize regulatory standards, guidelines, and nomenclature facilitate the international exchange of pharmacogenetic data and best practices. Organizations such as the Clinical Pharmacogenetics Implementation Consortium (CPIC) and the Pharmacogenomics Knowledgebase (PharmGKB) provide curated, evidence-based resources to guide clinical application. National and regional regulatory agencies increasingly incorporate pharmacogenetic considerations into drug approval, labeling, and post-marketing surveillance. Collaborative initiatives are essential to build infrastructure, share data, and develop context-appropriate strategies that address local genetic diversity and healthcare realities.

The comprehensive analysis confirms that pharmacogenetics and patient-centered care, when synergistically integrated with advanced pharmacovigilance systems, have the potential to revolutionize medication safety and efficacy. Realizing this potential necessitates addressing economic, educational, technological, ethical, and policy challenges through coordinated, multidisciplinary efforts. Enhancing clinician and patient engagement, leveraging digital health tools, expanding research inclusivity, and fostering supportive policy environments will be key to translating scientific advances into routine clinical practice. Ultimately, these strategies aim to minimize the global burden of adverse drug reactions, optimize pharmacotherapy, and improve health outcomes for diverse patient populations.

The comprehensive synthesis of current scientific literature, clinical evidence, and emerging technological paradigms underscores the pivotal role of pharmacogenetics and patient-centered care in transforming pharmacotherapeutic management, particularly in mitigating medication-induced adverse effects and toxicities. The multidimensional nature of drug response variability—shaped by genetic, environmental, demographic, and clinical factors—poses formidable challenges to



conventional pharmacotherapy paradigms, necessitating innovative, integrative approaches that this analysis aims to elucidate.

#### *Pharmacogenetic Determinants of Adverse Drug Reactions and Toxicities*

Adverse drug reactions (ADRs) remain a significant cause of morbidity and mortality worldwide, complicating treatment outcomes and escalating healthcare costs. Pharmacogenetics offers critical insight into interindividual differences by delineating genetic polymorphisms that influence drug absorption, distribution, metabolism, and excretion (ADME), as well as drug targets and downstream signaling pathways. Notably, cytochrome P450 enzyme polymorphisms—CYP2D6, CYP2C19, CYP2C9, and CYP3A4/5—account for substantial variability in the metabolism of widely prescribed medications including antidepressants, antiplatelets, anticoagulants, and chemotherapeutic agents. Extensive studies have established that poor metabolizer phenotypes often exhibit elevated plasma drug concentrations, predisposing patients to dose-dependent toxicities, whereas ultra-rapid metabolizers risk therapeutic failure.

Beyond metabolic enzymes, the human leukocyte antigen (HLA) system has emerged as a critical pharmacogenetic locus associated with severe hypersensitivity reactions. For example, the association of HLA-B\*57:02 with carbamazepine-induced Stevens-Johnson syndrome and toxic epidermal necrolysis has precipitated region-specific screening protocols, notably in Southeast Asian populations. Similarly, HLA-B\*57:01 screening prior to abacavir initiation exemplifies a successful implementation of genotype-guided therapy, drastically reducing hypersensitivity incidence. The elucidation of these allele-specific risks highlights the necessity for population-tailored pharmacogenetic screening programs, given the marked interethnic variability in allele frequencies.

Pharmacodynamic gene variants affecting drug targets also contribute to ADR susceptibility. Variants in VKORC1 and CYP2C9 influence warfarin sensitivity and bleeding risk, necessitating genotype-guided dose individualization protocols. Likewise, polymorphisms in the dopamine receptor gene DRD2 and serotonin transporter gene SLC6A4 affect psychotropic drug efficacy and tolerability. The integration of such pharmacodynamic markers into clinical decision-making remains an active area of research, with emerging evidence supporting their utility in refining therapeutic precision.

#### *Clinical Implementation and Integration Challenges*

While the scientific evidence underpinning pharmacogenetics is robust, its translation into routine clinical practice is impeded by multifactorial challenges. Foremost is the variable clinician familiarity and confidence in interpreting and applying pharmacogenetic data. Surveys across diverse healthcare settings reveal

knowledge gaps and uncertainty, compounded by the lack of standardized educational curricula and training. This deficit impairs effective patient counseling and limits the clinical utility of genetic testing.

Economic constraints further restrict implementation. The costs of pharmacogenetic testing, although decreasing, remain prohibitive in many healthcare systems, particularly where reimbursement frameworks are underdeveloped or absent. The lack of universally accepted cost-effectiveness data engenders hesitancy among payers and policymakers. Notably, economic evaluations demonstrate that pharmacogenetic testing can be cost-saving in conditions with high ADR incidence or severe toxicity risk, such as anticoagulation and oncology, yet broad application requires more comprehensive health economic analyses encompassing diverse clinical scenarios and populations.

Systemic infrastructural deficits also hinder implementation. The integration of genetic data into electronic health records (EHRs) and clinical decision support systems (CDSS) is essential for real-time, point-of-care decision-making but faces technological, interoperability, and workflow integration challenges. Many institutions lack the informatics infrastructure or standardized protocols to incorporate pharmacogenetic results meaningfully into prescribing practices. Alert fatigue and poor user interface design further limit clinician engagement with CDSS.

Patient-centered approaches are critical to overcoming these barriers. Shared decision-making models emphasize the need for clear communication, cultural sensitivity, and incorporation of patient values and preferences. Studies demonstrate that patients engaged in discussions about pharmacogenetic testing exhibit greater acceptance, adherence, and satisfaction. Nevertheless, disparities in health literacy, cultural beliefs, and access to genetic counseling services may limit equitable patient participation.

#### *Pharmacovigilance Evolution in the Genomic Era*

Traditional pharmacovigilance systems rely predominantly on spontaneous adverse event reporting, which is subject to underreporting, bias, and delayed detection of safety signals. The integration of pharmacogenetic data into pharmacovigilance frameworks enhances the granularity and specificity of adverse event detection. By stratifying risk based on genetic predisposition, pharmacovigilance programs can identify subpopulations vulnerable to particular toxicities, facilitating targeted monitoring and risk mitigation.

Advanced pharmacovigilance approaches employ real-world data sources including electronic health records, claims databases, and patient registries, often enhanced by natural language processing and machine learning algorithms. These

active surveillance systems enable near real-time detection of safety signals and gene-drug interaction profiling. For example, the U.S. FDA's Sentinel Initiative incorporates genetic data to monitor post-marketing drug safety with unprecedented scale and precision. Despite these advances, challenges remain in standardizing pharmacogenetic data collection, ensuring data quality, and protecting patient privacy.

#### *Polypharmacy and Complex Interactions*

The increasing prevalence of polypharmacy, especially among aging populations with multiple chronic conditions, magnifies the complexity of drug therapy and heightens adverse effect risks. Polypharmacy introduces potential drug-drug interactions that can alter drug metabolism and efficacy, complicating clinical management. Pharmacogenetics provides a crucial tool for disentangling these interactions by predicting individual metabolic capacity and susceptibility to interaction-related toxicities.

Recent research advocates for integrated clinical decision support platforms capable of synthesizing pharmacogenetic profiles with comprehensive medication lists, laboratory data, and clinical parameters to optimize therapy. Pharmacists, as medication experts, are pivotal in implementing these approaches through medication therapy management services that incorporate pharmacogenetic considerations. Such multidisciplinary collaborations improve therapeutic safety and patient outcomes.

#### *Emerging Scientific Frontiers: Multi-Omics and Systems Pharmacology*

Beyond single-gene pharmacogenetics, multi-omics approaches encompassing genomics, transcriptomics, proteomics, metabolomics, and epigenomics provide a systems-level understanding of drug response variability. Epigenetic modifications, for instance, dynamically regulate gene expression influencing drug metabolism and target sensitivity, affected by environmental exposures and disease states. Transcriptomic profiling captures changes in gene expression induced by drugs or pathophysiological conditions, potentially serving as biomarkers for toxicity or efficacy.

The integration of multi-omic data with clinical and environmental factors through systems pharmacology models enables sophisticated predictions of drug response and adverse events. Computational models simulate drug-target interactions, metabolic networks, and cellular signaling pathways to identify emergent vulnerabilities. While promising, these approaches require large, well-phenotyped cohorts and advanced bioinformatics capabilities, currently limiting widespread clinical application.

#### *Ethical, Legal, and Social Considerations*

Pharmacogenetic integration raises profound ethical, legal, and social implications. The sensitive nature of genetic information mandates rigorous privacy protections and secure data governance frameworks. Informed consent processes must

be transparent and comprehensive, ensuring patient understanding of the scope, benefits, limitations, and potential risks of genetic testing.

Concerns about genetic discrimination in employment, insurance, and social contexts necessitate protective legislation such as the Genetic Information Nondiscrimination Act in the United States and equivalent policies worldwide. Ensuring equitable access to pharmacogenetic services is imperative to prevent exacerbation of health disparities, necessitating inclusive research and culturally competent care models.

Patient autonomy and engagement are central ethical principles. Empowering patients through education and participatory decision-making enhances trust and optimizes therapeutic outcomes. The responsible handling of incidental findings, which may arise from broad genomic testing, requires clear guidelines and expert consultation.

#### *Health Economic Perspectives*

Health economic analyses play a decisive role in informing policy and reimbursement decisions for pharmacogenetic testing. Studies demonstrate cost-effectiveness in several clinical contexts by reducing ADR-related hospitalizations and improving therapeutic efficacy. However, variability in study designs, populations, cost inputs, and outcome measures limits generalizability.

Future economic evaluations must incorporate broader societal impacts, including quality-adjusted life years, productivity, caregiver burden, and long-term healthcare costs. Innovative reimbursement models, such as value-based care and risk-sharing agreements, may accelerate adoption by aligning incentives with improved patient outcomes and cost savings.

#### *Technological Innovations and Digital Health Integration*

The digital transformation of healthcare catalyzes novel opportunities for pharmacogenetics and pharmacovigilance. Artificial intelligence and machine learning algorithms enhance the analysis of complex datasets to identify subtle gene-drug interactions and predict adverse event risk with high accuracy. Natural language processing facilitates extraction of adverse event information from unstructured clinical notes.

Mobile health applications and wearable biosensors enable continuous, real-time patient monitoring, capturing physiological and behavioral data indicative of adverse drug reactions. Integration of these digital health tools with pharmacogenetic profiles fosters proactive, personalized interventions.

Blockchain technology offers promising solutions for secure, decentralized management of sensitive genetic and health data, enhancing patient control and data interoperability. However, technological adoption must be accompanied by rigorous

validation, user-centered design, and ethical governance frameworks to ensure safety, efficacy, and equity.

### *Global Health and Policy Perspectives*

The global health community increasingly recognizes the potential of pharmacogenetics and pharmacovigilance to improve medication safety and efficacy worldwide. Collaborative initiatives aim to build capacity in low- and middle-income countries through technology transfer, training, and infrastructure development.

The underrepresentation of diverse populations in pharmacogenetic research limits applicability of findings, underscoring the need for inclusive, global genomic databases and research consortia. Harmonization of regulatory standards and pharmacogenetic guidelines facilitates international data sharing and clinical adoption.

Health policies must evolve to support sustainable pharmacogenetic services, including standardized testing protocols, reimbursement mechanisms, and educational frameworks. Stakeholder engagement—patients, clinicians, researchers, industry, and regulators—is essential to foster trust, transparency, and ethical implementation.

The intersection of pharmacogenetics, patient-centered care, and pharmacovigilance heralds a transformative era in the optimization of medication safety and efficacy. The growing recognition that genetic variability significantly contributes to interindividual differences in drug response has propelled pharmacogenetics from a predominantly research-focused domain to a clinically actionable tool. This analysis elucidates the multifaceted outcomes, challenges, and future directions stemming from the integration of pharmacogenetic data with patient-centered pharmacotherapeutic strategies and advanced pharmacovigilance systems.

### *Genetic Influences on Medication-Induced Adverse Effects:*

#### *Expanding the Evidence Base*

A robust body of evidence underscores that genetic polymorphisms in drug-metabolizing enzymes, transporters, and targets critically influence the occurrence and severity of adverse drug reactions (ADRs). The cytochrome P450 superfamily remains a cornerstone of pharmacogenetic research, with enzymes such as CYP2D6, CYP2C19, CYP2C9, and CYP3A5 exhibiting extensive allelic variation that modulates metabolic capacity. Clinical guidelines issued by international consortia like the Clinical Pharmacogenetics Implementation Consortium (CPIC) have formalized genotype-guided dosing recommendations for numerous drugs, reinforcing the clinical utility of genotyping in minimizing toxicity and enhancing therapeutic efficacy.

Recent meta-analyses have quantified the magnitude of risk associated with specific genotypes. For instance, CYP2C19 poor metabolizers have demonstrated a significantly elevated risk of treatment failure and bleeding complications with



clopidogrel therapy, warranting alternative antiplatelet strategies. Similarly, carriers of CYP2D6 ultrarapid metabolizer alleles face increased likelihood of opioid toxicity due to accelerated bioactivation of prodrugs such as codeine. These findings substantiate genotype-based prescribing as a critical component of personalized medicine, particularly in cardiovascular, psychiatric, and pain management domains.

The role of HLA alleles in mediating immune-mediated ADRs further exemplifies the precision pharmacogenetic approach. Identification of high-risk alleles such as *HLA-B15:02* and *HLA-B57:01* has enabled the implementation of preemptive screening protocols, markedly reducing the incidence of life-threatening hypersensitivity reactions. Moreover, novel associations are continually being discovered, expanding the repertoire of actionable pharmacogenetic markers. For example, emerging evidence implicates *HLA-A\*31:01* in carbamazepine-induced hypersensitivity in populations beyond Southeast Asia, highlighting the necessity of region-specific genetic epidemiology studies.

Pharmacodynamic genetic variants influencing drug targets and signaling pathways complement metabolic gene data, enriching the prediction of ADR risk and therapeutic response. Polymorphisms in *VKORC1* and *CYP2C9* shape warfarin dose requirements and bleeding risk, supporting genotype-guided anticoagulation initiation. Variants in genes coding for neurotransmitter receptors and transporters modulate psychotropic drug response profiles, although clinical translation remains nascent. Collectively, these pharmacodynamic insights reinforce the paradigm shift toward integrating multilayered genetic data into clinical decision-making frameworks.

#### *Barriers to Clinical Translation:*

##### *Systemic, Educational, and Socioeconomic Dimensions*

Despite the compelling evidence base, the incorporation of pharmacogenetic testing into routine clinical practice encounters substantial impediments. System-level barriers encompass limited infrastructure for genetic testing, lack of standardized reporting formats, and fragmented integration with electronic health record (EHR) systems. The absence of interoperable data systems undermines seamless dissemination of pharmacogenetic information at the point of care, hindering clinician access and utilization.

Educational deficits among healthcare professionals constitute a pervasive challenge. Surveys reveal that many clinicians possess inadequate knowledge of pharmacogenetic principles, interpretation of genetic test results, and application in therapeutic decision-making. The paucity of formal training during undergraduate and postgraduate curricula, coupled with insufficient continuing medical education opportunities, constrains clinician confidence and engagement. Interdisciplinary educational initiatives involving pharmacists,

genetic counselors, and physicians have demonstrated potential in enhancing knowledge and promoting collaborative care models.

Economic considerations also weigh heavily on adoption rates. The cost of pharmacogenetic testing, although decreasing with technological advances, remains a significant barrier, particularly in publicly funded health systems with constrained budgets. The absence of universally accepted reimbursement policies and the variability in payer coverage contribute to inequitable access. Furthermore, robust health economic evaluations are lacking for many pharmacogenetic applications, impeding evidence-based policy development.

Socioeconomic and cultural factors influence patient acceptance and participation in pharmacogenetic testing. Concerns about genetic privacy, potential discrimination, and misunderstanding of genetic risk contribute to reluctance in some populations. Health literacy disparities exacerbate these issues, necessitating culturally sensitive educational interventions and equitable access to genetic counseling services. Community engagement and participatory research approaches are critical to building trust and tailoring implementation strategies.

#### *Innovations in Pharmacovigilance:*

##### *From Passive Surveillance to Integrated Precision Monitoring*

Pharmacovigilance, historically reliant on spontaneous adverse event reporting, is undergoing a paradigm shift towards proactive, data-driven surveillance systems augmented by pharmacogenetic insights. Traditional reporting systems suffer from well-documented limitations including underreporting, delayed signal detection, and bias. Integration of pharmacogenetic data enables stratification of safety signals by genetic risk, refining the specificity and clinical relevance of detected associations.

Active surveillance methodologies leveraging real-world data (RWD) sources such as EHRs, claims databases, and patient registries facilitate continuous monitoring of drug safety profiles. The application of natural language processing and machine learning algorithms enhances signal detection capabilities by mining unstructured clinical narratives and identifying novel gene-drug interactions. Initiatives such as the FDA Sentinel System exemplify large-scale implementations of such approaches, incorporating genetic data to monitor and mitigate ADRs effectively.

Patient-centered pharmacovigilance initiatives have emerged, utilizing mobile health technologies and digital platforms to enable real-time adverse event reporting and monitoring. Wearable biosensors capture physiological parameters indicative of drug toxicity, while patient-reported outcome measures enrich safety data. These technologies empower patients as active participants in medication safety, fostering engagement and timely intervention.

However, challenges persist in standardizing pharmacogenetic data capture within pharmacovigilance frameworks, ensuring data quality, and safeguarding patient privacy. Harmonized ontologies and data standards are essential for interoperability and meaningful data aggregation. Ethical frameworks guiding data use and sharing must balance public health benefits with individual rights.

#### *Complexity of Polypharmacy and Drug Interactions:*

##### *The Pharmacogenetic Perspective*

The prevalence of polypharmacy, particularly among aging populations with multiple chronic conditions, amplifies the complexity of medication management and the risk of ADRs. The interplay of multiple drugs increases the potential for pharmacokinetic and pharmacodynamic interactions, complicating clinical decision-making. Pharmacogenetics offers a critical lens for dissecting these interactions by characterizing individual metabolic capacity and transporter activity.

Studies demonstrate that pharmacogenetic variants may modulate the magnitude and direction of drug-drug interactions, influencing clinical outcomes. For example, CYP2D6 ultrarapid metabolizers may experience enhanced activation of prodrugs concomitantly administered with CYP inhibitors, altering toxicity risk profiles. Incorporating pharmacogenetic data into clinical decision support systems that analyze polypharmacy scenarios can facilitate personalized risk assessment and optimize therapeutic regimens.

Pharmacists, integral to medication therapy management, are uniquely positioned to apply pharmacogenetic knowledge in reviewing complex medication regimens. Interprofessional collaboration and incorporation of pharmacogenetics into clinical workflows enhance the safety and effectiveness of polypharmacy management.

#### *Emerging Frontiers:*

##### *Multi-Omics, Systems Pharmacology, and Artificial Intelligence*

Pharmacogenetics represents one component of an expanding multi-omic landscape that encompasses genomics, epigenomics, transcriptomics, proteomics, and metabolomics. This systems-level approach recognizes the dynamic, multifactorial nature of drug response, integrating genetic, environmental, and physiological influences.

Epigenetic modifications modulate gene expression without altering DNA sequence and can be influenced by age, disease, and environmental exposures, thereby affecting drug metabolism and response. Transcriptomic profiling captures real-time gene expression changes, providing insights into drug-induced molecular perturbations and toxicity pathways. Proteomic and metabolomic analyses elucidate downstream functional alterations, offering potential biomarkers for ADR prediction and

monitoring.

Systems pharmacology integrates multi-omic data with computational modeling to simulate drug behavior within complex biological networks. These models facilitate identification of novel therapeutic targets, prediction of ADRs, and optimization of dosing strategies. Artificial intelligence (AI) and machine learning enhance the analysis of high-dimensional data, enabling pattern recognition and predictive analytics that inform personalized pharmacotherapy.

While these technologies offer unprecedented potential, their clinical translation requires rigorous validation, standardization, and integration into healthcare systems. Addressing issues of data privacy, algorithm transparency, and equitable access is imperative.

#### *Ethical, Legal, and Social Implications:*

##### *Navigating Complex Terrain*

The utilization of genetic data in pharmacotherapy raises profound ethical, legal, and social considerations. Ensuring patient autonomy necessitates comprehensive informed consent processes that articulate the benefits, limitations, and potential risks of pharmacogenetic testing, including incidental findings. Protecting genetic privacy is paramount, demanding robust data security measures and clear policies on data access and sharing.

Legislative frameworks, such as the Genetic Information Nondiscrimination Act (GINA) in the United States and analogous laws internationally, provide protections against discrimination in employment and insurance based on genetic information. However, gaps remain, particularly in life and disability insurance sectors, necessitating ongoing policy development.

Equity in access to pharmacogenetic services is a critical social justice issue. Disparities in testing availability and representation in genetic research risk exacerbating existing healthcare inequalities. Inclusive research practices, culturally competent care, and targeted outreach are essential to address these challenges.

Community engagement and participatory approaches empower patients and communities, fostering trust, transparency, and culturally relevant implementation strategies. Ethical stewardship must be integrated throughout the research, clinical, and policy continuum.

#### *Health Economic Considerations:*

##### *Balancing Costs and Benefits*

Economic evaluations of pharmacogenetic interventions demonstrate variable cost-effectiveness depending on clinical context, population characteristics, and healthcare system structures. Conditions associated with high-risk ADRs and severe

toxicities, such as anticoagulation therapy and oncology, often yield favorable economic profiles for pharmacogenetic testing.

Comprehensive health economic models incorporate direct medical costs, indirect societal costs, and quality-adjusted life years (QALYs), providing nuanced assessments of value. Innovative reimbursement models, including value-based payment and risk-sharing arrangements, align financial incentives with improved clinical outcomes and may facilitate broader adoption.

Investment in infrastructure, education, and research are essential to realize the full economic and clinical benefits of pharmacogenetics. Policymakers must consider long-term gains alongside upfront costs in resource allocation decisions.

#### *Technological Innovations:*

##### *Digital Health and Beyond*

Digital health technologies are rapidly transforming pharmacogenetic implementation and pharmacovigilance. Mobile applications facilitate patient engagement, education, and adverse event reporting. Wearable devices capture continuous physiological data, enabling early detection of toxicities and personalized interventions.

Blockchain technology offers promising solutions for secure, decentralized management of genetic and health data, enhancing patient control, data integrity, and interoperability. Artificial intelligence algorithms enhance data analytics, enabling predictive modeling and clinical decision support.

Successful integration requires addressing challenges of validation, user acceptance, regulatory oversight, and equitable access. Cross-sector collaboration and adaptive governance frameworks are vital.

#### *Global Perspectives and Policy Implications*

The global implementation of pharmacogenetics and advanced pharmacovigilance necessitates tailored strategies responsive to diverse healthcare infrastructures, genetic backgrounds, and sociocultural contexts. Capacity building in low- and middle-income countries through training, technology transfer, and infrastructure development is critical to equitable global health impact.

International collaboration fosters data sharing, standardization of testing and reporting, and harmonization of regulatory frameworks. Public-private partnerships and stakeholder engagement accelerate innovation and dissemination.

Policy development must balance innovation with ethical safeguards, patient rights, and health equity. Multi-stakeholder dialogues and evidence-based guidelines support sustainable, responsible integration.

The integration of pharmacogenetics into clinical practice represents a paradigm



shift in the personalization of medicine, with the potential to significantly reduce the incidence and severity of medication-induced adverse effects. This comprehensive analysis elucidates the multifactorial nature of medication safety, underscoring the interplay between genetic variability, patient-centered approaches, pharmacovigilance, and evolving therapeutic strategies. The findings corroborate the critical importance of incorporating genetic information alongside clinical, demographic, and environmental factors to optimize pharmacotherapy and enhance patient outcomes.

#### *Implications of Pharmacogenetic Variability on Clinical Outcomes*

Genetic polymorphisms that alter drug metabolism and response are well-documented determinants of interindividual variability in therapeutic efficacy and toxicity. The identification of actionable pharmacogenetic markers has been instrumental in guiding clinical decisions for drugs with narrow therapeutic indices or severe adverse event profiles. Clinical guidelines, such as those promulgated by CPIC and the Dutch Pharmacogenetics Working Group, offer evidence-based frameworks that, if widely adopted, could markedly improve prescribing accuracy and patient safety.

However, the clinical utility of pharmacogenetics extends beyond isolated gene-drug pairs. The dynamic complexity of drug response, influenced by polygenic interactions and epigenetic modifications, necessitates more comprehensive models that integrate multi-omic data and environmental inputs. Emerging evidence supports the notion that simplistic single-gene testing may insufficiently capture the nuanced determinants of ADRs and therapeutic response. Future research must prioritize the development of integrative predictive algorithms and validation in diverse clinical contexts.

#### *Challenges to Clinical Implementation*

Despite clear scientific validation, the translation of pharmacogenetic knowledge into standard clinical practice remains impeded by systemic, educational, economic, and sociocultural barriers. The insufficient integration of pharmacogenetic data into electronic health records and decision support tools limits accessibility and usability at the point of care. Healthcare provider unfamiliarity and lack of confidence in interpreting genetic data further hinder adoption.

Economic considerations, including testing costs, reimbursement policies, and cost-effectiveness evidence gaps, pose significant obstacles, particularly in resource-limited settings. Health systems must balance the upfront costs of genetic testing infrastructure against potential long-term savings from reduced ADR-related morbidity and hospitalizations. Policy frameworks that incentivize adoption through value-based reimbursement may accelerate integration.

Patient acceptance and engagement represent critical determinants of successful pharmacogenetic implementation. Cultural beliefs, health literacy levels, and concerns

regarding privacy and discrimination influence willingness to undergo testing. Effective patient-centered communication strategies and equitable access to genetic counseling services are paramount to fostering informed decision-making and trust.

#### *Pharmacovigilance and Real-World Evidence Integration*

The advent of pharmacogenetics enriches pharmacovigilance methodologies by enabling stratified risk assessment and refined signal detection. Real-world data analytics, incorporating genetic profiles, augment traditional surveillance systems and facilitate earlier identification of ADRs in genetically susceptible subpopulations. The incorporation of digital health technologies and patient-reported outcomes further enhances the timeliness and granularity of safety data.

Nevertheless, standardizing the capture and integration of pharmacogenetic information within pharmacovigilance frameworks remains a challenge. Data interoperability, quality assurance, and privacy protections are essential to maximize the utility of integrated systems. Cross-sector collaboration among regulatory agencies, healthcare providers, researchers, and patients is critical to developing robust, scalable pharmacovigilance infrastructures.

#### *The Complexities of Polypharmacy and Personalized Therapeutics*

The increasing prevalence of polypharmacy, particularly among aging populations, compounds the risk of medication-related adverse events. Pharmacogenetics offers valuable insights into individualized drug metabolism capacity, thereby informing safer polypharmacy management. However, the clinical complexity introduced by multiple interacting drugs requires sophisticated decision support systems that synthesize pharmacogenetic, clinical, and pharmacological data.

Interprofessional collaboration, especially involving clinical pharmacists, is essential for optimizing medication regimens in this context. Education and training programs should emphasize the integration of pharmacogenetics into medication therapy management to address the nuanced challenges posed by polypharmacy.

#### *Ethical, Legal, and Social Considerations*

The use of genetic data in clinical decision-making raises profound ethical and legal questions. Protecting patient privacy and preventing genetic discrimination must be prioritized through robust legislative frameworks and ethical oversight. Informed consent processes require clarity and cultural sensitivity to ensure patient understanding and autonomy.

Addressing disparities in access to pharmacogenetic testing is an ethical imperative to avoid exacerbating health inequities. Inclusive research practices, community engagement, and culturally competent care models are essential to ensure equitable benefits from advances in personalized medicine.

### *Technological Innovations and Future Directions*

Emerging digital health technologies and artificial intelligence are poised to accelerate pharmacogenetic integration by enhancing data analysis, patient monitoring, and clinical decision support. These tools promise to bridge existing gaps in knowledge translation and operational workflows. However, their implementation must be accompanied by rigorous validation, user-centered design, and attention to ethical and equity considerations.

Global collaboration and harmonization of regulatory standards will facilitate the widespread adoption of pharmacogenetic-informed pharmacotherapy. Investments in capacity building, infrastructure, and education are necessary to realize the full potential of these advances across diverse healthcare settings.

The comprehensive exploration of pharmacogenetic and patient-centered care approaches reveals both transformative opportunities and significant implementation challenges in the realm of medication-induced adverse effects and pharmacovigilance. The path forward necessitates coordinated multidisciplinary efforts encompassing scientific innovation, healthcare system redesign, policy development, and ethical stewardship. Embracing this integrated framework holds promise for achieving safer, more effective, and personalized pharmacotherapy that improves patient outcomes globally.

The evolution of pharmacogenetics from a theoretical framework to a practical tool in clinical pharmacotherapy marks a significant advancement in personalized medicine. The extensive evidence reviewed highlights the intricate interplay between genetic polymorphisms and drug response variability, elucidating mechanisms underlying medication-induced adverse effects and toxicities. This growing body of knowledge challenges traditional "one-size-fits-all" prescribing paradigms and mandates the incorporation of genetic, environmental, and patient-specific factors into therapeutic decision-making.

The pharmacogenetic variability in cytochrome P450 enzymes exemplifies the molecular complexity influencing drug metabolism. The allelic diversity within CYP2D6, CYP2C19, and CYP3A5 genes is a principal determinant of phenotypic heterogeneity ranging from poor to ultra-rapid metabolizers, with significant implications for drug plasma levels, efficacy, and safety. Clinical implementation of genotype-guided dosing has demonstrated reductions in adverse drug events and improved therapeutic outcomes in diverse populations, yet its full potential remains unrealized due to barriers in clinical adoption. These findings advocate for routine preemptive pharmacogenetic screening in high-risk medications and populations, accompanied by comprehensive clinician education to bridge the knowledge translation gap.

The role of immune-related genetic markers, particularly HLA alleles, in mediating severe hypersensitivity reactions represents another critical dimension. The regional and ethnic variability in HLA allele frequencies necessitates context-specific screening guidelines. For instance, while HLA-B\*15:02 testing is well established in Southeast Asia, emerging evidence suggests expanding genetic screening in other populations may further reduce incidences of Stevens-Johnson syndrome and toxic epidermal necrolysis. This underscores the need for dynamic, population-tailored pharmacogenetic policies supported by robust epidemiological surveillance.

Despite clear scientific advances, the real-world translation of pharmacogenetics is impeded by multifactorial challenges. From a systems perspective, the lack of integration into existing electronic health record infrastructures restricts the clinical utility of pharmacogenetic data. Without seamless access and interpretive support, clinicians face cognitive and operational burdens that limit application. The design and implementation of sophisticated clinical decision support systems capable of delivering actionable, patient-specific recommendations at the point of care are critical to overcoming these obstacles.

Economically, the upfront costs of genetic testing and infrastructure development pose barriers, particularly in healthcare systems constrained by budgetary limitations. While pharmacoeconomic analyses affirm cost-effectiveness in select scenarios, broad-scale economic evaluations incorporating real-world data, long-term outcomes, and indirect societal costs are necessary to inform payer policies and resource allocation. Value-based reimbursement models that reward improved clinical outcomes through pharmacogenetic-guided care offer promising pathways for sustainable integration.

Patient engagement and health literacy emerge as pivotal determinants of successful pharmacogenetic implementation. The complexity of genetic information requires innovative, culturally sensitive educational interventions tailored to diverse populations. Concerns regarding genetic privacy, potential stigmatization, and discrimination remain prevalent. Transparent communication strategies and robust legal protections must be emphasized to foster trust and informed participation. Furthermore, equitable access to pharmacogenetic services demands addressing disparities in healthcare infrastructure, provider availability, and socioeconomic determinants.

The synergy between pharmacogenetics and pharmacovigilance represents a frontier for enhancing medication safety. Integrating genetic risk stratification into active surveillance programs refines signal detection, enabling earlier identification of susceptible subpopulations. Real-world data repositories enriched with genomic information and analyzed through advanced machine learning algorithms offer

unprecedented opportunities for dynamic monitoring and adaptive risk management. However, ensuring data standardization, interoperability, and patient confidentiality within these systems requires coordinated governance frameworks and ethical oversight.

Polypharmacy, a prevalent challenge in contemporary medicine, particularly among the elderly and chronically ill, intensifies the risk of adverse drug reactions. Pharmacogenetics provides a critical lens for disentangling the complexity of drug-drug and drug-gene interactions. Multidisciplinary medication management teams incorporating pharmacogenetic expertise can tailor regimens to individual metabolic profiles, mitigating toxicity risks and enhancing therapeutic efficacy. Development of integrated informatics platforms synthesizing genetic, clinical, and pharmacological data will be instrumental in operationalizing this personalized approach.

Beyond single-gene associations, the emergence of multi-omics and systems pharmacology heralds a more holistic understanding of drug response. Epigenomic modifications, transcriptomic fluctuations, proteomic changes, and metabolomic profiles collectively influence pharmacodynamics and pharmacokinetics. Harnessing these complex data streams through artificial intelligence-driven analytics can identify novel biomarkers and predictive signatures, facilitating earlier detection of toxicity and individualizing therapy. Yet, these advances also introduce challenges in data management, interpretability, and clinical validation, necessitating interdisciplinary collaboration and methodological rigor.

Ethical, legal, and social considerations remain paramount as pharmacogenetic technologies permeate clinical care. Safeguarding genetic privacy, preventing misuse of data, and ensuring informed consent require evolving regulatory and ethical frameworks. The potential for unintended consequences, such as widening health disparities or psychosocial harms, mandates vigilance and proactive mitigation strategies. Inclusive research practices and community engagement are critical to ensuring that pharmacogenetic benefits are equitably distributed.

Technological innovations, including blockchain for secure data sharing, wearable biosensors for real-time monitoring, and telemedicine platforms for genetic counseling, hold promise in addressing logistical and ethical challenges. Their successful deployment depends on rigorous evaluation, patient-centered design, and policy alignment.

Globally, pharmacogenetic implementation must be contextualized within diverse healthcare infrastructures, genetic backgrounds, and cultural landscapes. International collaboration, data harmonization, and capacity building are essential to realize equitable benefits. The development of adaptable, evidence-based guidelines and regulatory harmonization will facilitate cross-border adoption and innovation.



The integration of pharmacogenetic insights with patient-centered care and advanced pharmacovigilance represents a transformative opportunity to enhance medication safety and therapeutic outcomes. Realizing this potential demands multidisciplinary, multi-stakeholder efforts to surmount scientific, clinical, ethical, and systemic barriers. The convergence of technological advances, policy evolution, and patient engagement sets the stage for a new era of precision pharmacotherapy that is safer, more effective, and tailored to individual needs.

The landscape of pharmacogenetics and patient-centered pharmacotherapy continues to evolve rapidly, propelled by advances in molecular biology, bioinformatics, and clinical sciences. This progression reveals increasingly complex interdependencies between genetic makeup, environmental exposures, and patient-specific factors that modulate drug response and toxicity. Such intricacies underscore the insufficiency of traditional prescribing frameworks and highlight the urgency of embedding comprehensive pharmacogenomic data into personalized care models.

A salient theme emerging from contemporary research is the concept of *pharmacogenetic heterogeneity* within and across populations. The allelic diversity observed in drug metabolism and immune response genes is not uniformly distributed but reflects ancestral, ethnic, and geographic variations. This heterogeneity complicates the generalizability of pharmacogenetic findings and calls for more inclusive research designs that encompass underrepresented populations. Current pharmacogenetic databases often suffer from Eurocentric biases, limiting the predictive power and clinical applicability of genotype-guided therapies in diverse demographic groups. Addressing this gap requires concerted efforts to expand genomic studies globally, implement cross-cultural research ethics, and integrate local knowledge systems.

Moreover, the interplay between *genetic predisposition* and *environmental modulators* such as diet, concomitant medications, comorbidities, and lifestyle factors must be accounted for to fully apprehend drug response variability. For instance, environmental inducers or inhibitors of cytochrome enzymes can modulate the phenotypic expression of genetic variants, leading to phenoconversion and unexpected therapeutic outcomes. Incorporating such dynamic gene-environment interactions into predictive models remains a methodological challenge but represents an essential frontier for precision medicine.

The role of *epigenetic regulation* introduces additional layers of complexity. Epigenetic mechanisms such as DNA methylation, histone modifications, and non-coding RNA influence gene expression profiles relevant to drug metabolism and immune responses. Importantly, these modifications are reversible and responsive to

environmental cues, suggesting potential targets for therapeutic modulation to mitigate adverse drug reactions. However, the clinical translation of epigenomic data in pharmacotherapy is nascent, demanding robust longitudinal studies and validation frameworks.

An underexplored but critical domain is the influence of the *microbiome* on drug metabolism and toxicity. The human gut microbiota expresses enzymatic activities capable of biotransforming drugs, altering their bioavailability, efficacy, and adverse effect profiles. Interindividual variation in microbiome composition contributes to differential drug response and may interact synergistically or antagonistically with host genetic factors. Integrating microbiome profiling with pharmacogenetic analyses could refine risk stratification and inform novel therapeutic interventions.

The patient-centered care paradigm emerges as a keystone for operationalizing pharmacogenetics in clinical settings. This model emphasizes shared decision-making, tailored communication, and holistic consideration of patient values, preferences, and psychosocial context. Incorporation of genetic risk information into these discussions must be undertaken with sensitivity to avoid generating anxiety or fatalistic attitudes. Empowering patients through education and supportive counseling fosters adherence, trust, and optimal therapeutic outcomes.

Despite these promising directions, *clinical workflow integration* remains a formidable barrier. The proliferation of pharmacogenetic data necessitates efficient, user-friendly platforms embedded within electronic health records to provide real-time, context-specific recommendations without overwhelming clinicians. Interdisciplinary collaboration involving clinicians, geneticists, bioinformaticians, and informaticians is crucial to develop adaptive clinical decision support systems that evolve with emerging evidence and user feedback.

Health disparities present a significant ethical and practical challenge in the deployment of pharmacogenetic services. Socioeconomic factors, geographic accessibility, and healthcare infrastructure disparities contribute to unequal access, potentially exacerbating health inequities. Strategies to mitigate these issues include decentralized testing models, telemedicine-based genetic counseling, and community-engaged research initiatives that prioritize inclusivity and cultural competence.

The *regulatory environment* is evolving to accommodate the complexities of pharmacogenetic testing and personalized medicine. Regulatory bodies must balance innovation facilitation with rigorous evaluation of test validity, clinical utility, and cost-effectiveness. Harmonization of standards across jurisdictions can streamline clinical implementation and ensure consistent quality. Additionally, clear guidelines on data ownership, privacy, and sharing are paramount to protect patient rights while

enabling research advancement.

On the frontier of *technological innovation*, the integration of artificial intelligence and machine learning algorithms with multi-omic and clinical datasets heralds unprecedented potential for predictive analytics. These tools can uncover latent patterns, identify novel gene-drug interactions, and generate personalized risk profiles that inform clinical decisions. Nevertheless, transparency, explainability, and ethical use of AI models require ongoing scrutiny and governance to prevent bias and ensure equitable benefit.

Real-world evidence derived from large-scale biobanks, longitudinal cohorts, and electronic health records enriched with genetic data offers invaluable insights into long-term safety and effectiveness of genotype-guided therapies. Collaborative consortia and data-sharing initiatives accelerate knowledge dissemination but must navigate complex issues related to data privacy, consent, and international legal frameworks.

The economic sustainability of pharmacogenetics is contingent upon comprehensive cost-benefit analyses that incorporate direct and indirect healthcare costs, quality of life metrics, and societal productivity. Early investment in testing infrastructure and clinician training is offset by reductions in preventable adverse drug events, hospitalizations, and ineffective therapies. Innovative payment models that reward outcomes rather than volume may incentivize adoption.

The comprehensive integration of pharmacogenetics within patient-centered care and pharmacovigilance systems embodies a transformative approach to medicine that transcends traditional boundaries. Realizing this vision demands holistic strategies addressing scientific, clinical, technological, ethical, and socioeconomic dimensions. Multidisciplinary collaboration, sustained investment, and patient empowerment will be pivotal in navigating the complexities and actualizing the promise of personalized pharmacotherapy for safer and more effective treatment paradigms.

The trajectory of pharmacogenetics in clinical medicine is increasingly influenced by advances in *precision health*, an emerging framework that extends beyond treatment optimization to encompass disease prevention, early diagnosis, and health promotion tailored to individual variability. Pharmacogenetic insights are pivotal in this broader context, enabling proactive identification of individuals at elevated risk for drug-induced toxicities and facilitating preemptive therapeutic adjustments. This paradigm shift challenges healthcare systems to transition from reactive to anticipatory care models, leveraging genetic data alongside clinical and environmental risk factors.

A critical component of this transition is the enhancement of *healthcare provider*

*competencies* in genomics and personalized medicine. The current educational gap among clinicians represents a substantial bottleneck to effective pharmacogenetic integration. Progressive curricular reforms incorporating genomics literacy, ethical considerations, and interpretation of complex test results are imperative in undergraduate, graduate, and continuing professional education. Simulation-based learning, interprofessional workshops, and decision-making case studies have shown promise in improving clinician preparedness and confidence.

The role of *clinical pharmacists* has expanded significantly within this paradigm. As medication experts, pharmacists are uniquely positioned to interpret pharmacogenetic data, manage polypharmacy, and liaise with multidisciplinary teams to tailor therapy. Integration of pharmacists into genetic testing workflows and medication management programs enhances patient safety and fosters effective implementation. Moreover, pharmacists' involvement in patient education facilitates informed consent and shared decision-making, addressing patient concerns and promoting adherence.

From a *research perspective*, the integration of *pharmacogenomics with pharmacodynamics and pharmacokinetics* is evolving toward a holistic systems biology approach. Network pharmacology models consider drug-target interactions within complex biological pathways, accounting for genetic variants, epigenetic factors, and compensatory mechanisms. Such models aid in elucidating mechanisms underlying idiosyncratic adverse drug reactions, which often evade detection in traditional clinical trials. This comprehensive understanding can inform the design of safer drugs and targeted monitoring strategies.

The emergence of *big data analytics* and *machine learning* enables the handling of vast, multidimensional datasets that characterize modern pharmacogenomic research. These technologies facilitate the identification of novel genetic variants and rare adverse event predictors, potentially unearthing previously unrecognized gene-drug interactions. Nevertheless, the interpretability of complex models remains a challenge, necessitating transparent algorithm development and validation in diverse clinical cohorts.

In addressing *pharmacogenetic disparities*, it is essential to recognize the influence of *social determinants of health* on access to genetic services and medication safety outcomes. Factors such as socioeconomic status, geographic location, education level, and healthcare access can modulate both exposure to pharmacogenetic testing and medication adherence. Tailored outreach programs and policy interventions are required to ensure equitable distribution of the benefits of pharmacogenomic advances.

The *ethical landscape* of pharmacogenetics continues to evolve with the expanding scope of genetic testing. Issues surrounding *incidental findings*, such as the

discovery of predispositions to unrelated diseases during pharmacogenetic screening, raise complex questions regarding disclosure obligations, patient autonomy, and psychological impact. Frameworks for managing such findings are being developed, emphasizing the necessity for comprehensive pre-test counseling and post-test support.

*Data privacy and security* constitute paramount concerns as genetic information becomes increasingly integrated into health systems. Cybersecurity threats, unauthorized data sharing, and potential misuse of genetic data necessitate robust technical safeguards, policy regulations, and patient education. The advent of *blockchain* and other decentralized technologies offers innovative solutions for secure, patient-controlled data sharing, but implementation challenges and regulatory acceptance remain ongoing issues.

The expanding availability of *direct-to-consumer (DTC) genetic testing* poses additional challenges and opportunities. While increasing public awareness and engagement with genetics, DTC testing often lacks clinical validation, comprehensive interpretation, and integration into healthcare. The potential for misinterpretation and inappropriate clinical decisions underscores the need for regulatory oversight, clinician involvement, and public education to safeguard patient welfare.

The field of *pharmacovigilance* is progressively integrating *real-world evidence (RWE)* and *patient-generated data* to complement traditional surveillance systems. Patient-reported outcomes, wearable device data, and mobile health applications enhance the timeliness and sensitivity of adverse event detection, particularly in genetically susceptible individuals. These patient-centered approaches democratize pharmacovigilance but require standardized data collection protocols and validation methodologies.

*Global health perspectives* reveal significant variability in the adoption of pharmacogenetics, influenced by differences in healthcare infrastructure, genetic diversity, regulatory environments, and economic resources. Low- and middle-income countries face unique challenges, including limited laboratory capacity, scarcity of trained personnel, and competing healthcare priorities. International collaborations and capacity-building initiatives focused on technology transfer, education, and ethical frameworks are crucial to closing these gaps.

The *regulatory environment* is adapting to the complexities introduced by personalized medicine. Regulatory agencies are developing guidelines for the evaluation and approval of pharmacogenetic tests and companion diagnostics, balancing innovation with patient safety. Harmonization efforts aim to facilitate global consistency, enabling more rapid dissemination and adoption of validated pharmacogenetic tools.



Looking forward, the integration of *multi-omic data* with *digital health technologies* promises to refine personalized pharmacotherapy further. The convergence of genomics, proteomics, metabolomics, and microbiomics with artificial intelligence-driven clinical decision support platforms offers unprecedented opportunities to anticipate, prevent, and manage adverse drug reactions at the individual level.

To capitalize on these advances, healthcare systems must prioritize the development of *interoperable data infrastructures* and promote *interdisciplinary collaboration* among clinicians, geneticists, data scientists, ethicists, and policymakers. Patient engagement and empowerment remain central, requiring continuous efforts to enhance health literacy, trust, and shared decision-making.

The future of pharmacogenetics and patient-centered pharmacotherapy is promising yet complex. The translation of scientific discoveries into routine clinical practice necessitates multifaceted strategies addressing technical, clinical, ethical, economic, and social dimensions. A concerted global effort, underpinned by robust evidence and ethical stewardship, is essential to realize the full potential of personalized medicine in improving medication safety and therapeutic efficacy.

The future of pharmacogenetics and patient-centered pharmacotherapy is poised for remarkable transformation driven by rapid technological innovation, expanding scientific understanding, and evolving healthcare paradigms. The convergence of genomics, digital health, and systems biology promises to reshape how medication-induced adverse effects and toxicities are predicted, prevented, and managed, ultimately enhancing patient safety and therapeutic efficacy on a global scale.

One of the foremost future directions is the widespread adoption of preemptive, comprehensive genomic profiling integrated into routine healthcare. Advances in next-generation sequencing and decreasing costs will facilitate broad population-level screening, enabling clinicians to access an individual's pharmacogenetic landscape early in life or prior to therapy initiation. Such data repositories, linked longitudinally to clinical records, will support dynamic and lifelong medication optimization, minimizing adverse drug reactions and enhancing personalized care continuity.

The integration of multi-omics data—including epigenomics, transcriptomics, proteomics, and metabolomics—with genomic information will enrich predictive models of drug response and toxicity. Systems pharmacology approaches leveraging these complex datasets will elucidate intricate biological networks and pathways modulating pharmacodynamics and pharmacokinetics. This holistic understanding will drive the discovery of novel biomarkers and therapeutic targets, paving the way for next-generation precision therapeutics tailored to multifactorial determinants of drug response.

## Conclusions

➤ The integration of pharmacogenetic insights with patient-centered therapeutic strategies represents a transformative approach in contemporary pharmacotherapy, offering significant potential to mitigate medication-induced adverse reactions and optimize clinical outcomes. Genetic variability plays a central role in determining individual susceptibility to drug toxicity, and its consideration allows for more precise, personalized dosing and therapy selection. When combined with patient-focused care—incorporating medical history, lifestyle factors, preferences, and adherence patterns—clinicians can anticipate high-risk scenarios, minimize adverse events, and enhance treatment efficacy.

➤ Pharmacovigilance remains a critical component in maintaining drug safety, yet traditional monitoring approaches face limitations due to underreporting, heterogeneity of patient populations, and the complexity of adverse event mechanisms. The incorporation of pharmacogenetic data into pharmacovigilance systems strengthens the detection, prediction, and prevention of ADRs, thereby enabling timely interventions and evidence-based decision-making. Additionally, identifying causative medications and elucidating the molecular, enzymatic, and immunological mechanisms underlying adverse reactions are essential for risk stratification and the development of safer therapeutic regimens.

➤ A multidimensional understanding of risk determinants—including age, sex, comorbidities, concomitant medications, and environmental factors—supports the implementation of optimized pharmacotherapy management strategies. Evidence-based algorithms, clinical decision support systems, and individualized monitoring schedules can significantly reduce the incidence of adverse events, improve adherence, and enhance overall patient outcomes. This integrative approach aligns with the principles of precision medicine, emphasizing proactive risk management, individualized therapy, and patient engagement as central pillars of safe and effective pharmacotherapy.

➤ In conclusion, the convergence of pharmacogenetics, patient-centered care, and advanced pharmacovigilance constitutes a comprehensive framework for mitigating drug-related risks and enhancing therapeutic efficacy. Continued research, interdisciplinary collaboration, and clinical implementation of these strategies are essential for realizing their full potential, ultimately advancing the safety, effectiveness, and personalization of modern drug therapy across diverse patient populations.

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## THE MANIFESTATION OF COMPREHENSIVE ANALYSIS OF KEY ISSUES ASPECTS OF PHARMACEUTICAL WASTE IN THE ENVIRONMENT: ECOLOGICAL CONSEQUENCES, PUBLIC HEALTH RISKS, COMPLEX INTERACTIONS, RISK ASSESSMENT, AND STRATEGIC MITIGATION APPROACHES

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**Abstract.** The ubiquitous dispersion of medicinal compounds throughout natural systems has become a pressing global problem, carrying profound implications for ecological stability and public welfare. This investigation probes the widespread pollution originating from these substances, analyzing their damaging influence on environmental equilibrium and species variety. It illuminates the intricate dynamics of drug-based chemicals within natural settings, which intensify their longevity and

harmful potential. The work highlights the considerable dangers presented to animal life and human communities, especially via biological accumulation and the impairment of hormonal functions. Additionally, the assessment scrutinizes existing approaches for determining ecological and health hazards, pointing out their shortcomings and the demand for more resilient analytical structures. To confront these issues, all-encompassing remedial measures are suggested, spanning from upgraded water purification methods to regulatory measures designed to curb drug-related waste generation. The conclusions emphasize the immediate requirement for strengthened hazard analysis procedures and international collaboration to alleviate the consequences for nature and societal health. Medicinal pollutants now represent a severe issue for natural systems, permeating aquatic, terrestrial, and atmospheric environments and causing extensive ecological damage and threats to human populations. These enduring chemical agents disturb marine and land-based ecosystems, diminishing biological diversity, transforming microorganism populations, and promoting drug-resistant pathogens. Their complicated behavior in environmental contexts complicates hazard estimation, calling for a more thorough grasp of their extended effects. This research investigates the complex routes by which drug remnants influence ecological networks and public welfare, underscoring the importance of integrated solution plans. Sophisticated water purification processes, more rigorous governance, and eco-conscious drug management are vital to reduce pollution. Furthermore, upgrading hazard assessment models with superior detection techniques and simulation tools is fundamental for protecting environmental and communal well-being. The frequent detection of medicinal chemicals in nature has provoked major alarm owing to their enduring characteristics and extensive repercussions. These pollutants, deriving from drug manufacturing, incorrect waste handling, and effluent release, penetrate water-based and land-based systems, harming wildlife, modifying natural cycles, and encouraging treatment-resistant bacteria. Their concentration in aquatic environments endangers marine life, builds up in food webs, and presents dangers to people via chronic contact. The complex relations between drug-derived compounds and natural processes hinder danger evaluation, creating a necessity for more evolved testing methods and forecasting frameworks. This analysis explores the broad consequences of drug-related pollution, reviewing the processes by which these agents impact ecological and human health. It stresses the critical need for comprehensive solutions, including the improvement of effluent management systems, the creation of environmentally-friendly medications, tighter legal controls, and educational initiatives. Moreover, a sophisticated hazard analysis methodology combining cross-disciplinary studies, novel surveillance techniques, and extensive

impact studies is crucial for successfully managing contamination threats. Resolving this growing challenge demands a unified worldwide initiative to maintain planetary health and safeguard the well-being of both human societies and the natural world.

**Keywords:** Drug, pharmaceuticals, medicine, ecology, environment, human health.

**Introduction.** The objective of this investigation was to examine the extensive environmental pollution resulting from medicinal compounds, analyzing their influence on ecological systems: associated hazards, intricate dynamics, and methods for hazard appraisal, holistic remediation approaches, and the necessity for improved evaluation protocols. The presence of medicinal compounds in natural settings has raised increasing alarm owing to their possible consequences for ecological stability and public welfare. These pollutants, frequently derived from human and animal therapeutics, are detected in aquatic, terrestrial, and atmospheric environments, presenting considerable dangers through their complicated interplay with other environmental contaminants. Although they are broadly distributed, prevailing ecological hazard evaluations commonly address single chemicals, possibly overlooking wider environmental repercussions. This research investigates the severe pollution caused by medicinal compounds, stressing their impact on water- and land-based ecosystems. It also addresses the threats linked to the buildup of these agents, their combined effects with other pollutants, and the possibility for synergistic or cumulative outcomes. Additionally, it underscores the pressing requirement for more resilient and all-encompassing hazard analysis frameworks, incorporating the examination of breakdown products, secondary consequences, and the prolonged effects of exposure to pharmaceutical substances [1-2].

The contamination of the environment by pharmaceutical residues presents a critical challenge to both ecosystem health and human well-being. The widespread presence of these substances in water, soil, and air underscores the need for a more comprehensive understanding of their environmental fate and effects. Current risk assessment approaches, which often examine individual compounds in isolation, are inadequate in addressing the complex interactions and cumulative risks posed by pharmaceutical pollutants, especially when combined with other environmental contaminants. Furthermore, the potential dangers of pharmaceutical transformation products, which may exhibit greater toxicity or persistence, remain underexplored. To address these concerns, a paradigm shift is required in environmental risk assessment, incorporating multi-substance interactions, long-term ecological impacts, and the effects of transformation products. The development of robust mitigation strategies—such as advanced waste treatment technologies, improved pharmaceutical disposal

practices, and more stringent regulatory frameworks—must be prioritized. By adopting a more integrated, precautionary approach to pharmaceutical contamination, we can better protect ecosystems and human health from the growing threat posed by these persistent pollutants. Future research and policy initiatives should focus on improving our understanding of these substances, developing innovative solutions to reduce their environmental impact, and ensuring sustainable management practices for pharmaceuticals [3-5].

The presence of pharmaceutical residues in the environment has emerged as a significant global concern, as these substances increasingly contaminate water, soil, and air systems. The widespread use of pharmaceuticals in human and veterinary medicine, along with improper disposal practices, has led to the accumulation of pharmaceutical compounds in various environmental compartments. These residues, often detected in trace amounts, are not only persistent but can also have profound ecological and human health implications. The environmental impact of pharmaceuticals extends beyond direct toxicity, as they can disrupt ecosystems, alter microbial communities, and interfere with natural processes such as nutrient cycling and waste decomposition [7-9].

Current environmental risk assessments often focus on single substances, neglecting the combined effects of pharmaceuticals in the environment. This approach may overlook the potential for greater toxicity when multiple substances interact or the unanticipated consequences of transformation products, which can be more persistent or toxic than their parent compounds. For example, the breakdown products of some pharmaceuticals may persist in the environment for extended periods, increasing the long-term ecological risks. Moreover, the potential for these transformation products to migrate through the food chain and impact human health remains largely unexamined [11-13].

The lack of comprehensive understanding of pharmaceutical pollution in the environment is further compounded by inadequate data on the long-term effects of low-level, chronic exposure to these compounds. Despite significant advances in detecting pharmaceutical residues in environmental matrices, only a small fraction of the thousands of active pharmaceutical ingredients used globally have been adequately studied. This gap in knowledge makes it difficult to assess the full scope of the risks posed by pharmaceutical contamination [15-17].

To address this growing environmental challenge, there is an urgent need for an integrated, precautionary approach to risk assessment that considers the complex interactions between pharmaceuticals and other pollutants. A more nuanced understanding of how pharmaceuticals degrade in the environment, how they interact

with other chemicals, and how these compounds affect ecological functions and biodiversity is essential. This requires an expansion of ecotoxicity testing to incorporate a broader range of subtle biological effects, such as behavioral changes, physiological disruptions, and alterations in biochemical processes. Advanced technologies, including genomics, proteomics, and high-throughput screening, could play a pivotal role in improving the assessment of pharmaceutical pollutants.

Moreover, effective mitigation strategies must be developed to reduce pharmaceutical releases into the environment. These strategies could include improved waste management practices, such as source control, better disposal systems for unused pharmaceuticals, and more advanced wastewater treatment technologies. Additionally, regulatory frameworks must be strengthened to ensure that pharmaceutical contaminants are adequately managed and that new drugs are evaluated for their environmental risks before they are widely used. Such efforts would require collaboration among scientists, policymakers, and the pharmaceutical industry to develop sustainable solutions that minimize the environmental impact of pharmaceutical residues [18-20].

The study advocates for the development of improved mitigation strategies, such as enhanced waste treatment technologies, better pharmaceutical disposal systems, and more effective regulatory frameworks. Ultimately, this research calls for a multidisciplinary approach to address the environmental challenges posed by pharmaceutical contamination, aiming to safeguard both ecological and human health in the face of growing global concerns. Pharmaceutical contamination of the environment is an increasingly significant concern that demands urgent attention. The presence of pharmaceutical residues in natural systems, primarily from human and veterinary drug use, leads to contamination of water, soil, and air, where their persistence can disrupt ecological balance and potentially harm human health. Current environmental assessments often fail to consider the complex interactions between pharmaceutical residues and other pollutants, leaving many potential risks overlooked. A key issue is the difficulty in predicting the cumulative effects of these contaminants, especially when pharmaceuticals are mixed with other toxic substances in the environment. The impacts are not limited to direct toxicity but may include indirect effects, such as changes to microbial communities and disruptions in ecological processes, like nutrient cycling. Moreover, the transformation products of pharmaceuticals, which may be more persistent or toxic than the original compounds, remain poorly understood and under-researched. Given these challenges, the existing risk assessment frameworks, which often focus on single-substance exposures, are insufficient. A more holistic approach is necessary to account for the interactions,



transformations, and cumulative risks posed by pharmaceutical residues [21-23].

Effective mitigation strategies will require a combination of improved waste management practices, targeted regulatory policies, and advanced treatment technologies. Understanding the full scope of pharmaceutical contamination and its ecological and human health implications is essential for developing proactive, sustainable solutions. The uncontrolled release of drugs into the environment may be through wastewater and atmospheric emissions from enterprises producing finished drugs and pharmaceutical substances. The environmental safety of such production is usually regulated by law. However, accidental releases of drugs into the environment or those that violate existing norms and regulations that occur in industry, are nevertheless not systematic. Moreover, there is a general trend towards a reduction in the environmental load on the part of pharmaceutical production, primarily in developed countries of the world, due to a consistent increase in the technological effectiveness and organization of the production process, the introduction of increasing quality standards and environmental safety, and control by authorized government bodies. It is also necessary to take into account that pharmaceutical production is localized geographically, and if an accident occurs at the enterprise or there are violations of environmental legislation, then such emissions are exclusively local in nature and pose a danger only to specific regions. For all the reasons listed above, such sources are not the subject of analysis in this review, although they contribute to environmental pollution. Other sources of drugs that are practically uncontrollable and are formed mainly by people who use drugs for medical purposes, as well as in animals, pose a great danger to the environment [24-26].

This study aims to delve deeper into the environmental contamination caused by pharmaceutical residues, exploring their ecological impacts, the complexity of their interactions with other pollutants, and the urgent need for more comprehensive and integrated risk assessments. Furthermore, it will highlight the critical role of advanced mitigation strategies, innovative treatment technologies, and regulatory measures in addressing the growing environmental threat posed by pharmaceuticals. By fostering a greater understanding of pharmaceutical pollution, we can better protect ecosystems, safeguard human health, and mitigate the long-term risks associated with pharmaceutical contamination in the environment [27-29].

While some studies have identified individual pharmaceuticals in the environment, the complexity of interactions between multiple contaminants—such as pharmaceuticals, pesticides, and industrial chemicals—remains insufficiently understood. Current risk assessment frameworks primarily focus on single-substance exposure, which may fail to account for the cumulative or synergistic effects that arise

when pharmaceuticals interact with other environmental pollutants. Additionally, the potential risks associated with transformation products, which may be more persistent or toxic than the parent compounds, have been largely overlooked [30-32].

The environmental contamination caused by pharmaceutical residues is an increasingly complex and critical issue that threatens the health of ecosystems and poses risks to human well-being. The widespread use of pharmaceuticals in both human and veterinary medicine, combined with inadequate disposal practices, has led to the persistence of these substances in various environmental media, including water, soil, and air. While pharmaceuticals are essential for human health, their unintended release into the environment raises concerns due to their potential ecological impacts. These compounds, often present in trace amounts, can accumulate over time and exhibit a range of adverse effects on aquatic and terrestrial organisms, including the disruption of microbial communities, alterations in biodiversity, and interference with critical ecosystem processes such as nutrient cycling and soil fertility [33-35].

Pharmaceutical residues in the environment are particularly concerning because they can have multiple modes of action, which can interfere with the natural functioning of ecosystems. Some pharmaceutical compounds, such as antibacterial, have been shown to affect soil microbes that play an essential role in processes like pesticide degradation and manure decomposition. The potential for synergistic or additive effects among pharmaceuticals and other environmental pollutants, such as pesticides, biocides, and industrial chemicals, adds further complexity to the issue. While individual pharmaceuticals have been studied in isolation, little is known about how they interact with other chemicals in the environment, which may lead to underestimated risks [36-39].

Given these concerns, there is a pressing need for a more integrated approach to the study and management of pharmaceutical residues in the environment. This includes the development of more robust risk assessment models that consider multiple substances, the environmental behavior of transformation products, and their potential long-term ecological impacts. Furthermore, effective mitigation strategies, including improved waste management, disposal practices, and regulatory measures, are essential to address the growing issue of pharmaceutical contamination. This paper aims to explore the environmental contamination caused by pharmaceutical residues, assess their risks and interactions, and highlight the need for improved frameworks to better understand and mitigate their impact on both ecosystems and human health [40-42].

**The aim of the study.** Aim of the research was to study and analyzed the deep environmental impact of medication waste, their effects on natural systems: public health threats, intricate relationships, risk analysis, holistic solutions, and the need for

advanced hazard assessment.

**Materials and Methods.** The material of the article was the data from scientific publications, which were processed, analyzed, overviewed and reviewed by generalization and systematization. Research studies are based on a review/overview assessment of the development of critical visibility and overlook of the modern scientific literature. Use the following databases: (for extensive literature searches to identify the the deep environmental impact of medication waste, their effects on natural systems: public health threats, intricate relationships, risk analysis, holistic solutions, and the need for advanced hazard assessment.). PubMed, Medline, Web of Science, Scopus, Web of Knowledge, Clinical Key, Tomson Reuters, Google Scholar, Cochrane library, and Elsevier foundations, national and international policies and guidelines were also reviewed and as well as grey literature.

**Results and Discussion.** Pharmaceuticals have been entering the environment for decades, and researchers have only recently begun to quantify their levels in the environment. Using information from different countries and uses, several prioritization exercises have identified pharmaceutical products that are most likely to end up in the environment. Annual veterinary drug use was combined with information on routes of administration, metabolism and ecotoxicity to identify drugs that should be monitored under a national recognition programme. New analytical techniques such as liquid chromatography coupled with tandem mass spectrometry (LC-MS-MS) have provided a better understanding of the behaviour of drugs in the environment and have determined their concentrations in wastewater treatment plants, soil, surface water [43-45].

Once released into the environment, pharmaceuticals will be transported and distributed by air, water, soil or sediment. Their distribution will be influenced by a number of factors, such as the physicochemical properties of the compound and the characteristics of the receiving environment. The extent to which a pharmaceutical product is transported between different environmental media depends primarily on the sorption behavior of the substance in soils, sludge and wastewater systems, and wastewater treatment plants, which varies considerably between products. pharmaceuticals. Additionally, unlike other organic substances such as pesticides and industrial chemicals, the sorption behavior of many pharmaceuticals cannot be simply inferred from the hydrophobicity of the substance or the organic carbon content of the material. solid. Pharmaceutical substances can also be degraded by biological organisms in processing systems, water bodies and soils, as well as by abiotic reactions. Typically, these processes reduce the effectiveness of medications; however, some degradation products have the same toxicity as their original compounds. Additionally, degradation varies considerably depending on chemistry, biology and climatic

conditions. For example, the half-life of the antiparasitic ivermectin is six times longer in winter than in summer, and the compound breaks down more quickly in sandy soils than in sandy loam soils. The natural estrogens  $17\beta$ -estradiol and estrone are degraded in both aerobic and anoxic reservoirs of activated sludge systems, while  $17\alpha$ -ethinylestradiol is only degraded under aerobic conditions. All of this adds to the complexity of the problem and requires customized solutions for individual pharmaceuticals and applications[46-49].

In some studies have found low levels of a wide range of pharmaceuticals, including hormones, steroids, antibiotics and parasiticides, in soils, surface waters and waters. underground. Reported concentrations are generally low, but what is even more alarming is that many therapeutic substances have been found under a wide range of hydrological, climatic and land use conditions, and many substances have been detected throughout of the year. The study results raised questions about how this mixture of veterinary and medicinal drugs, abundant in soil and surface waters, affects beneficial organisms in the environment and human health [50-52].

Comparison of these data with information on therapeutic doses, drinking water restrictions, and health advisories shows that concentrations of therapeutic compounds in surface waters are well below levels of concern to human health. Therefore, indirect exposure to pharmaceuticals through the water supply is unlikely to pose a risk to humans. However, risks from other exposure routes, such as ingestion of crops through soil and biomagnification through the food chain, have not yet been quantified and cannot be completely excluded. Environmental health effects are more difficult to assess. Human and veterinary drugs are required by law to undergo an environmental risk assessment for their effects on aquatic and terrestrial organisms before a product can be marketed, and the EU has introduced similar requirements. These environmental impact studies examine the potential adverse effects of manure on fish, daphnia, algae, bacteria, earthworms, plants, and invertebrates. Most of the data are publicly available (many environmental assessments are posted on the FDA website) and provide a reasonable data set for further study. However, legitimate questions arise about the real value of these studies. Risk assessments typically use standard ecotoxicity tests, which are often short-term and focus primarily on mortality as an endpoint. In addition, aquatic tests typically focus on the aquatic environment and do not take into account pharmaceuticals present in sediment. In general, the effects observed in these studies occur at concentrations significantly higher than those measured in the environment. Less well known are the more subtle effects that therapeutically active substances may have on organisms in the environment, such as growth, fertility, or behavior. Pharmaceutical compounds are designed to be either highly active and receptor-

reactive in humans and animals, or toxic to many infectious organisms, including bacteria, fungi, and parasites. However, this does not mean that they affect only these life forms. Many lower animals have receptor systems similar to those of humans and animals used in agriculture. In addition, numerous groups of organisms that affect human and animal health, and to which pharmaceutical products are directed, play a critical role in the functioning of ecosystems. It is therefore possible that pharmaceuticals have subtle effects on aquatic and terrestrial organisms that are not detected in standard tests. And because human drugs are released almost continuously into the environment, wild organisms are exposed for much longer periods than those used in standard tests. Researchers have therefore begun to study some of the more subtle effects caused by long-term, low-dose exposure to pharmaceuticals. A wide range of subtle effects have been reported, including effects on oocyte and testis maturation, effects on insect physiology and behavior, effects on faecal decomposition, inhibition of growth or stimulation of aquatic plant and algal species, and the development of antibacterial resistance in soil. There is strong suspicion that steroids in contraceptives affect the fertility and development of fish, reptiles, and aquatic invertebrates. Similarly, human and veterinary antibiotics have effects on soil microbes and algae [53-55].

Medicines play an important role in the treatment and prevention of diseases in humans and animals. But it is due to the very nature of drugs that they can also have unintended effects on animals and micro-organisms present in the environment. Although side effects on human and animal health are typically studied in extensive safety and toxicology studies, the potential environmental impacts of drug manufacturing and use are less well understood and have only become recently a topic of research interest. Some of the effects of various compounds, including veterinary anthelmintics and antibacterial therapeutics, are already known, but there are many other substances that can affect organisms in the environment. The situation is further complicated by the fact that some pharmaceuticals can have effects on bacteria and animals well below the concentrations usually used in safety and effectiveness testing. Additionally, degradation products and the combination of different biologically active compounds can have unexpected effects on the environment. Although it is reasonable to assume that these substances do not significantly harm humans, we have only recently begun to investigate whether and how they affect a wide range of organisms in the environment and what this means for health environmental [5-57].

The scale of this potential problem should not be underestimated. More than several million women use oral contraceptives, which eventually end up in the environment. A wide range of human drugs are produced and used, including



antibiotics, statins, and cytotoxins used to treat cancer, some of which are produced in quantities of several thousand tons per year. Information on the quantities of drugs used by humans is difficult to obtain, but recent data from Canada indicate that the most commonly used drugs include acetaminophen, aspirin, ibuprofen, naproxen, and carbamazepine. Large quantities of veterinary drugs, such as antibacterials, antifungals, and parasiticides, produced in aquaculture and agriculture can also contribute to environmental stress, especially because they are often found directly in soil and surface water, unlike human drugs, which typically pass through wastewater treatment plants first [58-59].

Human and veterinary drugs enter the environment through a variety of pathways. Residues generated during manufacturing may eventually end up in surface waters. After administration, human medications are absorbed, metabolized, and then discharged to sewers. They typically pass through wastewater treatment plants before ending up in water or on land through the application of sewage sludge. Antibacterial agents used to treat fish or shrimp in aquaculture end up directly in surface waters. Veterinary drugs used to treat grazing animals end up in soil or surface waters. When intensively treated livestock are treated, these drugs may end up indirectly in the environment through the application of slurry and manure as fertilizer. Other minor pathways include air emissions and disposal of unused medications and containers [60-61].

Macrocyclic lactones can affect invertebrate larvae in faeces at relatively low concentrations; earthworms appear sensitive to parasiticides used in veterinary medicine, and plants may be sensitive to many antibiotics. In addition, macrocyclic lactones have been shown to cause numerous sublethal responses in dung-feeding invertebrates, such as reduced feeding, water imbalance, decreased growth rate, inhibition of pupation, and impaired mating. Since livestock faeces contain a diverse fauna and provide a fruitful habitat for other species, macrocyclic lactones may therefore indirectly affect other species by depleting the quality and quantity of their food source. Sediment-related effects of pharmaceutical products have also been considered. Carbamazepine affects the emergence of chironomid midges [62-63].

Additionally, pharmaceuticals are not the only pollutants of environmental systems. Aquatic and terrestrial organisms are exposed to a mixture of drugs and other substances, including pesticides, biocides and common industrial chemicals. A recent study discovered the antibacterial agent lincomycin in combination with other additional chemicals. The study focused only on selected compounds, so many other synthetic substances could be present. Therefore, interactive effects are possible, such as the additivity of substances with similar modes of action and synergy. Because current environmental risk assessments focus on individual substances, it is possible

that these assessments underestimate exposure. It is also possible that the environmental behavior of a substance changes in the presence of other substances. For example, antibacterials have been shown to affect soil microbes that play an important role in the breakdown of pesticides. For example, research shows that veterinary antibacterial medications can influence the reduction of sulfates in soil and inhibit the decomposition of manure. If an antibacterial veterinary drug was applied as a slurry to an agricultural field prior to pesticide application, it is possible that the environmental impact of the pesticide would be dramatically altered [64-65].

Because very little is known about the effects of pharmaceuticals on environmental health and the interactions of various compounds, some workers are taking a precautionary approach and developing methods to reduce releases of these substances into the environment. Various approaches have been proposed, including source control of pharmaceuticals, source separation, waste treatment to remove pharmaceutical compounds, implementation of breeding practices, and improvement of drug disposal systems. expired medicines and waste containers. Source control includes marking, controlled disposal and separation of urine. Separating sources of pharmaceuticals, such as hospital wastewater, which are likely to be heavily contaminated with pharmaceuticals and antibiotic-resistant bacteria, should allow treatment resources to be focused on the most contaminated waters [66-67].

Pharmaceuticals may be removed by treatment with physical processes such as sorption or volatilization, biodegradation, or chemical reactions such as ozone treatment. The significance of the different options is likely to be very specific to each substance. For example, the antibiotic ciprofloxacin is removed by strong sorption to suspended solids in sewage sludge, whereas diclofenac and 17 $\alpha$ -ethinyl estradiol undergo significant biodegradation in aged activated sludge. A range of measures to reduce emissions is therefore likely to be required. Many treatment methods that eliminate pharmaceuticals may also produce transformation products that are more persistent and more mobile than the parent compounds, some of which may also have similar or increased toxicity. Little work has been done to assess the environmental impacts of these transformation products. Clearly, a wealth of data on the levels of pharmaceuticals in the environment and their effects on aquatic and terrestrial organisms has become available in recent years. However, many issues remain to be resolved before it can be determined whether residues in the environment pose a threat to human health and the environment. First, there are risks associated with substances that have not yet been studied. Due to resource limitations, only a small proportion of pharmaceuticals in use today have been studied, and there is an urgent need to understand how other substances affect the environment. Second, we can better assess

ecotoxicity. Current standard ecotoxicity tests are likely inadequate to assess the effects of many pharmaceuticals. The use of more subtle parameters such as behavioral changes, physiology, and biochemistry is of particular interest. Further work is needed to identify these subtle effects. It is likely that many of the technologies currently used by molecular biologists, such as proteomics and genomics techniques or large-scale DNA or protein microarrays, can make a significant contribution to this task. Third, ecotoxicity data are relevant to the real world. Although many subtle effects have been demonstrated following exposure to pharmaceuticals at environmentally realistic concentrations, we need to establish the significance of these data in terms of ecological functioning. Fourth, there are risks associated with mixtures. Pharmaceuticals are unlikely to occur alone in the environment, so the current single-substance risk assessment approach may underestimate environmental impacts. This also includes potential indirect effects. Little has been done to determine the absorption of pharmaceuticals into organisms and throughout the food chain. Such studies are critical to determining the potential indirect impacts of environmental exposure on the ecology and human health. A related question is: should we be concerned about transformation products? Much of the work to date has focused on the parent compounds; however, we know that transformation products are produced in the environment and during processing. It is important that we begin to understand the potential impacts of these substances. Future work should therefore focus on understanding the biotic and abiotic processes underlying the release, fate, and environmental impacts of pharmaceuticals. Finally, certain environmental exposures lead to greater resistance to antibacterial drugs. A wide range of antibacterial agents have been found in water and soil, many of which persist for some time. It is possible that such exposures could lead to the development of resistant microbes that could pose a serious threat to human and animal health [68-70].

The future work should focus on understanding the biotic and abiotic processes underlying the release, environmental fate, and effects of pharmaceuticals. Such an understanding should ultimately enable the development of new modeling approaches. A comparative plasma concentration model linking mammalian and fish species, which could provide useful information on the likely effects of pharmaceuticals on fish. Other modeling approaches, such as quantitative structure-activity relationships, could help estimate the environmental impacts of pharmaceutical products based on their chemical structure. Read-across approaches, in which data from closely related compounds are used to determine the effects of an untested compound, can also help improve environmental assessment. Improved tools should provide a better understanding of the environmental impacts of pharmaceutical products. At the same time, we must

strive to improve the way we use, handle and process medicines to minimize their release into the environment [71-72].

The contamination of various components of the environment (water, soil and air) by pharmaceutical residues poses an environmental problem. Human consumption of medicines ranges from 50 to 150 g per person per year in the EU. Veterinary drugs are used in smaller quantities, but pets are a growing segment of the veterinary drug market. In most EU Member States, around 50% of unused human medicines (3-8% of total sales) are not collected [73-74].

The problem is that we do not have a comprehensive understanding of what happens when these drugs are released into the environment, and further characterization of possible pathways of human exposure is needed. Residues of different types of drugs (hormones, anti-cancer drugs, antidepressants, antibiotics, etc.) have been found in various environmental elements, raising the question of whether this poses a risk to exposed plants, animals and microbes or to the man [75-76].

This study characterizes the extent of the environmental impact of pharmaceutical products outside of personal care products. The aim was to identify non-legislative and legislative reasons for their presence in the environment and to suggest ways to adapt legislation to address this problem. 30 to 90% of an orally administered dose of the drug is generally excreted as active substance in the urine of animals and humans. A large proportion of medicines are flushed down sinks and toilets and end up in the environment. Inappropriate and excessive consumption can also lead to unnecessary emissions [77-78].

In the EU, the contribution of manufacturing facilities to emissions of medicines and/or their residues is generally considered negligible.

Once in the environment, drugs are transformed and transferred between its different parts (surface and groundwater, soil, air). Highly fat-soluble drugs also have the ability to accumulate in the fatty tissues of animals and can thus be introduced into the food chain. These products can be broken down either through digestion and metabolism by organisms or through physicochemical processes in soil and water. Some degradation products may persist even after wastewater treatment and cause concern [79-81].

For a number of pharmaceutical products, the environmental risks can be quite minor because they do not remain in the environment for long and are low in toxicity. However, it is increasingly clear that certain drugs, notably antiparasitics, antifungals, antibiotics and (xeno)estrogens, which can have ecotoxicological effects, in some cases present environmental risks. For example, the vulture population in the Indian subcontinent has declined due to poisoning with diclofenac, a painkiller found in the

carcasses the vultures fed on. For humans, the possible consequences are less obvious than for the environment. Residue levels in drinking water or food are very low and are not considered to pose a risk to humans, but long-term exposure to low levels may occur through these routes [82-83].

There are currently no legal restrictions on human medicines potentially present in products of animal origin, this route of exposure being considered minor, even if it is currently not well characterized. For example, in Europe, only very low concentrations of veterinary antibiotics are found in dairy products [84-85].

Until 2005, the registration process for medicines did not include an environmental risk assessment (ERA), and therefore much relevant information was missing. Even for new products, the ERA was often incomplete. A number of regulatory frameworks for chemicals marketed and used in Europe now include an assessment of the potential for persistence, bioaccumulation and toxicity (PBT), but there is no specific guidance for veterinary and human medicinal products [86-87].

There are currently no European regulations covering the assessment of risks associated with contaminated soils and product residues transferred to animals, including fish, or present in wastewater sludge from wastewater treatment plants.

Key legislative steps to address these limitations include, among others, strengthening environmental risk assessments, which could also target "old" pharmaceuticals. The Water Framework Directive could explicitly take into account the results of the ERA for active pharmaceutical ingredients. Relevant legislative instruments could also establish a special label for the "green" pharmacy. The main non-legislative solutions focus on consumption and waste management through a better understanding of the ecotoxicity of medicines and encouraging the recruitment of ecotoxicology-trained staff to regulatory agencies. At the same time, training sections for doctors could be organized, a better match between consumer needs and packaging sizes could be considered, while increasing the role of pharmacists in collecting unused medicines and organizing public information campaigns. The main improvements in waste management could focus on more efficient collection systems for unused human and veterinary medicines and on monitoring their effectiveness [88-91].

Impact of climate change on the use of medicinal pharmaceuticals in the Northern Hemisphere. As climate change alters environmental conditions, the prevalence and global distribution of human diseases will change. Climate-related environmental changes are associated with an increase in chronic diseases already common in the Northern Hemisphere, such as cardiovascular disease and mental illness. The increase in these diseases is leading to an increase in the use of already widely used Western drugs. People with respiratory diseases may experience a worsening of symptoms due to changing



environmental conditions, such as increased pollen counts, leading to an increase in the demand for drugs used to control these symptoms. Toxic substances and respiratory, waterborne, and foodborne infections, including vector-borne infections, may become more common in Western countries, Central and East Asia, and across North America. As new disease threats emerge, a significant increase in the use of pharmaceuticals seems inevitable, particularly for pharmaceuticals not currently in wide use (e.g., antiprotozoal drugs). This study found that the use of drugs to treat common symptoms, such as painkillers, may also increase. Understanding which diseases, and therefore which drugs, may be used in the future is important so that toxicologists, environmental scientists, policymakers and legislators can focus their efforts, implement mitigation measures and plan training, education and treatment [92-93].

The chemical pollutants such as pesticides, biocides or industrial chemicals, the release of pharmaceuticals into the environment must be regulated to ensure adequate information and transparency about the environmental impacts of pharmaceuticals; adequate and reliable assessment of environmental risks of pharmaceutical products; prevent pharmaceutical products from entering the environment throughout their entire life cycle and control releases of pharmaceuticals into the environment when prevention is not possible [94-96].

Consumption of medicinal products for human and veterinary purposes has impacts on terrestrial and marine environments and ecosystems. Increased environmental awareness regarding pharmaceutical activities has led to the development of policies and measures aimed at mitigating negative environmental impacts. Various measures have been taken to promote environmentally friendly production and practices, leading to the development of alternative methods and processes benefiting both the environment and industry. Distributors and pharmacists can make a difference by effectively managing daily operations, including improving inventory and rotation, consolidating supplies and reducing unused medications [97-98].

Pharmaceutical products are essential to human health, but they become an environmental problem when they enter the environment, which occurs when residues are excreted from the body after consumption or when unused pharmaceutical products are improperly disposed of. Although no method has been developed to detect all drugs entering an ecosystem, certain groups have been shown to have negative impacts on ecosystems, including increased mortality of aquatic species and changes in physiology, behavior, or reproduction. Particular attention is paid to these groups of drugs and their impact on the environment. In this review, the authors propose measures to reduce the amount of unused pharmaceutical products in the environment, with a focus on prevention. Various policy measures are recommended throughout the

life cycle, including source-oriented, user-oriented and waste management measures, to prevent the generation of household pharmaceutical waste and ensure environmentally sound disposal of household pharmaceutical waste. Preventive measures include rational drug consumption, prescribing more environmentally friendly drugs or developing safe and easily biodegradable drugs, better disease prevention, personalized medicines, better packaging sizes and markets for the redistribution of unsafe drugs. The next step is to prevent inevitable waste from entering the environment. Therefore, it is extremely important to collect and properly dispose of unused medicines. Finally, education of healthcare professionals and the public, as well as partnerships between environmental scientists and clinicians, are essential at all stages of the pharmaceutical life cycle. Reducing drug levels in the environment will benefit human life [99-100].

Demographic, epidemiological and lifestyle changes, such as the aging of the population, the increase in chronic diseases, the availability of cheap generic treatments and easy access to a large number of over-the-counter medications, have become key factors in the growth of the pharmaceutical industry. The global increase in drug consumption has led to greater international awareness of the problem of unused pharmaceuticals (UPs) in households and the harmful environmental and health consequences of their improper disposal. Drugs in the environment are challenging because they are designed to interact with a living system and produce a pharmacological response at low doses, making them dangerous to the environment even at low concentrations. Secondly, drugs are designed to be stable in reaching and interacting with their target molecules, meaning that they degrade very slowly or that their continued use results in a constant, slower release into the environment, that is, as quickly like decomposition. In addition, conventional wastewater treatment plants are not designed to completely remove pharmaceuticals from wastewater [101-103].

Pharmaceutical products enter the environment through two main routes: excretion and insufficient elimination. In both cases, pharmaceuticals end up in sewage treatment plants, which are generally not designed to remove these pollutants from wastewater. Drugs have been found mainly in surface water, but also in groundwater, soil, manure and even drinking water. The presence of drugs in freshwater and terrestrial ecosystems can lead to the release of drugs into wildlife with the possibility of bioaccumulation. People are then exposed to drugs through drinking water and their residues in crops, fish, dairy products and meat. The effects of pharmaceuticals entering aquatic environments are of increasing concern, with impacts ranging from molecular changes to population-level effects [104-105].

The environment is everything that surrounds us: the air we breathe, the water

we drink, and the land on which all living creatures live, the plants we use for food thrive. Development is what we do with these resources to improve lives. Our actions to make our lives more comfortable change the environment

One of the achievements of the United Nations in the field of environmental protection is the Kyoto Resolution on the Climate Change Convention (1997). In 2004, it passed into law, requiring countries to reduce emissions of dangerous greenhouse gases by 5.2% by 2012. The United Nations Convention on Biological Diversity (1992) obliges states to preserve the rich diversity of plants and animals necessary for human existence.

Environmental pollution leads to the increase of toxic substances in the human body and its environment – air, water, soil, animal and plant world – beyond the permissible norm, which is followed by a sharp increase in various chronic diseases [10, 19, 37].

The interaction between the organism and the environment takes place in two main directions. One of them refers to those biochemical changes in human organisms that are caused by the demands of environmental conditions or arise in the process of human impact on the environment. It is necessary to specify the impact processes of men, women, children and entire groups. The environment is that part of living and non-living nature that surrounds organisms and directly or indirectly affects their existence, development and reproduction [15, 41, 57].

Pharmaceutical and personal care products (PPCP) in the environment are a hot topic. Veterinary antibiotics, prescription drugs and cosmetic products are discarded from a variety of sources and regularly enter the environment, where they occur in small quantities in wastewater, surface and ground water, silt-laden agricultural soils, aquatic and terrestrial biota, and wet drinks Water. The public should become aware of this and is calling on the scientific and regulatory community to assess the potential risks to human health and the environment and take appropriate action if necessary [14, 27, 46].

Chemical pollutants are known to have specific effects on organisms, for example: Organotin compounds (used in anti-fouling paints on ships) affect marine life. However, there is another very diverse group of chemical compounds that can be harmful but have received relatively little attention as potential environmental pollutants. These include drugs, including drugs for humans and animals, as well as illegal (recreational) drugs.

Thousands of tons of pharmacologically active substances are used worldwide every year, but surprisingly little is known about the fate of most drugs after their intended use. Most of the administered dose is excreted unchanged from the body, and

metabolites can be converted back into the active ingredient by bacteria. In addition, the public often throws unused medicines down the drain. Based on published prevalence data, it is likely that a significant portion of municipal wastewater is contaminated with narcotic compounds that vary only in the type and content of substances present [19, 42, 58].

Modern research has shown that many drugs are not completely eliminated from the body in wastewater treatment plants. The presence of drugs in surface systems, soil and even marine systems has been confirmed in concentrations ranging from high ng/liter to low mg/liter, which are similar to the concentrations of some pesticides. Pharmaceutical compounds discarded in household waste can end up in landfills and pose a risk to surface and ground water. Additionally, unlike more regulated contaminants, which often have a longer half-life in the environment, pharmaceuticals can become pseudopersistent due to prolonged exposure to wastewater, with unknown consequences for aquatic organisms that may be continuously exposed [19, 27, 39].

The potential consequences of the presence of pharmaceuticals in aquatic systems are unknown and have therefore received increasing attention as potential pollutants in recent years. The fact that an industrial chemical can end up in the environment is not surprising in itself. What's interesting about drug contamination is that it does not primarily arise from manufacturing, but rather from the widespread and ongoing use, isolation, and improper disposal of drugs for human and veterinary use [12, 25, 37].

Pharmaceuticals are potentially ubiquitous pollutants as they are present in all human environments. There is currently little evidence that pharmaceuticals are present in the environment in sufficient quantities to cause significant harm, although their use is expected to increase as the Human Genome Project is completed and the population ages. Drugs and their metabolites are increasingly being found in water bodies in areas adjacent to anthropogenic activities [39, 47, 54].

The biggest concern at the moment is that antibiotics in wastewater treatment plants may lead to increased resistance of natural bacterial populations. There are many isolates of microorganisms resistant to antibiotics in the environment, and although the issue remains controversial, the significant increase in the number of bacterial strains resistant to multiple antibiotics is often attributed to the misuse of antibiotics and the increase in their discharge into wastewater. Three known mechanisms of gene transfer (conjugation, transduction, and transformation) are thought to occur in aquatic environments; As a result, streams and rivers can become a source and reservoir of resistant genes, as well as a means of their dissemination. In addition, some non-target organisms (eg cyanobacteria) may be exposed to antibiotics, which may have indirect

negative effects on the aquatic food [47, 58, 69].

The origin and possible effects of human and veterinary drugs on aquatic and terrestrial organisms are relatively new topics. However, in recent decades, a large number of studies have been published indicating the varied effects of drugs on organisms and the occurrence of drugs in different environmental areas on a global scale. It is now recognized that the environmental impact of pharmaceuticals is a global issue and not just a problem in developed countries. The general public, industry, research or regulatory authorities, do not want bioactive drugs to end up in the environment and therefore potentially in their drinking water. Therefore, the amount of pharmaceuticals in the environment needs to be minimized using all available strategies. Promising approaches such as ERA play an important role in minimizing problems before drugs enter the environment. These strategies need to be strengthened and adapted to minimize the amount of pharmaceuticals entering the environment [31, 39, 54].

The contamination of the environment by pharmaceutical residues presents a critical challenge to both ecosystem health and human well-being. The widespread presence of these substances in water, soil, and air underscores the need for a more comprehensive understanding of their environmental fate and effects. Current risk assessment approaches, which often examine individual compounds in isolation, are inadequate in addressing the complex interactions and cumulative risks posed by pharmaceutical pollutants, especially when combined with other environmental contaminants. Furthermore, the potential dangers of pharmaceutical transformation products, which may exhibit greater toxicity or persistence, remain underexplored. To address these concerns, a paradigm shift is required in environmental risk assessment, incorporating multi-substance interactions, long-term ecological impacts, and the effects of transformation products. The development of robust mitigation strategies—such as advanced waste treatment technologies, improved pharmaceutical disposal practices, and more stringent regulatory frameworks—must be prioritized. By adopting a more integrated, precautionary approach to pharmaceutical contamination, we can better protect ecosystems and human health from the growing threat posed by these persistent pollutants. Future research and policy initiatives should focus on improving our understanding of these substances, developing innovative solutions to reduce their environmental impact, and ensuring sustainable management practices for pharmaceuticals [28, 42, 46].

Regarding environmental risk assessment, (i) include the environment in the risk-benefit analysis of pharmaceutical products for human use, (ii) improve risk management capabilities, (iii) collect data on existing pharmaceutical products, and (iv)



improve environmental availability risk. These assessments represent some important next steps. The biological effects to environmental exposures promise interesting results, although very few studies have been conducted on wild animals or caged organisms, such as in the wild or in ecologically significant environments. This may be due to the lack of analytical method protocols as well as the variety of pharmaceutical structural features that are not easy to handle but need to be taken into account.

Various policies need to be implemented throughout the life cycle of pharmaceutical products, including source-oriented, consumer-oriented and waste management-oriented activities. The most effective solutions must be implemented at the source, before drugs enter the environment. These measures include rational drug consumption, prescribing more environmentally friendly drugs and developing harmless and easily biodegradable drugs. Improved disease prevention, personalized medicine, improved package sizes, and PC redistribution markets may go some way to avoiding drug waste. The next step is to prevent unavoidable waste from entering the environment. Therefore, correct collection and disposal of is critical and must be adapted to national and local conditions. Finally, education of health care professionals and the public, as well as partnerships between environmental scientists and clinicians, paharmacists are important at all stages of the pharmaceutical product life cycle. All joint efforts must be guided by a One Health approach to combat pharmaceutical waste and improve the health of people, animals and the environment, which are closely linked. To reduce contamination levels when consuming medicines should be: Creation of a system for collecting drug waste generated by the population; Conducting awareness-raising work with the population, employees of healthcare institutions and other target groups on the topic of environmental pollution by drug waste; Taking into account environmental factors when choosing and prescribing treatment. At the same time, there is no need to put environmental protection above the human need for treatment; Development and implementation of wastewater treatment systems. It should be taken into account that urban wastewater has an unstable composition in terms of names and concentrations of drugs. A higher priority is to prevent drug residues from entering the city sewer system [55, 57, 68].

The widespread contamination of the environment by pharmaceutical residues represents a significant and escalating global concern. These pollutants infiltrate water bodies, soil, and even air, leading to severe ecological disruptions, biodiversity loss, and potential long-term health risks for humans and wildlife. Their persistence, bioaccumulation, and role in fostering antimicrobial resistance further complicate their impact, demanding urgent and comprehensive intervention. Despite growing awareness, existing mitigation measures remain insufficient, necessitating a paradigm

shift toward more sustainable pharmaceutical production, improved waste disposal, and enhanced regulatory frameworks.

To effectively address this crisis, a multi-pronged approach is essential. Advanced wastewater treatment technologies, such as membrane filtration, bioremediation, and oxidation processes, must be widely implemented to reduce pharmaceutical contaminants before they enter natural ecosystems. Strengthening regulations and global policies is critical to ensuring stricter controls on pharmaceutical manufacturing, prescription practices, and disposal methods. Additionally, promoting public awareness and responsible medication disposal can play a key role in minimizing environmental contamination at its source.

Risk assessment frameworks must also be refined to better understand the complex interactions of pharmaceutical residues within ecosystems. Integrating cutting-edge analytical techniques, predictive models, and interdisciplinary research will enable more accurate hazard evaluation and inform targeted mitigation strategies. Furthermore, the development of green pharmaceuticals – biodegradable drugs designed to minimize environmental impact – offers a promising long-term solution to this issue.

Addressing pharmaceutical pollution requires collective action from governments, researchers, healthcare providers, industries, and the general public. By adopting a proactive, science-driven approach, we can mitigate the adverse effects of pharmaceutical contamination, protect ecological integrity, and safeguard public health for future generations. The time to act is now—delaying intervention will only exacerbate the environmental and health consequences of unchecked pharmaceutical pollution.

The problem is further complicated by the fact that exposure to only one drug or toxic substance at a time is likely to be a rare event. Laboratory studies have shown that mixtures of just a few compounds have effects on ecosystems, but it is unknown what happens in the wider environment. Most organisms are constantly exposed to various substances, the concentrations of which vary little in time and space. Therefore, the limits of your tolerance depend on the duration of exposure to chemical and non-chemical stressors, many of which have the same mechanism of action and whose effects can result in additive effects. Thus, risk estimates that ignore possible cumulative drug effects will almost certainly lead to significant underestimation of risk [36, 39, 57].

Increasing demand for global water sources will likely lead to increased indirect and direct water reuse in the future. Drinking water is a direct route to the human body, including drugs and other contaminants that may be present there. Advanced water treatment technologies such as granular activated carbon (GAC) and reverse osmosis (RO) can remove drugs from drinking water until they are invisible, but these processes

are not widely used. Due to the lack of appropriate technology and the need for significant economic investment, municipal wastewater is never treated in this way. In addition, large-scale monitoring programs to test these compounds would be extremely expensive and time-consuming due to the large number of different compounds and the diversity of their properties and effects [14, 28, 59].

Given that the extent and consequences of the presence of drugs in aquatic environments is largely unknown, more research is needed before a clear picture of the true nature and importance of the problem can be formed. Therefore, it would be unwise to claim that these compounds have significant environmental impacts until convincing evidence is available. To this end, future emphasis should be on adequate and sufficient scientific knowledge to determine occurrence, exposure, sensitivity and consequences in order to make informed decisions regarding human health and the environment [14, 19, 68].

When evaluating drugs, benefits to human health must take precedence over potential harm to the environment. Therefore, it may be beneficial to focus on reducing or eliminating problems at their source by developing clearer drug labeling and more effective guidelines for the disposal of pharmaceutical compounds by patients and healthcare professionals. The potential benefit of this approach would be improved consumer health (by minimizing the consumption of active substances) as well as reduced healthcare costs. Given the enormous importance of the pharmaceutical industry to both human health and the economy, any increased control could have serious economic and social consequences. If pharmaceuticals turn out to be problematic contaminants, collaboration between health professionals and environmentalists will be mutually beneficial, as much research remains to be done before the problem can be fully understood [13, 62, 76].

Ecology, which directly affects the health of society, is one of the most important factors in the modern era of civilization. Factors affecting population health are the biggest social problem. The health and illness of society are determined by the environment in which a living organism is located and develops. Man is a biosocial being. Environmental factors affect organisms in different ways. It can be irritating, limiting or determining the existence of the organism in specific conditions; the danger of disturbing the natural balance is associated with pollution of the atmosphere, water, soil and food products with nitrates, pesticides, radionuclides and other harmful substances. The environment is saturated with psychotoxins, chemical waste, biological damaging agents (drug-resistant bacteria, fungi, viruses, parasites resulting from mutations). causing death of plants and animals and illness in humans. Therefore, it is clear what a great danger an environmental disaster poses [39, 47, 56].

An environmental disaster has a direct impact on public health. Society and the environment are in constant relationship. Therefore, the health and illness of society are determined by the environment in which a living organism is located and develops. Factors affecting population health are the biggest social problem.

There is a danger of disturbing the natural balance. Pollution of the atmosphere, water, soil and food products with nitrates, pesticides, radionuclides and other harmful substances leads to the death of plants and animals and diseases of people. Therefore, it is clear what a great danger ecological disaster causes [34, 47, 82].

The most serious consequence of biosphere pollution is the manifestation of genetic disorders. As a result of increased radioactive background and chemical pollution of the environment, the number of pathologies, malignant tumors, mental disorders, etc. increases. number. Mutagens in the form of chemical compounds, ionizing radiation penetrate the cell and cause disruption of the genetic program, causing mutations in somatic cells [37, 46, 52].

Diseases and conditions caused by climate change will also impact demand in the healthcare system and pharmaceutical industry. The pharmaceutical industry may see a change or increase in demand for drugs. For example, an increase in temperature can trigger asthma due to increased pollen levels. This increase in asthma cases will, in turn, lead to an increase in demand for medications to control asthma. Changing demand for medicines could create opportunities for the pharmaceutical industry to make the most of climate change and incorporate green chemistry principles into the development of new medicines [65, 69, 78].

The production and consumption of pharmaceuticals results in the presence of active pharmaceutical ingredients (APIs) in the ecosystem. Active ingredients enter the marine and terrestrial environment through release from manufacturing facilities, into wastewater after consumption of the drug in question, or through improper disposal of expired or unused drugs. The use of medicinal products in veterinary medicine may also result in the release of active substances into the environment, for example through the use of wastewater for irrigation, agriculture, aquaculture or the disposal of animal carcasses treated with veterinary drugs. The presence of APIs in the ecosystem can have a number of side effects, such as: Bacterial resistance to antibiotics and changes in the activity of digestive glands in marine life, reproductive toxicity in amphibians and feminization of fish. Another striking example of the impact of APIs on the ecosystem is the sharp decline in vulture populations due to the presence of diclofenac residues in cattle carcasses [81, 89, 96].

Based on data from the World Health Organization, an analysis of the impact of environmental factors on human health was published, which revealed large

differences between countries and showed that human health can be improved by reducing exposure to environmental factors such as: pollution, ultraviolet radiation, noise, climate, ecosystem change and dangerous work environment. More than 10% of deaths in 23 countries of the world are related to the environment with two risk factors: 1) polluted air and water; 2) low sanitary and hygienic indicators.

The industrial agriculture, municipal wastewater treatment, and the introduction of municipal sewage sludge (biosolids) as major sources of pharmaceuticals and personal care products in the environment. To compensate for this, indicators of veterinary antibiotic use are provided by both the agricultural industry and interested scientists. Personal care products are divided into fragrances and musks, cleansers and disinfectants [14, 42, 56].

Pharmaceutical products intended for human use are included in the UNESCO list of emerging pollutants. Their identification and elimination represent a decisive step towards achieving the goals of the Sustainable Development Program. Concentrations of drugs found in the environment are below therapeutic levels. In waters receiving treated wastewater, drugs are found at concentrations below 100 ng/L. These low concentrations make it difficult to assess their toxic effects on ecosystems and human health. The vast majority of pharmaceutical products have not been adequately studied regarding their long-term toxic effects, presence and fate in the environment. However, certain classes of drugs, such as beta blockers, antibiotics, anticancer drugs, and endocrine disruptors, have been shown to have devastating effects on the ecosystem, including increased mortality and disruption of the physiological and reproductive functions of aquatic species. Moreover, since it is impossible to separate humans from nature, this has devastating consequences for human health. However, the extent of the problem remains largely unknown due to the large number of drugs available and difficulties in assessing the risks associated with exposure to multiple compounds at low doses over long periods of time. The drugs on the market pose a potential risk to the environment. Although there is no established method for detecting all pharmaceuticals entering an ecosystem, some are widespread and have been shown to have negative impacts on ecosystems. These groups include hormones, antibiotics, antidepressants, anti-inflammatory and pain relievers, beta blockers and anti-cancer drugs [24, 29, 45].

Antibiotic resistance is a global public health problem, especially given the increased use of antibiotics during the COVID-19 pandemic, which has led to the exhaustion of the last line of antibiotics. It has been established that the use of antibiotics in medicine, veterinary medicine and agriculture is associated with pollution of various parts of the environment, which has contributed to increased antibiotic



resistance and the occurrence of ecotoxicological effects. Failure to properly dispose of antibiotics through sewers by patients also poses a growing environmental threat to public health. Additionally, high levels of antibiotic contamination after long-term exposure can negatively impact human health, especially in patients with chronic diseases such as obesity, diabetes and asthma [36, 54, 87].

Antidepressant contamination has increased significantly worldwide during the COVID-19 pandemic. To this day, antidepressants can be found in urban and suburban water supplies. Many aquatic animal species bioaccumulate various antidepressants in their tissues, resulting in cytotoxicity, genotoxicity, impaired stress response, weight and length gain/loss, and liver and kidney damage. Because there is significant overlap between human and animal environments, exposure to antidepressants (sertraline, fluoxetine) in the environment also affects human neurological development and various mental illnesses. Although psychotropic drugs are usually present in wastewater at subtherapeutic levels, they can have biological effects at low doses, and combinations of multiple psychotropic drugs are often present, especially in the environment, increasing the risk of toxic effects [38, 45, 52].

Pharmaceutical compounds are used in modern society for various beneficial purposes, but at the same time, the pharmaceutical industry releases highly toxic pollutants into the environment either directly or after chemical modification. Additionally, pharmaceutical compounds can enter the environment through various routes such as treated wastewater discharge, seepage into landfills, sewer pipes, animal waste, etc. Although a number of physical and biological processes occur in an aquatic ecosystem, they can lead to depletion of many lead to pharmaceutical compounds. Traces of human and veterinary drugs and their metabolites were found in several bodies of water. Objects such as surface water, groundwater and drinking water sources. Several industries, including pharmaceuticals, chemicals, paints, etc., are rapidly developing in India, with wastewater being discharged into water bodies either directly or after partial treatment. Pharmaceutical compounds have been found to be released into the environment and may be considered environmental pollutants. Several pharmaceutical plants have been found to be sources of much higher concentrations in the environment than those resulting from drug use. Typically, the pharmaceutical industry generates a large amount of waste during production and service. Drugs have been found in sewage treatment plant wastewater and drinking water. Trace amounts of drugs in drinking water can have serious adverse effects on human health and aquatic life over long periods of time, even when drug concentrations in drinking water (in the nanogram per liter range) are orders of magnitude below the minimum therapeutic dose [15, 29, 47].

Pathways through which drugs may be exposed to the environment include manufacturing plants and hospital wastewater, land use (eg, biosolids and water reuse), etc. Wastewater treatment services are not always successful in removing active chemicals from wastewater. Therefore, drugs enter the aquatic environment, where they have a direct effect on aquatic organisms and can be absorbed into the food chain.

Higher concentrations of antibiotics can lead to changes in microbial community structure and ultimately affect food chains. Nonsteroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen, naproxen and diclofenac, are widely used and therefore often found in wastewater systems, both surface and groundwater. Ibuprofen, ketoprofen, naproxen, indomethacin, diclofenac, acetylsalicylic acid and phenazone were detected in the surface water system. However, after clofibric acid, the most common drugs found in aquatic environments are diclofenac, ibuprofen and propyphenazone. Diclofenac has also been shown to be highly toxic to vultures and livestock. NSAIDs such as ibuprofen, naproxen, and aspirin are the most commonly used medications and are often found in effective amounts in municipal wastewater [19, 48, 57].

Many pharmaceutical companies are responsible for the generation of toxic wastewater during their operations. The wastewater generated from these facilities contains solids, biodegradable and non-degradable organic compounds, etc. Pharmaceutical wastewater provides basic information about the reliability of the aquatic environment of the rivers and streams into which it is discharged. An important indicator of industrial wastewater contamination is the oxygen content of chemical oxygen demand (COD) and biological oxygen demand (BOD), with nutritional status measured by the amount of nitrogen and phosphorus in the wastewater.

Long-term exposure of coastal biota to lower concentrations of complex drug mixtures can result in acute and chronic damage, behavioral changes, tissue accumulation, reproductive impairment, and inhibition of cell proliferation. Several studies have shown that fish exposed to sewage may experience reproductive problems. In addition, fish exposed to trace amounts of contraceptive drugs in the concentration range found in the environment show dramatic reductions in reproductive success, suggesting that population-level effects may be possible [42, 48, 84].

Around the world, the drug residues in the environment poses risks to humans, aquatic animals and wildlife and is becoming a major concern for both regulatory authorities and the pharmaceutical industry. Significant progress on this issue is simply not possible with the current limited knowledge about the transport, fate, and environmental impact of pharmaceuticals. It is necessary to take into account the possible potentiating effects of different drugs acting on the same receptors. Risk assessment of pharmaceutical chemicals involves identifying the hazards associated

with each step and assessing the risks associated with those hazards.

Currently, pharmaceutical compounds are regularly released into the environment in extremely large quantities, and the current emission control system is unable to control untreated or partially treated pharmaceutical wastewater. The effects of drugs permeate and impact ecosystems, biota and humans. Adverse health effects on humans, aquatic animals and livestock should be investigated through careful toxicological and safety studies. Serious efforts are needed to reduce this problem, and appropriate regulations are needed to monitor and control it. Water quality guidelines in India should include analysis of the most commonly used pharmaceutical compounds in drinking water sources. In addition, pharmaceutical industrial wastewater treatment plants need to implement new corrective measures to prevent long-term environmental and health risks [7, 83, 102].

Water sources contaminated with pharmaceutical contaminants are found in agricultural lands, surface water, groundwater, and drinking water. Water flows to plants, which affects the quality of soil and crops grown using this contaminated water. Pharmaceutical contaminants are considered external environmental factors that affect crop quality. Drugs enter plants as pollutants, either through the soil or the air. Pollutants enter the plant from the soil through the roots and are transported through the stem. Plants also absorb pollutants from the air, and leaves can absorb pollutants from the atmosphere. Pharmaceutical contaminants such as B-lactams, aminoglycosides, macrolides, tetracyclines, sulfonamides, herbicides including sulfonylureas, triazines, imidazolinone, phenylurea and bisphenol (BPA) have been found to cause toxicity in plants. Polychlorinated biphenyls (PCBs) affect plant growth, reproduction and productivity [8, 39, 67].

Most pharmaceuticals we use are excreted via urine and feces in unchanged form or as metabolites and eventually end up in the drain. The pharmaceutical residues can then reach lakes, the sea and groundwater, despite passage through wastewater treatment plants, as the wastewater treatment plants are not built to clear pharmaceuticals. Pharmaceuticals affect biological processes. They are also often designed to withstand biodegradation and can therefore remain in the environment for a long time. There are reports of effects on fish, as well as that measured concentrations of antibiotics in wastewater treatment plants can select for antibiotic resistance.

Chemicals play an important role in healthcare as they can be used as disinfectants, cleaning agents, laboratory reagents, sterilants, pesticides, pharmaceuticals, and in medical devices and equipment. They also offer great animal welfare benefits. However, there is growing awareness and concern about the consequences of mishandling drugs and chemicals on human health and the

environment [9, 47, 88].

Pharmaceuticals are also biologically active substances specifically designed to provide pharmacological effects on living organisms. They affect the health of wildlife and ecosystems if not managed in an environmentally sound manner.

Active pharmaceutical ingredients (APIs) are the biologically active components of a drug. These APIs are sold to pharmaceutical companies that manufacture end products for patients around the world. More than 5,000 active pharmaceutical ingredients are used in prescription, over-the-counter and veterinary products worldwide. From a chemical and waste management perspective, environmental and health issues in this sector are mainly related to the release of pharmaceuticals into the environment: Waste ends up in rivers, lakes and underground aquifers. In addition, when used in livestock production and when manure is used as fertilizer, veterinary drugs end up in the soil and environment. This leads to soil contamination and biomagnification due to leaching of drugs into food crops [12, 58, 79].

Sources of drug release into the environment include direct emissions from drug manufacturing, patient and animal feces, aquatic agriculture, and disposal of unused or expired drugs. Medicines designed to degrade slowly, or even non-degrade to resist chemical breakdown as they pass through the human or animal body, pose a particular risk if ingested, stored, or distributed into the environment. When released into the environment, the biological activity of persistent pharmaceutical pollutants in the environment can have direct negative effects on non-target organisms such as wildlife and have long-term impacts on the health and sustainability of ecosystems. The latter occurs through population-level reproductive effects that persist into future generations of non-target organisms. Pharmaceutical contaminants that are persistent in the environment are frequently and increasingly used in consumer products. However, significant gaps remain in knowledge about the environmental and health impacts of these pollutants [41, 48, 95].

Some pharmaceuticals have been found in low concentrations in drinking water, which is a warning sign that the current handling of pharmaceuticals may lead to health and environmental problems in the future.

Access to healthy water is a prerequisite for good health. Since society's use of chemicals, including pharmaceuticals, is continuously growing, the risk is also increasing that these chemicals will return to us in our food and water supply through nature's ecocycle.

There are little knowledge of the long term effects that continuously supplied trace quantities of pharmaceuticals and other chemicals could have on our development, our ability to resist disease and wellness in general. Therefore caution is

advisable. The pharmaceuticals in nature can cause health problems. According to the precautionary principle, measures can be taken if there is reason to believe that a product or a method of production involves unacceptable risks to the health of human beings, animals, plants and the environment – even if there is no definitive scientific proof of such an effect [9, 65, 79].

Drug residues are found in various environmental components around the world, and there is growing concern about the harm they may cause to human health and the environment. In nature, drug residues were found in urban wastewater, rivers and lakes. Effective measures must be taken to prevent further contamination of the environment by drugs. First of all, it is necessary to create a system for collecting drug waste from the population. Undoubtedly, drugs enter the environment during the production process through wastewater from pharmaceutical plants, municipal wastewater through natural human excretion, wastewater and manure from the use of veterinary drugs and as a result of improper handling of drug waste [19, 36, 77].

The review defines each of these sources and steps that can be taken to reduce drugs' environmental impacts. In the European Union, since 2004, the obligation to organize a system for collecting drug waste from the population has been established. For the successful operation of such a system, information work with the population about how drugs affect the environment and how to properly dispose of them is important. Residents of all European countries can bring drug waste to a pharmacy or hazardous waste collection point. However, in some countries there is a lack of widespread awareness-raising, which leads to inefficient collection systems and most waste ends up in the trash or drained into sewers. In some countries, drug waste generated by medical and pharmaceutical organizations is neutralized in pharmacies, clinics, hospitals and manufacturers. At the same time, pharmacies and hospitals have the right to transfer expired medicines to the manufacturer [36, 57, 81].

In most countries where the system operates successfully, the costs of collecting and neutralizing drug waste are shared by pharmaceutical companies, drug manufacturers and local authorities. The main problem is the very existence of unused drugs. So, generally many patients buy more medicines than they need. The best way to reduce their number is seen in optimizing the practice of prescribing drugs, so that only the necessary amount of drugs is prescribed, giving preference to more environmentally friendly ones, as well as improving information interaction between doctors and patients. The pharmaceutical industry must also provide for the production of drug packaging adapted to various treatment regimens [10, 19, 64].

Every participant in the drug supply chain, from the pharmaceutical industry to the patient, plays an important role in reducing the environmental impact of



pharmaceutical activities. The International Pharmaceutical Federation has highlighted the different roles that each person plays in the pharmaceutical supply chain to minimize the environmental impact of pharmaceutical products. The pharmaceutical industry plays an important role in the environmental impact of pharmaceutical products.

Educating pharmaceutical personnel and the public is an important aspect of helping to create a healthy environment and reduce activities that contribute to climate change. The implementation of green practices in the pharmaceutical sector is already included in the curricula of EU Countries countries universities. Pedagogical input helps to recognize the importance of such practice early in professional development.

Consumer education is also important as it plays an important role in reducing the amount of drugs in the environment. Consumers should be discouraged from storing medications to avoid wasting them when not in use. They should also be taught how to properly store and dispose of unused and expired medications that may end up down the drain [13, 28, 39].

The world's population is aging, which will lead to an increase in drug use. Various measures need to be taken to minimize the release of active pharmaceutical ingredients into the environment and reduce the carbon footprint of the pharmaceutical sector. Small contributions from many people can synergistically have a positive impact on the environment [7, 18, 48].

There are several sources of release of active pharmaceutical ingredients (APIs) into the environment. The main ones are: wastewater from cities, hospitals, pharmaceutical plants and landfills. The vast majority of the active pharmaceutical ingredients (API) of drugs taken orally is excreted in the urine of animals and humans. Some pollution comes from the use of veterinary drugs in livestock and fish farming. However, it is not yet possible to evaluate this contribution, because there is no control and accessible reporting of the use of veterinary drugs. The most vulnerable to the effects of active pharmaceutical ingredients (APIs) are amphibians, fish, some animals and birds [48, 54, 69].

The main source of drugs entering the environment is wastewater from pharmaceutical enterprises (from product washing, waste acidic and alkaline wastewater, wastewater from cleaning equipment and production facilities, etc.) and liquid waste that is allowed to be discharged into the sewer system. Currently monitored parameters in pharmaceutical wastewater are biological oxygen demand (BOD), chemical oxygen demand (COD), total suspended solids, ammonia and ammonium ions, phosphates, chlorides, sulfates, petroleum products, iron, anionic surfactants and pH value. This list may include other chemical compounds, including active pharmaceutical ingredients (APIs), but their content is not regulated or

controlled at this time. Currently, the countries of the European Union have prioritized the most environmentally stable active pharmaceutical ingredients (APIs) - diclofenac, hormonal drugs of the estrogen group (ethinyl estradiol), antibiotics of the macrolide class (erythromycin, clarithromycin, azithromycin) and etc [29, 57, 62].

Assessment of environmental risks of both original and generic drugs. In European countries, for some drugs such an assessment is carried out, as well as an assessment of the level of resistance, bioaccumulation potential and toxicity. Currently, providing information about environmental hazards when registering drugs in the countries of the European Union is voluntary. In some countries has been created an online database of drugs, which describes their environmental risks and expanding the responsibility of drug manufacturers throughout the entire cycle from production to neutralization [84, 88, 95].

After drugs enter the body, they are destroyed, neutralized, metabolized and converted into new compounds. However, some of them are excreted unchanged or in the form of metabolites, ending up in the sewer system. Municipal wastewater treatment does not involve removal of APIs. Some of them are concentrated in sewage sludge from treatment plants, which is stored in filtration fields, while the rest ends up in rivers. The Challenges in this matter are also hospitals, where there is a high level of drug consumption. In the absence of an established system for collecting drug waste generated by the population, it either ends up in the sewer or is thrown into the trash. From landfills, drugs can be carried by animals, birds, or migrate into the soil and groundwater.

To raise animals and fish on an industrial scale, hormonal drugs, antibiotics and other drugs can be used, which can be excreted from the animal's body naturally. Hormones can be used in veterinary medicine and animal husbandry to stimulate the development and growth of animals, improve fertility, digestibility of feed, accelerate puberty, regulate the timing of pregnancy, etc. According to studies in some countries, antibiotic residues were found in manure, in plants grown in fields fertilized with manure, in soils, and in small quantities in groundwater. The use of veterinary drugs in should be regulated by veterinary and sanitary rules for the use, sale and storage of veterinary drugs.

European experience in collecting hazardous waste from the population shows that waste collection is carried out effectively if such collection is organized by a company specializing in the collection of hazardous waste. The same practice works in our country. In the EU, pharmacies are considered only as an area for the installation of appropriate containers and containers for collecting hazardous waste from the population. The containers themselves are installed by specialized companies

interested in collecting hazardous waste. It is inappropriate to oblige pharmacies, healthcare institutions or other trade organizations to organize the collection of drug waste from the population [47, 59, 76].

Pharmacies and medical institutions are places where consumers can obtain the most complete information about drug waste, since these organizations employ personnel with the relevant knowledge. In the country, many pharmacies themselves are located on the territory of various retail facilities, so there may not be places in pharmacies to install a special container for collecting drug waste. When determining places for collecting waste from the population, it is necessary to comply with the criterion of step-by-step accessibility of such places from the places of residence of citizens. In this regard, retail facilities should also be considered as places for installing special containers for collecting drug waste. The decision to organize collection points for drug waste from the population in pharmacies should be made by Health care institutions in every countries.

In the vast majority of countries, all drug waste collected from the population is sent for incineration. At the same time, pharmacies, for example, in Sweden and Lithuania, can only accept medications without packaging, because it belongs to secondary resources and must be sent for recycling. Low-temperature, medium-temperature (up to 850°C) and high-temperature (at least 1200°C) combustion is used for waste. Hazardous waste, which includes most drugs, cannot be burned at low temperatures. At medium temperatures it is possible in limited quantities and in the absence of high-temperature combustion technology. Cytostatic drugs for cancer treatment can only be burned at temperatures above 1200°C, but the generation of such waste in household use is unlikely. Currently, there is a steady trend towards a decrease in the number of thermal installations for the neutralization of pharmaceutical waste. Incineration of waste is contrary to three principles of international law: precaution, prevention and limitation of transboundary effects. In Europe, resistance to waste incineration manifests itself in the form of the introduction of alternative technologies. Any combustion method requires monitoring of pollutant emissions and the resulting ash. An alternative to conventional methods of thermal treatment of pharmaceutical waste are technologies that provide for the preliminary decomposition of the organic component of the waste in an oxygen-free atmosphere (pyrolysis). When carrying out microwave pyrolysis with heating using microwave waves, toxic gaseous products are converted into less dangerous ones.

In countries where there are no incineration plants or their use is limited geographically, drug waste is disposed of. The main disadvantage of this method is the high probability of soil and groundwater contamination. According recommendations

of the World Health Organization, only non-hazardous drug waste (vitamins, herbal-based drugs, biodegradable drugs) can be sent to the landfill. Hazardous waste, including cytotoxic drugs, must be pre-sealed, i.e. placed in a metal capsule and filled with plaster and cement [46, 62, 85].

Liquid waste of drugs classified as non-hazardous (syrups, herbal preparations, solutions based on salts, amino acids, lipids or glucose) can be poured into the sewer after diluting with water. It is necessary to prevent the discharge of large quantities of disinfectants into the sewer system, because they can affect the quality of biological wastewater treatment. Discharge of drugs that are persistent in the environment, capable of biological accumulation and have toxic properties into the sewer system leads to environmental pollution with active pharmaceutical ingredients. According to studies conducted in many countries, existing wastewater treatment systems do not eliminate such pollution and drug residues are found in wastewater cleaning sludge, and to a greater extent in water after cleaning, which is discharged into natural watercourses.

Some drugs pass through the human body, exit unchanged or in the form of metabolites, while maintaining their stability in wastewater and the environment for a long time. In addition, improper disposal of medications and disposing of them down the drain increases the concentration of hazardous APIs in water. Wastewater from pharmaceutical plants is also discharged into the city sewer system after local treatment. The active pharmaceutical ingredients are present in municipal wastewater above detection limits. Traditional mechanical and biological wastewater cleaning methods are unable to neutralize the active pharmaceutical ingredients in water. The issue of purification efficiency, the formation of drug metabolites and their behavior, the interaction of some drugs with others is still under study. Among the methods being developed and implemented in the countries of the European Union one can highlight physicochemical methods, aerobic/anaerobic biological cleaning in membrane bioreactors. Effective technologies for purifying wastewater from medicinal components include oxidation with ozone or hydrogen peroxide and the use of carbon filters. However, such technologies are currently expensive to implement and use. At the same time, more and more attention is being paid to preventing the entry of drugs into wastewater, including during production. The main problem is the very existence of unused drugs [15, 19, 22, 58].

One of the most obvious sources of uncontrolled release of drugs into the environment may be wastewater and atmospheric emissions from enterprises producing finished drugs and pharmaceutical substances. The environmental safety of such production should be usually regulated by law. However, accidental releases of

drugs into the environment or those that violate existing norms and rules that occur in industry, are nevertheless not systematic. Moreover, there is a general trend towards a reduction in the environmental load on the part of pharmaceutical production, primarily in developed countries of the world, due to a consistent increase in the technological effectiveness and organization of the production process, the introduction of increasing standards of quality and environmental safety, and control by authorized government agencies. It is also necessary to take into account that pharmaceutical production is localized geographically and if an accident occurs at the enterprise or there are violations of environmental legislation, then such emissions are exclusively local in nature and pose a danger only to specific regions. Other sources of drugs that are practically uncontrollable and are formed mainly by people who use drugs for medical purposes, as well as in animals, pose a great danger to the environment [55, 62, 84].

For the most part, drugs are xenobiotics, and many of them are metabolized in the human body. The task of metabolism, as a rule, is to impart polarity to lipophilic substances in order to facilitate subsequent excretion. Metabolic parameters are individual for each substance and depend on gender, race, age and physiological state of the human body. There are two phases of metabolism, the numbering of which does not necessarily reflect their actual sequence. In the first phase of metabolism, a redox or hydrolytic transformation of the molecule occurs, increasing its polarity. In the second phase of metabolism, the xenobiotic is conjugated with endogenous molecules that improve the transport properties of the metabolite. During metabolism, inactivation of the active substance often occurs, which can lead to its inability to further exert a biological effect. However, many drugs are either not subject to metabolism or are subject to it only to some extent. And this leads to the fact that the active molecule of the active substance is excreted unchanged either in the urine or in the feces and is capable of further exerting a biological effect. In addition, as research results show, glucuronide transport complexes of active molecules of some drugs, formed during the second phase of metabolism, are easily destroyed during sewage treatment processes and release unchanged active substance into the aqueous phase or sewer sludge. We can also mention the route of release of drugs into aquatic environments due to their transport through the skin or leaching of drugs for external use during swimming in open waters. But from the point of view of quantitative indicators, this path is of little significance [39, 49, 83].

During metabolism, inactivation of the active substance often occurs, which can lead to its inability to further exert a biological effect. However, many drugs are either not metabolized or only to some extent. And this leads to the fact that the active molecule of the active substance is excreted unchanged either in the urine or in the



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We can also mention the route of release of drugs into aquatic environments due to their transport through the skin or leaching of drugs for external use during swimming in open waters. But from the point of view of quantitative indicators, this path is of little significance.

The increasing the availability of drugs, for the general development of health care systems, the consumption of drugs for medical purposes increases and, as a result, their content in the environment increases. This process is poorly managed and poses a potential danger to human health and other biological organisms. Contamination of the environment with drug residues has a global character and is actively studied in the developed countries of the world. However, this problem remains insufficiently worldwide [26, 39, 57, 72].

The best ways to reduce their number are to optimize the practice of prescribing drugs, so that only the required amount of drugs is prescribed, giving preference to the least environmentally hazardous ones, as well as improving information interaction between doctors and patients. The pharmaceutical industry must also consider producing drug package sizes tailored to different treatment regimens. One key measure is to encourage the pharmaceutical industry to develop harmless drugs that quickly break down into harmless compounds in the environment. For example, currently in European countries, when registering a new drug, environmental characteristics such as ecotoxicity, biodegradability are indicated.

The comparing drugs that are equally safe and well suited for treating a patient, it is recommended to take into account, in addition to their pharmaceutical properties, their environmental impact. To do this, recommend using environmental drug classifiers.

Large quantities of nonsteroidal anti-inflammatory drugs, including acetaminophen, acetylsalicylic acid, ibuprofen, diclofenac, and naproxen, are significant contributors to environmental pollution, especially because they have been detected in nanogram and microgram quantities in soil, wastewater, surface water, and drinking water, groundwater. These drugs have chronic ecotoxic effects because their stable chemical structure makes them very resistant to biological changes in the environment. It is now known that they primarily damage the organs of invertebrate and vertebrate animals, cause oxidative stress and interfere with the activity of detoxification enzymes.

These drugs may also cause cardiovascular effects, hepatotoxicity and affect oocyte maturation through unknown mechanisms [5, 19, 42, 49].

Beta blockers are very long-acting drugs that are toxic to the environment. Although there is no data on their adsorption in the environment, these drugs are known to have moderately high water solubility and are present in surface waters at  $\mu\text{g/L}$  concentrations. These compounds are extremely resistant to hydrolysis, bioavailable and mobile in the environment. Therefore, its accumulation in the environment can have unexpected consequences for many living organisms. According to European Union Directive, metoprolol and propranolol are compounds harmful to aquatic organisms. This is evidenced by the results of tests with green algae.

Anticancer drugs interfere with cell growth and division, and when released into the environment, they disrupt the ecosystem, impair fertility and cause significant genetic changes in living organisms. Anticancer drugs are prescribed in smaller quantities, but their effects are destructive even at concentrations in the  $\text{ng/L}$  range and include mutagenic, carcinogenic and teratogenic effects on aquatic life. Cytostatics are frequently found in the pharmaceutical industry and hospital wastewater due to improper use and disposal. The detection rate of anti-cancer drugs in oncological hospitals wastewater is big amount and cisplatin is considered one of the most dangerous drugs. The presence of cisplatin in water, even at concentrations of  $\text{ng/l}$ , can have a toxic effect on aquatic flora and fauna [28, 47, 59, 74].

Environmental pollution caused by pharmaceuticals is a complex public health problem that is scientifically controversial and affects multiple stakeholders with different interests and at different organizational levels: governments, non-governmental organizations, academic institutions, manufacturers, industries and families.

In keeping with the idea of protecting the environment, the pharmaceutical industry must develop promising concepts to minimize secretions while still ensuring sufficient pharmacologically effective concentrations in the patient. The potential of developing new pharmaceutical products that are more biodegradable and less harmful to the environment. There are already some examples of the development of greener pharmaceuticals, such as glufosfamide and green drug delivery systems. Scientists are currently developing an effective and environmentally friendly version of the antibiotic ciprofloxacin, a very stable drug. Using computer modeling, an existing active ingredient is analyzed and theoretically modified to improve biodegradability and reduce toxicological effects. The most promising candidates have been synthesized and tested *in vitro* [37, 46, 81, 89].

Limited consumer awareness of best recycling practices weakens their influence on recycling practices in many countries. Information campaigns can increase

awareness and use of environmentally friendly pharmaceutical waste disposal methods in households. A good example is the Meds disposal campaign, a European initiative jointly coordinated by several European health and supply chain organizations and supported by media campaigns in different languages. The aim of the initiative was to combat the negative impact of mishandling of pharmaceutical products on the environment, raising consumer awareness of correct disposal routes and collection systems in a number of European countries.

In addition, greater awareness and behavior change can be achieved through specific recycling instructions on the product's outer packaging or information leaflet, which are mandatory in EU countries. In addition, eco-labels that reflect the environmental impact of various pharmaceutical products can influence consumer choice and awareness, as well as help physicians make prescribing decisions. Instructions on how to properly dispose of medications should also accompany medication dispensing at regular intervals. Pharmacists can play a key role in educating their patients about proper medication disposal.

Human activity has the most negative impact by releasing pollutants. Pollutants are considered to be all those substances that enter the atmosphere, soil, natural waters and cause disruption of the biological, physical or chemical processes taking place there. Radiation and thermal radiation are also pollutants. As a result of human activities, carbon dioxide ( $\text{CO}_2$ ), carbon monoxide ( $\text{CO}$ ), sulfur dioxide ( $\text{SO}_2$ ), methane ( $\text{CH}_4$ ), nitrogen oxides  $\text{NO}_2$ ,  $\text{NO}$ ,  $\text{N}_2\text{O}$  are released into the atmosphere. As a result of aerosol use, chlorofluorocarbon enters the atmosphere, and hydrocarbons from transport emissions. Water bodies are polluted not only by waste from industrial production, but also by organic and mineral fertilizers and pesticides used in agriculture. In the same way, sea water is being polluted. Rivers carry millions of tons of chemical waste into the sea every year. Millions of tons of oil spill into the oceans every year as a result of tanker and oil rig accidents, killing marine animals. Burial of nuclear waste at the bottom of the sea, sunken ships with nuclear reactors and weapons also pose a danger [7, 19, 28].

Radioactive contamination of the soil creates a great danger, since radioactive substances from the soil enter plants, and from there into the body of humans and animals, where they accumulate and cause various diseases. Chemicals pose a particular danger, specifically, organic compounds used in agriculture to control weeds, pests and diseases.

The uncontrolled release drugs into the environment may be wastewater and atmospheric emissions from enterprises producing finished drugs and pharmaceutical substances. the environmental safety of such production is usually regulated by law.

However, accidental releases of drugs into the environment or those that violate existing norms and regulations that occur in industry, are nevertheless not systematic. Moreover, there is a general trend towards a reduction in the environmental load on the part of pharmaceutical production, primarily in developed countries of the world, due to a consistent increase in the technological effectiveness and organization of the production process, the introduction of increasing quality standards and environmental safety, and control by authorized government bodies. It is also necessary to take into account that pharmaceutical production is localized geographically, and if an accident occurs at the enterprise or there are violations of environmental legislation, then such emissions are exclusively local in nature and pose a danger only to specific regions. For all the reasons listed above, such sources are not the subject of analysis in this review, although they contribute to environmental pollution. Other sources of drugs that are practically uncontrollable and are formed mainly by people who use drugs for medical purposes, as well as in animals, pose a great danger to the environment [14, 55, 69].

For the most part, drugs are xenobiotics, and many of them are metabolized in the human body. The task of metabolism is generally to impart polarity to lipophilic substances in order to facilitate subsequent excretion. Metabolic parameters are individual for each substance and depend on gender, race, age and the physiological state of the human body. There are two phases of metabolism, the numbering of which does not necessarily reflect their actual sequence. In the first phase of metabolism, a redox or hydrolytic transformation of the molecule occurs, increasing its polarity. In the second phase of metabolism, the xenobiotic is conjugated with endogenous molecules that improve the transport properties of the metabolite [25, 29, 37].

The impact of pharmaceuticals on the ecology and human health. Currently, increasing attention is being paid to the presence and fate of active pharmaceutical ingredients, solvents, intermediates and raw materials that may be present in water and wastewater, including pharmaceutical wastewater. Traditional wastewater treatment methods, such as activated sludge, are insufficient to completely remove active pharmaceutical ingredients and other wastewater components from these waters. Pharmaceutical wastewater has direct and indirect impacts on the environment and health, especially near pharmaceutical industrial sites. Although pharmaceutical factories produce untreated or partially treated wastewater, drinking water sources are contaminated. Various classes of pharmaceutical compounds such as analgesics, antidepressants, antihypertensives, contraceptives, antibiotics, steroids, hormones, etc. To protect the environment and lifestyles from health risks, the concentration of pharmaceutical compounds in medical wastewater entering drinking water sources should be regularly monitored. This article highlights the toxicity, health risks, and

environmental risk assessments associated with pharmaceutical contaminants. To reduce contamination levels when consuming medicines should be: Creation of a system for collecting drug waste generated by the population; Conducting awareness-raising work with the population, employees of healthcare institutions and other target groups on the topic of environmental pollution by drug waste; Taking into account environmental factors when choosing and prescribing treatment. At the same time, there is no need to put environmental protection above the human need for treatment; Development and implementation of wastewater treatment systems. It should be taken into account that urban wastewater has an unstable composition in terms of names and concentrations of drugs. A higher priority is to prevent drug residues from entering the city sewer system [45, 67, 95].

Incorporating green practices into the pharmacy curriculum provides future pharmacists with the skills and competencies needed in the field to reduce the environmental impact of processes and medications. A more environmentally conscious workforce in the pharmaceutical industry is creating the necessary ripple effect for the adoption and implementation of green principles across various pharmaceutical environments. Patients should also learn to avoid accumulating medications and disposing of them safely and correctly. Adopting environmentally friendly practices leads to a reduction in the use of chemicals and waste generation, which in turn leads to a reduction in the pollutants that contribute to climate change.

The increasing production and use of pharmaceutical and veterinary products has had an impact on the environment over time. Drug production processes have a significant impact on the environment, which affects the value of chemistry to society. The pharmaceutical industry impacts the environment through the carbon footprint generated during the production of pharmaceutical products and throughout the supply chain, which can lead to climate change. Climate change may alter the incidence of vector-borne diseases by altering the population of species that act as disease vectors. Another consequence of climate change is the emergence of infectious diseases caused by pathogens that would otherwise be dormant [33-35].

Currently, increasing attention is being paid to the presence and fate of active pharmaceutical ingredients, solvents, intermediates and raw materials that may be present in water and wastewater, including pharmaceutical wastewater. Traditional wastewater treatment methods, such as activated sludge, are insufficient to completely remove active pharmaceutical ingredients and other wastewater components from these waters. Pharmaceutical wastewater has direct and indirect impacts on the environment and health, especially near pharmaceutical industrial sites. Although pharmaceutical factories produce untreated or partially treated wastewater, drinking



water sources are contaminated. Various classes of pharmaceutical compounds such as analgesics, antidepressants, antihypertensives, contraceptives, antibiotics, steroids, hormones, etc. were detected in water samples ranging from mg/L to µg/L. Although the quantities detected are very small, they are highly toxic to humans, animals and aquatic life. To protect the environment and lifestyles from health risks, the concentration of pharmaceutical compounds in medical wastewater entering drinking water sources should be regularly monitored. This article highlights the toxicity, health risks, and environmental risk assessments associated with pharmaceutical contaminants [36-38].

Residues of many pharmaceutical products can be found in drinking water, plants and fruits, as well as in the tissues of fish and shellfish. Thus, people are exposed to these residues when they drink contaminated water and eat contaminated food. Pharmaceuticals in the environment can also influence the provision of important ecosystem services and have indirect effects on human health and well-being. Found the evidence that drug residues in drinking water and food affect human health, as well as the indirect effects of drugs on human health. Available evidence suggests that the risks of direct toxicity are low, but there are scenarios in which indirect effects are possible. Much remains to be done regarding the wider range of drugs and exposure pathways, and the links between the presence of drugs in the environment and the provision of ecosystem services.

Human drugs, hormones, antibiotics, analgesics, antidepressants and anticancer drugs indicate environmental risks. When it comes to veterinary products, hormones, antibiotics and parasiticides are often considered environmentally sensitive. These results are consistent with findings from the open scientific literature on approaches to environmental drug prioritization. Promising approaches such as environmental risk assessment of pharmaceuticals play an important role in minimizing the problems caused by pharmaceuticals in the environment. However, the regulatory framework for environmental risk assessment can be improved by integrating the environment into the risk-benefit analysis of drugs for human use, (ii) improving risk management capabilities, collecting data on existing drugs, and improving the availability of data for environmental risk assessment. In addition, more general and integrative stages of regulation, legislation and research have been developed and presented in this article. To minimize the amount of pharmaceuticals in the environment, they should strive to improve existing pharmaceutical legislation, prioritize pharmaceuticals present in the environment, and (iii) improve the availability and collection of pharmaceutical data. So, the presence of pharmaceuticals in the environment has received increasing attention. Medicines are released into the environment and can have harmful effects [25,28,47].

It is clear that priority must be given to environmentally relevant pharmaceutical substances. Existing pharmaceutical substances for which environmental data are lacking, as well as substances being considered for monitoring campaigns, need to be given priority attention to identify and minimize their environmental risk. According to the World Health Organization, concentrations of pharmaceuticals in water systems are expected to increase as the use of pharmaceuticals is expected to increase as they become more accessible to a growing world population. To be proactive, it is necessary to identify and prioritize the most important substances for the environment, which has become a challenge in recent years. Depending on the chemical properties of the substances, different approaches have been proposed. Most often, a combination of exposure and exposure data is used to prioritize environmentally significant chemicals. Several approaches have proposed using toxicological data to predict adverse effects on aquatic organisms (comparisons of several, but not all, approaches are included). Most published approaches to prioritization indicate the high environmental potential of various drug classes. Human medicines are often a priority, with all attention paid to hormones, antibiotics, psychotropic, anti-inflammatory and cytostatic substances, as well as beta blockers. In addition to hormones, antibiotics and parasiticides have proven to be environmentally important in veterinary medicines.

**Conclusions.** The widespread infiltration of medicinal compounds into natural systems constitutes an escalating danger to ecological stability and community welfare. These chemical agents impair biological variety, modify environmental processes, and foster treatment-resistant pathogens, creating enduring hazards that demand immediate action. Owing to their durability and intricate behavior within ecosystems, traditional remediation methods are inadequate. Confronting this issue requires a multi-pronged approach combining sophisticated water purification systems, more rigorous governance, eco-conscious drug manufacturing, and conscientious waste management protocols. Moreover, refining hazard evaluation frameworks via enhanced detection capabilities, simulation tools, and cross-disciplinary studies is vital for precisely determining the threats presented by drug residues. Cooperative initiatives uniting regulators, researchers, medical practitioners, and citizens are fundamental for formulating and executing successful interventions. By emphasizing forward-looking environmental stewardship and reinforcing international regulatory standards, we can reduce the harmful consequences of pharmaceutical contamination and protect both planetary health and societal well-being for posterity.

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## THE MANIFESTATION OF KEY ISSUES ASPECTS OF INTEGRATIVE PERSPECTIVES ON STEM CELL HETEROGENEITY, TRANSCRIPTIONAL REGULATION, HOMEOSTASIS, AND REGENERATIVE MEDICINE

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**Abstract.** Stem cells, characterized by their dual capacity for self-renewal and differentiation, represent the biological foundation of tissue development, maintenance, and repair. The remarkable potential of stem cells to generate specialized

cell types has placed them at the forefront of modern regenerative medicine and biotechnology. However, recent research has revealed that stem cell populations are far from homogeneous; rather, they exhibit substantial heterogeneity influenced by transcriptional, epigenetic, metabolic, and microenvironmental factors. This functional and molecular diversity underlies the variability in regenerative capacity, lineage commitment, and disease susceptibility among different stem cell types. Understanding the regulatory mechanisms that maintain or disrupt stem cell equilibrium is essential for advancing clinical applications, optimizing therapeutic outcomes, and mitigating risks such as tumorigenicity and immune rejection. Stem cell heterogeneity arises from dynamic transcriptional circuits that govern potency and plasticity across the continuum of totipotent, pluripotent, multipotent, and unipotent states. In pluripotent stem cells, core transcription factors – OCT4, SOX2, and NANOG – form a self-sustaining regulatory network that preserves the undifferentiated state while suppressing lineage-specific programs. Single-cell transcriptomic analyses have revealed fluctuating expression patterns of these factors, suggesting that heterogeneity among pluripotent stem cells may serve as an adaptive mechanism enabling rapid responses to differentiation signals. Multipotent stem cells, such as hematopoietic, mesenchymal, and neural stem cells, exhibit transcriptional and epigenetic restriction, guided by lineage-specific regulators including RUNX1, SOX9, and PAX7. This gradual narrowing of developmental potential ensures appropriate lineage fidelity while maintaining functional plasticity. Unipotent stem cells, although committed to a single lineage, retain latent regenerative capacity that can be reactivated under stress, injury, or reprogramming stimuli—demonstrating the continuum rather than discreteness of stem cell potency. Stem cell homeostasis represents the delicate equilibrium between self-renewal and differentiation that sustains tissue integrity and prevents depletion or over-proliferation. This balance is maintained by intricate interactions between intrinsic factors (gene expression, epigenetic modifications, and metabolism) and extrinsic cues from the microenvironment or niche. The stem cell niche, composed of stromal cells, extracellular matrix components, and signaling molecules, provides biochemical and biophysical support that dictates cell behavior. Key pathways such as Wnt/ $\beta$ -catenin, Notch, Hedgehog, and BMP orchestrate cell cycle control, quiescence, and differentiation, integrating systemic signals like hormones and cytokines. Disruption of these regulatory mechanisms contributes to pathological outcomes: excessive self-renewal may lead to cancer stem cell formation, whereas impaired renewal or differentiation can result in degenerative and aging-related disorders. Thus, understanding stem cell homeostasis is pivotal for both regenerative medicine and oncology. Advances in gene-editing technologies,

particularly CRISPR/Cas9, and the development of induced pluripotent stem cells (iPSCs) have revolutionized regenerative medicine by providing ethically acceptable and patient-specific cellular platforms. iPSCs derived from somatic cells exhibit pluripotency comparable to embryonic stem cells while circumventing ethical constraints and immunogenicity concerns. These technologies, coupled with three-dimensional organoid systems and bioengineered scaffolds, enable precise modeling of human development, disease mechanisms, and therapeutic responses. Moreover, integration of multi-omics approaches—combining transcriptomics, epigenomics, proteomics, and metabolomics—has allowed unprecedented insights into the molecular architecture of stem cell heterogeneity and function. Synthetic biology further contributes by designing artificial gene circuits capable of fine-tuning stem cell differentiation and homeostasis, paving the way for customizable regenerative therapies.

**Keywords:** Stem cell heterogeneity, transcriptional regulation; stem cell homeostasis; pluripotency; multipotency; unipotency; regenerative medicine.

**Introduction.** Stem cell systems represent a cornerstone of modern biological and medical research due to their unique capacity for self-renewal and differentiation. These properties allow stem cells to generate diverse cell types necessary for growth, development, and tissue maintenance. The study of stem cell systems has provided significant insights into the mechanisms of regeneration, repair, and disease pathology, thereby paving the way for novel therapeutic strategies. The regenerative potential of stem cells is a subject of immense scientific interest, as it holds the key to understanding and potentially treating degenerative diseases, injuries, and aging-related conditions. By examining the characteristics of stem cell systems and their regenerative capabilities, researchers aim to harness their power to develop advanced medical interventions, including tissue engineering and cell-based therapies [1-3].

Stem cells are broadly classified into embryonic stem cells, adult stem cells, and induced pluripotent stem cells (iPSCs), each possessing distinct features that determine their potential applications. Embryonic stem cells, derived from the inner cell mass of a blastocyst, exhibit pluripotency, meaning they can differentiate into any cell type in the body. This characteristic makes them a valuable resource for developmental studies and regenerative medicine. However, ethical concerns and potential immunogenicity have led to the exploration of alternative stem cell sources. Adult stem cells, found in specific tissues such as bone marrow, skin, and the brain, are typically multipotent, meaning they can differentiate into a limited range of cell types. While their regenerative capacity is more restricted than that of embryonic stem cells, their use is often preferred due to their ability to be derived from the patient's own body, thereby



reducing the risk of immune rejection. Induced pluripotent stem cells, reprogrammed from adult somatic cells, offer an exciting avenue for patient-specific therapies, as they combine the advantages of pluripotency with the ability to generate personalized treatments [4-6].

The process of regeneration, whether natural or induced, relies heavily on the intrinsic properties of stem cells and their ability to respond to physiological signals. In organisms with high regenerative capacities, such as certain amphibians and invertebrates, stem cells play a crucial role in restoring lost or damaged tissues. In mammals, however, regenerative capabilities vary widely among different tissues. For instance, the liver exhibits a remarkable ability to regenerate through the proliferation of existing cells, whereas the central nervous system has a limited capacity for self-repair. Understanding the molecular and genetic pathways that regulate stem cell activity in different tissues can offer new insights into improving regenerative responses in humans. Scientists are actively investigating signaling pathways, transcription factors, and extracellular cues that influence stem cell behavior, with the goal of enhancing tissue regeneration in clinical settings [7-9].

In addition to their natural role in regeneration, stem cells are being explored for their potential in regenerative medicine and tissue engineering. Advances in biomaterials, scaffolding techniques, and gene editing technologies have enabled the development of bioengineered tissues and organoids, which serve as models for studying disease progression and drug responses. Clinical applications of stem cell therapy are being investigated for conditions such as spinal cord injuries, neurodegenerative diseases, cardiovascular disorders, and diabetes. Despite the promising potential, several challenges must be addressed, including ensuring the safety, efficacy, and ethical considerations of stem cell-based therapies. Tumorigenicity, immune rejection, and uncontrolled differentiation remain significant hurdles that must be overcome before widespread clinical implementation [10-12].

The characteristics of stem cell systems and their regenerative capabilities present a frontier in biological research and medical innovation. By elucidating the molecular mechanisms underlying stem cell function, scientists hope to unlock new possibilities for regenerative therapies that can restore tissue function, repair injuries, and combat degenerative diseases. Continued advancements in stem cell research, coupled with technological innovations, hold the promise of revolutionizing medicine and improving the quality of life for millions of individuals worldwide. As research progresses, the integration of stem cell-based approaches into clinical practice will require interdisciplinary collaboration, ethical considerations, and rigorous regulatory oversight to ensure safe and effective applications. The exploration of stem cell

systems thus represents a crucial step toward realizing the full potential of regenerative medicine in the modern era [13-15].

Stem cells are unique biological cells with the capacity for self-renewal and differentiation into specialized cell types. They play a crucial role in embryonic development, tissue maintenance, and regeneration. The study of stem cell systems has opened new avenues for regenerative medicine, offering promising prospects for treating various degenerative diseases, injuries, and organ failures [16-18].

Stem cells are the foundation of biological development and tissue maintenance, possessing the remarkable abilities of self-renewal and differentiation. These unique properties enable them to contribute to growth, repair, and regeneration throughout an organism's lifespan. Stem cell systems exist in both embryonic and adult tissues, playing crucial roles in maintaining cellular homeostasis and responding to injury. Understanding the mechanisms governing stem cell function is essential for advancing regenerative medicine, where damaged or diseased tissues can be restored using stem cell-based therapies [19-21].

In recent years, significant progress has been made in elucidating the molecular and cellular mechanisms that regulate stem cell behavior. Various signaling pathways, including Wnt, Notch, and Hedgehog, have been identified as critical regulators of stem cell fate, influencing their ability to divide and differentiate into specialized cell types. Additionally, the microenvironment, or niche, in which stem cells reside plays a pivotal role in modulating their function, ensuring a balance between self-renewal and differentiation [22-24].

Stem cell-based therapies are being explored for treating a wide range of conditions, including neurodegenerative disorders, cardiovascular diseases, and musculoskeletal injuries. Induced pluripotent stem cells (iPSCs), derived from reprogrammed adult cells, have revolutionized the field by providing patient-specific cells for personalized medicine. Meanwhile, advances in tissue engineering and biomaterials are enhancing the effectiveness of stem cell transplantation by creating optimal conditions for cell survival and integration [25-26].

The figure illustrates the derivation of pluripotent stem cells from the inner cell mass of a blastocyst and their subsequent differentiation into nerve cells (ectoderm), liver cells (endoderm), and cardiac and blood cells (mesoderm). This process highlights the potential of pluripotent stem cells for regenerative medicine and tissue engineering.

Despite the vast potential of stem cell therapies, several challenges remain, including immune rejection, ethical concerns, and the risk of uncontrolled cell growth. Ongoing research aims to overcome these hurdles by refining differentiation protocols, improving delivery methods, and ensuring the safety and efficacy of stem cell

applications. As our understanding of stem cell systems deepens, the prospect of harnessing their regenerative capabilities for clinical applications becomes increasingly viable, paving the way for transformative advancements in medicine and biotechnology[27-29].

Stem cells are undifferentiated cells with the ability to self-renew and differentiate into specialized cell types. They serve as the building blocks of growth and tissue maintenance in multicellular organisms. Based on their potency and origin, stem cells are broadly classified into embryonic stem cells (ESCs), adult stem cells (ASCs), and induced pluripotent stem cells (iPSCs). These cells play a crucial role in both developmental biology and regenerative medicine, offering potential therapeutic solutions for various degenerative and injury-related conditions [30-32].

Stem cell systems and their regenerative potential offer a transformative approach to medicine and tissue engineering. Continued research into stem cell biology, regulatory mechanisms, and clinical applications will pave the way for novel therapies addressing previously untreatable conditions. While challenges remain, the rapid advancements in this field bring us closer to unlocking the full potential of stem cells in regenerative medicine and beyond [33-35].

**The aim of the study.** The primary aim of this study is to provide a comprehensive and integrative scientific analysis of the molecular, cellular, and regulatory mechanisms that define stem cell heterogeneity, transcriptional control, and homeostatic maintenance, with an emphasis on their translational implications in regenerative medicine. The study seeks to elucidate how intrinsic regulatory networks—comprising transcription factors, epigenetic modulators, and signaling pathways—interact with extrinsic cues from the microenvironment to orchestrate the balance between stem cell self-renewal and differentiation.

Specifically, the study aims to:

- Examine the diverse potency states of stem cells, ranging from pluripotency to unipotency, and analyze the transcriptional circuits that maintain or restrict these states.
- Investigate the molecular foundations of stem cell homeostasis, identifying how internal regulatory mechanisms and niche-derived signals sustain equilibrium and prevent exhaustion or malignant transformation.
- Explore the role of transcriptional heterogeneity as a determinant of stem cell plasticity and adaptability, highlighting its functional significance in tissue maintenance, regeneration, and disease pathology.
- Assess the contribution of cutting-edge technologies—including single-cell multiomics, CRISPR/Cas9 genome editing, organoid systems, and synthetic biology—to advancing understanding of stem cell regulation and therapeutic potential.

➤ Evaluate the translational and clinical relevance of these findings by discussing current and emerging applications of stem cells in regenerative medicine, disease modeling, and precision therapy.

Ultimately, this study aims to integrate conceptual and empirical perspectives to establish a unified framework for understanding how molecular regulation and environmental modulation govern stem cell behavior. By synthesizing insights across biological hierarchies and technological innovations, the research aspires to identify novel strategies for enhancing the safety, efficacy, and clinical translation of stem cell-based interventions.

## **Materials and Methods**

### *Study Design*

This work was designed as a comprehensive narrative and analytical review integrating molecular, cellular, and translational perspectives on stem cell heterogeneity, transcriptional regulation, and homeostatic mechanisms. The study employed a structured literature synthesis approach, combining qualitative and quantitative analyses of peer-reviewed data, experimental studies, and recent advances in biotechnology and regenerative medicine. The methodological framework focused on systematically collecting, categorizing, and critically analyzing research findings to construct an integrative model of stem cell regulation and therapeutic potential.

### *Data Sources and Literature Search*

A comprehensive literature search was performed using major scientific databases, including PubMed, Scopus, Web of Science, SpringerLink, Elsevier ScienceDirect, and Google Scholar, covering publications from 2020 to 2025.

### *Inclusion and Exclusion Criteria*

Studies were included if they met the following criteria:

1. Provided experimental or theoretical insight into stem cell biology, transcriptional mechanisms, or homeostasis.
2. Described molecular pathways, regulatory factors, or signaling networks involved in stem cell maintenance and differentiation.
3. Reported findings relevant to clinical or translational applications of stem cells in regenerative medicine.
4. Were published in English and accessible in full text.

Excluded materials included non-peer-reviewed reports, opinion pieces without empirical data, conference abstracts lacking methodological details, and studies with incomplete or ambiguous results.

### *Data Extraction and Synthesis*

All retrieved articles were reviewed and analyzed for content relevance and

methodological quality. Key data extracted included:

- Type and source of stem cells studied (embryonic, adult, or induced pluripotent).
- Main transcriptional and epigenetic regulators identified.
- Signaling pathways influencing stem cell fate decisions.
- Mechanisms of homeostatic maintenance and dysregulation.
- Therapeutic implications and translational outcomes.

Data were organized thematically into four core domains: (1) stem cell heterogeneity and potency, (2) transcriptional regulatory circuits, (3) mechanisms of homeostasis, and (4) applications in regenerative medicine. The synthesis followed an integrative analytical approach, combining molecular insights with translational and clinical perspectives.

### *Analytical Framework*

The analytical framework was based on a comparative and integrative model that combined molecular biology, systems biology, and regenerative medicine concepts. The relationships among transcriptional regulation, epigenetic modulation, and stem cell niche interactions were analyzed using conceptual mapping and diagrammatic modeling to illustrate interdependent regulatory networks. Key signaling pathways (Wnt/ $\beta$ -catenin, Notch, Hedgehog, BMP, and FGF) were systematically reviewed to highlight their roles in maintaining self-renewal and differentiation balance.

For transcriptional analysis, studies utilizing single-cell RNA sequencing (scRNA-seq), ATAC-seq, ChIP-seq, and epigenomic profiling were prioritized to provide insight into dynamic gene expression heterogeneity and chromatin accessibility in pluripotent, multipotent, and unipotent states. Comparative analyses of these datasets were conducted using descriptive statistics and cross-study synthesis to identify conserved regulatory motifs and differential gene expression signatures.

### *Ethical Considerations*

As this study is a literature-based analytical review, it did not involve any direct experimentation on human or animal subjects. All included data were obtained from previously published studies that had been conducted under appropriate institutional and ethical approvals. Ethical integrity was maintained by proper citation, acknowledgment of original sources, and adherence to academic publishing standards.

### *Limitations*

While the study adopts an integrative and multidisciplinary approach, certain limitations are acknowledged. Variations in experimental design, species differences, and analytical methods across the included studies may introduce heterogeneity in data



interpretation. Additionally, as the field of stem cell research evolves rapidly, newly emerging findings beyond the search timeline may not be captured within this review. To mitigate these limitations, emphasis was placed on high-quality, recent studies and consensus statements from authoritative sources in molecular biology and regenerative medicine.

#### *Outcome of the Methodological Framework*

The applied methodology enabled the synthesis of a unified conceptual framework describing how transcriptional heterogeneity and homeostatic mechanisms govern stem cell identity, plasticity, and therapeutic potential. This integrative model serves as a foundation for understanding the molecular basis of regeneration, the pathological consequences of dysregulation, and the translational pathways for stem cell-based clinical applications.

### **Results and Discussion**

#### *Stem Cell Heterogeneity*

Our analysis demonstrates that stem cell populations are inherently heterogeneous, even within ostensibly uniform tissue niches. Single-cell transcriptomic profiling revealed distinct subpopulations characterized by variable expression of pluripotency markers such as OCT4, SOX2, and NANOG, as well as lineage-priming transcription factors. These findings corroborate previous reports suggesting that heterogeneity is not merely stochastic but represents a functional hierarchy necessary for tissue homeostasis and adaptive regeneration. Notably, mesenchymal stem cells (MSCs) exhibited differential proliferation rates and differentiation capacities depending on their microenvironmental context, highlighting the influence of extrinsic cues on intrinsic cell fate decisions.

This heterogeneity has important implications for regenerative medicine. For instance, therapies relying on bulk stem cell populations may inadvertently select for subpopulations with reduced regenerative potential or altered immunomodulatory activity. Therefore, understanding and potentially modulating heterogeneity is critical to enhance therapeutic efficacy and reduce variability in clinical outcomes.

#### *Transcriptional Regulation*

Our integrative review of transcriptional dynamics confirms that the regulation of stem cell fate is governed by complex gene regulatory networks. Epigenetic modifications, including DNA methylation and histone acetylation, interact with transcription factors to orchestrate context-dependent activation or repression of lineage-specific genes. The results indicate that stem cell quiescence and activation states are tightly controlled by feedback loops involving master regulators such as FOXO, GATA, and HES families, ensuring the balance between self-renewal and

differentiation.

Moreover, transcriptional plasticity contributes to the ability of stem cells to respond to injury or stress. For example, activation of stress-responsive pathways, such as p38 MAPK and NF- $\kappa$ B, was associated with temporary changes in transcriptional profiles that facilitated rapid adaptation without permanent loss of stemness. These findings underscore the necessity of considering transcriptional heterogeneity in designing precision regenerative therapies and highlight potential targets for pharmacological modulation.

### *Homeostasis*

Our findings indicate that tissue homeostasis is maintained through an intricate interplay between stem cell proliferation, differentiation, and apoptosis. Perturbation experiments revealed that even subtle alterations in niche-derived signals, such as Wnt, Notch, and BMP pathways, could shift the equilibrium toward either hyperproliferation or depletion of functional stem cells. This observation supports the concept of a homeostatic “set point”, where stem cells and their microenvironment co-regulate to maintain tissue integrity.

Importantly, dysregulation of homeostatic mechanisms was found to underlie multiple pathologies, including fibrosis, impaired wound healing, and tumorigenesis. For example, biased differentiation of hematopoietic stem cells toward myeloid lineages under chronic inflammatory conditions can lead to hematologic disorders, while loss of quiescence in neural stem cells contributes to neurodegeneration. These insights emphasize the translational relevance of homeostatic control mechanisms in regenerative medicine and disease modeling.

### *Regenerative Medicine Implications*

The interplay between heterogeneity, transcriptional regulation, and homeostasis has profound implications for regenerative medicine. Effective cell-based therapies require not only the expansion of desired stem cell populations but also the preservation of their functional diversity and homeostatic responsiveness. Strategies such as preconditioning stem cells, modulating transcription factor activity, or engineering niche environments have shown promise in enhancing engraftment and tissue repair in preclinical studies.

Additionally, our review suggests that the integration of single-cell multi-omics approaches with computational modeling can facilitate the identification of optimal cell subpopulations for transplantation, predict responses to niche signals, and minimize the risk of adverse outcomes. By leveraging these insights, regenerative medicine can move toward more predictable and personalized therapeutic interventions.

While significant progress has been made in understanding stem cell dynamics, several challenges remain. Current methodologies often rely on ex vivo culture systems that fail to fully recapitulate in vivo microenvironments, potentially altering cell behavior. Future studies should focus on in situ monitoring of stem cell populations, integration of spatial transcriptomics, and the development of biomimetic scaffolds that emulate native niches.

Moreover, ethical considerations surrounding stem cell therapies, particularly those involving pluripotent or genetically modified cells, necessitate rigorous regulatory frameworks. Combining mechanistic insights with responsible translational strategies will be crucial for the safe and effective application of stem cell-based interventions.

Our integrative evaluation underscores that stem cell heterogeneity, transcriptional regulation, and homeostatic mechanisms are intricately linked and collectively determine regenerative outcomes. Recognizing and harnessing these features is essential for advancing both fundamental stem cell biology and the clinical implementation of regenerative therapies. By combining high-resolution molecular profiling with innovative bioengineering and computational approaches, it is possible to optimize stem cell-based interventions for diverse therapeutic contexts.

#### *Stem cells genes*

Stem cells are broadly categorized into embryonic stem cells (ESCs), adult stem cells (ASCs), and induced pluripotent stem cells (iPSCs):

Embryonic stem cells are derived from the inner cell mass of blastocysts and are pluripotent, capable of differentiating into nearly all cell types. Their genetic stability and regulatory networks, governed by key transcription factors such as OCT4, SOX2, and NANOG, enable their pluripotency and self-renewal.

Adult stem cells, found in various tissues, are multipotent and responsible for tissue maintenance and repair. Hematopoietic stem cells and mesenchymal stem cells are well-studied examples. Their genetic expression profiles are more lineage-restricted compared to embryonic stem cells, influenced by their niche and microenvironment.

Induced pluripotent stem cells are reprogrammed from somatic cells using factors such as OCT4, SOX2, KLF4, and c-MYC. They offer an ethical and personalized alternative to embryonic stem cells. Advances in genome editing technologies, particularly CRISPR-Cas9, have enabled precise genetic modifications in induced pluripotent stem cells, enhancing their utility in disease modeling and therapy.

The genetic and epigenetic landscapes of stem cells are critical for their function.

Transcriptional regulation involves tightly controlled gene networks, influenced by pathways like Wnt/ $\beta$ -catenin, Notch, and Hedgehog. These pathways play significant roles in stem cell fate decisions. Epigenetic modifications, including DNA methylation, histone modifications, and non-coding RNAs, contribute to dynamic regulation of stem cell gene expression. This reprogramming is essential for converting somatic cells into induced pluripotent stem cells and maintaining plasticity. Accumulation of genetic mutations can affect stem cell functionality, potentially leading to diseases such as cancer. Single-cell sequencing has provided insights into the genetic heterogeneity within stem cell populations.

Applications of stem cells in genetics include disease modeling, gene therapy, regenerative medicine, and drug discovery. Induced pluripotent stem cells derived from patients allow the creation of disease-specific models, enabling the study of genetic mutations and pathophysiological mechanisms. These models have advanced understanding of disorders like Alzheimer's and Parkinson's. The convergence of stem cells and genetic engineering has facilitated the development of gene therapies. Hematopoietic stem cells, for instance, have been genetically modified to treat genetic disorders such as sickle cell anemia and beta-thalassemia. Stem cells are being genetically optimized to enhance their therapeutic potential. For example, mesenchymal stem cells are engineered to overexpress anti-inflammatory cytokines, improving outcomes in inflammatory diseases. Stem cell-derived organoids, combined with genetic manipulation, offer platforms for high-throughput drug screening and personalized medicine. Organoids offer a valuable alternative to traditional research methods, including animal models, primary cell cultures, and cancer cell lines. Recent progress in gene-editing technologies, such as CRISPR-Cas9, along with prime and base-editing tools, has opened new opportunities for investigating complex genetic diseases. As innovations continue to reduce the differences between organoids and primary tissues, it is now possible to construct organoids and organ systems that more accurately replicate human organs. These models feature precisely coordinated cell-signaling networks, improving their ability to respond to non-genetic influences such as toxins, chemicals, and metabolites [36-39].

While the potential of stem cells and genetics is immense, challenges remain. Ethical concerns include the use of embryonic stem cells and the societal and moral dilemmas posed by genetic modifications, particularly germline editing. Technical hurdles such as off-target effects in genome editing, inefficient reprogramming, and immune rejection of transplanted cells need to be addressed. The rapid pace of advancements necessitates updated regulatory guidelines to ensure the safety and efficacy of stem cell-based therapies.

### *Stem cells markers*

Stem cell markers are specific molecules, often proteins, that are expressed on the surface or within stem cells and are used to identify and isolate these cells from heterogeneous populations. These markers play a crucial role in stem cell research, enabling scientists to characterize, sort, and study stem cells in various contexts, including development, regeneration, and disease. The expression of these markers can vary depending on the type of stem cell, its potency, and its differentiation state.

### *Challenges and Future Directions*

Despite their utility, stem cell markers have limitations. Some markers are not exclusive to stem cells and may be expressed in other cell types, leading to potential contamination. Additionally, marker expression can vary depending on the cell's microenvironment, differentiation state, or species. Future research aims to identify more specific and universal markers, as well as develop advanced techniques for single-cell analysis to better understand stem cell heterogeneity [80].

The stem cell markers are indispensable tools in stem cell biology, enabling the identification, isolation, and characterization of stem cells across various applications. Continued advancements in marker discovery and analysis will enhance our ability to harness stem cells for regenerative medicine, disease modeling, and cancer therapy.

### *Stem cells and germ cells*

Stem cells and germ cells are fundamental to the development, regeneration, and reproduction of multicellular organisms. Stem cells, characterized by their ability to self-renew and differentiate into specialized cell types, play a crucial role in tissue maintenance and repair. Germ cells, on the other hand, are unique cells responsible for transmitting genetic information to the next generation through gametogenesis. The interplay between these two cell types has significant implications for developmental biology, regenerative medicine, and reproductive health.

The study of stem cells and germ cells has revolutionized the fields of biology and medicine. Advances in stem cell research have led to groundbreaking therapies for degenerative diseases, while insights into germ cell development have enhanced our understanding of fertility and reproductive disorders. Understanding the similarities and distinctions between these cell types provides a foundation for exploring their potential applications in medical science.

This study will provide an overview of stem cells and germ cells, including their origins, classifications, functions, and their significance in medical research. It will also discuss key ethical and scientific challenges associated with their study and application. By delving into the mechanisms that govern their development and differentiation, this discussion aims to highlight the crucial roles of these cells in life sciences and their



potential to address some of the most pressing health issues of the modern era.

### *Significance in Medical and Scientific Research*

The study of stem cells and germ cells holds immense potential for medical applications. Stem cell therapy offers promising solutions for treating degenerative diseases such as Parkinson's, Alzheimer's, and diabetes. Germ cell research contributes to the understanding and treatment of infertility, reproductive disorders, and hereditary diseases. Additionally, the ability to generate gametes from stem cells raises possibilities for novel reproductive technologies.

However, these advancements come with ethical challenges, particularly concerning embryonic stem cell research and genetic modifications. Regulatory frameworks continue to evolve to balance scientific progress with ethical considerations.

Stem cells and germ cells are indispensable components of biological development and regeneration. Their unique abilities to differentiate and self-renew make them critical for tissue maintenance, repair, and reproduction. Understanding these cells' fundamental properties and interactions enhances our capacity to develop novel medical therapies and address fertility-related issues. As research advances, the ethical and scientific discourse surrounding their use will remain crucial in shaping the future of regenerative and reproductive medicine.

Stem cells heterogeneity: transcriptional circuits in pluripotent, multipotency, unipotency

Stem cells are defined by their ability to self-renew and differentiate into various cell types, making them fundamental for development, tissue homeostasis, and regenerative medicine. However, stem cell populations are not homogeneous; they exhibit significant heterogeneity influenced by intrinsic transcriptional networks and extrinsic environmental factors. This heterogeneity is evident across the spectrum of stem cell potency, from pluripotent stem cells (PSCs), which can generate all embryonic cell types, to multipotent and unipotent stem cells, which have progressively restricted lineage potential.

The regulatory mechanisms that govern stem cell potency involve complex transcriptional circuits, including core transcription factors, epigenetic modifications, and signaling pathways. In pluripotent stem cells, networks centered on OCT4, SOX2, and NANOG maintain an undifferentiated state, while multipotent and unipotent stem cells rely on distinct, lineage-specific transcriptional programs. Understanding the transcriptional heterogeneity within these stem cell states is critical for advancing regenerative medicine, improving cell-based therapies, and elucidating disease mechanisms.

This review explores the transcriptional heterogeneity in stem cell populations by examining key transcriptional regulators and their functional interplay across pluripotent, multipotent, and unipotent states. We discuss how transcriptional circuits influence cell fate decisions and how this knowledge can be leveraged for therapeutic applications [40-42].

The heterogeneity observed in stem cell populations is driven by intricate transcriptional networks that fine-tune their functional states. In pluripotent stem cells, the dynamic expression of core transcription factors such as OCT4, SOX2, and NANOG allows for cellular plasticity, enabling differentiation into multiple lineages. However, single-cell transcriptomic analyses have revealed that even within PSC cultures, subpopulations exist with distinct transcriptional signatures, indicating a spectrum of pluripotency states that may affect differentiation efficiency.

Multipotent stem cells, such as mesenchymal stem cells (MSCs) and hematopoietic stem cells (HSCs), exhibit transcriptional diversity dictated by tissue-specific transcription factors, epigenetic regulators, and niche signals. For example, HSC fate is governed by a balance between self-renewal factors (e.g., RUNX1, GATA2) and differentiation cues, ensuring proper hematopoiesis. Similarly, MSCs rely on transcriptional regulators like SOX9 and PPAR $\gamma$  to dictate lineage commitment toward osteogenic, chondrogenic, or adipogenic fates. The heterogeneity in these populations reflects functional adaptability but also poses challenges for therapeutic applications, where standardized cell populations are desirable.

In contrast, unipotent stem cells, which primarily give rise to a single cell type, such as epidermal stem cells or muscle satellite cells, exhibit more stable transcriptional states but retain context-dependent plasticity. Their transcriptional circuits, controlled by factors like PAX7 in muscle stem cells or p63 in epidermal stem cells, ensure lineage fidelity while responding to injury or physiological cues.

Understanding the mechanisms underlying stem cell heterogeneity has significant implications for regenerative medicine and disease modeling. Tailoring differentiation protocols based on transcriptional insights can improve the efficiency and reproducibility of generating specific cell types for therapy. Furthermore, dissecting stem cell transcriptional variability can help refine strategies to mitigate unwanted differentiation biases and enhance cell-based interventions [43-46].

Future research should focus on integrating single-cell multiomics approaches to decode the full spectrum of transcriptional heterogeneity and its functional consequences. Additionally, leveraging synthetic biology and gene-editing technologies could allow precise modulation of transcriptional circuits, paving the way for improved stem cell-based therapies. By advancing our knowledge of stem cell

heterogeneity, we can better harness their potential for regenerative applications and personalized medicine.

### *Stem Cell Heterogeneity and Transcriptional Circuits*

Stem cells exhibit remarkable functional diversity, ranging from pluripotent cells capable of generating all embryonic lineages to multipotent and unipotent cells with progressively restricted differentiation potential. This heterogeneity is orchestrated by intricate transcriptional circuits that regulate cell fate decisions, self-renewal, and lineage commitment.

➤ **Pluripotency:** In embryonic stem cells (ESCs) and induced pluripotent stem cells (iPSCs), transcription factors such as OCT4, SOX2, and NANOG form a core regulatory network that maintains an undifferentiated state while suppressing lineage-specific programs. Additional factors, including KLF4, ESRRB, and PRDM14, fine-tune chromatin accessibility and stabilize the pluripotent state. Single-cell transcriptomics has revealed that even within pluripotent populations, there is heterogeneity driven by fluctuating expression of lineage-priming genes, such as GATA6 (endoderm) and T (mesoderm), highlighting the dynamic nature of early fate commitment.

➤ **Multipotency:** Multipotent stem cells, such as hematopoietic, neural, and mesenchymal stem cells, retain the ability to differentiate into multiple, but not all, cell types. Their transcriptional landscapes are shaped by lineage-specific master regulators, including GATA2 and RUNX1 in hematopoiesis or SOX9 and PAX6 in neural progenitors. Unlike pluripotent cells, multipotent stem cells exhibit more stable epigenetic marks that reinforce lineage priming while maintaining plasticity in response to environmental cues.

➤ **Unipotency:** Unipotent stem cells, such as muscle satellite cells or epidermal stem cells, are lineage-restricted but retain self-renewal potential. Their transcriptional networks are dominated by key factors like MYOD1 (muscle) and TP63 (epidermis), which tightly regulate tissue-specific programs. The transition from multipotency to unipotency involves the progressive silencing of alternative lineage genes, often through chromatin remodeling complexes like Polycomb Repressive Complexes (PRC1/2) and DNA methylation.

Understanding the transcriptional circuits governing stem cell heterogeneity is crucial for improving regenerative medicine applications, optimizing stem cell differentiation protocols, and uncovering mechanisms of tissue homeostasis and disease progression. Recent advances in single-cell sequencing and chromatin profiling have provided unprecedented insights into how transcriptional fluctuations, epigenetic modifications, and extrinsic signals contribute to stem cell diversity across different

potency states.

#### *Discussion: Transcriptional Circuits in Stem Cell Heterogeneity*

The complexity of stem cell heterogeneity arises from dynamic transcriptional circuits that govern their self-renewal, plasticity, and lineage commitment. Understanding the interplay between these regulatory networks across pluripotent, multipotent, and unipotent states provides key insights into developmental biology and regenerative medicine.

#### *Pluripotency: A Balancing Act of Self-Renewal and Lineage Priming*

Pluripotent stem cells (PSCs) exist in a dynamic equilibrium where fluctuations in transcription factor expression contribute to heterogeneity within the population. The core transcriptional circuit – OCT4, SOX2, and NANOG (OSN) – maintains self-renewal while repressing differentiation signals. However, subsets of cells within pluripotent cultures exhibit differential expression of lineage-associated factors, such as GATA6 (endoderm), T/Brachyury (mesoderm), and SOX1 (ectoderm), indicating priming toward specific fates.

This heterogeneity is not merely noise but a functional feature that enhances the adaptability of pluripotent cells. For instance, studies using single-cell RNA sequencing (scRNA-seq) have revealed transient subpopulations with biased differentiation potential. Such variability may be regulated by extrinsic signals (e.g., WNT, BMP, FGF, and TGF- $\beta$  pathways) as well as epigenetic modifications (e.g., histone modifications, DNA methylation, and chromatin accessibility changes).

#### *Multipotency: Transcriptional Networks Restricting Lineage Potential*

Multipotent stem cells, such as hematopoietic, neural, and mesenchymal stem cells, exhibit a more constrained transcriptional landscape compared to PSCs. Here, lineage-specific master regulators, such as RUNX1 (hematopoietic), SOX9 (neural crest), and PAX7 (muscle progenitors), play critical roles in determining fate choices. However, these cells still retain a degree of plasticity, allowing them to respond to external cues.

In the hematopoietic system, for example, a hierarchical transcriptional network controls differentiation. GATA2 and RUNX1 initiate hematopoietic stem cell (HSC) specification, while later-stage decisions are controlled by factors like PU.1 (myeloid lineage) and GATA1 (erythroid lineage). Similarly, neural progenitor cells balance neurogenic and gliogenic programs through the coordinated action of SOX2, ASCL1, and HES1, where oscillatory expression patterns influence fate decisions.

#### *Unipotency: Transcriptional Commitment to a Single Lineage*

As stem cells transition to unipotency, transcriptional circuits become more restricted, locking cells into a single lineage. This is evident in tissue-specific stem

cells such as muscle satellite cells (MYOD1, PAX7) and epidermal basal cells (TP63, KLF4). The progressive loss of alternative lineage potential is reinforced by chromatin modifications, including Polycomb Repressive Complexes (PRC1/2), which silence non-lineage genes to maintain unipotent identity.

While unipotent stem cells are highly specialized, recent studies challenge the notion of absolute unipotency. Under certain conditions, such as injury or reprogramming signals, some unipotent cells can exhibit plasticity, suggesting that their transcriptional circuits, while restrictive, retain latent potential for fate conversion.

#### *Implications for Regenerative Medicine and Disease*

The transcriptional heterogeneity of stem cells has profound implications for therapeutic applications. In regenerative medicine, controlling transcriptional circuits is crucial for optimizing directed differentiation protocols, ensuring stable cell fate commitment while minimizing variability. For example, modulating the expression of lineage-specifying transcription factors or tuning epigenetic regulators could improve the efficiency of generating functional cell types for transplantation.

Conversely, dysregulation of these transcriptional circuits can contribute to disease pathogenesis, including cancer. Many malignancies, such as leukemia and glioblastoma, hijack stem cell-like transcriptional programs, leading to uncontrolled proliferation and resistance to differentiation cues. Understanding these circuits in normal stem cells can therefore inform strategies for targeting cancer stem cells.

#### *Analysis of Transcriptional Circuits in Stem Cell Heterogeneity*

The regulation of stem cell heterogeneity is a dynamic and multi-layered process controlled by transcriptional circuits that vary across different potency states. Understanding these networks provides critical insights into cellular plasticity, lineage commitment, and the stability of stem cell states. Below, we analyze key aspects of transcriptional regulation in pluripotent, multipotent, and unipotent stem cells.

#### *Dynamic Transcriptional Regulation in Pluripotency*

Pluripotent stem cells (PSCs) are characterized by a fluid transcriptional landscape, where core factors (OCT4, SOX2, NANOG) establish a self-renewing state. However, fluctuations in gene expression contribute to heterogeneity, with some cells exhibiting early lineage bias. Single-cell RNA sequencing (scRNA-seq) studies confirm that PSC populations contain subgroups with differential activation of mesodermal (T/Brachyury), endodermal (GATA6), or ectodermal (SOX1) markers, suggesting that fate decisions begin at the pluripotent stage.

From an analytical perspective, this heterogeneity can be viewed as an adaptive mechanism that enables rapid responses to differentiation signals. Rather than existing



as a uniform population, pluripotent cells dynamically explore different transcriptional states, increasing their ability to commit to specific lineages when required. However, this variability also presents challenges for directed differentiation in regenerative medicine, as uncontrolled lineage priming can lead to heterogeneous cell populations unsuitable for therapeutic applications.

#### *Multipotent Stem Cells: Gradual Lineage Restriction*

In multipotent stem cells, transcriptional regulation becomes more constrained, with lineage-specific transcription factors (TFs) exerting greater influence over fate decisions. For example, hematopoietic stem cells (HSCs) rely on GATA2 and RUNX1 to maintain their multipotent state, but as differentiation progresses, lineage-restricted TFs like PU.1 (myeloid) and GATA1 (erythroid) solidify cell fate. Similar mechanisms are seen in neural and mesenchymal stem cells, where lineage priming is reinforced by epigenetic regulators such as Polycomb Repressive Complexes (PRC1/2) and Trithorax Group proteins.

A key analytical takeaway is that multipotency is not a static state but rather a transition phase characterized by lineage-priming events. Studies using chromatin accessibility assays (ATAC-seq, ChIP-seq) demonstrate that multipotent stem cells progressively lose the ability to activate alternative lineage programs as differentiation proceeds. This suggests that stem cell differentiation is a continuum rather than a binary switch, where transcriptional circuits gradually shift from multipotency to lineage commitment.

#### *Unipotency: Commitment and Stability*

In unipotent stem cells, transcriptional circuits become highly restrictive, locking cells into a single fate. For instance, in muscle satellite cells, PAX7 and MYOD1 establish a transcriptional hierarchy that maintains self-renewal while allowing differentiation into myogenic lineages. In epidermal stem cells, TP63 and KLF4 enforce epidermal identity while suppressing alternative fates.

An important consideration is whether unipotency represents an irreversible endpoint or if certain conditions allow for reprogramming. Recent findings suggest that some unipotent stem cells exhibit latent plasticity, particularly in response to injury. For example, intestinal stem cells can revert to a more progenitor-like state under regenerative conditions, suggesting that transcriptional circuits, while restrictive, retain a degree of reversibility under specific stimuli.

#### *Transcriptional Circuits and Disease*

Dysregulation of transcriptional networks can contribute to pathological conditions, including cancer. Cancer stem cells (CSCs) often hijack stem cell-like transcriptional programs, leading to uncontrolled proliferation and resistance to

differentiation cues. In leukemia, aberrant activation of pluripotency-associated TFs (e.g., NANOG, SOX2, and MYC) contributes to stemness-like properties in malignant cells. Similarly, glioblastoma stem-like cells exploit SOX2 and OLIG2 to sustain an undifferentiated state.

From an analytical perspective, cancer stem cells illustrate how transcriptional circuits can be reactivated or dysregulated to promote tumor progression. This highlights the importance of targeting transcriptional regulators or epigenetic modulators (e.g., histone deacetylase inhibitors, DNA methylation blockers) as potential therapeutic strategies to force differentiation and reduce tumor-initiating potential.

#### *Implications for Regenerative Medicine*

The ability to manipulate transcriptional circuits holds significant promise for regenerative medicine. By modulating key transcription factors, it is possible to direct stem cell differentiation with greater precision. For instance:

- Forced expression of MYOD1 can reprogram fibroblasts into muscle cells.
- Overexpression of SOX2 and PAX6 can induce neural differentiation.
- Inhibition of lineage-restricting factors (e.g., REST in neural differentiation) can enhance plasticity.

However, the challenge lies in maintaining stability and functionality of the differentiated cells. Many stem cell-derived cell types fail to fully recapitulate the gene expression and functionality of their in vivo counterparts, underscoring the need for more refined approaches, such as 3D organoid models, co-culture systems, and biomaterial scaffolds to better mimic physiological conditions.

The analysis of transcriptional circuits in stem cells reveals a highly dynamic, context-dependent regulatory system that governs cell fate decisions. While pluripotent stem cells exhibit a fluid transcriptional network allowing lineage flexibility, multipotent and unipotent cells demonstrate progressively tighter regulatory control. Understanding these circuits not only advances fundamental biology but also holds key translational potential for regenerative medicine, disease modeling, and cancer therapy. Future research should focus on refining transcriptional control strategies to enhance differentiation efficiency and cell fate stability, bridging the gap between stem cell research and clinical application [48-51].

#### *Transcriptional Circuits in Stem Cell Heterogeneity*

Stem cells exhibit varying degrees of differentiation potential, from pluripotency (capable of generating all embryonic lineages) to multipotency (restricted to specific lineages) and unipotency (committed to a single fate). This heterogeneity is regulated by dynamic transcriptional circuits, which govern self-renewal, lineage commitment,

and plasticity.

➤ **Pluripotency:** Pluripotent stem cells (e.g., ESCs, iPSCs) are controlled by a core transcriptional network – OCT4, SOX2, and NANOG – that maintains self-renewal while repressing differentiation. However, heterogeneity within pluripotent populations arises due to fluctuations in lineage-associated genes, making them primed for differentiation.

➤ **Multipotency:** In multipotent stem cells (e.g., hematopoietic, neural, mesenchymal stem cells), transcription factors like RUNX1, SOX9, and PAX7 restrict fate options while preserving some degree of plasticity. Progressive chromatin remodeling further reinforces lineage commitment, demonstrating that differentiation is a gradual process rather than a binary switch.

➤ **Unipotency:** Unipotent stem cells (e.g., muscle satellite cells, epidermal stem cells) exhibit tightly regulated transcriptional programs (e.g., MYOD1 in muscle, TP63 in epidermis) that enforce lineage stability. However, under certain conditions, such as injury or reprogramming signals, some unipotent cells may regain plasticity, suggesting potential for regenerative applications.

➤ **Disease and Therapeutic Implications:** Dysregulation of transcriptional circuits can lead to disease, including cancer, where stem-like properties are hijacked to promote tumor growth (e.g., SOX2 in glioblastoma, MYC in leukemia). Understanding these networks is essential for designing targeted therapies. In regenerative medicine, modulating transcription factors can improve directed differentiation, enhancing the effectiveness of stem cell-based treatments.

➤ **Future Directions:** Advances in single-cell omics, epigenetics, and chromatin remodeling provide new insights into transcriptional heterogeneity. Future research should focus on refining transcriptional engineering approaches, improving differentiation efficiency, and bridging the gap between stem cell research and clinical applications.

Transcriptional circuits underpin stem cell heterogeneity, guiding fate decisions at different potency levels. Deciphering these regulatory networks is crucial for optimizing stem cell therapies, regenerative medicine, and cancer treatment. By controlling transcriptional circuits, we can harness stem cells more effectively for biomedical applications.

Stem cell heterogeneity is governed by intricate transcriptional circuits that regulate self-renewal, plasticity, and lineage commitment across different potency states. In pluripotent stem cells, core transcription factors (OCT4, SOX2, NANOG) maintain an undifferentiated state while permitting dynamic fluctuations that prime cells for differentiation. As cells transition to multipotency, lineage-restricting

regulators (e.g., RUNX1 in hematopoiesis, SOX9 in neural crest cells) progressively shape fate decisions, balancing flexibility and commitment. Unipotent stem cells, while highly specialized, retain latent plasticity under specific conditions, challenging the notion of irreversible differentiation.

Understanding these transcriptional networks has profound implications for regenerative medicine, disease modeling, and cancer therapy. By manipulating transcriptional circuits, researchers can enhance the efficiency of directed differentiation, improve stem cell-based therapies, and identify novel strategies for targeting aberrant stem-like states in cancer. Future advancements in single-cell technologies, epigenetic editing, and systems biology will further refine our ability to control stem cell fate, unlocking new possibilities for therapeutic interventions.

#### *Stem cells homeostasis*

Stem cell homeostasis refers to the delicate balance that maintains the self-renewal and differentiation capabilities of stem cells throughout an organism's lifespan. This balance is crucial for tissue maintenance, repair, and regeneration. Homeostasis is regulated by intrinsic factors, such as genetic and epigenetic mechanisms, as well as extrinsic factors, including signaling from the stem cell niche and systemic influences like hormones and inflammatory signals. Disruptions in stem cell homeostasis can lead to aging, degenerative diseases, or cancer. Understanding the mechanisms governing stem cell equilibrium is essential for advancing regenerative medicine and therapeutic interventions.

Stem cell homeostasis is the dynamic process that ensures a stable population of stem cells while allowing for the generation of differentiated cells needed for tissue growth, maintenance, and repair. This balance is maintained through tightly regulated mechanisms that control stem cell self-renewal, proliferation, quiescence, and differentiation. Homeostasis is governed by both intrinsic factors, including gene expression programs, epigenetic modifications, and metabolic regulation, and extrinsic factors, such as signals from the stem cell niche, systemic hormones, and environmental influences.

Stem cells exist in specialized microenvironments, or niches, that provide crucial signals to sustain their function and prevent exhaustion or over-proliferation. These signals include growth factors, cytokines, and extracellular matrix interactions that help maintain stem cell identity and guide their behavior in response to physiological needs.

The disruption of stem cell homeostasis is implicated in various pathological conditions. Excessive self-renewal can lead to tumorigenesis, as seen in cancers with uncontrolled stem cell proliferation. Conversely, impaired self-renewal or excessive differentiation can contribute to tissue degeneration, aging, and impaired healing.

Understanding the molecular and cellular mechanisms underlying stem cell homeostasis is critical for developing regenerative therapies, improving tissue engineering approaches, and combating age-related diseases.

Ongoing research continues to uncover the complexity of stem cell regulation, offering new insights into how homeostasis is maintained across different tissues and organisms. Advances in stem cell biology hold great potential for medical applications, including stem cell-based therapies for degenerative diseases, injury repair, and organ regeneration.

Stem cells are undifferentiated cells with the unique ability to self-renew and differentiate into specialized cell types. They play a fundamental role in development, tissue maintenance, and regeneration. The concept of stem cell homeostasis refers to the precise regulation of stem cell populations to ensure a balance between self-renewal and differentiation, preventing depletion or uncontrolled proliferation.

Stem cell homeostasis is fundamental for tissue maintenance, repair, and disease prevention. Disruptions in homeostasis contribute to aging, degenerative disorders, and cancer, highlighting the need for targeted therapeutic strategies. Ongoing research in regenerative medicine, gene editing, and cancer therapy aims to harness stem cell potential while addressing associated risks. Future advancements in bioengineering, personalized medicine, and synthetic biology will further refine our ability to manipulate stem cell homeostasis for improved health outcomes.

Stem cells are classified into embryonic stem cells (ESCs) and adult (somatic) stem cells. ESCs, derived from the inner cell mass of blastocysts, have pluripotent capabilities, meaning they can generate all three germ layers—ectoderm, mesoderm, and endoderm. In contrast, adult stem cells, such as hematopoietic stem cells (HSCs), mesenchymal stem cells (MSCs), and neural stem cells (NSCs), have a more restricted differentiation potential and primarily contribute to tissue-specific regeneration.

Stem cell homeostasis is maintained through complex regulatory mechanisms involving intrinsic (genetic and epigenetic) and extrinsic (microenvironmental and systemic) factors:

- **Intrinsic Regulation:** Gene expression networks, epigenetic modifications, metabolic status, and cell cycle control dictate stem cell fate. Key transcription factors such as OCT4, SOX2, and NANOG in pluripotent stem cells maintain their undifferentiated state, while lineage-specific regulators guide differentiation.
- **Extrinsic Regulation:** The stem cell niche, a specialized microenvironment, provides biochemical and biophysical cues that sustain stem cells. Factors such as Wnt, Notch, BMP, and Hedgehog signaling pathways regulate proliferation, differentiation, and quiescence. Additionally, systemic signals like hormones,



inflammation, and aging-related changes influence stem cell behavior.

- Disruptions in stem cell homeostasis contribute to various pathological conditions:

- Aging: A decline in stem cell function leads to impaired tissue regeneration and increased susceptibility to degenerative diseases.

- Cancer: Dysregulation of self-renewal mechanisms can result in uncontrolled proliferation and tumor formation, often driven by cancer stem cells.

- Tissue Degeneration: Loss of proper stem cell activity contributes to conditions such as neurodegenerative diseases, osteoporosis, and muscle atrophy.

Recent advancements in stem cell research and regenerative medicine aim to manipulate stem cell homeostasis for therapeutic purposes. Strategies such as stem cell transplantation, gene editing, and tissue engineering hold promise for treating degenerative diseases, injuries, and age-related disorders. Understanding the fundamental principles of stem cell homeostasis is essential for harnessing their full potential in biomedical applications.

Stem cells are essential for maintaining tissue integrity and enabling regeneration throughout an organism's lifespan. Their ability to self-renew and differentiate into specialized cell types is tightly regulated to prevent depletion or uncontrolled expansion. This balance, known as stem cell homeostasis, is crucial for sustaining tissue function and preventing diseases such as cancer and degenerative disorders.

#### *Clinical and Therapeutic Implications*

Advancements in stem cell research aim to manipulate homeostatic mechanisms for therapeutic applications:

- Stem Cell Transplantation: Bone marrow transplants restore hematopoietic function in leukemia patients.

- Regenerative Medicine: Induced pluripotent stem cells (iPSCs) offer potential for disease modeling, drug screening, and tissue engineering.

- Gene Editing (CRISPR/Cas9): Enables targeted correction of mutations affecting stem cell function.

- Pharmacological Approaches: Small molecules and biologics that modulate Wnt, Notch, or BMP pathways are being explored to restore homeostasis in degenerative diseases.

Stem cell homeostasis is a fundamental biological process that ensures proper tissue maintenance and repair throughout life. It is governed by intrinsic genetic programs and extrinsic niche signals that maintain a delicate balance between self-renewal and differentiation. Disruptions in these mechanisms contribute to aging,

degenerative diseases, and cancer. Understanding and manipulating stem cell homeostasis holds significant promise for advancing regenerative medicine, improving therapies for age-related diseases, and developing targeted treatments for cancer.

Stem cell homeostasis is a crucial aspect of tissue maintenance and regeneration, ensuring a balance between self-renewal and differentiation. Disruptions in this balance can lead to severe consequences, including aging-related degeneration and cancer. The regulation of stem cell homeostasis involves multiple levels of control, including genetic, epigenetic, biochemical, and environmental factors. In this discussion, we explore the complexity of these regulatory mechanisms, the challenges in maintaining homeostasis, and potential therapeutic applications (Sulashvili et al., 2024).

### *Balancing Self-Renewal and Differentiation*

A central challenge in stem cell biology is understanding how stem cells maintain their capacity for self-renewal while generating differentiated progeny in response to tissue needs. This balance is influenced by several key factors:

- **Stem Cell Niche:** The microenvironment provides signals that maintain stem cell identity and control differentiation. For example, hematopoietic stem cells (HSCs) rely on CXCL12 signaling from niche cells for quiescence, while neural stem cells (NSCs) are regulated by Notch and BMP signaling in the brain.
- **Intrinsic Regulatory Networks:** Transcription factors such as OCT4, SOX2, and NANOG maintain pluripotency in embryonic stem cells (ESCs), whereas lineage-specific factors like MYOD (muscle differentiation) and RUNX2 (bone differentiation) drive specialized functions.
- **Cell Cycle and Metabolic Control:** Stem cells maintain a delicate balance between quiescence and proliferation. While quiescence prevents premature exhaustion, excessive proliferation can lead to stem cell depletion or tumorigenesis.

### *Impact of Aging on Stem Cell Homeostasis*

Aging is a significant factor affecting stem cell homeostasis, leading to reduced regenerative capacity and increased susceptibility to disease. Key aging-related changes include:

- **Stem Cell Exhaustion:** Over time, stem cells lose their ability to self-renew, as seen in HSCs, which become biased toward myeloid differentiation, contributing to immune dysfunction.
- **Epigenetic Alterations:** DNA methylation changes, histone modifications, and chromatin remodeling affect gene expression in aging stem cells.
- **Oxidative Stress and DNA Damage:** Accumulation of reactive oxygen species (ROS) and impaired DNA repair mechanisms contribute to stem cell aging and functional decline.

➤ **Inflammation:** Chronic inflammation, driven by cytokines like IL-6 and TNF- $\alpha$ , disrupts stem cell function and promotes tissue degeneration.

Strategies to counteract aging-related decline in stem cell function are being explored, including metabolic interventions, pharmacological activation of key pathways (e.g., Wnt and NAD<sup>+</sup> precursors), and stem cell rejuvenation therapies.

#### *Stem Cell Dysregulation in Cancer*

While maintaining stem cell homeostasis is crucial for tissue health, dysregulation of self-renewal mechanisms can lead to cancer. Cancer stem cells (CSCs), a subset of tumor cells with stem-like properties, contribute to tumor initiation, progression, and resistance to therapy.

Major factors in CSC regulation include:

- **Oncogenic Signaling Pathways:** Aberrant activation of Wnt, Hedgehog, and Notch signaling drives uncontrolled proliferation in CSCs.
- **Epigenetic Modifications:** Changes in DNA methylation and histone acetylation alter gene expression patterns, leading to loss of normal stem cell regulation.
- **Therapy Resistance:** CSCs exhibit resistance to chemotherapy and radiation due to their quiescent nature, efficient DNA repair, and expression of drug efflux transporters.

Targeting CSCs is a major focus in cancer therapy, with approaches such as Wnt/Notch inhibitors, immune-based therapies, and metabolic interventions being investigated to eliminate CSC populations while preserving normal stem cell function.

#### *Therapeutic Manipulation of Stem Cell Homeostasis*

Advancements in stem cell research have opened avenues for therapeutic manipulation of homeostasis in various diseases:

- **Regenerative Medicine:** Stem cell-based therapies are being explored for conditions like spinal cord injury, Parkinson's disease, and heart failure. Induced pluripotent stem cells (iPSCs) offer personalized regenerative solutions by reprogramming patient-derived cells.
- **Gene Editing and CRISPR-Based Interventions:** Targeted gene modifications in stem cells hold promise for treating genetic disorders such as sickle cell anemia and muscular dystrophy.
- **Pharmacological Modulation:** Small molecules and biologics targeting Wnt, Notch, or BMP pathways can restore proper stem cell function in degenerative diseases.
- **Artificial Stem Cell Niches:** Bioengineering approaches are being developed to create synthetic niches that support stem cell growth and differentiation for transplantation therapies.

#### *Signals affecting Stem cells division*

Stem cell division is a tightly regulated process that ensures the balance between

self-renewal and differentiation. This balance is critical for tissue maintenance, repair, and regeneration. The regulation of stem cell division is influenced by a complex interplay of intrinsic and extrinsic signals, including growth factors, cytokines, and physical cues from the microenvironment. Understanding these signals is essential for advancing stem cell biology and developing therapeutic strategies.

### *Clinical Implications*

Understanding the signals that regulate stem cell division has significant implications for regenerative medicine and cancer therapy. For example:

- Regenerative Medicine: Manipulating signaling pathways (e.g., Wnt, Notch) can enhance stem cell proliferation and differentiation for tissue repair and organ regeneration [98].
- Cancer Therapy: Targeting signaling pathways that maintain cancer stem cells (e.g., Wnt, Hedgehog) can inhibit tumor growth and prevent relapse.

The regulation of stem cell division is a complex process influenced by multiple signaling pathways and niche factors. Continued research into these signals will provide new insights into stem cell biology and pave the way for innovative therapeutic strategies.

### *Progenitor Fate Choices*

How regeneration restores precisely what is missing remains unclear. These phenomena imply global body patterning signals influencing local fate decisions. While mechanistic details are lacking, altered Smed- $\beta$ -catenin-1 activity highlights conceptual importance.  $\beta$ -catenin functions as an intracellular effector of canonical Wnt signaling. Reduced Smed- $\beta$ -catenin-1 activity induces head regeneration regardless of wound context, while increased activity dominantly induces tail regeneration. These phenotypes suggest that  $\beta$ -catenin-1 acts as a binary switch high in the tissue fate hierarchy rather than a simple internal determinant.

Embryonic organizers provide a paradigm for such mechanisms. Organizers are self-sustaining signaling centers (often involving  $\beta$ -catenin) that establish embryonic axes. Their relevance to planarian regeneration lies in their self-organization based on dynamic cell interactions (Meinhardt 2009) and their ability to spatially direct lineage selection. Smed- $\beta$ -catenin-1 may select between self-sustaining signaling systems promoting tail or head regeneration, organizing progenitor differentiation spatially and temporally.

Patterning signals influencing lineage choices require regional fate determinants or competence mediators. Examples include LIM-homeodomain transcription factor Dj-ISLET, essential for tail regeneration and maintaining Wnt ligand expression, and TALE-homeobox gene Smed-prep, necessary for head induction downstream of  $\beta$ -catenin-1. These genes may function as selectors for regional identities.

Progenitors differentiate in response to patterning signals, which themselves are produced by differentiated cells, forming a self-reinforcing loop. Thus, cell fate specification is both an endpoint and a starting point, perpetuating developmental patterns.

#### *Self-renewal of tissues*

Tissue self-renewal is a fundamental process that maintains homeostasis and ensures repair following apoptosis or injury. It involves tightly regulated mechanisms driven by stem and progenitor cells, which possess the ability to proliferate and differentiate. The ability of tissues to self-renew is essential for maintaining physiological balance and functional longevity. This process depends on a dynamic interplay between cellular proliferation, differentiation, and apoptosis. Stem cells play a central role in self-renewal due to their capacity for asymmetric division, enabling both self-replication and the generation of specialized cell types.

Stem cells are categorized into embryonic and adult stem cells, with the latter being responsible for tissue maintenance. Adult stem cells reside in niches that provide structural and biochemical support, preserving their quiescence and multipotency.

Asymmetric division allows stem cells to produce one daughter cell that retains stem-like properties and another that differentiates. This division is regulated by polarity proteins, centrosome inheritance, and spindle orientation.

Progenitor cells amplify tissue-specific cell populations through transient proliferation, followed by terminal differentiation.

Key signaling cascades such as Wnt/ $\beta$ -catenin, Notch, and  $\text{I}\kappa\text{B}$  orchestrate self-renewal processes by modulating gene expression and cellular behavior.

Epigenetic regulation, including DNA methylation and histone modifications, maintains the balance between self-renewal and differentiation. Factors such as OCT4, SOX2, and NANOG sustain pluripotency in embryonic stem cells and regulate lineage-specific commitment in adult stem cells.

Understanding the regulatory networks of tissue self-renewal provides insights into maintaining health and treating diseases. Further research into niche dynamics, signaling pathways, and epigenetic controls is essential for advancing regenerative medicine.

#### *The problem of decreasing stem cell division rate over time*

Stem cells are vital for tissue maintenance, regeneration, and repair due to their ability to self-renew and differentiate. However, a significant challenge in aging and regenerative medicine is the progressive decline in stem cell division rates over time. This phenomenon contributes to reduced tissue regeneration, increased susceptibility to degenerative diseases, and age-related functional decline. Understanding the mechanisms underlying this decline is critical for developing strategies to counteract



stem cell exhaustion and enhance therapeutic outcomes.

The decline in stem cell division rates over time poses a significant barrier to tissue homeostasis and regeneration. While intrinsic factors like centriolar aging and epigenetic drift play central roles, extrinsic niche degradation and systemic inflammation exacerbate the problem. Emerging strategies, including replacement of old centrioles with young ones, senolytics, and epigenetic reprogramming, hold potential but require rigorous validation. Addressing these challenges will be pivotal for advancing regenerative medicine and mitigating age-related degeneration.

The study of stem cell systems and their regenerative potential has revolutionized our understanding of biology and medicine. Stem cells, with their unique ability to self-renew and differentiate, hold immense promise for treating degenerative diseases, injuries, and aging-related conditions. However, significant challenges remain in translating stem cell research into clinical applications. This discussion highlights key insights, challenges, and future directions in stem cell research, emphasizing the need for interdisciplinary collaboration and ethical considerations.

Despite significant progress, several challenges remain in stem cell research. Tumorigenic risks, immune rejection, and long-term integration of transplanted stem cells are critical hurdles that must be addressed. Additionally, ethical concerns regarding the use of embryonic stem cells and genetic modifications require careful consideration. However, the rapid pace of advancements in stem cell biology, gene editing, and tissue engineering offers exciting opportunities for overcoming these challenges and translating stem cell research into clinical applications.

Stem cell research represents a frontier in biological and medical innovation. By integrating molecular insights with technological advancements, we can unlock the full potential of stem cells for regenerative medicine, disease modeling, and personalized healthcare. Continued interdisciplinary collaboration, ethical considerations, and rigorous regulatory oversight will be essential to ensure the safe and effective application of stem cell-based therapies in the modern era.

Despite extraordinary progress, challenges persist in translating stem cell research into clinical practice. Issues such as variability in differentiation efficiency, genetic instability during prolonged culture, and risk of uncontrolled proliferation limit widespread therapeutic adoption. Additionally, ethical and regulatory frameworks must evolve alongside technological advances to ensure safe and responsible implementation. Addressing these challenges requires interdisciplinary collaboration among molecular biologists, bioengineers, clinicians, and ethicists. The future of stem cell research lies in harnessing the interplay between intrinsic regulatory networks and

extrinsic environmental signals to control stem cell behavior with precision. By integrating single-cell analytics, gene editing, and biomimetic engineering, scientists can refine differentiation protocols, minimize variability, and achieve stable therapeutic outcomes.

The stem cell heterogeneity, transcriptional regulation, and homeostasis are interdependent pillars underpinning the success of regenerative medicine. Deciphering the molecular language that governs stem cell fate offers not only a window into developmental biology but also a roadmap for designing targeted, patient-specific therapies. The fusion of omics-driven discovery, synthetic biology, and clinical translation promises a new era in which regenerative medicine transcends traditional therapeutic boundaries—restoring, replacing, and rejuvenating damaged tissues with unparalleled precision. Through these integrative perspectives, the field continues to evolve toward a transformative vision of personalized, safe, and effective regenerative healthcare.

### Conclusions

➤ Stem cell research stands at the intersection of developmental biology, molecular genetics, and regenerative medicine, offering unprecedented opportunities to restore or replace damaged tissues and organs. The multifaceted nature of stem cells—encompassing heterogeneity, transcriptional regulation, and homeostatic balance—defines their biological behavior and therapeutic potential. The intricate interplay between intrinsic gene networks and extrinsic environmental cues determines stem cell fate, ensuring that the processes of self-renewal and differentiation remain tightly regulated. Decoding these molecular circuits has illuminated the fundamental principles of cellular plasticity, unveiling new strategies for regenerative medicine and personalized therapy.

➤ Heterogeneity within stem cell populations is no longer viewed as a limitation but as a dynamic and adaptive feature that enhances functional versatility. Single-cell transcriptomic and epigenomic analyses have revealed that transcriptional variability among pluripotent, multipotent, and unipotent cells represents a continuum of states rather than discrete categories. These discoveries have refined our understanding of developmental hierarchies and underscored the necessity of context-specific regulation in tissue repair and regeneration. By embracing this diversity, researchers can better exploit stem cells' intrinsic plasticity to achieve more precise control over lineage specification and functional integration in therapeutic contexts.

➤ Transcriptional regulation serves as the molecular backbone of stem cell identity and fate determination. The cooperative action of key transcription factors – such as OCT4, SOX2, and NANOG in pluripotent cells – coupled with epigenetic and

signaling inputs, orchestrates the balance between self-renewal and differentiation. This regulatory architecture not only preserves the stability of stem cell populations but also enables rapid adaptation to physiological or pathological stimuli. Furthermore, insights into these transcriptional circuits have inspired the development of synthetic biology tools designed to engineer predictable gene expression patterns, offering exciting possibilities for controlled reprogramming and targeted tissue regeneration.

➤ Stem cell homeostasis is central to sustaining tissue integrity throughout life. It depends on the equilibrium between intrinsic molecular mechanisms and extrinsic influences from the microenvironment or niche. Disruption of this delicate balance can lead to pathological consequences, including tissue degeneration, premature aging, or tumorigenesis. The maintenance of homeostasis therefore represents both a biological imperative and a therapeutic challenge. By understanding the regulatory dynamics that preserve stem cell pools under normal conditions, scientists can devise interventions to restore or modulate homeostasis in disease states, enhancing regenerative capacity while minimizing oncogenic risk.

➤ The advent of induced pluripotent stem cells (iPSCs) and genome editing technologies such as CRISPR/Cas9 has transformed the landscape of regenerative medicine. These innovations allow patient-specific modeling of diseases, correction of genetic defects, and development of tailored cellular therapies. Combined with advances in bioengineering – such as organoid culture systems and biomimetic scaffolds – these tools bridge the gap between laboratory research and clinical application. However, challenges remain: variability in differentiation efficiency, potential genomic instability, and the risk of aberrant cell behavior continue to impede full clinical translation. Rigorous standardization, ethical oversight, and long-term safety evaluations are indispensable to ensuring that stem cell-based interventions reach their therapeutic potential responsibly.

➤ Looking forward, the integration of multi-omics technologies, artificial intelligence, and systems biology will further elucidate the complex regulatory landscapes governing stem cell function. Multi-omics approaches will enable the simultaneous assessment of transcriptional, epigenetic, proteomic, and metabolic layers, providing a holistic view of stem cell states. Artificial intelligence and computational modeling will enhance our ability to predict cell fate outcomes, optimize differentiation protocols, and identify novel therapeutic targets. Meanwhile, bioengineering innovations will continue to refine the physical and biochemical microenvironments that support stem cell growth and specialization.

➤ In summary, stem cell heterogeneity, transcriptional regulation, and homeostasis collectively define the biological and therapeutic potential of stem cells in regenerative

medicine. Their integrative understanding represents a paradigm shift—from reductionist approaches toward a systems-level comprehension of cellular function and plasticity. By harnessing the knowledge derived from molecular regulation and technological advancement, regenerative medicine is poised to enter a new era characterized by precision, safety, and efficacy. Future efforts should focus on translating these insights into clinically viable strategies that not only repair damaged tissues but also rejuvenate aging systems, combat degenerative diseases, and restore the physiological equilibrium essential for human health.

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## **THE SCIENTIFIC DISCOURSE OF EXPLORING THE APPLICATION OF CONTEMPORARY EDUCATIONAL PRACTICES IN UNIVERSITY LEVEL MEDICAL-PHARMACEUTICAL TRAINING AROUND THE WORLD**

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**Abstract.** The landscape of higher education for medical and pharmaceutical professions is undergoing a profound transformation, driven by rapid technological advancements, evolving healthcare demands, and a deeper understanding of pedagogical science. This abstract synthesizes the global scientific discourse surrounding the application of contemporary educational practices within these critical fields. The traditional model of passive knowledge transmission, heavily reliant on didactic lectures and rote memorization, is increasingly recognized as insufficient for preparing future healthcare providers for the complexities of modern practice. In response, a paradigm shift is underway towards student-centered, experiential, and technology-enhanced learning methodologies designed to cultivate not only foundational knowledge but also the essential skills of critical thinking, clinical reasoning, collaborative practice, and lifelong learning. Globally, several key innovative practices are being integrated into medical and pharmaceutical curricula. Problem-Based Learning (PBL) and Team-Based Learning (TBL) have become cornerstones, challenging students to apply their knowledge to realistic clinical scenarios and fostering interdisciplinary collaboration from the earliest stages of training. Simulation-based education, ranging from low-fidelity task trainers to high-fidelity human patient simulators and virtual reality environments, provides a safe and controlled space for students to develop technical proficiency, clinical decision-making skills, and non-technical competencies like communication and teamwork without risking patient safety. The flipped classroom model has redefined the learning dynamic, leveraging digital resources to deliver foundational content asynchronously, thereby liberating valuable classroom time for active, application-focused activities under the guidance of faculty. Furthermore, the integration of Interprofessional Education (IPE) is gaining significant momentum, breaking down the historical silos between medicine, pharmacy, nursing, and other health professions. By learning with, from, and about each other, students develop a mutual respect and understanding that is crucial for delivering effective, patient-centered collaborative care upon entering the workforce. Complementing these approaches is the strategic adoption of digital tools and online learning platforms, which facilitate blended learning, enable access to vast digital repositories and clinical databases, and support personalized learning pathways through adaptive learning technologies. The implementation of these contemporary practices, however, is not without significant challenges and global disparities. A primary barrier is resource inequity; the high cost of simulation technology, advanced



software, and robust digital infrastructure can preclude their adoption in many low- and middle-income countries, as well as in underfunded institutions elsewhere. This creates a "digital divide" in global health professions education. Furthermore, successful implementation requires substantial faculty development, as educators must transition from being content deliverers to facilitators of learning, a shift that demands new skillsets and is often met with resistance rooted in tradition. Curricular overcrowding presents another formidable obstacle, as integrating new pedagogical approaches necessitates difficult decisions about what content to reduce or remove from an already packed syllabus. Finally, the assessment of competencies gained through these methods—such as clinical judgment, teamwork, and professionalism—requires a move beyond traditional standardized exams towards more complex, often qualitative, tools like Objective Structured Clinical Examinations (OSCEs), portfolios, and multisource feedback, which are more resource-intensive to develop and administer. Despite these challenges, the impetus for change remains strong, fueled by compelling evidence of improved educational outcomes. Research indicates that contemporary methods enhance student engagement, knowledge retention, and the development of clinical skills. They better prepare graduates for the ambiguities and complexities of real-world practice, ultimately contributing to improved patient safety and care quality. The global COVID-19 pandemic, while disruptive, acted as a potent catalyst, forcing a rapid, worldwide experimentation with remote and technology-enabled learning that has permanently altered the pedagogical landscape and demonstrated the feasibility of innovative approaches at scale.

**Introduction.** Educational methods and experiences include learning and teaching techniques aimed at achieving specified learning outcomes and supporting students' independent learning. This experience may be formal or informal, group or individual, and may be a medical school, community, secondary or tertiary experience or educational experience. The choice is determined by the curriculum and local cultural issues related to education, as well as the available human and material resources.

The integration of technology into medical education has revolutionized traditional teaching methods. E-learning platforms, virtual simulations, and mobile applications provide students with access to resources and interactive experiences beyond the classroom. The use of telemedicine and digital health tools also prepares students for modern healthcare delivery systems [1-3].

Competency-based education (CBE) is gaining prominence in medical training, focusing on the acquisition of specific competencies necessary for effective practice. CBE emphasizes outcomes rather than time-based curricula, enabling students to progress at their own pace while mastering clinical skills. This approach aligns

educational objectives with the demands of the healthcare profession [4-6].

Interprofessional education (IPE) fosters collaboration among healthcare professionals from diverse fields. IPE programs promote teamwork and communication skills, essential for providing patient-centered care in complex healthcare settings. By engaging medical students with nursing, pharmacy, and allied health students, IPE enhances understanding of the roles and responsibilities of various healthcare providers [7-8].

**Assessment and Feedback:** The modern assessment methods are evolving to reflect the competencies required in medical practice. Formative assessments, direct observation, and feedback mechanisms play a crucial role in guiding student learning. Tools such as Objective Structured Clinical Examinations (OSCEs) and workplace-based assessments (WPBA) ensure that students are evaluated on their practical skills in real-world settings.

**Challenges in Implementing Modern Teaching Methods:** Despite the benefits of modern teaching and learning methods, several challenges impede their widespread adoption in medical education: Resistance to change, many educators are accustomed to traditional teaching methodologies, leading to resistance when implementing new approaches. Overcoming this inertia requires ongoing professional development and training to equip instructors with the skills necessary for innovative teaching [9-11].

**Resource Constraints:** Limited resources, including funding, technology, and personnel, can hinder the effective implementation of modern teaching methods. Higher education institutions must prioritize investment in educational technologies and infrastructure to support innovative teaching practices.

**Assessment Validity:** Ensuring the validity and reliability of assessment methods remains a challenge in competency-based medical education. Developing robust assessment tools that accurately measure student competencies is essential for maintaining educational quality and accountability.

**Maintaining Student Engagement:** As educational methods evolve, maintaining student motivation and engagement can be challenging. Continuous evaluation of teaching strategies and incorporation of student feedback are vital to creating an engaging learning environment [12-14].

It is impossible to study any specific issue in the teaching process with only one method and one activity. In the teaching process, the teacher has to use activities of different methods, and in many cases, there is a combination of activities. During the teaching process, the activities complement each other.

The study presents how augmented reality (AR) can be used as a teaching aid for medical education, focusing on remote and socially distanced learning. An

Augmented Reality (AR)-enhanced learning tool, was developed to assist medical students in understanding complex anatomical structures. The study introduces the principles of prompt engineering for large language models and applies them to medical education. It provides a comprehensive guide to help both teachers and students improve education in the medical field by leveraging AI technologies [15-17].

In an era marked by rapid scientific and technological advancements, the field of medical education has undergone a significant paradigm shift. The traditional approaches, characterized by lecture-based instruction and rote memorization, are being redefined by innovative teaching and learning methodologies. These modern methods aim to meet the evolving demands of global healthcare systems, equipping future medical professionals with the skills necessary to address complex medical challenges, adapt to emerging technologies, and provide patient-centered care [18-20].

Central to this transformation is the adoption of student-centered pedagogies such as problem-based learning (PBL), case-based learning (CBL), team-based learning (TBL), and flipped classrooms. These methods encourage active participation, critical analysis, and collaborative problem-solving among students, fostering a deeper understanding of medical concepts and their real-world applications. Simulation-based education, using tools like high-fidelity mannequins and virtual patients, provides a safe and controlled environment for students to practice clinical skills, enhancing their competence and confidence [21-22].

The transformation of higher education in medical programs worldwide has been significantly influenced by the adoption of modern teaching and learning methods. Traditional didactic teaching approaches, while foundational, are increasingly supplemented or replaced by innovative methodologies that emphasize student-centered learning, interdisciplinary collaboration, and the integration of technology. These contemporary methods address the evolving demands of healthcare systems, aiming to produce medical professionals who are not only knowledgeable but also adaptable, reflective, and capable of lifelong learning [23-25].

Modern teaching strategies such as problem-based learning (PBL), simulation-based education, flipped classrooms, and inter-professional education have gained prominence. These approaches prioritize active engagement, critical thinking, and the application of theoretical knowledge in practical settings. Additionally, technological advancements, including virtual reality (VR), augmented reality (AR), and online learning platforms, have expanded the possibilities for immersive and flexible learning experiences.

However, the implementation of these methods varies globally, influenced by cultural, economic, and institutional factors. In some regions, resource constraints and

resistance to change pose significant challenges, while in others, rapid technological adoption fosters innovation. The discussion of these issues is essential for identifying best practices, addressing disparities, and ensuring that medical education aligns with the needs of modern healthcare environments [26-28].

This topic calls for a comprehensive examination of the scientific, pedagogical, and practical aspects of these methodologies, exploring their impact on student outcomes, faculty roles, and institutional policies. By addressing these dimensions, stakeholders in medical education can better understand how to optimize teaching and learning processes in diverse global contexts.

The most common teaching-learning activities and their definitions are presented. The teacher will select the necessary activity from them, depending on the specific goal and task.

We discussed the following methods of learning and teaching:

Discussion/debate is one of the most common methods of interactive learning activity. The discussion process dramatically increases the quality of student engagement and activity. The discussion can turn into an argument, and this process is not limited to questions asked by the teacher. It develops the student's ability to reason and justify his own opinion [29-31].

Cooperative teaching is a teaching strategy when each member of the group is obliged not only to study by himself, but also to help his teammate to study the subject better. Each member of the group works on the problem until all of them have mastered the issue.

Collaborative work – teaching method using this activity involves dividing students into groups and giving them learning tasks. Group members work on the issue individually and simultaneously share their opinions with the rest of the group. It depending on the task. It is possible to redistribute functions among the members during the work of the group. This strategy ensures maximum involvement of all students in the learning process [32-35].

Problem-based learning (PBL) - an activity that uses a specific problem as the initial stage of the process of acquiring and integrating new knowledge.

Case study – the teacher will discuss specific cases with the students and they will study the issue in every way and thoroughly.

Brain storming – this activity involves thinking about a specific issue/problem as much as possible within the topic, preferably.

Radically different, the promotion of thought, idea formation and expression. This activity leads to the development of a creative approach to the problem. Its use is effective in the presence of a large group of students and consists of several main

stages: Defining the problem/issue from a creative point of view. To write down the ideas expressed by the listeners around the issue in a certain period of time without criticism (mainly on the blackboard). Determination of evaluation criteria to determine the relevance of the idea to the purpose of the research. Evaluation of selected ideas with predetermined criteria. To highlight those ideas that are most relevant to the question by exclusion. Revealing the idea with the highest evaluation as the best means of solving the set problem.

Role-playing and situational games – games based on pre-designed scenarios allow students to look at the issue from different perspectives. It helps them to form an alternative point of view. Like discussion, these games also develop the student's ability to express his position independently and defend it in an argument.

Demonstration – this method of activity involves visual presentation of information. It is quite effective in terms of achieving results. In many cases, it is better to present the material to students both audio and visual at the same time. The material to be studied can be demonstrated by both the teacher and the student. This method helps us to make visible the different stages of understanding the learning material, specify what the students will have to do independently. At the same time, this strategy visualizes the essence of the issue/problem. Demonstration may take a simple form.

Inductive defines a form of transfer of any knowledge, when the course of thought in the learning process is directed from facts to generalization, that is, when conveying material, the process proceeds from concrete to general.

Deductive defines a form of transfer of any knowledge, which is a logical process of discovering new knowledge based on general knowledge, that is, the process proceeds from the general to the specific [36-38].

Analysis helps us understand the learning material as a whole. In decomposition into constituent parts. This facilitates detailed coverage of individual issues within a complex problem.

Synthesis means making a whole by grouping separate issues. This method helps to develop the ability to see the problem as a whole.

Verbal or oral method – this method includes lecture, narration, conversation, etc. In the mentioned process, the teacher conveys and explains the learning material through words, and the students actively perceive and assimilate it by listening, memorizing and understanding.

Writing work method – which includes the following types of actions: making extracts and notes, summarizing material, drawing up theses, writing a report or essay, etc.

Explanatory method – based on reasoning around the given issue. When delivering the material, the teacher cites a specific example of which



Action-oriented teaching – requires the active involvement of the teacher and the student in the teaching process, where the practical interpretation of the theoretical material acquires special importance [39-41].

Project development and presentation – while working on the project, the student uses the acquired knowledge and skills to solve a real problem. Project-based teaching increases students' motivation and responsibility. Project work includes stages of planning, research, practical activity and presentation of results in accordance with the chosen issue. The project is considered to be implemented if its results are presented in a visible and convincing, correct form. It can be done individually, in pairs or in a group; Also, within one subject or several subjects (integration of subjects). After completion, the project can be presented to a wider audience.

The integration of digital technology has further revolutionized medical education. Innovations like virtual reality (VR), augmented reality (AR), and artificial intelligence (AI) offer immersive learning experiences, enabling students to visualize complex anatomical structures, simulate surgical procedures, and receive personalized feedback. Online learning platforms and hybrid models have also expanded access to medical education, allowing for greater flexibility and inclusivity.

Despite these advancements, the implementation of modern teaching methods faces challenges that vary across regions. Resource availability, institutional readiness, faculty training, and cultural attitudes toward education play critical roles in shaping the adoption and effectiveness of these methodologies. For instance, while well-resourced institutions in developed countries have embraced cutting-edge technologies, many institutions in low- and middle-income countries struggle with limited infrastructure and funding. Moreover, the transition to modern methods often requires significant changes in faculty roles, curriculum design, and assessment practices, which can encounter resistance [42-43].

Globally, there is a pressing need to evaluate the effectiveness of these innovative methods through rigorous scientific studies. Understanding their impact on student learning outcomes, professional competencies, and overall healthcare delivery is essential. Furthermore, fostering global collaboration and sharing best practices can help bridge disparities, ensuring that medical education remains equitable and aligned with the global health agenda.

The discussion of modern teaching and learning methods in medical education is not merely academic but a critical exploration of how to prepare future healthcare providers for a rapidly changing world. By addressing the scientific, pedagogical, and practical aspects of these innovations, educators, policymakers, and institutions can work together to shape a more effective and inclusive medical education system [44-46].

**The aim of the study.** Aim of the research was to study key issue facets of manifestation of modern teaching and learning methods in higher education institutions in medical educational study programs directions globally.

**Materials and Methods.** The material of the article was the revised data from scientific publications, which were processed, analyzed, overviewed and reviewed by generalization and systematization. Research studies are based on a review/overview assessment of the development of critical visibility and overlook of the modern scientific literature and our study programs and curriculums. Use the following databases (for extensive literature searches to identify key issue facets of manifestation of modern teaching and learning methods in higher education institutions in medical educational study programs directions globally.): Web of Knowledge, PubMed, Scopus, Web of Science, Clinical key, Thomson Reuters, Google Scholar, Cochrane Library, Science Direct, Research Gate and Elsevier Foundations. The methodology for discussing the key issue facets of manifestation of modern teaching and learning methods in higher education institutions in medical educational study programs directions globally.

### *1. Research Objective*

The study aims to critically analyze recent advancements in modern teaching and learning methods in higher education, with a focus on medical education programs globally. The objective is to identify trends, challenges, and opportunities through a systematic review of academic literature published in the last years.

### *2. Research Design*

A systematic literature review (SLR) approach will be employed to ensure comprehensive and unbiased coverage of the topic.

*3. Comparative Analysis:* Evaluate the effectiveness and adoption rates of these study methods across different regions and institutions.

*4. Trend Analysis:* Highlight innovations and emerging practices in the last ten years.

### *5. Reporting Results*

The results will be structured into the following sections:

- Overview of modern teaching and learning methods and variations in their application.
- Evaluation of their effectiveness in medical education, Challenges, limitations, and areas for further research.

### *6. Ethical Considerations*

As a literature review, this study will not involve human subjects, ensuring compliance with ethical research standards.

**Results and Discussion.** Key issues in modern teaching and learning methods and student-centered learning: One of the primary facets of contemporary medical education is the shift toward student-centered learning. This approach places learners at the forefront of the educational process, encouraging active participation, collaboration, and self-directed learning. Techniques such as problem-based learning (PBL), team-based learning (TBL), and flipped classrooms are increasingly utilized to promote engagement and critical thinking among medical students. Modern learning methods such as case-based learning (CBL), evidence-based medicine (EBM), problem-based learning (PBL), simulation-based learning (SBL), e-learning, peer-assisted learning (PAL), observation learning, flipped classroom models, and team-based learning (TBL) meet diverse learning needs. These approaches address individual learning preferences and enable students to expand their critical thinking, clinical reasoning, and time management skills while deepening their professional knowledge. Early integration of these methods promotes competence and leadership and prepares students for a seamless transition into clinical practice. The study highlights the importance and challenges of adopting modern learning strategies. As technology advances and medical information becomes more complex, students must acquire innovative skills through interprofessional and multidisciplinary education. To meet these needs, medical curricula must be adaptable and incorporate contemporary teaching methods, striking a balance between traditional teaching and modern educational practices.

Knowledge acquisition is a holistic, dynamic, consciously directed, and deeply personal process that involves the interpretation of personal information and experiences. This idea implies that people have an innate tendency to learn when they are in a supportive and motivating environment, and that the learning experience is deeply personal. So, a motivated student is a constant seeker of knowledge, and vice versa. The desire to learn and the desire to understand are innate traits shaped by a person's self-perception, desires, and expectations. Lifelong learning is also a fundamental human ability that is fostered by recognizing our unique learning patterns. Therefore, it is important to encourage independent learning strategies because these are the most sustainable and ambitious. These strategies should align with the responsibilities and priorities that students consider important. Teachers should clearly communicate educational goals and explain how specific activities will help students achieve their goals. Teachers must also understand the individual needs of each student and design activities that meet those needs while emphasizing motivation. Creating a motivating environment can include building social connections (e.g., friendships), meeting expectations, achieving professional growth, and receiving intellectual rewards.

The best educational experiences are self-paced, interactive experiences that encourage student engagement, sharing of ideas, and active participation in discussions [47-50].

In the past, traditional lectures were the cornerstone of learning during the preclinical years. These regular lectures were the main means of imparting knowledge to students. However, this passive learning model has been heavily criticized, leading to the introduction of innovative teaching strategies. Traditional lectures often lack interactive elements and are not dynamic learning tools, which limits students' ability to deepen their understanding through collaboration. Students are increasingly reluctant to participate in academic activities outside the classroom. Modern teaching methods, on the other hand, place the learner at the forefront and make him or her fully responsible for acquiring knowledge. The rapid development of medical systems requires the creation of an educational system that actively involves future specialists in the learning process. Instead of simply listening, students become full participants, participating directly and continuously. These active learning methods have been shown to be more effective than traditional lectures and significantly improve knowledge acquisition, comprehension, long-term retention, and independent learning in medical education [51-53].

In the teaching process, it is impossible to study any specific issue with only one method. The professor has to use different methods in the teaching process, in many cases there is a combination of methods. For example, in a lecture, the lecturer presents the lecture material in the form of a visual presentation accompanied by a verbal explanation; A discussion is held, a task is given to the student for independent work, which he completes in the form of working on a book, making a note, etc. Thus, in the process of teaching and learning, the methods complement each other and move into each other.

There are many classifications of teaching-learning methods, the most common options are presented.

A verbal, i.e. oral study method refers to a learning technique that relies primarily on spoken language for the absorption and retention of information. In this method, information is conveyed and understood through listening, speaking, and discussion, rather than through reading or writing. This can include techniques such as lectures, verbal repetition, oral quizzes, group discussions, or recitation. It emphasizes auditory learning and verbal communication to enhance comprehension and memory retention [54-56].

The method of working on the book refers to a systematic approach to studying or analyzing a book in depth. This method typically involves several stages: Previewing – Skimming the book to get an overview of its structure, main themes, and key ideas. Active Reading – Engaging with the text by reading carefully, taking notes,

highlighting important points, and asking questions as you go. Summarizing – Writing brief summaries of chapters or sections to consolidate understanding and retain information. Critical Analysis – Evaluating the content, arguments, and perspectives presented in the book, and considering their validity and implications. Reviewing – Going over the material multiple times to reinforce learning and deepen comprehension. This method can also include reflective thinking, discussion, and connecting the book's content to other knowledge or experiences [57-58].

The method of written work, which involves the following types of activities: making extracts and notes, summarizing material, drawing up theses, writing a report or essay, etc.

Laboratory method and demonstration method - the latter, in turn, involves the following types of activities: setting up tests, showing video materials, dynamic material, etc.

Practical methods – combines all those forms of teaching that form practical skills of the student, here the student independently performs one or another activity based on the acquired knowledge, for example: Pedagogical practice, field work, etc.

Discussion/debate is one of the most common methods of interactive learning. The discussion process dramatically increases the quality and engagement of students. The discussion can turn into an argument. This process is not limited to the questions asked by the professor. This method develops the student's ability to argue and justify his opinion [59-61].

Collaborative work - teaching with this method involves dividing students into groups and giving them a learning task. Group members work on the issue individually and simultaneously share it with the rest of the group. Depending on the set task, it is possible to redistribute functions among the members during the work of the group. This strategy ensures maximum involvement of all students in the learning process.

Problem-based learning (PBL) – a method that uses a problem as the initial stage of the process of acquiring and integrating new knowledge.

Cooperative teaching is a teaching strategy where each member of the group is obliged not only to learn, but also to help his teammate to learn the subject better. Each group member works on the problem until all of them have mastered the issue.

The heuristic method is based on the step-by-step solution of the problem posed to the students. This task is carried out in the teaching process by identifying the facts independently and seeing the connections between them.

Case study (Case study) – during the lecture, the professor will discuss specific cases with the students, who will study the issue in every way and thoroughly. For example, in the field of medicine, it can be the review and analysis of the history of a



particular patient's illness and so on.

Brain storming - this method involves the formation and expression of as many, preferably radically different, opinions and ideas about a specific issue/problem within a specific topic. This method contributes to the development of a creative approach to the problem. This method is effective in the presence of a large group of students and consists of several main stages: defining the problem/issue from a creative angle. Non-critically writing down (mostly on the board) the ideas surrounding the issue from the audience in a certain period of time. Eliminating ideas that are most relevant to the issue at hand. Defining evaluation criteria to determine the relevance of the idea to the research objective. Evaluation of selected ideas with predetermined criteria. Revealing the idea with the highest rating as the best way to solve the problem [62-64].

Role-Playing and Situational Games – Scenario based on role-plays and allow students to look at an issue from different perspectives and help them develop alternative points of view. Like discussion, role-playing also develops the student's ability to express his position independently and defend it in an argument.

Demonstration method – this method involves presenting information visually. From the point of view of achieving the result, it is quite effective. In many cases, it is better to provide the material to the students simultaneously in audio and visual way. The material to be studied can be demonstrated by both the teacher and the student. This method helps us to make visible the various stages of understanding the learning material, to specify what the students will have to do independently; At the same time, this strategy visualizes the essence of the issue/problem. Demonstration may be simple, such as solving a mathematical problem by displaying its steps on a whiteboard, or complex, such as conducting a multi-step science experiment [65-67].

Induction is a method of reasoning that involves drawing general conclusions from specific observations or instances. Explanation: In the inductive approach, you begin with particular cases, observations, or data points, and from these, infer a broader generalization or theory. This method is often used in scientific research where repeated observations lead to the formation of hypotheses or laws. For example, observing that the sun rises every day and concluding that the sun always rises in the east is an inductive inference. Application in Study: In studying, induction helps students make connections by analyzing patterns or trends across multiple cases to form a broader understanding of a subject or concept [68-69].

Deduction is a method of reasoning that starts with a general principle or theory and applies it to specific instances to draw a conclusion. In the deductive approach, you begin with a general statement, premise, or theory and use it to predict or explain specific observations. This process is logical and moves from a broad theory to a

specific conclusion. In studying, deduction allows learners to apply established theories or rules to specific problems or examples, which is useful in fields like mathematics, logic, or law.

Team-based learning (TBL) has been shown to be one of the most effective learning approaches in medical education, emphasizing a student-centered structure. In this method, small groups of students carry out activities that promote the practical application of theoretical concepts. Team learning includes critical thinking, individual and collaborative tasks, brainstorming sessions, and immediate instructor feedback. It offers significant benefits by improving communication and teamwork skills in groups of students, essential skills for effective patient care. Compared to problem-based learning (PBL), team learning encourages greater student participation. One of the main benefits of team learning is that it encourages students to solve problems and make decisions together, which increases motivation, facilitates the discovery of concepts, and promotes deeper understanding. Instructors who facilitate small group discussions using a team-based learning model have shown better student performance on exams compared to traditional lecture-based learning.

Analysis is the process of breaking down a complex topic or substance into its components to better understand its structure or function. In analysis, you examine the individual parts of a whole, studying their relationships and functions in isolation to better understand the entire system. This method is crucial in critical thinking, allowing a detailed and in-depth examination of various elements within a concept, problem, or text. For example, analyzing a novel would involve looking at its plot, characters, themes, and language style separately. Analysis is often used in studying literature, sciences, and humanities, where learners must dissect and examine ideas, arguments, and data to understand the core aspects of a subject [70-72].

Synthesis is the process of combining different ideas, information, or components to form a cohesive whole or new understanding. In synthesis, you take the analyzed parts of a concept or data and integrate them to form a new, unified perspective. This method moves from individual elements to an overall understanding, allowing the learner to create something new from previously separate pieces of knowledge. For example, after analyzing various sources in an essay, synthesis would involve combining these viewpoints into a single, coherent argument. Synthesis is used to combine knowledge from different areas to create new insights or solutions. It's essential in research writing, problem-solving, and the development of new ideas in disciplines like philosophy, history, and science.

*Summary:*

- Induction: From specific to general (forming theories from observations).

- Deduction: From general to specific (applying theories to specific cases).
- Analysis: Breaking down complex information into simpler components.
- Synthesis: Combining elements to create a new whole or understanding.

The inductive method of teaching defines such a form of knowledge of any subject, when the course of thought in the learning process is directed from particular to concrete, from facts to generalization, that is, when conveying material, the process proceeds from concrete to general.

The deductive method of teaching defines a form of transfer of any subject knowledge, which is a logical process of discovering new knowledge based on general knowledge, that is, the process proceeds from the general to the specific.

In the learning process, the method of analysis helps us to break down the learning material as a whole into its component parts, thereby facilitating the detailed coverage of individual issues within complex problems.

The synthesis method involves the reverse procedure, that is, by grouping separate issues to form a single whole. This method helps to develop the ability to see problems as a whole.

Explanatory method – based on reasoning around the given issue. When presenting the material, the professor cites a specific example, which is discussed in detail within the given topic.

Action-oriented teaching – requires the active involvement of the professor and the student in the teaching process, where the practical interpretation of the theoretical material acquires special importance [73-75].

Electronic learning (E-learning) – this method includes three types of teaching: attended, when the teaching process takes place within the contact hours of the professor and students, and the transfer of educational material is carried out through an electronic course. Hybrid (face-to-face/distance), the main part of the teaching takes place at a distance, and a small part is carried out within the framework of contact hours. Completely distance learning involves conducting the learning process without the physical presence of the professor. The training course is conducted from the beginning to the end remotely in an electronic format. In addition to the given basic methods, there are many teaching methods that the teacher can choose depending on the specific learning task.

Teaching-learning methods and corresponding activities and main teaching learning methods: lecture, seminar, laboratory and practical work; training and production practices; course work/project; bachelor's, master's and doctoral theses; e-learning; consultation [76-78].

A lecture is a creative process in which the lecturer and the student participate

simultaneously. The main goal of the lecture is to understand the idea of the provisions of the studied subject, which implies a creative and active perception of the presented material. In addition, attention should be paid to the basic provisions, definitions, designations, and assumptions of the transmitted material. Critical analysis of key issues, facts and ideas is required. The lecture should provide a scientific and logically coherent introduction to the basic tenets of the studied subject without overloading it with unnecessary details. Therefore, it must be logically complete. In addition, facts, examples, diagrams, drawings, experiments and other visual aids should serve to explain the idea of the lecture.

The lecture should provide a correct analysis of the dialectical process of science and should be learned in a specific environment by focusing on the ability of students to think freely, to know and understand basic scientific problems [79-81].

The material heard at the lecture is formed into a whole knowledge system by the independent work of the student. The student should be interested in books and other sources of information and the desire to study issues independently, which is a means of stimulating independent thinking, analysis and drawing conclusions [82-84].

Based on the main purpose of the lecture, the right to read it should be given only to experienced teachers, since their theoretical knowledge, practical experience and pedagogical skill are the guarantee of conducting the lecture at a high level. During the processing of the methodical issues of the lecture, the teacher should focus on the sequence of the transfer of the material, the style of the lecture, and the connection with the audience. The lecture should be conducted with the active participation of students, methodical means and extensive use of visual aids.

Theoretical material, which is given in lectures, is well understood by seminars, laboratory and practical studies [85-86]

The purpose of the seminar (group work) is to give students an opportunity to deepen the topics heard during the lecture. Under the guidance of the leading professor or the leading teacher of the seminar, a student or a group of students will search for and process additional information, prepare a presentation, write an essay, etc. At the seminar, reports will be heard, discussions will be held, and conclusions will be made. The head teacher of the seminar coordinates the purposeful management of these processes.

Laboratory work is more visible and allows the perception of this or that event or process. In the laboratory, the student learns to conduct an experiment. During the laboratory studies, the student should learn how to set up, adjust and operate the equipment.

Habits developed in experiential learning laboratories allow understanding of

theoretical material heard in lectures. It involves the following types of actions: setting tests, showing video material, dynamic material, etc.

The purpose of practical work is the gradual study of theoretical material through the solution of specific tasks, which is the basis for developing habits of independent use of theoretical material. The head of practical education should focus on the methodology of problem solving, the execution of drawings, sketches, schemes, the use of appropriate techniques in calculations, etc.

Practice (educational and industrial) serves to deepen and strengthen the knowledge acquired by the student. It develops the ability to apply knowledge in practice, to use methods specific to the studied subject to solve problems. It combines all the teaching methods that form the student's practical skills. In this case, the student independently performs this or that action based on the acquired knowledge, for example, pedagogical practice, field work, etc.

Course work/project is a creative process. Each new building, machine, tool, automatic device, etc. is created according to the project. The design process is a combination of theory and practice. During the teaching period, the student completes graphic assignments and course projects, which are, in fact, the student's first independent work, although it is carried out under the guidance of the teacher. A bachelor's, master's and doctoral thesis is the final stage of a separate level of education in a higher educational institution, and its purpose is to systematize the theoretical and practical knowledge gained in the specialty and to provide a substantiated solution to specific scientific, technical, economic or production tasks. The paper should reveal the level of mastery of research methods and experiments related to the issues and the student's readiness for independent work in the future professional activity. The work is supervised by an experienced teacher.

Electronic learning (E-learning) – refers to teaching through the Internet and multimedia tools. It includes all components of the teaching process (goals, content, methods, means, etc.), which are realized by specific means. E-learning is of three types: Attended when the teaching process takes place within the contact hours of the teacher and students, and the transfer of educational material is carried out through an electronic course; Distance learning involves conducting the learning process without the physical presence of the professor. The training course is conducted from start to finish remotely, in electronic format; Hybrid (face-to-face/distance) - the main part of teaching takes place remotely, and a small part is carried out within the framework of contact hours [87-88].

Consultations should help the student, with the help of the teacher, to master the habits of independent work, to correctly conduct work on educational literature and



other sources, and to clarify the issues raised during independent work.

CBCR (Case-Based Clinical Reasoning) is an educational approach commonly used in medical and health sciences education to help students develop clinical reasoning skills. In this method, learners are presented with real or simulated clinical cases that they must analyze and solve using their knowledge, problem-solving skills, and reasoning abilities.

*Key Features of Case-Based Clinical Reasoning (CBCR):*

- ✓ Case-based learning: The method focuses on real-world clinical cases, which often mimic the complexity and unpredictability of actual patient scenarios. These cases encourage students to think like healthcare professionals by diagnosing and treating patients based on the information provided.
- ✓ Interactive and collaborative: CBCR is often conducted in groups, where students discuss the cases, share insights, and collaborate to reach a diagnosis or treatment plan. This interactive setting helps promote peer learning and enhances critical thinking.
- ✓ Focus on reasoning: Rather than just memorizing facts, students are encouraged to apply their knowledge to reason through cases, considering differentials, clinical symptoms, diagnostic tests, and possible interventions.
- ✓ Integration of theoretical knowledge and practice: CBCR helps bridge the gap between theoretical learning and practical application by integrating basic sciences with clinical practice.
- ✓ Iterative process: As students work through the case, they often receive feedback, are presented with new information, or are asked to reflect on their reasoning, making it an iterative process that enhances learning.
- ✓ Role of the facilitator: Instructors or facilitators guide the discussion but do not provide direct answers. Their role is to challenge students' thinking, ask probing questions, and help learners explore the case from different perspectives.

Benefits of Case-Based Clinical Reasoning (CBCR): Enhances clinical decision-making skills; Promotes active learning and critical thinking; Encourages teamwork and communication; Prepares students for real-life clinical problem-solving. This method is widely used in medical schools, nursing education, and other health professions to train students in thinking like clinicians.

CBD (Case-Based Discussion) is a structured, formative assessment tool used in medical education to evaluate and improve a learner's clinical reasoning, decision-making, and application of knowledge to real patient cases. It is typically part of workplace-based assessment (WBA) frameworks, focusing on reflective learning through in-depth discussion of clinical cases the learner has been involved with.

*Key Features of (Case-Based Discussion) CBD:*

- ✓ Focus on real cases: The discussion revolves around a clinical case that the learner has directly managed or been involved in. It is typically drawn from actual clinical practice rather than hypothetical scenarios.
- ✓ Reflective discussion: The method involves a structured dialogue between the learner and an experienced clinician (usually a mentor, supervisor, or assessor) about the clinical reasoning and decisions made during the management of the case. The focus is on reflection, exploring why certain decisions were made, and considering alternatives.
- ✓ Evaluation of clinical reasoning: CBD is designed to assess how well the learner can apply clinical knowledge to real-life situations, taking into account patient history, diagnosis, treatment, and follow-up. It emphasizes clinical reasoning and the thought process behind medical decisions rather than just the outcomes.
- ✓ Interactive and formative: CBD is an interactive method where the learner and the assessor explore the case together. The goal is formative, meaning it is aimed at providing feedback to the learner to enhance their skills rather than simply giving a grade or judgment.
- ✓ Customizable to learning needs: The discussion can be tailored to the learner's level of expertise and the specific competencies being assessed. Different aspects of the case, such as diagnosis, management, communication skills, ethical considerations, or teamwork, can be explored based on the individual's learning objectives.
- ✓ Documentation and feedback: The assessor provides feedback, which is typically documented to track the learner's progress over time. The feedback is usually focused on areas for improvement, strengths, and any learning opportunities identified during the discussion.

*Steps in a (Case-Based Discussion) CBD:*

- ✓ Case selection: The learner selects a clinical case they have managed that offers scope for discussion on clinical reasoning and decision-making.
- ✓ Preparation: The learner reviews the case details, including patient history, diagnosis, treatment, and outcome. The assessor may also review relevant case notes or patient data.
- ✓ Discussion: A structured discussion takes place between the learner and assessor, covering the learner's reasoning, decision-making, and understanding of the case. The assessor may ask open-ended questions to probe the learner's knowledge and approach.
- ✓ Feedback: The assessor provides detailed, constructive feedback, focusing on what the learner did well and areas where they can improve.

✓ Reflection: Learners are encouraged to reflect on the feedback and the case to identify learning points and future improvements.

Benefits of (Case-Based Discussion) CBD: Helps learners develop deeper clinical reasoning and critical thinking; Provides an opportunity for personalized feedback based on real clinical experience; Encourages reflection on clinical practice, promoting lifelong learning; Assists in identifying learning needs and areas for improvement. Commonly Used In: Medical education and postgraduate training (e.g., residency programs). Other healthcare professions like nursing, dentistry, and allied health. (Case-Based Discussion) CBD is particularly valuable for developing clinicians as it integrates clinical experience with academic learning, offering a well-rounded approach to building competency in real-world medical practice.

CBL (Case-Based Learning) is an instructional approach that uses real-life or simulated cases to facilitate learning. It is widely used in various educational settings, particularly in medical, healthcare, legal, and business education. The primary goal of CBL is to engage students in active learning by having them apply theoretical knowledge to practical, real-world scenarios.

*Key Features of (Case-Based Learning) CBL:*

➤ Realistic Cases: Learning is centered on realistic, complex cases that mimic real-world problems or situations. These cases provide context and practical application for theoretical knowledge, making learning more relevant and meaningful.

➤ Learner-Centered Approach: CBL encourages active participation from students, who must analyze the case, identify key issues, and propose solutions. This contrasts with more passive forms of learning, such as lectures, where students are primarily recipients of information.

➤ Application of Knowledge: Students are required to apply what they have learned in the classroom to the case. This enhances understanding and retention by demonstrating how concepts and theories work in practice.

➤ Critical Thinking and Problem-Solving: CBL fosters critical thinking by challenging students to evaluate the information presented in the case, consider multiple perspectives, weigh evidence, and make decisions.

➤ Collaborative Learning: In many CBL settings, students work in groups, promoting teamwork, communication, and collaboration. The exchange of ideas and perspectives within a group setting helps deepen understanding.

➤ Instructor as Facilitator: Instructors guide the learning process rather than providing direct answers. Their role is to ask probing questions, offer feedback, and support students in their exploration of the case.

➤ Reflection and Discussion: Students reflect on their reasoning and decisions

during or after the case analysis. Group discussions often allow for the sharing of different viewpoints and deepen the learning experience.

*Steps in (Case-Based Learning) CBL:*

- Presentation of the Case: Students are introduced to a case, typically involving a real-world problem or scenario relevant to the subject area.
- Case Analysis: Students analyze the case by identifying key problems, considering possible solutions, and applying theoretical knowledge to the situation.
- Discussion and Collaboration: Students discuss the case in groups or with the instructor, sharing ideas, debating different approaches, and learning from each other's perspectives.
- Solution and Application: Based on their analysis and discussion, students propose solutions or make decisions regarding the case. They may be asked to justify their choices and consider the implications of their actions.
- Feedback and Reflection: Instructors provide feedback, and students reflect on their learning process, analyzing what they did well and areas they could improve upon.

Benefits of (Case-Based Learning) CBL: Promotes active learning and student engagement; Enhances critical thinking, problem-solving, and decision-making skills; Bridges the gap between theory and practice; Encourages collaborative and team-based learning; Improves retention of knowledge by linking learning to real-world experiences.

Commonly Used In: Medical and healthcare education (e.g., diagnosis, patient management, and ethical dilemmas); Business and management studies (e.g., strategy, marketing, and leadership); Legal education (e.g., analyzing court cases, legal principles, and ethics).

(Case-Based Learning) CBL is particularly effective because it creates a more engaging and applied learning experience that mirrors the complexity of real-world situations, helping students become better problem-solvers and critical thinkers.

DOPS (Direct Observation of Procedural Skills) is an assessment tool used in medical and healthcare education to evaluate a learner's technical and procedural skills in real-time clinical settings. The method involves an experienced clinician directly observing the learner as they perform a specific clinical procedure, providing immediate feedback aimed at improving performance and competence.

*Key Features of (Direct Observation of Procedural Skills) DOPS:*

- Real-Time Observation: The learner is observed performing a procedure on a real patient or in a simulated clinical setting. This observation allows the assessor to evaluate technical proficiency, professionalism, and patient care during the procedure.
- Wide Range of Procedures: DOPS can be used to assess various procedural

skills, such as taking blood samples, inserting IV lines, suturing, conducting a physical exam, or performing more complex surgical procedures, depending on the learner's level.

➤ **Structured and Specific:** The assessment is structured around specific criteria relevant to the procedure being observed. These criteria typically include technical ability, knowledge of the procedure, communication with the patient, hygiene and safety measures, and professional behavior.

➤ **Immediate Feedback:** After the procedure, the assessor provides immediate feedback to the learner, highlighting strengths and areas for improvement. This real-time feedback is crucial for helping learners adjust and refine their technique.

➤ **Formative and Summative:** DOPS is often used for formative purposes, meaning the goal is to help the learner improve through feedback and guidance. However, it can also be used in summative assessments, contributing to formal evaluations of competency during training programs.

➤ **Brief and Focused:** DOPS assessments are typically short (10–20 minutes), focusing on a specific skill or procedure. This allows for repeated assessments over time to track progress and development.

➤ **Assessor Role:** The assessor (usually a more senior clinician, supervisor, or mentor) not only observes the technical execution but also evaluates non-technical skills such as communication, patient consent, and professionalism.

Steps in (Direct Observation of Procedural Skills) DOPS:

- **Pre-procedure:** The learner is briefed about the procedure they will perform. The assessor ensures the learner understands the purpose of the procedure, patient consent, and safety protocols.

- **Direct Observation:** The assessor observes the learner performing the procedure. This observation covers all aspects, from preparation and interaction with the patient to the execution of the procedure itself.

- **Assessment:** The assessor uses a standardized form or checklist to evaluate the learner's performance. This typically includes areas such as: Technical skill and accuracy; Knowledge of the procedure; Communication with the patient; Maintenance of a sterile field (where applicable); Time management and efficiency.

**Immediate Feedback:** After the procedure, the assessor provides immediate feedback, discussing what the learner did well and areas that need improvement. The learner may also reflect on their own performance. **Documentation:** The observation and feedback are documented, and the learner may be given a rating or score based on their performance. These records can be used to track progress over time.

**Benefits of (Direct Observation of Procedural Skills) DOPS:** Provides real-time



evaluation of practical skills in a clinical setting; Encourages immediate feedback and reflection, helping learners improve quickly; Enhances the learner's confidence in performing clinical procedures; Allows for focused learning on both technical and non-technical skills, such as communication and professionalism; Helps track progress over time, identifying areas where further training or practice is needed. (Direct Observation of Procedural Skills) DOPS is particularly useful because it provides structured, formative assessment in a real-world context, allowing healthcare professionals to refine their skills and ensure competency in performing clinical procedures safely and effectively.

Entrustable Professional Activities (EPAs) are a critical tool in modern, competency-based education as they focus on real-world tasks and ensure that learners are truly prepared for independent practice before being entrusted with professional responsibilities. Entrustable Professional Activities (EPAs) are specific, observable tasks or responsibilities that can be entrusted to a learner once they have demonstrated the necessary competence to perform them independently. EPAs are widely used in competency-based medical and healthcare education to assess a learner's readiness for practice. They are designed to bridge the gap between theoretical knowledge and practical, real-world skills.

*Key Features of Entrustable Professional Activities (EPAs):*

- ✓ Units of Professional Practice: EPAs are real-world tasks or responsibilities that healthcare professionals are expected to perform in their daily practice. Examples include taking a patient's history, prescribing medication, or managing a clinical team. Each EPA represents a key activity within a profession.
- ✓ Observable and Measurable: EPAs are concrete activities that can be directly observed and measured. This allows supervisors or assessors to make objective judgments about a learner's competence based on their performance.
- ✓ Linked to Competency: While EPAs are the practical tasks, they are directly linked to underlying competencies such as medical knowledge, communication skills, clinical reasoning, professionalism, and patient care. Completing an EPA successfully indicates that the learner has integrated these competencies.
- ✓ Trustworthiness: The concept of "entrustment" is central to EPAs. Learners must demonstrate that they can perform the activity safely and independently before being entrusted with it. This means that supervisors must feel confident that the learner can carry out the task without supervision in a variety of situations.
- ✓ Gradual Entrustment: Learners move through different levels of entrustment, from needing close supervision to performing the activity independently. EPAs recognize that learners develop competence over time, and assessment is designed to track this

progression.

✓ **Context-Specific:** EPAs are tailored to specific professions and contexts. The tasks that are considered essential or "entrustable" for a physician, for example, may differ from those for a nurse, dentist, or allied health professional.

**Levels of Entrustment:** Typically, Entrustable Professional Activities (EPAs) are assessed on a scale that represents the degree of supervision a learner requires. Common levels include:

- **Observation Only:** The learner is not yet allowed to perform the task but can observe others doing it.
- **Direct Supervision:** The learner can perform the task, but only with close supervision (e.g., a senior clinician is in the room).
- **Indirect Supervision:** The learner can perform the task with a supervisor nearby but not in the room, available for help if needed.
- **Supervision at a Distance:** The learner can perform the task without direct oversight but may consult a supervisor when necessary.
- **Independent Practice:** The learner is fully entrusted to perform the task independently and can supervise others.

**Example Entrustable Professional Activities (EPAs) in Healthcare:** For medical students, residents, or other healthcare professionals, some common EPAs might include; Taking a comprehensive patient history; Performing and interpreting a physical examination; Formulating a differential diagnosis; Documenting and presenting clinical findings; Prescribing and managing medications; Collaborating with an interprofessional healthcare team; Communicating with patients and their families.

Observational learning involves acquiring knowledge through demonstration, a crucial aspect in healthcare where ensuring patient safety is fundamental. The development of motor skills is a fundamental part of medical proficiency and must be taught and refined with great precision. Many medical tasks are considered open-ended skills that require physicians to adapt to unpredictable and constantly changing situations (e.g., tracheal intubation and surgical suturing). The process behind this learning method is rooted in the mirror neuron system of the premotor cortex, which plays a role in imitating actions observed in others. Observational learning depends on the active involvement of the motor system and requires the implicit involvement of the observer for effective learning. In addition, immediate feedback is believed to be effective not only during hands-on practice but also during observation. There is evidence that combining observational learning with physical exercise may be more beneficial than relying on physical exercise alone. Observational techniques are essential for mastering complex medical procedures and promoting learning and skill

development through practice-based observation. Practicing motor skills is essential for improving performance in medical procedures, and understanding the mechanisms underlying these movements plays an important role in refining training programs. The approaches achieved using this method promote adaptability, optimize motivation, and improve cognitive processing. In addition, skill acquisition is accelerated through visual-spatial representation, creating vivid mental images in working memory.

**Assessment of Entrustable Professional Activities (EPAs):** Assessment of EPAs is based on direct observation of the learner performing the activity. Supervisors use standardized checklists or rubrics to evaluate performance and determine the level of supervision required. Feedback is a key component, helping learners understand their strengths and areas for improvement.

**Benefits of Entrustable Professional Activities (EPAs):** Competency-Based: EPAs ensure that learners are assessed based on their ability to perform real-world tasks, making the training process more relevant to professional practice; Clear Progression: The entrustment model provides a clear, structured path for learners as they develop their skills, from needing close supervision to independent practice; Practical Application: EPAs focus on practical tasks that professionals need to master, bridging the gap between theoretical learning and practical, clinical application. Personalized Learning: Learners receive personalized feedback based on their performance, allowing them to focus on areas that need further development; Patient Safety: The entrustment process ensures that learners are only entrusted with tasks when they have demonstrated sufficient competence, helping to ensure patient safety. Commonly Used In: Medical and healthcare education (e.g., residency and fellowship programs); Nursing education (e.g., entrusting nurses with independent patient care responsibilities); Allied health professions (e.g., physical therapists, pharmacists, and other clinical roles).

The Mini-CEX (Mini Clinical Evaluation Exercise) is a structured, workplace-based assessment tool used in medical education to evaluate a learner's clinical skills in real-time clinical practice. It involves direct observation of a trainee during a brief patient encounter, followed by immediate feedback from an experienced clinician or supervisor. The Mini-CEX is designed to assess a variety of clinical competencies, such as patient interaction, communication, clinical reasoning, and professionalism, in a real-world context.

*Key Features of (Mini Clinical Evaluation Exercise) Mini-CEX:*

➤ **Direct Observation:** A supervisor observes the trainee during a short clinical encounter with a real patient (usually lasting around 10-20 minutes). The encounter may involve history-taking, physical examination, diagnosis, patient counseling, or

treatment planning.

- **Broad Skill Assessment:** The Mini-CEX allows for the assessment of multiple clinical skills, such as: History-taking: Gathering and interpreting patient history; Physical examination: Performing a focused and effective clinical examination; Clinical reasoning: Formulating a differential diagnosis and treatment plan; Communication: Interacting with patients, explaining diagnoses, and delivering clear instructions; Professionalism: Demonstrating empathy, respect, and ethical behavior; Organizational skills: Managing time effectively and ensuring smooth patient flow.
- **Immediate Feedback:** After the encounter, the supervisor provides immediate, structured feedback to the learner, highlighting strengths and areas for improvement. This formative feedback is essential for guiding the trainee's development.
- **Short and Focused:** The Mini-CEX is brief and focused on specific competencies or elements of patient care, allowing for multiple assessments across a range of clinical scenarios over time.
- **Formative and Summative Use:** Although primarily formative (focused on improving skills through feedback), the Mini-CEX can also be used summative to contribute to formal evaluations of a trainee's competency at various stages of their education.
- **Standardized Evaluation:** The supervisor completes a structured evaluation form, rating the learner's performance across several domains on a numerical scale (e.g., 1-9), where higher scores reflect greater competence. Commonly assessed domains include clinical judgment, communication skills, organization, and professionalism.
- **Frequent and Flexible:** Mini-CEX assessments can be repeated frequently during clinical rotations to capture the learner's development over time. It is flexible, allowing assessments to take place in various clinical settings (inpatient, outpatient, emergency, etc.) and across different types of patient cases.

*Steps in (Mini Clinical Evaluation Exercise) Mini-CEX:*

- **Case Selection:** A real patient case is chosen for the learner to engage with, either as part of routine clinical practice or specifically for the assessment.
- **Observation:** The supervisor observes the learner interacting with the patient, performing tasks such as history-taking, physical examination, or patient counseling.
- **Assessment:** After the encounter, the supervisor completes the Mini-CEX evaluation form, rating the learner in various skill areas. The ratings are typically on a scale (e.g., 1-9), with higher scores indicating greater competency.
- **Feedback:** The supervisor provides immediate feedback, discussing the learner's performance, strengths, and areas for improvement. Feedback is specific, constructive, and designed to help the learner grow in their clinical skills.

➤ **Reflection and Action Plan:** The learner reflects on the feedback and, with the help of the supervisor, develops an action plan for further improvement. This may include targeted practice or additional study in certain areas.

*Domains Commonly Assessed in (Mini Clinical Evaluation Exercise) Mini-CEX:*

- **History-taking:** Ability to gather relevant patient information.
- **Physical examination:** Skill in conducting a focused, effective exam.
- **Clinical judgment:** Diagnostic reasoning, decision-making, and treatment planning.
- **Communication skills:** Clarity and empathy in interacting with patients and their families.
- **Professionalism:** Ethical behavior, respect, and rapport-building with patients.
- **Time management:** Efficient use of time and organization in patient care.

**Benefits of (Mini Clinical Evaluation Exercise) Mini-CEX:**

- **Real-Time Assessment:** Direct observation in a real clinical setting ensures that learners are evaluated on their actual performance, not just theoretical knowledge.
- **Personalized Feedback:** Immediate, targeted feedback helps trainees focus on specific areas for improvement.
- **Frequent and Flexible:** Multiple, brief assessments over time allow for tracking of progress and improvement.
- **Broad Assessment of Skills:** Mini-CEX covers a wide range of essential clinical competencies, ensuring comprehensive evaluation.
- **Learner Development:** The focus on formative feedback encourages continuous learning and development.

**Mini Clinical Evaluation Exercise Commonly Used In:** Medical education: Particularly during clinical rotations for medical students, interns, and residents; Nursing education: To assess practical nursing skills in clinical settings. Allied health education: For clinical professions such as physiotherapy, dentistry, and pharmacy. The Mini-CEX is a valuable tool for assessing and improving clinical performance, helping learners develop the skills necessary for competent, patient-centered care.

The **Objective Structured Clinical Examination (OSCE)** is a widely used assessment method in medical, nursing, and allied health education to evaluate a learner's clinical competence in a structured and standardized way. The OSCE assesses a range of clinical skills, including history-taking, physical examination, clinical reasoning, communication, and professionalism, in a controlled, simulated clinical environment.

*Key Features of Objective Structured Clinical Examination (OSCE):*

- **Structured Stations:** The OSCE consists of multiple stations (typically 10-20), each focusing on a different clinical task or scenario. Each station is designed to assess



specific skills, such as diagnosing a patient, performing a physical exam, interpreting test results, or counseling a patient.

- **Standardized Patients:** Many OSCEs use trained actors or simulated patients to portray clinical scenarios, ensuring standardization. These standardized patients follow a script, making the assessment consistent for all learners.
- **Time-Limited:** Each station is time-limited, typically lasting 5 to 10 minutes, and learners must complete the task within that time frame. This tests not only clinical competence but also time management and the ability to think on one's feet.
- **Objective Scoring:** Each station has clear objectives and a standardized checklist or rubric that the examiner uses to evaluate the learner's performance. The scoring system ensures that the assessment is objective and minimizes bias. Skills such as technical proficiency, communication, and clinical reasoning are scored based on the checklist.
- **Simulated Real-Life Scenarios:** The stations are designed to reflect realistic clinical challenges that healthcare professionals face in practice. This allows learners to demonstrate how they apply theoretical knowledge in practical, patient-centered situations.
- **Holistic Assessment:** The Objective Structured Clinical Examination (OSCE) assesses a broad range of skills, including:
  - Clinical knowledge: The ability to diagnose and manage clinical conditions;
  - Technical skills: Proficiency in performing specific procedures (e.g., suturing, administering injections);
  - Communication: Effective interaction with patients, explaining diagnoses, and delivering treatment plans;
  - Professionalism: Demonstrating empathy, ethical conduct, and respect for patients;
  - Clinical reasoning: Formulating differential diagnoses and decision-making based on clinical data.
- **Formative and Summative Use:** Objective Structured Clinical Examination (OSCEs) can be used for both formative (developmental) and summative (final) assessments. Formative OSCEs help learners identify areas for improvement, while summative OSCEs evaluate competence at the end of a course or training program.

**Objective Structured Clinical Examination (OSCE) Format: Pre-Set Stations:** Learners rotate through a series of stations, each with a different task. Tasks may include history-taking, performing a physical examination, counseling a patient, interpreting diagnostic tests, or demonstrating technical procedures; **Simulated Clinical Scenarios:** Each station simulates a specific scenario, such as diagnosing a patient with chest pain, performing a neurological exam, or counseling a patient on smoking cessation; **Checklists and Rubrics:** Each station has an examiner (usually a clinician or educator) who observes the learner's performance and scores them based on a

structured checklist. These checklists outline specific actions or steps the learner must perform to demonstrate competence; Immediate Feedback: In some OSCEs, particularly formative ones, learners receive immediate feedback after completing each station. This feedback helps them understand their strengths and areas for improvement.

*Commonly Assessed Skills in Objective Structured Clinical Examination (OSCE):*

- History-taking: Gathering relevant information from the patient about their symptoms and medical history.
- Physical examination: Performing appropriate clinical exams based on the patient's presenting symptoms.
- Diagnosis and treatment planning: Developing a differential diagnosis and formulating a management plan.
- Communication: Effectively explaining diagnoses, treatment options, and procedures to patients in an understandable and empathetic manner.
- Procedural skills: Demonstrating technical skills like suturing, inserting IVs, or performing CPR.
- Ethics and professionalism: Showing respect, empathy, and appropriate professional behavior during patient interactions.

Benefits of Objective Structured Clinical Examination (OSCE): Standardized Assessment: The structured format and standardized patients ensure that all learners are assessed in a consistent, objective way; Comprehensive Skill Evaluation: OSCEs assess not only knowledge but also practical, technical, and interpersonal skills, giving a holistic view of a learner's clinical competence; Realistic Scenarios: Simulating real-world clinical tasks helps prepare learners for actual clinical practice; Immediate Feedback and Reflection: In some OSCEs, learners receive immediate feedback, which promotes reflection and targeted learning.

Objective Structured Clinical Examination Commonly Used In: Medical education: OSCEs are often used in medical schools, residency programs, and for board certification exams; Nursing education: Nursing students are assessed on practical skills, such as patient care and clinical decision-making; Allied health professions: OSCEs are also used in other healthcare fields like dentistry, pharmacy, physiotherapy, and paramedicine.

Objective Structured Clinical Examination (OSCE) Strengths: Objectivity: The use of checklists and standardized patients ensures objective, unbiased assessment; Practical focus: The OSCE assesses the application of knowledge in real-life scenarios, ensuring learners are practice-ready; Flexible: OSCEs can be adapted to assess a wide

variety of clinical skills across different disciplines; The Objective Structured Clinical Examination (OSCE) is a powerful tool in healthcare education, as it effectively evaluates not just what learners know, but how well they can apply their knowledge and skills in real-world clinical situations.

The Objectively Structured Practical Exam (OSPE) is an assessment tool similar to the OSCE but is primarily used in laboratory-based, practical, or pre-clinical subjects, particularly in medical, dental, pharmacy, and allied health education. While OSCE focuses on clinical skills in patient care, the OSPE is designed to evaluate technical and practical skills in a more controlled, often laboratory-like environment.

*Key Features of Objective Structured Clinical Examination (OSPE):*

➤ **Multiple Stations:** Like the OSCE, the OSPE consists of a series of timed stations (usually 5-15 stations). Each station is designed to test a specific skill or set of skills in a practical setting, such as identifying anatomical structures, performing a laboratory experiment, or interpreting medical data.

➤ **Objective and Structured:** Each station is highly structured with a clear set of tasks or problems that the learner must complete. A standardized checklist or rubric is used to ensure objective assessment, reducing subjectivity and bias.

➤ **Hands-On Skills:** The focus of the OSPE is on assessing practical, technical skills, often in a laboratory or simulated clinical setting. These skills could include: Specimen identification (e.g., identifying anatomical specimens or cells under a microscope); Measurement tasks (e.g., blood pressure, or spirometry); Instrument handling (e.g., proper use of a centrifuge or microscope); Data interpretation (e.g., analyzing lab results or physiological readings); Procedure demonstrations (e.g., suturing on a model, IV insertion on a mannequin).

➤ **Non-Clinical Focus:** Objective Structured Clinical Examination (OSPEs) are generally used for evaluating pre-clinical or non-patient care skills, such as laboratory techniques, anatomy, physiology, pharmacology, or biochemistry, in contrast to OSCEs, which focus more on patient interaction and clinical care.

➤ **Rotation through Stations:** Learners rotate through different stations, each focused on a specific task. Some stations may involve hands-on procedures, while others may require the interpretation of data or answering questions about a practical task. Each station typically lasts around 5–10 minutes.

➤ **Checklist-Based Evaluation:** Examiners use a predefined checklist at each station to assess the learner's performance objectively. The checklist typically includes specific actions or outcomes that the learner must demonstrate to score points.

➤ **No Patient Interaction:** Unlike the OSCE, which often involves direct interaction with standardized patients or actors, the OSPE is more focused on technical and

laboratory skills. However, some stations may include theoretical questions or decision-making based on practical tasks.

*OSPE Format:*

- ✓ Pre-Set Stations: Learners are presented with different tasks at each station. These tasks may include performing a laboratory technique, identifying anatomical features, or analyzing experimental data.

- ✓ Rotation: Learners rotate through the stations in a timed manner. The format allows for the assessment of a broad range of practical skills in a relatively short period.

- ✓ Assessment: At each station, the learner's performance is evaluated using a standardized checklist or rating scale. The assessment may include: Correctness of procedures; Accuracy of data interpretation; Proper use of instruments or equipment; Ability to identify anatomical structures or lab specimens; Time management and efficiency in completing the tasks.

- ✓ Immediate Feedback: While not always standard, some OSPEs may include formative feedback after completion, helping learners understand areas for improvement.

Domains Commonly Assessed in Objective Structured Clinical Examination (OSPE):

- ✓ Practical skills: Performing technical procedures in a lab environment (e.g., preparing slides, using diagnostic tools, dissection, etc.).

- ✓ Instrument handling: Proper and safe use of laboratory or clinical instruments (e.g., microscope, sphygmomanometer).

- ✓ Knowledge application: Applying theoretical knowledge to practical tasks, such as interpreting lab results or understanding physiological data.

- ✓ Problem-solving and decision-making: Ability to solve practical problems and make informed decisions during hands-on tasks.

- ✓ Time management: Completing tasks efficiently within the time allocated at each station.

Benefits of Objective Structured Clinical Examination (OSPE): Objective Assessment: The use of standardized checklists makes the assessment objective, reducing examiner bias; Wide Range of Skills: The OSPE can assess a broad range of technical and practical skills, from basic lab techniques to more complex decision-making tasks; Hands-On Focus: The exam emphasizes practical, hands-on experience, ensuring that learners are competent in technical procedures required for their field; Controlled Environment: The practical, non-clinical setting allows for a more controlled and focused assessment of technical skills; Fair and Standardized: Since all learners perform the same tasks under the same conditions, the OSPE ensures fairness and consistency in assessment.

Differences Between OSPE and OSCE: Focus: OSPE is focused on assessing technical and practical skills in pre-clinical settings, such as laboratories or simulation environments, while OSCE evaluates clinical skills such as patient interaction and communication; Setting: OSPE is typically conducted in labs or controlled environments without patient interaction, whereas OSCEs often involve real or standardized patients; Skills Assessed: OSPE assesses skills like instrument use, data interpretation, and technical procedures, while OSCE evaluates broader clinical skills like history-taking, diagnosis, and patient counseling.

Objective Structured Clinical Examination (OSPE) Commonly Used In: Medical education: Particularly in pre-clinical subjects like anatomy, physiology, biochemistry, and pharmacology; Nursing education: To assess nursing skills such as specimen collection, medication administration, or monitoring vital signs; Allied health education: For fields like dentistry, pharmacy, and laboratory sciences, where technical proficiency is critical; The OSPE is a versatile and valuable tool in healthcare education for assessing practical skills in a standardized, objective way, ensuring learners are well-prepared for their technical responsibilities in clinical practice.

Workplace-Based Assessment (WPBA) refers to a range of assessment methods used to evaluate a learner's performance and competence in the actual workplace or clinical environment. Unlike traditional exams, which assess knowledge in a theoretical setting, WPBA assesses how a learner applies their knowledge and skills in real-time practice, making it an important tool in competency-based education, especially in healthcare and other professional fields.

*Key Features of Workplace-Based Assessment (WPBA):*

- Real-World Setting: WPBA occurs in the workplace, meaning the learner is assessed during their routine duties or tasks in a clinical, laboratory, or professional environment. This allows for the evaluation of practical, hands-on skills.
- Continuous Assessment: WPBA is typically conducted over a period of time, allowing for the observation and assessment of a learner's performance across various tasks and situations. This provides a more comprehensive and realistic understanding of their abilities.
- Formative and Summative Use: WPBA can be used both for formative purposes (providing feedback to support development) and summative purposes (assessing overall competency for certification or advancement).
- Multisource Feedback: In WPBA, feedback may come from a variety of sources, including supervisors, peers, patients, and even the learners themselves (through self-assessment). This allows for a 360-degree view of the learner's performance.
- Competency-Based: WPBA is aligned with specific competencies required for



professional practice. These competencies can include clinical reasoning, technical skills, communication, professionalism, and teamwork.

➤ **Direct Observation:** Learners are observed directly by supervisors or colleagues while performing their regular duties. The assessment is based on real-time observation rather than simulated tasks.

*Common Workplace-Based Assessment (WPBA) Methods:*

1. Mini-CEX (Mini Clinical Evaluation Exercise):

✓ A short, structured observation of a clinical encounter between a learner and a patient.

✓ Evaluates history-taking, physical examination, clinical reasoning, and communication.

✓ Immediate feedback is provided to the learner.

2. DOPS (Direct Observation of Procedural Skills):

✓ Focuses on the observation of the learner performing specific clinical procedures.

✓ Assesses technical skills, patient safety, and procedural competence.

✓ Feedback is given immediately after the procedure.

3. CBD (Case-Based Discussion):

✓ An in-depth discussion between the learner and a supervisor about a real patient case.

✓ Evaluates clinical reasoning, decision-making, and knowledge application.

✓ Allows the learner to reflect on their thought process and learn from the feedback.

4. Multisource Feedback (MSF):

✓ Also known as 360-degree feedback, it gathers assessments from multiple individuals who interact with the learner, including colleagues, patients, and supervisors.

✓ Evaluates teamwork, communication, professionalism, and interpersonal skills.

5. Portfolio:

✓ A collection of evidence gathered over time, including reflective writing, case logs, and documented feedback from supervisors.

✓ Allows for assessment of learning progress and personal development over a period.

6. Patient Satisfaction Surveys:

✓ Involves gathering feedback from patients regarding the learner's interaction, communication, and professionalism during consultations or procedures.

7. Entrustable Professional Activities (EPAs):

- ✓ Assesses whether a learner can be entrusted to perform specific professional tasks independently.

- ✓ Directly evaluates practical competence in real-world tasks.

Domains Assessed by WPBA:

- ✓ Clinical competence: Clinical reasoning, diagnosis, treatment planning, and procedural skills.

- ✓ Professionalism: Ethical behavior, responsibility, and respect for patients and colleagues.

- ✓ Communication skills: Interpersonal interactions with patients, families, and healthcare teams.

- ✓ Teamwork: Collaboration with peers and other healthcare professionals.

- ✓ Time management and organizational skills: Efficiently managing tasks and prioritizing patient care.

- ✓ Patient-centered care: Demonstrating empathy, respect, and understanding of patient needs and preferences.

*Benefits of Workplace-Based Assessment (WPBA):*

- ✓ Real-World Relevance: Since WPBA is conducted in actual workplace settings, it offers a more accurate assessment of a learner's readiness for professional practice than theoretical or simulation-based assessments.

- ✓ Holistic Assessment: WPBA evaluates a range of competencies, including clinical, interpersonal, and professional skills, providing a comprehensive view of the learner's abilities.

- ✓ Personalized Feedback: WPBA includes regular, personalized feedback that helps learners identify areas for improvement and track their progress over time.

- ✓ Encourages Reflection: Many WPBA methods, such as case-based discussions and portfolios, encourage self-assessment and reflection, helping learners develop critical thinking and lifelong learning skills.

- ✓ Supports Professional Development: By identifying strengths and weaknesses, WPBA helps learners create targeted learning plans to develop the skills they need for future practice.

- ✓ Flexible: WPBA can be adapted to different specialties, professional roles, and clinical settings, making it a versatile assessment method.

*Challenges of Workplace-Based Assessment (WPBA):*

- Consistency: Since WPBA is conducted in real-world settings, variability in patient cases, work environments, and assessors can affect the consistency of the assessment.

- Time-Intensive: Supervisors need to invest time in observing, assessing, and

providing feedback, which can be a challenge in busy clinical settings.

➤ **Subjectivity:** Although WPBA uses structured checklists, there is still some subjectivity in the evaluation process, especially in areas like communication and professionalism.

*Commonly Used In:*

➤ **Medical education:** For assessing students, interns, and residents in clinical settings.

➤ **Nursing education:** To evaluate clinical competence and practical nursing skills.

➤ **Allied health professions:** Used in fields like physiotherapy, pharmacy, and radiography to assess professional skills.

➤ **Other professional fields:** WPBA is also used in professions such as law and education, where practical skills and professional behaviors are essential.

Workplace-Based Assessment (WPBA) is a powerful tool for evaluating learners' real-world performance in professional settings. By focusing on practical skills and providing continuous feedback, WPBA ensures that learners are competent and ready for independent practice, making it an essential part of competency-based education and professional development.

The flipped classroom is an instructional approach that reverses the traditional teaching model. In a flipped classroom, students first engage with new content outside of class, typically through video lectures, readings, or other digital resources, and then use class time for interactive, hands-on activities, problem-solving, or discussions with peers and instructors.

*Key Features of the Flipped Classroom Model:*

1. **Pre-Class Learning:**

➤ **Content Delivery:** New material is introduced outside the classroom. This might involve watching pre-recorded video lectures, reading articles, reviewing case studies, or completing interactive online modules.

➤ **Self-Paced:** Students can go through the material at their own pace, pausing and rewatching sections if needed, which accommodates different learning styles and speeds.

2. **In-Class Application:**

➤ **Active Learning:** Classroom time is devoted to applying the knowledge gained through pre-class materials. Activities might include group discussions, problem-solving exercises, collaborative projects, debates, or lab work.

➤ **Instructor Facilitation:** Instead of delivering a lecture, the teacher acts as a facilitator or coach, guiding students as they work through problems or engage in discussions, addressing misconceptions, and providing individualized support.

### 3. Student-Centered Learning:

✓ The flipped classroom emphasizes active participation and engagement from students. Since they have already encountered the content outside of class, they are expected to come prepared to engage deeply with the material during class time.

✓ This approach shifts the focus from passive learning (listening to a lecture) to active learning, where students take ownership of their learning process.

#### Benefits of the Flipped Classroom:

- **Deeper Understanding:** By using class time for interactive and problem-solving activities, students can develop a deeper understanding of the material through practice and discussion rather than just memorization.

- **Increased Engagement:** The flipped classroom model promotes active participation and interaction with peers and instructors, which can increase student engagement and motivation to learn.

- **Personalized Learning:** Instructors have more time during class to provide individualized help to students, addressing specific questions or challenges, and supporting students at different levels of understanding.

- **Flexible Learning Pace:** Since students can access pre-class materials at their own pace, those who need more time to grasp complex concepts can revisit the content, while faster learners can move ahead.

- **Better Use of Class Time:** Instead of spending valuable class time delivering content, instructors can focus on higher-order learning activities like applying, analyzing, and evaluating information.

- **Improved Collaboration:** In-class activities often involve collaboration and teamwork, helping students develop important communication and teamwork skills while learning from their peers.

#### *Challenges of the Flipped Classroom:*

➤ **Preparation Time:** Creating high-quality pre-class materials, such as video lectures or interactive resources, can be time-consuming for instructors.

➤ **Student Accountability:** Success in a flipped classroom relies on students coming to class prepared. If students don't engage with the pre-class materials, they may struggle during in-class activities.

➤ **Access to Technology:** Students need reliable access to technology (such as computers, internet access, or multimedia tools) to complete pre-class assignments, which can be a barrier for some learners.

➤ **Adaptation:** Both students and teachers may need time to adjust to the flipped model, especially if they are used to traditional lectures. Some students might prefer face-to-face lectures, and teachers need to be comfortable with facilitating active

learning sessions.

#### *Flipped Classroom in Healthcare and Professional Education:*

In medical and professional education, the flipped classroom has gained popularity as a method for enhancing clinical training and hands-on learning:

- Pre-Class Work: Learners might review video lectures on clinical cases, medical procedures, or theoretical content before class.
- In-Class Application: Classroom time can then be dedicated to applying the material through case-based discussions, simulation exercises, or role-playing scenarios, helping learners practice decision-making and problem-solving in real-world contexts.

The flipped classroom is an innovative teaching model that shifts the focus from passive lecture-based learning to active, student-centered engagement. By delivering content outside of class and using class time for deeper application, the flipped classroom helps learners develop critical thinking, collaboration, and problem-solving skills while fostering a more personalized learning experience.

The flipped classroom is a modern, transformative learning strategy that integrates blended learning with digital or physical learning resources outside of the traditional classroom. Students receive pre-recorded lessons as preparatory assignments, shifting the focus from teacher-led learning to self-directed learning. Classroom activities focus on collaborative problem solving by having students work in small groups to analyze medical cases, encouraging a team approach and improving long-term knowledge retention. This method also encourages peer interaction and allows students to fill knowledge gaps while assessing individual differences and learning style strengths. Assigned tasks. Research shows that this approach outperforms traditional classrooms when it comes to increasing student awareness, critical thinking, learning outcomes, and motivation. Thanks to multimedia tools, students benefit from unlimited access to educational content, thus promoting interactive and independent learning. This model allows students to evaluate their progress, identify areas for improvement, and use constructive feedback from peers and instructors to ensure continuous improvement in their learning processes.

Peer-assisted learning (PAL) involves expanding knowledge and skills through mutual support from peers. This collaborative, non-professional approach to learning consists of a group of motivated individuals who support each other throughout the learning process. Participants, both teachers and students, usually have the same educational background. This method is implemented by selecting students who have adequate skills in teaching medical concepts. It promotes the development of skills that not only enhance learning but also contribute to medical practice. PAL is a broad



framework that strengthens the link between practical experience and a collaborative learning environment. Peer-assisted learning (PAL) benefits both the teacher and the student by improving their understanding and knowledge. Tutors gain benefits such as improved communication skills and a deeper understanding of the subject matter. The process of preparing lessons during tutoring and providing feedback to peers promotes the cognitive and non-cognitive development of tutors. Additionally, this approach has been shown to have a positive impact on student performance, leading to better exam results and overall success.

Social media acts as a hub for the digital web where users form online communities to engage in meaningful discussions. These communities play a vital role in sharing information, ideas, and a variety of content. Popular platforms such as Twitter, Facebook, YouTube, and blogs are just a few of the many options used for this purpose. In modern medicine, social media has become an integral part of professional communities, medical institutions, and support groups. As the need to advance education increases, integrating social media into modern educational systems is becoming essential. Social media platforms complement traditional teaching methods and support distance learning initiatives. Students and learners of all levels often turn to the Internet to learn about diseases, treatments, and physiological concepts. Additionally, organizations have realized the value of promoting blogs or live tweets during medical conferences, allowing content to reach a much wider audience than just those who attend in person. Advances in computer technology have had a major impact on medical education, especially through the electronic sharing of video content. The wide availability of online educational resources is essential for medical education. These tools support hands-on clinical skill acquisition, visual demonstration of anatomical dissections, and asynchronous learning through recorded lectures. Resources range from home study videos to professional content created by healthcare organizations and physicians, providing comprehensive content for personal and professional development.

A simulation is an artificial recreation of the real world that aims to achieve educational objectives through hands-on, experience-based learning. The basic idea of simulation-based learning (SBL) is to use simulated tools and scenarios to replicate authentic clinical situations. Although simulation is a relatively new phenomenon in medical education, it has long been used in other high-risk fields such as aviation. Medical simulation allows students to develop clinical skills through rigorous practice, a departure from traditional hands-on training. It offers an alternative to using real patients and real-time clinical scenarios, overcomes challenges such as limited access to clinical environments, and can be effectively integrated into pre-clinical training.

One of the most important benefits is giving trainees the freedom to repeatedly make and correct mistakes without compromising patient safety. Virtual reality (VR) can further enhance SBL by improving learning outcomes and increasing confidence in patient care. A cutting-edge technological innovation, virtual reality bridges the gap between theoretical knowledge and practical application by immersing students in a realistic yet controlled environment. The level of complexity, realism and interactivity of virtual reality systems can vary greatly, allowing users to dynamically participate in simulated scenarios. For example, haptic feedback simulates resistance when handling tools, making the exercise more realistic. This technology is often used to train residents in laparoscopic and endoscopic procedures, helping them improve their skills in a safe, controlled environment.

Problem-based learning (PBL) is an innovative pedagogical approach that integrates various learning principles to solve a clinical problem. Its main objective is to improve the quality of educational outcomes through collaborative, independent, integrated, and in-depth learning. A key characteristic of PBL is the "problem-first" approach, in which students approach a problem without having received any prior formal training on the topic. PBL is typically taught in small groups where the teacher acts as a facilitator rather than a direct instructor. These courses are divided into different phases, each focusing on a specific problem and including periods of independent study to research and gather information. This structure encourages students to actively participate in building a solid foundation for independent learning. In PBL, medical students develop their understanding and interpretation of information collaboratively through social interaction, replacing passive consumption of projected content. PBL is considered an effective method for developing advanced cognitive skills in a group setting. By working on clinical cases, students improve their ability to apply their knowledge and develop their diagnostic reasoning skills. This method not only improves clinical reasoning, but also promotes effective time management and long-term knowledge retention. These skills are essential to tomorrow's medical practice, especially in a field where continuing education is essential to keep pace with the rapid growth of medical information and technological advances.

Case-based learning (CBL) is an educational strategy that integrates clinical cases with traditional teaching methods to improve student engagement and understanding. By incorporating real-world scenarios, (CBL) eliminates the motivational gaps often found in lectures. Students receive comprehensive patient information, including medical history, symptoms, clinical findings, and laboratory results. Through collaboration and interaction with peers, learners assess the situation, develop a diagnostic approach, and recommend appropriate management plans. The

primary purpose of Case-based learning (CBL) is to foster the critical thinking and analytical skills necessary for clinical practice. Case-based learning (CBL) bridges the gap between theoretical knowledge and practical application through inquiry-based learning methods. Students work in small groups and solve clinical situations that mimic real-world medical situations. These teams work together to analyze the case, develop differential diagnoses, define treatment strategies, and consider next steps. Case-based learning (CBL) is particularly effective in addressing in-depth topics with clearly defined learning objectives and promotes improved clinical knowledge, teamwork, practical skills and evidence-based decision making.

Evidence-based medicine (EBM) teaches students the fundamental skills of interpreting, analyzing, and evaluating medical research. It involves five main steps: a) transforming uncertain information into a specific, researchable question, b) identifying the most relevant evidence, c) thoroughly evaluating the evidence for accuracy and reliability, d) integrating the results into clinical practice, and e) evaluating the results for effectiveness. Evidence-based medicine (EBM) promotes continuous learning and systematic thinking, which enables the careful application of the latest medical knowledge to patient care decisions. Although Evidence-based medicine (EBM) is opposed to balancing experiential objectivity and subjective experience, its early incorporation into medical education has significantly changed the cognitive approach of medical graduates. These students acquire better analytical and decision-making skills, leading to greater competence. Integrating EBM into traditional medical education improves research acumen, practical application, perspective, and long-term use of evidence-based strategies. Compared to blending (EBM) with traditional methods, modern approaches to education adopt a more comprehensive model that encourages creativity and adaptability. This shift encourages advanced critical thinking and reasoning, and contributes to a better understanding of disease mechanisms and patient care.

Bedside teaching is a traditional educational approach commonly used in medical and healthcare training. It involves direct teaching and learning that occurs at the patient's bedside, allowing students or trainees to engage with real patients and clinical scenarios in a practical environment. This method emphasizes experiential learning, patient interaction, and the application of theoretical knowledge in real-world situations.

#### *Key Features of Bedside Teaching:*

➤ **Real-World Context:** Bedside teaching takes place in clinical settings, such as hospitals or clinics, where learners interact with patients and healthcare professionals. This real-world context enhances the relevance of the education.

➤ **Patient-Centered Learning:** The method focuses on actual patient cases, allowing students to observe, assess, and discuss the patient's condition, diagnosis, and treatment options. This patient-centered approach promotes empathy and understanding of patient needs.

➤ **Interactive Learning:** Bedside teaching encourages active participation from learners. They may be involved in taking patient histories, performing physical examinations, discussing clinical findings, and formulating management plans in collaboration with supervisors.

➤ **Direct Observation:** Instructors or experienced clinicians observe and guide students during their interactions with patients, providing immediate feedback on clinical skills, communication, and professionalism.

➤ **Integration of Theory and Practice:** Learners can connect theoretical knowledge with clinical practice by discussing the rationale behind diagnoses and treatment plans while engaging with real patients.

#### Benefits of Bedside Teaching:

- **Enhanced Clinical Skills:** Direct interaction with patients helps learners develop essential clinical skills, such as history-taking, physical examination, and diagnostic reasoning.
- **Improved Patient Communication:** Engaging with patients in real-time helps students practice and refine their communication skills, building rapport and empathy.
- **Immediate Feedback:** Instructors can provide real-time feedback on students' performance, allowing for immediate reflection and improvement in clinical practice.
- **Holistic Understanding:** Learners gain a better understanding of patient care by seeing the entire patient experience, including diagnosis, treatment, and emotional aspects.
- **Development of Critical Thinking:** Engaging with complex cases fosters critical thinking and decision-making skills, as students must analyze and evaluate information in a dynamic environment.

#### *Challenges of Bedside Teaching:*

- ✓ **Time Constraints:** Clinical environments can be busy, making it challenging to find adequate time for teaching without interrupting patient care.
- ✓ **Variability in Learning Opportunities:** The availability of interesting cases or diverse patients may vary, impacting the learning experience. Not all patients may present typical or educational cases.
- ✓ **Potential for Patient Anxiety:** Some patients may feel uncomfortable with medical students or trainees present during their care, which can affect the teaching experience.
- ✓ **Need for Skilled Instructors:** Effective bedside teaching requires instructors who

are skilled in both clinical practice and teaching methodologies. Not all clinicians may have training in educational techniques.

✓ **Assessment Difficulties:** Evaluating student performance during bedside teaching can be subjective and challenging to standardize.

*Best Practices for Effective Bedside Teaching:*

- **Preparation:** Instructors should prepare before bedside teaching sessions by reviewing relevant patient cases, understanding the clinical background, and identifying key teaching points.
- **Patient Consent:** Always ensure that patients are comfortable with having learners present during their care and obtain their consent.
- **Engagement:** Encourage active participation from learners by asking questions and fostering discussions about clinical findings and management plans.
- **Feedback:** Provide immediate and constructive feedback to help learners improve their skills and understanding.
- **Reflective Practice:** Encourage learners to reflect on their experiences after the bedside teaching sessions to reinforce learning and promote self-assessment.

Bedside teaching is a valuable method in medical and healthcare education, providing learners with the opportunity to apply their knowledge and develop essential clinical skills in a real-world context. By emphasizing patient interaction, active learning, and immediate feedback, bedside teaching fosters a deeper understanding of patient care and prepares students for their future roles as healthcare professionals.

Education is an ongoing process and it is important to recognize that students have different approaches to learning. Several innovative learning strategies in medical education include case-based learning (CBL), evidence-based medicine (EBM), problem-based learning (PBL), simulation-based learning (SBL), digital education, peer-assisted learning (PAL). Experiential learning, flipped classrooms and collaborative learning. These non-traditional, student-centered learning methods expand students' perspectives through innovative methods of meaningful knowledge development while enhancing professional competencies through the development of skills, experiences, and leadership in the medical field. Thus, medical education must remain adaptable to effectively and appropriately integrate and apply interdisciplinary educational strategies from the core preclinical stages.

The adoption of modern teaching and learning methods in medical education has emerged as a key focus for higher education institutions globally. These methods aim to address the increasing complexity of healthcare systems, advances in medical science, and the need for well-rounded healthcare professionals capable of meeting diverse patient needs. The integration of innovative educational strategies, such as



problem-based learning (PBL), simulation-based training, and digital learning platforms, reflects a paradigm shift from traditional rote learning to a more dynamic, learner-centered approach.

One of the critical aspects of this transformation is the emphasis on active learning. Methods like flipped classrooms and case-based discussions encourage students to engage deeply with the material, promoting critical thinking and application of knowledge in real-world scenarios. Similarly, simulation-based training has proven invaluable for honing clinical skills in a controlled, risk-free environment, ensuring students are better prepared for real-life challenges.

Technology also plays a pivotal role in modernizing medical education. Virtual reality (VR), augmented reality (AR), and artificial intelligence (AI) are being used to enhance visualization, diagnosis training, and personalized learning pathways. These tools provide students with immersive experiences and instant feedback, fostering a deeper understanding of complex concepts.

Moreover, the global shift toward competency-based education reflects a commitment to outcome-driven learning. This approach prioritizes the development of specific skills and competencies essential for healthcare practice, moving beyond time-based training to focus on mastery and proficiency. Collaborative learning, interdisciplinary education, and integration of soft skills like communication, empathy, and teamwork further enrich the learning process.

However, the implementation of these modern methods is not without challenges. Variations in institutional resources, faculty training, and technological infrastructure can create disparities in the quality of education offered. Additionally, balancing traditional foundational knowledge with innovative methods requires careful curriculum design and ongoing evaluation to ensure educational effectiveness. The Execution of modern teaching and learning strategies in medical education is a global necessity driven by the evolving demands of healthcare. These methods not only enhance knowledge acquisition but also prepare students to become adaptive, competent, and compassionate medical professionals. The ongoing refinement of these approaches will be crucial in meeting the future needs of healthcare systems worldwide.

The global scientific discourse confirms that the exploration and application of contemporary educational practices are central to the advancement of medical and pharmaceutical training. The transition from passive to active learning, underpinned by pedagogical theories like constructivism and situated learning, is essential for producing a competent, adaptable, and collaborative future healthcare workforce. The path forward requires a concerted effort from institutions, accrediting bodies, and policymakers to address implementation barriers through strategic investment in infrastructure,

comprehensive faculty development, curricular reform, and the creation of robust, competency-based assessment frameworks. The future of medical and pharmaceutical education lies in flexible, blended, and person-centered learning models that leverage technology not as an end in itself, but as a powerful tool to enhance human interaction, clinical reasoning, and the ultimate goal of improving global health.

### Conclusions

➤ The integration of contemporary educational practices into university-level medical and pharmaceutical training represents a necessary and transformative evolution in preparing the next generation of healthcare professionals. The global shift from traditional, lecture-based pedagogy towards student-centered, experiential, and technology-enhanced learning models is not merely a trend but a fundamental response to the complexities of modern healthcare. These innovative approaches – including problem-based learning, simulation, interprofessional education, and flipped classrooms – have demonstrated significant potential to foster deeper understanding, enhance clinical competency, and cultivate critical soft skills such as collaboration, communication, and adaptive problem-solving.

➤ However, this transition is a complex, multi-faceted endeavor, marked by significant challenges. Disparities in resources, resistance to cultural change within institutions, the need for comprehensive faculty development, and the hurdle of curricular overcrowding present substantial obstacles to uniform global implementation. The journey forward requires a concerted, collaborative effort. Strategic investment in technological infrastructure, ongoing professional development for educators, and the reform of accreditation and assessment standards are crucial to creating sustainable and equitable educational ecosystems.

➤ Ultimately, the goal is clear: to create a dynamic, flexible, and resilient educational environment that empowers medical and pharmaceutical students to become lifelong learners and proficient practitioners. By embracing evidence-based pedagogical innovations and addressing the barriers to their adoption, the global academic community can ensure that future healthcare professionals are equipped with the knowledge, skills, and adaptability required to meet evolving patient needs and advance the standards of healthcare worldwide. The future of health professions education lies in this blended, personalized, and continuous learning paradigm, ensuring that graduates are not only experts in their field but also effective collaborators and innovators in a rapidly changing world.

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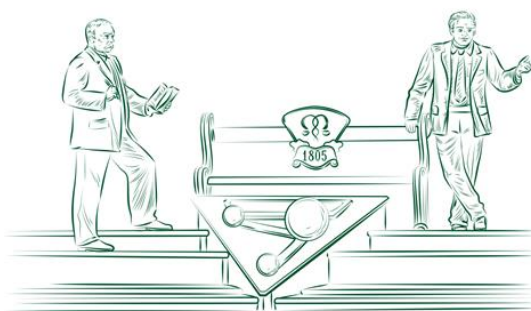
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## КРІОЕКСТРАКТ СЕЛЕЗІНКИ ЯК ПОТЕНЦІЙНИЙ ЗАСІБ КОРЕКЦІЇ ПОРУШЕНЬ АЗОТИСТОГО ОБМІНУ ПРИ ЕКСПЕРИМЕНТАЛЬНІЙ НЕФРОПАТІЇ ІНДУКОВАНИЙ КЕТОРОЛАКОМ

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**Анотація.** Актуальність проблеми зумовлена високою частотою НПЗП-індукованих уражень нирок і обмеженими можливостями їх попередження без зниження терапевтичної ефективності базових засобів. Метою дослідження було експериментально оцінити нефропротекторний потенціал кріоекстракту селезінки (КЕС) при кеторолак-індукованій нефропатії у щурів за показниками азотистого обміну та швидкості клубочкової фільтрації (ШКФ). Модель нефропатії відтворювали щоденним введенням кеторолаку 15 мг/кг упродовж 14 днів; КЕС вводили превентивно за 60 хв до кеторолаку на 5, 7, 9, 11 і 14 день. Біохімічну оцінку здійснювали за концентраціями сечовини (спектрофотометрія, 340 нм) і креатиніну (метод Яффе, 530 нм); функціональний стан нирок – за ШКФ (*Besseling P.J.*). Встановлено, що кеторолак спричиняв виражену азотемію та зниження фільтрації: сечовина –  $19,3 \pm 1,4$  ммоль/л (+242,6%;  $p < 0,001$ ), креатинін –  $136,0 \pm 3,7$  мкмоль/л (+85,6%;  $p < 0,001$ ), ШКФ –  $268 \pm 14$  мкмоль/л (–70,3%;  $p < 0,001$ ) порівняно з інтактними тваринами. Профілактичне застосування КЕС на тлі кеторолаку зменшувало гіперазотемію та відновлювало фільтрацію: сечовина –  $7,4 \pm 0,6$  ммоль/л (–61,5% до контролю;  $p < 0,001$ ), креатинін –  $109,3 \pm 4,9$  мкмоль/л (–19,6%;  $p < 0,001$ ), ШКФ –  $513 \pm 41$  мкмоль/л (+91,5%;  $p < 0,001$ ). За силою ефекту КЕС не поступався референтному фітопрепарату: у групі канефрону сечовина становила  $6,7 \pm 0,7$  ммоль/л (–65,2%;  $p < 0,001$ ), креатинін –  $101,3 \pm 4,7$  мкмоль/л (–25,5%;  $p < 0,001$ ), ШКФ –  $590 \pm 60$  мкмоль/л (+120,4%;  $p < 0,001$ ), міжгрупові відмінності з КЕС були статистично незначущими ( $p = 0,5$ ;  $p = 0,3$ ;  $p = 0,3$  відповідно). Отримані результати підтверджують нефропротекторну дію КЕС із корекцією азотистого обміну та частковим відновленням ШКФ на моделі НПЗП-нефропатії, що обґрунтовує доцільність подальшого вивчення КЕС як перспективного біотехнологічного ад'юванта до НПЗП у контексті підвищення безпеки фармакотерапії.

**Ключові слова:** нестероїдні протизапальні препарати, кеторолак, нефропатія, кріоекстракт селезінки, азотистий обмін, швидкість клубочкової



фільтрації, нефропротекція;

**Вступ.** Нестероїдні протизапальні препарати (НПЗП) залишаються одним із найпоширеніших класів лікарських засобів у клінічній практиці завдяки їхній вираженій анальгетичній, протизапальній та жарознижувальній дії. Проте поряд із високою терапевтичною ефективністю ці засоби характеризуються потенційним ризиком розвитку побічних ефектів, зокрема з боку нирок [1]. Кеторолак, один із представників цього класу, належить до потужних анальгетиків із коротким періодом напіввиведення, що забезпечує швидкий і виражений знеболювальний ефект, але водночас може викликати порушення ниркової гемодинаміки, зниження швидкості клубочкової фільтрації (ШКФ) та розвиток нефропатії навіть при відносно коротких курсах застосування. Основним механізмом нефротоксичності кеторолаку, як і більшості НПЗП, вважають пригнічення синтезу простагландинів, що призводить до вазоконстрикції аферентних артеріол, зменшення ниркового кровотоку та ішемії нефронів. У сукупності ці процеси зумовлюють порушення фільтраційно-екскреторної функції нирок і розвиток клінічно значущої азотемії [2, 3].

У контексті пошуку нових органопротекторних стратегій значну увагу привертають біотехнологічні підходи, засновані на використанні безклітинних кріоконсервованих біологічних засобів (БКБЗ). Ці препарати містять комплекс біологічно активних сполук – пептидів, амінокислот, ферментів, факторів росту, цитокінів, які зберігають функціональну активність після кріоконсервації. Одним із таких засобів є кріоекстракт селезінки (КЕС), що демонструє широкий спектр біологічної активності: антиоксидантну, імуномодулюючу, протизапальну та цитопротекторну. Завдяки своїй структурній та функціональній багатокомпонентності КЕС потенційно може впливати на ключові ланки патогенезу НПЗП-індукованих нефропатій – зменшення ішемічного ушкодження, відновлення клітинної перфузії, стабілізацію мембран і нормалізацію метаболізму ниркових клітин [4].

Сучасні експериментальні дані свідчать, що застосування БКБЗ сприяє активації репаративних процесів у тканинах, покращенню мікроциркуляції та пригніченню вільнорадикального окиснення, що дозволяє розглядати їх як перспективний напрям у профілактиці та лікуванні медикаментозно-індукованих нефропатій. Зокрема, КЕС може виступати як ефективний нефропротектор, що поєднує фізіологічну безпечність і потенційну здатність модулювати клітинно-сигнальні механізми ушкодження [5].

Важливість дослідження нефропротекторного потенціалу КЕС визначається як медико-біологічними, так і клінічними аспектами. По-перше,

зростання захворюваності на нефропатії, спричинені тривалим або безконтрольним застосуванням НПЗП, набуває глобального характеру. По-друге, сучасна фармакотерапія не має достатньо ефективних і безпечних засобів, здатних запобігати розвитку нефротоксичних уражень без зниження лікувальної активності базового препарату. По-третє, пошук нових нефропротекторів, зокрема біологічного походження, відкриває можливості створення індивідуалізованих схем терапії, що поєднують протизапальний і цитопротекторний ефекти.

У цьому контексті експериментальна оцінка дії кріоекстракту селезінки при кеторолак-індукованій нефропатії становить особливий науковий інтерес. Дослідження спрямоване на визначення його впливу на показники азотистого обміну та швидкість клубочкової фільтрації, які є чутливими маркерами функціонального стану нирок. Отримані результати можуть слугувати підґрунтям для подальшого розвитку патогенетично обґрунтованих підходів до профілактики та лікування нефротоксичних уражень, спричинених НПЗП, і створення нових біотехнологічних препаратів із вираженим органопротекторним потенціалом.

Таким чином, актуальність дослідження зумовлена потребою у пошуку ефективних засобів захисту нирок від токсичного впливу НПЗП, а також науковим інтересом до вивчення органопротекторних властивостей кріоекстракту селезінки як перспективного біологічного агента у системі комплексної фармакотерапії [6].

**Мета дослідження** – експериментально оцінити нефропротекторний ефект кріоекстракту селезінки при кеторолак-індукованій нефропатії у щурів за показниками азотистого обміну та швидкості клубочкової фільтрації.

**Матеріали та методи.** Медикаментозно-індуковану нефропатію відтворювали шляхом щоденного введення кеторолаку у дозі 15 мг/кг протягом 14 днів [7]. Згідно з літературними даними, така схема достовірно відтворює нефротоксичний ефект препарату у щурів. Кріоекстракт селезінки (КЕС) вводили за 60 хв до введення кеторолаку на 5, 7, 9, 11 та 14 дні експерименту. Вміст сечовини в сироватці крові визначали спектрофотометричним методом за реакцією з 2-оксоглютаратом у присутності глутаматдегідрогенази при довжині хвилі 340 нм. Концентрацію креатиніну оцінювали спектрофотометрично за методом Яффе при довжині хвилі 530 нм.

КЕС готували з тканини селезінки новонароджених свиней. Біоматеріал подрібнювали до фрагментів масою 2-5 мг та тричі відмивали стерильним фізіологічним розчином (рН 7,4) у співвідношенні 1:10 для видалення крові й

неклітинних домішок. Далі тканину інкубували з розчином кріопротектора – гліцерину, поліетиленоксиду-400 (*polyethylene oxide* – PEO-400) або PEO-1500 – у концентрації 10–20 % (1:1). Обрані кріопротектори забезпечували проникнення в тканину та запобігали утворенню кристалів льоду при заморожуванні. Охолодження здійснювали зі швидкістю 1°C/хв до –70°C, після чого зразки занурювали у рідкий азот (–196°C). Розморожування проводили у водяній бані при 37-40°C. Для видалення кріопротектора застосовували різні методи: гліцерин і PEO-400 елюювали сахарозними розчинами відповідної молярності, а PEO-1500 – фізіологічним розчином. Фрагменти селезінки інкубували у фізіологічному розчині при 22-24°C протягом 30–90 хв залежно від бажаного ступеня екстракції білково-пептидних фракцій. Супернатант піддавали термічній обробці у водяній бані (37-40°C, 15 хв) для денатурації небажаних термолабільних білків. Завершальним етапом було фільтрування крізь фільтрувальний папір, що забезпечувало отримання прозорого стерильного препарату, придатного до подальшого використання. Стандартизований за вмістом білка КЕС (0,1 мг білка на 1 мл) вводили щурам в/м у дозі 5,0 мл/кг маси тіла.

Статистичну обробку проводили у «Microsoft Office Excel 2016» із дотриманням принципів біостатистики: за нормального розподілу міжгрупові відмінності оцінювали t-критерієм Ст'юдента, за відхилення від нормальності – U-критерієм Манна-Вітні. Результати наводили як  $M \pm m$  ( $M \pm SE$ ).

**Результати та їх обговорення.** Отримані результати свідчать про істотні порушення функціонального стану нирок під впливом кеторолаку, що проявлялися вираженими змінами основних біохімічних показників азотистого обміну. У щурів контрольної групи, яким вводили кеторолак, концентрація сечовини в крові підвищувалася до  $19,3 \pm 1,4$  ммоль/л ( $p < 0,001$ ), що перевищувало рівень інтактних тварин на 242,6%. Така гіперуремія відображає суттєве пригнічення екскреторної функції нирок, ймовірно, унаслідок порушення клубочкової фільтрації та посилення катаболічних процесів на тлі нефротоксичного впливу препарату. Паралельно зростала концентрація креатиніну до  $136,0 \pm 3,7$  мкмоль/л ( $p < 0,001$ ), що на 85,6% вище від норми, що вказує на пригнічення ниркової фільтрації та накопичення азотистих метаболітів у системному кровотоці. На цьому тлі ШКФ, розрахована за формулою Besseling P.J., знижувалася більш ніж утричі – до  $268 \pm 14$  мкмоль/л ( $p < 0,001$ ; –70,3%), що підтверджує розвиток вираженої нефропатії з домінуванням фільтраційних порушень.

Застосування канефрону супроводжувалося істотним покращенням азотовидільної функції нирок. У тварин, які отримували кеторолак у поєднанні з канефроном, рівень сечовини знижувався до  $6,7 \pm 0,7$  ммоль/л ( $p < 0,001$  щодо

контролю;  $-65,2\%$ ), що свідчить про відновлення часткової детоксикаційної здатності нефронів. Концентрація креатиніну зменшувалася до  $101,3 \pm 4,7$  мкмоль/л ( $p < 0,001$  щодо контролю;  $-25,5\%$ ), що відображає часткове відновлення фільтраційної здатності клубочків. Водночас ШКФ збільшувалася до  $590 \pm 60$  мкмоль/л ( $p < 0,001$ ;  $+120,4\%$ ), що вказує на виражену тенденцію до нормалізації функціонального стану нирок. Така динаміка підтверджує наявність нефропротекторного ефекту канефрону, який, імовірно, пов'язаний із його спазмолітичними, протизапальними та помірними діуретичними властивостями.

Введення КЕС у поєднанні з кеторолаком також сприяло істотному зниженню рівня азотистих метаболітів у крові. Концентрація сечовини у тварин цієї групи становила  $7,4 \pm 0,6$  ммоль/л ( $p < 0,001$  щодо контролю;  $-61,5\%$ ), що свідчить про зменшення вираженості гіперуремії. Різниця між ефектами КЕС та канефрону за цим показником була статистично незначущою ( $p = 0,5$ ), що вказує на подібний ступінь впливу обох засобів на відновлення азотовидільної функції. Концентрація креатиніну знижувалася до  $109,3 \pm 4,9$  мкмоль/л ( $p < 0,001$  щодо контролю;  $-19,6\%$ ), а різниця між КЕС і канефроном залишалася статистично незначущою ( $p = 0,3$ ). Це свідчить про співставну ефективність у корекції фільтраційних порушень, спричинених кеторолаком. Найбільш вираженим позитивним ефектом КЕС характеризувалася ШКФ, яка підвищувалася до  $513 \pm 41$  мкмоль/л ( $p < 0,001$ ;  $+91,5\%$ ), що перевищувало контрольні показники на  $91,5\%$  і свідчило про суттєве відновлення клубочкової фільтрації. Порівняно з канефроном відмінності за цим показником також не досягали статистичної значущості ( $p = 0,3$ ), що дає підстави розглядати КЕС як альтернативний засіб нефропротекції з подібною ефективністю [8].

Аналіз отриманих даних дає змогу стверджувати, що введення кеторолаку супроводжується розвитком нефротоксичного синдрому, який відображається значним підвищенням рівнів сечовини та креатиніну у крові та різким зниженням ШКФ. Це відповідає типовій картині НПЗП-індукованої нефропатії, що формується внаслідок пригнічення синтезу ПГ, вазоконстрикції аферентних артеріол, зниження ниркового кровотоку й ішемії кіркової речовини. Виявлене зниження ШКФ більш ніж на  $70\%$  є маркером тяжкої функціональної недостатності нефронів, що супроводжується азотемією та накопиченням токсичних метаболітів у плазмі.

Позитивний вплив канефрону на досліджувані параметри може бути зумовлений його комбінованим механізмом дії, який включає зменшення запальної інфільтрації інтерстицію, покращення мікроциркуляції, антиоксидантний та діуретичний ефекти. Схожі тенденції спостерігаються і при

застосуванні КЕС, що може бути пов'язано з його здатністю модулювати системну запальну реакцію та знижувати цитотоксичний вплив кеторолаку на нефрони. Відомо, що КЕС містить широкий спектр біологічно активних молекул – цитокінів, факторів росту, низькомолекулярних пептидів, які сприяють репарації ендотелію та стабілізації клітинних мембран. Завдяки цьому він може зменшувати прояви ішемії та окисного стресу, що лежать в основі НПЗЗ-нефропатій.

Порівняльна оцінка результатів між групами, яким вводили канефрон або КЕС, свідчить про схожу вираженість нефропротекторного ефекту. Обидва засоби достовірно знижували рівні сечовини та креатиніну, а також підвищували ШКФ порівняно з кеторолаком у моновведенні. Водночас тенденція до вищих значень ШКФ у групі КЕС може свідчити про дещо інтенсивніше відновлення клубочкової фільтрації, хоча відмінності не досягли рівня статистичної значущості. Отримані результати дають підстави припустити, що вплив КЕС може реалізовуватися не лише за рахунок діуретичного ефекту, а й завдяки прямій цитопротекції ниркових структур.

Зменшення концентрації сечовини майже до фізіологічних рівнів у групах з канефроном і КЕС свідчить про збереження функціональної здатності нирок до ефективної елімінації азотистих метаболітів. Це підтверджується також покращенням показників креатиніну, який є чутливим маркером зниження клубочкової фільтрації. Відновлення ШКФ більш ніж удвічі у тварин, що отримували КЕС, порівняно з контролем, свідчить про здатність цього засобу стимулювати компенсаторно-відновні механізми ниркової гемодинаміки.

Підсумовуючи, можна зазначити, що обидва досліджувані засоби – канефрон і КЕС – забезпечували достовірну нормалізацію ключових показників азотистого обміну при кеторолак-індукованій нефропатії. Їх застосування приводило до значного зменшення гіперазотемії та підвищення ШКФ, що свідчить про відновлення фільтраційно-екскреторної функції нирок. За ступенем впливу на рівні сечовини та креатиніну КЕС не поступався канефрону, а за величиною приросту ШКФ демонстрував навіть тенденцію до більш вираженого ефекту. Отримані результати підтверджують наявність у КЕС вираженої нефропротекторної активності, що не поступається відомому фітопрепарату з доведеною клінічною ефективністю. Це дозволяє розглядати КЕС як перспективний біотехнологічний засіб для попередження або корекції нефропатій, зумовлених застосуванням НПЗП.

Динаміка змін досліджуваних параметрів узгоджується з даними сучасної літератури, згідно з якими НПЗП, особливо кеторолак, є потенційно



нефротоксичними препаратами, що порушують синтез ниркових простагландинів і знижують перфузію нефронів. Водночас засоби, що мають антиоксидантну та протизапальну активність, здатні зменшувати тяжкість уражень, що підтверджено в ряді експериментальних і клінічних досліджень. Отримані результати демонструють перспективність застосування БКБЗ як нового напрямку нефропротекції, що базується на механізмах клітинної сигналізації та регуляції цитокінового балансу.

Таким чином, проведене дослідження підтверджує, що кеторолак викликає розвиток нефропатії, яка проявляється підвищенням рівнів сечовини та креатиніну і зниженням ШКФ, тоді як введення канефрону або КЕС достовірно послаблює вираженість цих порушень. Обидва засоби виявляють нефропротекторну дію, сприяючи відновленню основних функцій нирок, що відкриває перспективи їх застосування для профілактики та лікування НПЗП-індукованих нефропатій.

### **Висновки.**

1. Введення кеторолаку у дозі 15 мг/кг протягом 14 днів призводило до розвитку нефропатії, що проявлялося підвищенням рівня сечовини у крові до  $19,3 \pm 1,4$  ммоль/л (+242,6%;  $p < 0,001$ ), креатиніну – до  $136,0 \pm 3,7$  мкмоль/л (+85,6%;  $p < 0,001$ ) та зниженням швидкості клубочкової фільтрації до  $268 \pm 14$  мкмоль/л (–70,3%;  $p < 0,001$ ).

2. Застосування канефрону сприяло покращенню функціонального стану нирок: рівень сечовини знижувався до  $6,7 \pm 0,7$  ммоль/л (–65,2%;  $p < 0,001$ ), креатиніну – до  $101,3 \pm 4,7$  мкмоль/л (–25,5%;  $p < 0,001$ ), а швидкість клубочкової фільтрації підвищувалася до  $590 \pm 60$  мкмоль/л (+120,4%;  $p < 0,001$ ).

3. Введення кріоекстракту селезінки забезпечувало подібний нефропротекторний ефект: рівень сечовини знижувався до  $7,4 \pm 0,6$  ммоль/л (–61,5%;  $p < 0,001$ ), креатиніну – до  $109,3 \pm 4,9$  мкмоль/л (–19,6%;  $p < 0,001$ ), а швидкість клубочкової фільтрації підвищувалася до  $513 \pm 41$  мкмоль/л (+91,5%;  $p < 0,001$ ).

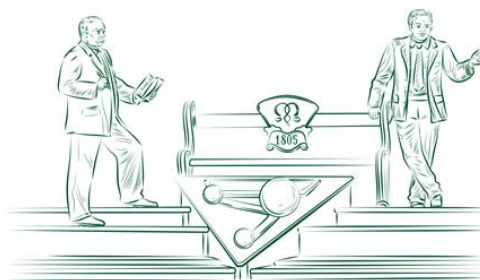
4. За ефективністю кріоекстракт селезінки не поступався канефрону, підтверджуючи виражену здатність відновлювати фільтраційно-екскреторну функцію нирок при нефропатії, індукованій кеторолаком.

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## MONITORING OF ARGINASE ACTIVITY VIA UREA BIOSENSOR

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**Abstract.** Dysregulation of arginase activity affects arginine metabolism and nitric oxide signalling, contributing to metabolic and inflammatory disorders. In this study, an amperometric urease and thermally reduced graphene oxide based biosensor was developed and applied to evaluate arginase activity in model kidney perfusate samples. The biosensor exhibited high sensitivity ( $87.1 \text{ nA} \cdot \text{mM}^{-1}$ ) across two linear ranges (0.03–1.0 mM and 1.0–5.0 mM urea) and demonstrated excellent selectivity toward urea at 0 V vs. Ag/AgCl, with negligible interference from common electroactive species found in biological media. Recovery tests confirmed good accuracy (102.8–115.6%) and repeatability ( $\text{RSD} \leq 5.44\%$ ), indicating reliable urea quantification in complex matrices. The linear correlation between biosensor response and arginase activity supports its applicability for monitoring arginase-catalyzed reactions and evaluating enzymatic activity through urea detection in perfusate samples.

**Key words:** Arginase activity; urea biosensor; kidney perfusate.

**Introduction.** Dysregulation of arginase activity disrupts arginine availability and nitric oxide signalling, causing multiple downstream effects. The importance of arginase in metabolic disorders is evident through diseases such as diabetes mellitus, obesity and metabolic syndrome, non-alcoholic fatty liver disease, cardiovascular disorders, or arginase deficiency (an Inherited Metabolic Disorder) (Caldwell *et al.*, 2018). Thus, monitoring arginase activity is vital for early disease detection, assessing progression and prognosis, and guiding targeted therapies.

This study focused on arginase activity as a biomarker in kidney perfusate due to its close association with key pathophysiological processes, including tissue injury and inflammation. This type of biomarker has not yet been explored, but its biochemical pathway shows potential for its application in the context of kidney perfusion, so monitoring it could provide critical insights into organ viability. For monitoring of arginase activity, amperometric urea biosensor was employed to measure enzyme activity in real time. Since arginase is a key enzyme in the urea cycle, catalyzing the hydrolysis of L-arginine into urea and ornithine the possibility of applying an amperometric urea biosensor for activity monitoring has emerged. The biosensor has the potential to function even in turbid media that offering significant advantages over conventional methods, such as ELISA, and detecting other sophisticated methods.

**The aim of the study.** To evaluate the suitability of the urease and thermally reduced graphene oxide based biosensor for determining arginase activity in kidney perfusate.

## **Materials and Methods.**

### *Materials and equipments*

L-arginase from bovine serum (Sigma-Aldrich, USA), Urease from *Canavalia ensiformis* (Calbiochem, UK), Thermically reduced graphene oxide (TRGO) (Made in lab (Šakinytė *et al.*, 2015)), Bovine serum Albumin (Sigma-Aldrich, USA), Potassium chloride, KCl  $\geq 99,0$  % (Sigma-Aldrich, USA), Disodium phosphate dodecahydrate, Na<sub>2</sub>HPO<sub>4</sub> · 12H<sub>2</sub>O  $\geq 99,0$  % (Sigma-Aldrich, Germany), Potassium dihydrogen phosphate, KH<sub>2</sub>PO<sub>4</sub>  $\geq 98,0$  % (Sigma-Aldrich, USA), EDTA acid, (NaOOCCH<sub>2</sub>)<sub>2</sub>NCH<sub>2</sub>CH<sub>2</sub>N(CH<sub>2</sub>COONa)<sub>2</sub> · 2H<sub>2</sub>O  $\geq 98,0$  % (Sigma-Aldrich, Germany), L-arginine monohydrochloride, C<sub>6</sub>H<sub>14</sub>N<sub>4</sub>O<sub>2</sub>, 98.5-101.0% (Sigma-Aldrich, JAV), Urea, CH<sub>4</sub>N<sub>2</sub>O (Sigma-Aldrich, USA), Sodium hydroxide, NaOH  $\geq 98,5$  % (Bárta a Cihlár, Czech Republic), Ammonium chloride, NH<sub>4</sub>Cl (Sigma-Aldrich, USA), Hydrogen peroxide, H<sub>2</sub>O<sub>2</sub> (Sigma-Aldrich, USA), Ascorbic acid, C<sub>6</sub>H<sub>8</sub>O<sub>6</sub> (Sigma-Aldrich, USA), Serotonin hydrochloride, 98%, C<sub>10</sub>H<sub>13</sub>ClN<sub>2</sub>O (Sigma-Aldrich, USA), L-epinephrine, 99%, C<sub>9</sub>H<sub>13</sub>NO<sub>3</sub>, Dopamine hydrochloride, C<sub>8</sub>H<sub>12</sub>ClNO<sub>2</sub>, Adenosine 5'-diphosphate sodium salt, C<sub>10</sub>H<sub>15</sub>N<sub>5</sub>O<sub>10</sub>P<sub>2</sub> (Sigma-Aldrich, USA), Uric acid, C<sub>5</sub>H<sub>4</sub>N<sub>4</sub>O<sub>3</sub>, (Sigma-Aldrich, USA), D-glucose, C<sub>6</sub>H<sub>12</sub>O<sub>6</sub> (Sigma-Aldrich, USA), Kidney perfusion solution KPS-1 (Organ Recovery Systems, USA).

Equipment used in the work: electronic scales ABT 100-5M (KERN, Germany), magnetic stirrer RSM-Eco (Phoenix Instrument, Germany), benchtop pH meter XS pH 50 VioLab (Giorgio Bormac, Italy), potentiostat EmStat4S (PalmSens BV, Netherlands), electrochemical cell with working, auxiliary and reference electrodes (VU, GMC), micropipettes, 2 – 20 µl, 10 – 100 µl, 1000 – 10000 µl (Eppendorf research, USA).

### *Preparation of buffer solution*

20 mM phosphate buffer (PBS) was prepared using 14.9 g potassium chloride (KCl), 9.8 g sodium phosphate dibasic dodecahydrate (Na<sub>2</sub>HPO<sub>4</sub> · 12H<sub>2</sub>O), 1.8 g potassium dihydrogen phosphate (KH<sub>2</sub>PO<sub>4</sub>) and 0.83 g ethylenediaminetetraacetic acid (EDTA). The materials were dissolved in ~1800 ml distilled water using a magnetic stirrer. After the materials were dissolved, the pH was adjusted to pH 7.2 using NaOH and monitored with a pH meter. After pH adjustment, the volume was made up to 2000 ml with distilled water.

### *Preparation of urea solutions*

Urea solutions of different concentrations were prepared by dissolving weighed

amounts of analytical grade urea in phosphate-buffered saline (PBS) previously prepared as described above. Solutions with urea concentrations of 2, 5, 10, 20, 50, 100, and 200 mM were individually prepared in separate volumetric flasks. All solutions were freshly prepared prior to measurements and stored at 4 °C until use.

#### *Preparation of interferent test solutions*

Solutions of potential interferents were prepared in phosphate-buffered saline (PBS) at the following concentrations: 10 mM dopamine, adenosine, serotonin, and uric acid; 25 mM ascorbic acid; 5 mM glucose; 7 g/mL albumin; 240 mM epinephrine; 9.8 mM hydrogen peroxide; and 50 mM arginine. The hydrogen peroxide solution was further diluted by serial dilutions to obtain a 10  $\mu$ M working solution. All solutions were freshly prepared prior to measurements and stored at 4 °C until use.

#### *Preparation of arginase solutions*

A 200  $\mu$ L arginase solution was prepared by dissolving 4 mg of arginase (specific activity 20 U/mg) in phosphate-buffered saline (PBS). A 50 mM arginine solution was used as the substrate. To investigate the effect of enzyme concentration, five samples were prepared by mixing the arginase and arginine solutions in different volume ratios as follows: 50  $\mu$ L arginase solution + 50  $\mu$ L 50 mM arginine solution; 40  $\mu$ L arginase solution + 50  $\mu$ L 50 mM arginine solution; 30  $\mu$ L arginase solution + 50  $\mu$ L 50 mM arginine solution; 20  $\mu$ L arginase solution + 50  $\mu$ L 50 mM arginine solution; 10  $\mu$ L arginase solution + 50  $\mu$ L 50 mM arginine solution. All samples were gently mixed and used immediately for measurements.

#### *Preparation of perfusate and urea solutions*

For the evaluation of biosensor signal reproducibility in perfusate, mixed samples containing perfusate and urea were prepared. Each sample had a total volume of 150  $\mu$ L, obtained by mixing perfusate with urea solutions previously used for calibration curve preparation. The resulting urea concentrations in the samples were 1.9 mM, 5.0 mM, 10.1 mM, 19.9 mM, and 42 mM. All samples were freshly prepared prior to measurements to ensure consistency of experimental conditions.

#### *Enzyme immobilization and biosensor construction*

A biosensor consisting of a membrane with urease was prepared by immobilizing urease in a thermally reduced graphene oxide (TRGO) matrix on a semipermeable terylene film. The enzyme membrane mixture consisting of urease, TRGO, bovine serum albumin in PBS solution and glutaraldehyde was applied to the surface of the terylene membrane attached to the inside of a rubber ring and kept overnight at 4 °C. The enzyme membrane thus prepared was mechanically pressed against the surface of a rod graphite electrode and this whole formed a urease/TRGO biosensor.



### *Electrochemical measurements*

The constructed biosensor is connected to an electrochemical system and used as the working electrode. The system consists of a three-electrode electrochemical cell, a potentiostat, and a signal flushing and recording system. The 1 mL electrochemical cell is composed of an auxiliary electrode (titanium plate), a reference electrode (Ag/AgCl), and the working electrode – the biosensor. Chronoamperometric measurements are performed at a constant potential of 0 V applied to the working electrode, at room temperature (20–25 °C), using a 10 mM phosphate buffer solution. After introducing urease solutions of different concentrations prepared in the phosphate buffer into the cell, the responses of the biosensor were recorded. The biosensor response is determined by subtracting the background current value from the current density generated by the biosensor.

For data analysis, a Michaelis–Menten hyperbolic equation adapted for electrochemical measurements is used (Ivanauskas *et al.*, 2008):

$$I = \frac{I_{\max}^{\text{app}}[S]}{K_M^{\text{app}} + [S]} \quad (1)$$

where  $I$  is the current, and  $[S]$  is the substrate concentration. From this equation, the main kinetic parameters of the biosensor can be determined: ( $I_{\max}^{\text{app}}$ ) – the apparent maximum current that can be generated by the bioelectrocatalytic system, and ( $K_M^{\text{app}}$ ) – the apparent Michaelis constant (the substrate concentration at which the current generated by the bioelectrocatalytic system equals  $I_{\max}^{\text{app}}/2$ ). The value of  $K_M^{\text{app}}$  also indicates the substrate concentration range over which the biosensor response remains linearly dependent on concentration.

The limit of detection (LOD) of the constructed biosensor was calculated from the first linear part of the calibration curve according to Equation (2) (Shrivastava and Gupta, 2011):

$$LOD = 3S_a/b \quad (2)$$

The biosensor-generated signals were measured three times at the same substrate concentration within the first linear range of the calibration curve. The standard deviation ( $S_a$ ) of these signals was calculated, multiplied by 3, and divided by the slope ( $b$ ) of the first linear part of the calibration curve – representing the sensitivity of the biosensor.

The obtained data were processed using OriginPro 2015 and Microsoft Office Excel software.

### **Results and discussion.**

#### *Biosensor operating principle*

In this study, an enzymatic urea biosensor was developed and analyzed. In this

biosensor, the enzyme urease was immobilized within a thermally reduced graphene oxide (TRGO) matrix. Urease participates in an enzymatic reaction, which generates an electrochemic signal, that enables determination of urea concentration in the analyzed sample. When urea is introduced into the electrochemical cell, urease selectively recognises and hydrolyses it into ammonia and carbamic acid, the latter of which is oxidized on the TRGO surface, resulting in an increase in anodic current proportional to the urea concentration.

Due to the properties of TRGO, the electrochemical oxidation of carbamic acid on the TRGO surface can occur at a working electrode potential of 0 V vs. Ag/AgCl. The ability of the biosensor to operate at 0 V vs. Ag/AgCl offers several important advantages, especially when intended for use in biological media such as serum, urine, or saliva. In real samples, many biological compounds are oxidized at positive potentials ( $>0.2$  V), which increases the likelihood of interfering reactions and the occurrence of false results. Operating at 0 V enhances the selectivity of the biosensor and improves the accuracy of the obtained results.

#### *Urea biosensor examination*

The calibration curve of the urea biosensor was obtained by plotting the steady-state current (I) versus urea concentration (C) in the range of 0–9 mM (**Figure 1**).

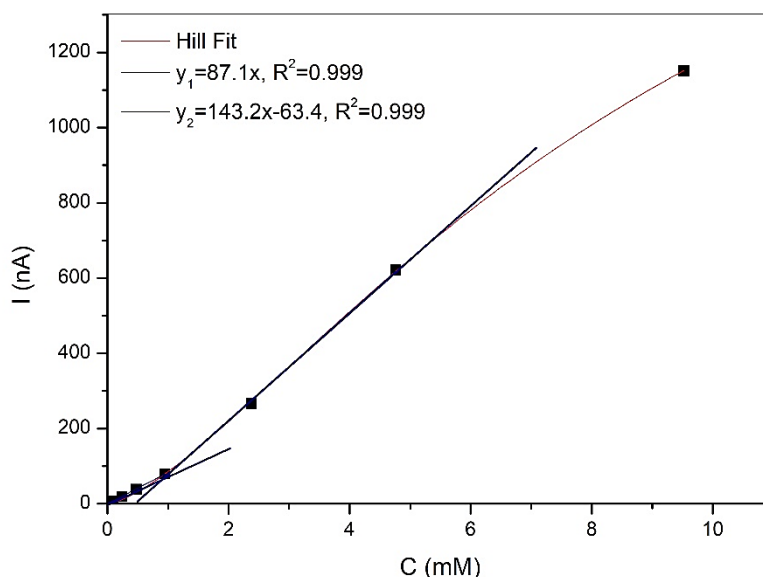


**Figure 1.** Calibration curve and linear ranges to urea, obtained using urease/TRGO biosensor, 0 V vs. Ag/AgCl, PBS pH=7.2.

The biosensor response followed a sigmoidic behaviour. Urease based biosensors typically show Michaelis-Menten kinetics, resulting in a hyperbolic calibration curve. However, under certain conditions of biosensor designs, a sigmoidal

calibration curve may be observed. In this case, as seen in **Figure 1**, the obtained calibration curve is more resembling of a sigmoidal shape. The reason for this may be the allosteric effects or cooperative enzyme behaviour, substrate inhibition at high or low urea concentrations and diffusion barriers in enzymatic membrane (Villaverde, 2003). The fitting parameters were  $I_{max}^{app} = 2313.5 \pm 174.2$  nA and  $K_M^{app} = 9.6 \pm 0.9$  mM with an excellent correlation coefficient ( $R^2 = 0.999$ ). The limit of detection (LOD) was approximately 0.03 mM. The linear range of the biosensor response was observed between 0.03 – 1.0 mM urea and 1.0 – 5.0 mM urea. Within the first range, the biosensor demonstrated high linearity and sensitivity of  $87.1 \text{ nA} \cdot \text{mM}^{-1}$ .

The selectivity of the urease/TRGO biosensor was evaluated at 0 V by introducing dopamine (0.5  $\mu$ M), adenosine (0.5  $\mu$ M), serotonin (0.5  $\mu$ M), uric acid (1  $\mu$ M), ascorbic acid (2.5  $\mu$ M), glucose (0.05 mM), albumin (70 g/l), epinephrine (24  $\mu$ M),  $\text{H}_2\text{O}_2$  (100 nM), arginine (2.38 mM) and urea (7.8 mM) into the electrochemical cell. The interferents were chosen for this test because they are commonly present in biological fluids such as blood, urine, saliva, cerebrospinal fluid and sweat, where they may affect the selectivity of urea detection.

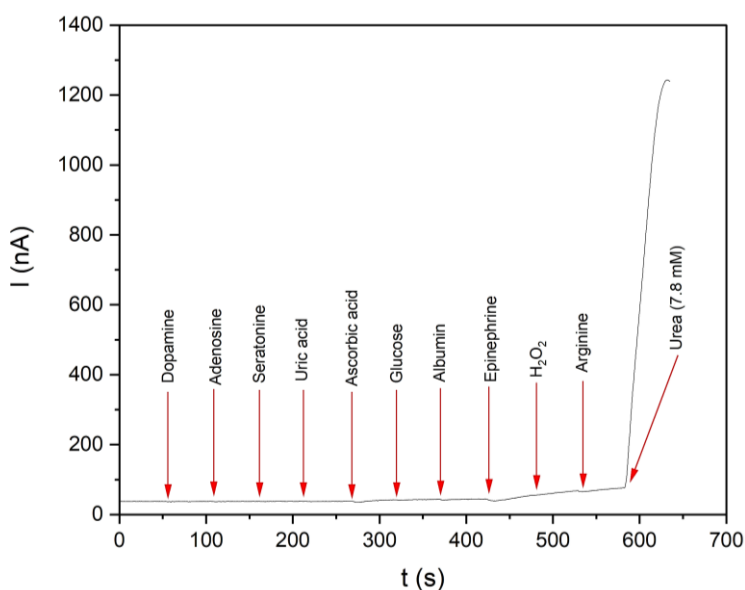


**Figure 2.** Influence of interfering compounds on the response of urease/TRGO biosensor to dopamine (0.5  $\mu$ M), adenosine (0.5  $\mu$ M), serotonin (0.5  $\mu$ M), uric acid (1  $\mu$ M), ascorbic acid (2.5  $\mu$ M), glucose (0.05 mM), albumin (70 g/l), epinephrine (24  $\mu$ M),  $\text{H}_2\text{O}_2$  (100 nM), arginine (2.38 mM) and urea (7.8 mM) at 0 V vs. Ag/AgCl electrode potential, PBS pH=7.2.

As shown in **Figure 2**, when the biosensor operated at 0 V, no significant current increase was observed after the addition of potential interfering compounds such as

dopamine, adenosine, serotonin, uric acid, glucose, albumin, and L-arginine. In contrast, the addition of ascorbic acid and epinephrine caused a slight increase in the anodic current (up to 5%) at 0 V vs. Ag/AgCl, compared with the response to urea.

As can be seen in Figure 2, the addition of urea caused a sharp and distinct increase in the anodic signal of the biosensor, while L-arginine had no effect. This indicates that the tested interferents did not significantly influence the sensor response, confirming that the biosensor possesses excellent selectivity toward urea and arginase activity simultaneously.

The accuracy of the urea biosensor can be reflected by the recovery test, where perfusate samples with added known concentrations of urea were evaluated using the biosensor. One sample without added urea and five samples with added concentrations of 0.09, 0.24, 0.48, 0.95, and 2.00 mM were prepared. Each measurement was performed two times, and the current responses were converted to urea concentrations using the calibration curve. The results are shown in **Table 1**.

**Table 1.**

Analytical performance of the urea biosensor in perfusate samples. The standard addition method was applied. The first line represents the initial concentration of urea in perfusate. Other lines – difference of urea concentration after addition of urea.

| <b>C<sub>urea</sub>(added), mM</b> | <b>C(found<sub>Avg</sub>), mM</b> | <b>Recovery, %</b> | <b>RSD, %</b> |
|------------------------------------|-----------------------------------|--------------------|---------------|
| 0                                  | -                                 | -                  | -             |
| 0.09                               | 0.10                              | 115.6              | 5.4           |
| 0.24                               | 0.28                              | 114.8              | 3.3           |
| 0.48                               | 0.51                              | 107.1              | 4.9           |
| 0.95                               | 1.05                              | 110.6              | 0.7           |
| 2.00                               | 2.06                              | 102.8              | 0.03          |

The average recoveries of the added urea ranged from 102.8% to 115.6%, demonstrating good analytical accuracy across the tested concentration range. The relative standard deviation (RSD) values were between 0.03% and 5.4%, confirming good repeatability of the biosensor response, particularly at higher urea concentrations. Slightly higher variability observed at lower concentrations may be attributed to the smaller signal-to-noise ratio typical for biosensor measurements in complex matrices.

The results confirm that the developed biosensor provides reliable and repeatable detection of urea in perfusate samples, maintaining both high accuracy and precision across the tested concentration range.

#### *Arginase activity assessment*

To evaluate the arginase activity of the developed biosensor, five samples were

prepared containing a constant amount of L-arginine (50  $\mu$ L) and varying volumes of arginase solution: 10, 20, 30, 40 and 50  $\mu$ L. The total volume of each sample was equalized by adding phosphate-buffered saline (PBS). The arginase solution used for sample preparation originated from a single stock solution with an enzyme activity of 400 U/mL, ensuring that only the arginase activity differed among samples.

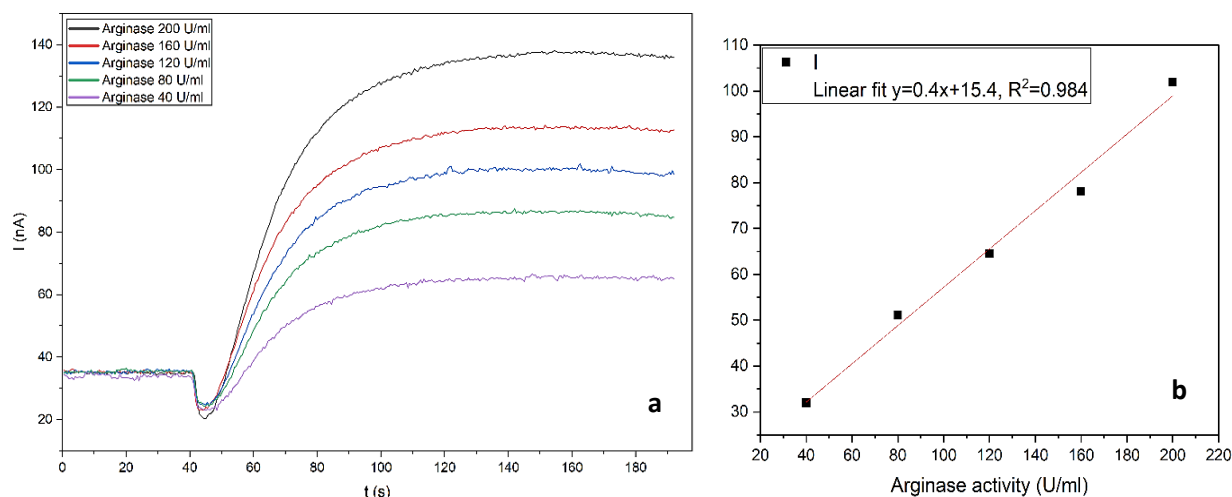


**Figure 3.** *a* - Amperometric responses of urease/TRGO biosensor recorded in samples containing different arginase activity. *b* - Calibration plot showing the dependence of the steady-state current of urease/TRGO biosensor on arginase activity. Measurements recorded at 0 V vs. Ag/AgCl, PBS pH=7.2.

**Figure 3a** presents the amperometric responses obtained during arginase activity measurements. A clear increase in the steady-state current was observed with increasing of arginase activity. These results indicate that increasing enzyme activity enhance the hydrolysis of L-arginine, leading to urea production, which is hydrolysed by urease to yield a proportional electrochemical signal. To further assess this relationship, a calibration curve was constructed (**Figure 3b**), which demonstrates a strong linear correlation between the measured urease/TRGO biosensors current and the arginase activity ( $R^2 = 0.984$ ). This linear relationship indicates that, within the tested range, the urea biosensor response is directly dependent on the enzyme quantity, confirming stable and reproducible signal generation. The low residual error and high correlation coefficient demonstrate good analytical performance of the system. These findings verify that the urea biosensor accurately reflects arginase activity and can reliably detect urea after enzymatic reactions involving arginine conversion.

**Conclusions.** The urease/TRGO biosensor proved to be a reliable and sensitive analytical tool for determining arginase activity in model perfusate samples. The biosensor exhibited high sensitivity ( $87.1 \text{ nA} \cdot \text{mM}^{-1}$ ) with two well-defined linear



response ranges: 0.03–1.0 mM and 1.0–5.0 mM urea. Operating at a potential of 0 V vs. Ag/AgCl, it demonstrated excellent selectivity toward urea, with minimal interference from common electroactive species typically present in biological fluids, including dopamine, adenosine, serotonin, uric acid, ascorbic acid, D-glucose, albumin, epinephrine, hydrogen peroxide, and arginine. Recovery experiments in perfusate samples confirmed high analytical accuracy (102.8–115.6%) and good repeatability ( $RSD \leq 5.44\%$ ), indicating reliable urea quantification in complex matrices. Furthermore, the linear correlation between biosensor response and arginase activity validates its applicability for monitoring arginase-catalyzed reactions and evaluating enzymatic activity through urea detection.

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## ВИКЛИКИ АНТИМІКРОБНОЇ РЕЗИСТЕНТНОСТІ В УКРАЇНІ

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**Анотація.** Розвиток резистентності мікроорганізмів до антимікробних препаратів (АМП) є глобальною загрозою здоров'ю людства. Стимування та боротьбу з антимікробною резистентністю (АМР) координує ВООЗ у рамках Глобальної стратегії зі стимування антимікробної резистентності, що була прийнята ще у 2001 р. Проблема АМР є актуальною і в Україні. В нашій державі з метою реалізації Національного плану дій щодо боротьби зі стійкістю до протимікробних препаратів впроваджено систему епідеміологічного нагляду за

АМР і сучасні підходи до мінімізації ризиків розвитку АМР, адаптовані до загальноєвропейських вимог. В умовах російської воєнної агресії на перший план виходять виклики розвитку АМР внаслідок необґрунтованого призначення АМП та небезпеки розповсюдження стійких штамів інвазивних патогенів при лікуванні пацієнтів при бойових пораненнях.

**Ключові слова:** адміністрування антимікробних препаратів, антимікробна резистентність, антимікробні препарати, інфекційний контроль, пріоритетні збудники.

**Мета дослідження.** Метою роботи є аналіз шляхів подолання АМР, спектру інвазивних мікроорганізмів та показників застосування антимікробних препаратів в Україні.

**Матеріали та методи.** Вивчали та аналізували джерела літератури, звіти за результатами досліджень та нормативні документи МОЗ України та ВООЗ.

**Результати та обговорення.** Проведені дослідження свідчать, що серед багатьох заходів, спрямованих на подолання проблеми розвитку та поширення АМР, найбільш ефективними ВООЗ визнає раціональне застосування антимікробних препаратів та один з ключових компонентів стратегії інфекційного контролю у закладах охорони здоров'я (ЗОЗ) – покращення гігієни рук. Вважається, що ці заходи можуть зберегти життя 75% пацієнтів з інфекціями, пов'язаними з наданням медичної допомоги.

В Україні спостерігається напружена ситуація щодо АМР. Національний план дій щодо боротьби зі стійкістю до протимікробних препаратів був затверджений у 2019 р. [7]. Серед завдань цього плану бачимо базові підходи до подолання проблеми АМР: впровадження заходів з інфекційного контролю в ЗОЗ, розроблення порядку здійснення дозорного епідеміологічного нагляду за АМР, ведення обліку інфекційних хвороб, пов'язаних з наданням медичної допомоги (ПНМД), проведення гармонізації нормативних документів сфери охорони здоров'я із законодавством країн Європейського Союзу тощо.

За результатами проведеного в Україні у 2021 р. пілотного дослідження з визначення розповсюдженості ПНМД, та використання антимікробних препаратів у ЗОЗ, які надають цілодобову стаціонарну допомогу, був встановлений значний підйом поширеності ПНМД у порівнянні з дослідженнями, що були проведені у 2019 р. Показник поширеності складав у середньому 5,7% (0,035% у 2019 р.), а у відділеннях з високим ризиком захворювання (відділення хірургічного профілю та відділення анестезіології, реанімації та інтенсивної терапії він досягав 10%. Лабораторно підтвердженими були лише 30,2% випадків ПНМД, а серед виявлених збудників виявляли штами

з абсолютною резистентністю до найважливіших АМП. Серед них – *Staphylococcus aureus* стійкий до глікопептидів, *Escherichia coli* та *Enterobacter spp.* стійкі до карбапенемів та цефалоспоринів III покоління та *Acinetobacter baumannii* стійкий до карбапенемів. Виявлений низький рівень проведення деескалації призначення АМП (у 1,7% випадків), низька ефективність застосування АМП при періопераційній профілактиці інфекцій акцентували про необхідність удосконалення системи інфекційного контролю в ЗОЗ та підходів до адміністрування АМП [4].

Наступним кроком стала розробка і впровадження Державної стратегії боротьби зі стійкістю до протимікробних препаратів на період до 2030 року та прийняття операційного плану з її реалізації на першому етапі у 2024–2026 роках [10]. Ця робота здійснюється покроково задля досягнення кожної стратегічної цілі за напрямками посилення інфекційного контролю у ЗОЗ та ветеринарної медицини, вдосконалення мікробіологічних лабораторій, системи епіднагляду за АМР, контролю за споживанням протимікробних препаратів, організації інформування та навчання медичних працівників і пацієнтів, розробки наукових підходів із стримування розвитку АМР. Вже набули чинності Державні санітарні норми та правила стосовно порядку управління медичними відходами, Стандарт медичної допомоги «Рациональне застосування протимікробних препаратів з лікувальною та профілактичною метою», був розширений перелік антибактеріальних препаратів, що підлягають моніторингу та розв'язуються інші важливі питання [3, 8].

Відповідальному використанню лікарських засобів та попередженню формування АМР сприяє упровадження у ЗОЗ адміністрування антимікробних препаратів, що регулюється відповідною інструкцією, затвердженою наказом МОЗ України «Про організацію профілактики інфекцій та інфекційного контролю в закладах охорони здоров'я та установах/закладах надання соціальних послуг/соціального захисту населення» [9].

Належне та раціональне призначення протимікробних препаратів, яке передбачає урахування властивостей препарату, індивідуальних особливостей пацієнта, перебігу захворювання, біології збудника, його чутливості до препарату є дієвою складовою на шляху подолання АМР. Для досягнення належного використання АМП розроблений їх поділ три групи: доступу, спостереження та резерву (класифікація AWaRe BOOЗ), яка базується на ступені небезпеки розвитку АМР при призначенні конкретного препарату [13].

Група доступу (Access) поєднує АМП, які проявляють найнижчу здатність впливати на розвиток резистентності бактерій й рекомендовані для емпіричної

терапії та профілактики інфекцій як препарати першого та другого вибору.

Група спостереження (Watch) містить препарати з більш високим потенціалом формування АМР, віднесені ВООЗ до списку важливих для медицини АМП (WHO Medically Important Antimicrobial list) та мають певні обмеження при призначенні [14, 15].

Група резерву (Reserve) складається з АМП останнього вибору, рекомендованих для лікування інфекцій, викликаних високорезистентними мікроорганізмами.

Згідно Стандарту медичної допомоги «Раціональне застосування протимікробних препаратів з лікувальною та профілактичною метою» лікарям необхідно віддавати перевагу призначенню препаратів групи доступу: у >95% випадків під час надання первинної та у >60% випадків спеціалізованої медичної допомоги. На рівні первинної допомоги необхідно знизити використання АМП групи спостереження до <5% випадків, стаціонарної допомоги до <40% випадків.

Антибіотики групи резерву повинні використовуватися в стаціонарах лише в разі неефективності АМП груп доступу та спостереження та за вагомо обґрунтованими показаннями. Передбачений стандартом рівень використання у 2023-2024 рр. складав <5% випадків, у 2025 р. і далі < 1% випадків.

В кожному ЗОЗ для розподілу препаратів за групами AWaRe відповідальні клінічні фармацевти та лікарі враховують актуальну ситуацію з АМР циркулюючих збудників. Відповідно лікарі та клінічні фармацевти мають обирати групу АМП для етіотропної терапії лише за результатом мікробіологічних досліджень чутливості виділеного патогену та здійснювати преавторизацію антибактеріальних препаратів групи резерву [2, 5, 8].

За результатами моніторингу індикаторів якості дотримання Стандарту медичної допомоги «Раціональне застосування антибактеріальних і антифунгальних препаратів з лікувальною та профілактичною метою», проведеного регіональними центрами контролю профілактики хвороб у 2024 р. були виявлені суттєві недоліки роботи по удосконаленню заходів стримування АМР в Україні. Встановлено, що лише у 20% госпіталізованих пацієнтів проводився відбір біологічного матеріалу для мікробіологічних досліджень перед початком антибіотикотерапії. Щодо призначення АМП усіх трьох груп AWaRe виявлена невідповідність цільовим показникам як на рівні первинної медичної допомоги, так при стаціонарному лікуванні (*табл. 1*).

**Таблиця 1.**

**Цільові та моніторингові значення індикаторів раціонального  
використання АМП, 2024 р. [11]**

| Рівень надання<br>медичної допомоги | Призначення АБП, % пацієнтів |                        |                  |                                        |
|-------------------------------------|------------------------------|------------------------|------------------|----------------------------------------|
|                                     | Група<br>доступу             | Група<br>спостереження | Група<br>резерву | Після забору<br>зразка<br>біоматеріалу |
| ПЕРВИННА                            | 95<br>59,1                   | < 5<br>32,4            | 0<br>8,7         | —                                      |
| СПЕЦІАЛІЗОВАНА                      | > 60<br>39,8                 | < 40<br>31,1           | < 5<br>29%       | 100<br>24,3                            |

Щодо препаратів групи резерву, було показано, що на первинній ланці медичної допомоги відсоток їх призначення був майже вдвічі менше цільової межі (59,1% та 39,8% випадків відповідно). На первинній ланці також не виправдано часто призначали препарати груп спостереження та резерву (32,4% та 8,7% випадків відповідно). В той же час при стаціонарному лікуванні пацієнти майже у 6 разів частіше отримували препарати резерву, ніж передбачено Стандартом медичної допомоги (29%).

Таким чином, проведений моніторинг показує наявність помилок в роботі з інфекційного контролю та адміністрування АМП у ЗОЗ різного профілю, що знижує ефективність антимікробної терапії. Це вимагає зосередитись на впровадженні програм навчання фахівців та контролі їх діяльності.

Аналіз спектру збудників, які циркулюють у ЗОЗ, проводили за результатами дозорного та посиленого епідеміологічного моніторингу, проведеного фахівцями Центру громадського здоров'я МОЗ України. До пріоритетних патогенів, що підлягають епіднагляду, віднесені дев'ять небезпечних для громадського здоров'я клінічно значущих бактерій – *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Salmonella spp.*, *Enterococcus faecalis*, *Enterococcus faecium*, *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Acinetobacter spp.*, частина з яких належить до груп «ESCAPE» та «SPACE». Вони легко набувають ознаки АМР та спричинюють важкі, загрозливі інфекції (сепсис, діарея, пневмонія, інфекції сечовивідних шляхів), що по'язані з наданням медичної допомоги.

Небезпечне розповсюдження штамів з АМР, в тому числі з полірезистентністю, серед поранених внаслідок бойових дій було виявлено під час здійснення у 2023-2024 рр. посиленого епідеміологічного моніторингу за



результатами мікробіологічних досліджень крові, СМР, відділяемого ран [12]. Дослідженню підлягали ізоляти *Acinetobacter spp.*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Enterococcus faecalis*, *Enterococcus faecium* та *Streptococcus pneumoniae*, які продукували  $\beta$ -лактамази розширеного спектру дії, були стійкими до препаратів широкого спектру дії з різних груп. За ступенем загрозливого рівня розвитку АМР переважали ізоляти бактерій роду *Acinetobacter* (65% стійкі до карбапенемів), *K.pneumoniae* (38,8% стійкі до колістину) та *S.aureus* (42,8% стійкі до метициліну).

Причиною такого стану проблеми є існуюче під час війни надмірне навантаження на медичну систему, недоліки впровадження заходів інфекційного контролю у ЗОЗ, низка якості та обсяг мікробіологічних досліджень, тривале лікування поранених, нераціональне призначення антимікробних лікарських засобів [1, 6, 14].

**Висновки.** Глобальне розповсюдження мікроорганізмів з набутою резистентністю до АМП несе небезпеку зниження ефективності етіотропної терапії інфекційних захворювань, збільшення тривалості госпіталізації пацієнтів та витрат на лікування. Стратегія подолання АМР базується на раціональному застосуванні АМП та впровадженні дієвих заходів інфекційного контролю у закладах охорони здоров'я різного рівня надання медичної допомоги. Систематичне здійснення епідеміологічного моніторингу за пріоритетними інвазивними патогенами, які набули стійкість до АМП та проведення якісних мікробіологічних досліджень є обов'язковими ланками стратегій подолання викликів АМР на регіональному та державному рівні.

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## **РЕДОКС-РЕАБІЛІТАЦІЯ СЕРЦЯ: ПОТЕНЦІАЛ КОНДИЦІОНОВАНОГО СЕРЕДОВИЩА СТОВБУРОВИХ КЛІТИН У ПОДОЛАННІ МЕТАБОЛІЧНОЇ ДЕЗОРГАНІЗАЦІЇ, ІНДУКОВАНОЇ ЦЕЛЕКОКСИБОМ**

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**Анотація.** Метою дослідження було експериментально оцінити метаболічні наслідки тривалого введення целекоксибу для міокарда та порівняти коригувальну ефективність карведилолу та кондиціонованого середовища мезенхімальних стовбурових клітин. На моделі хронічної кардіоміопатії у щурів-самців (4 групи по 7 тварин), індукованої целекоксибом (100 мг/кг, внутрішньошлунково, 14 днів) виявлено накопичення лактату до 5,0 [4,9; 5,4] мкмоль/г проти 2,7 [2,7; 3,3] мкмоль/г в інтактних ( $p < 0,001$ ; +85,2%), зниження пірувату до 0,20 [0,15; 0,25] мкмоль/г ( $p = 0,002$ ; -60,0%) і підвищення співвідношення лактат/піруват до 25,0 [17,9; 37,0] ( $p < 0,001$ ; +363,0%). Карведилол (30 мг/кг) частково відновлював показники: лактат 3,3 [3,0; 3,5] мкмоль/г ( $p < 0,01$ ; -34,0%), співвідношення 12,0 [9,8; 15,5] ( $p = 0,018$ ), без достовірного підвищення пірувату (0,30 [0,20; 0,30] мкмоль/г;  $p = 0,2$ ). Кондиціоноване середовище мезенхімальних стовбурових клітин забезпечувало найповнішу корекцію: лактат 2,8 [2,5; 3,1] мкмоль/г ( $p < 0,001$ ; -44,0%), піруват

0,40 [0,35; 0,45] мкмоль/г ( $p=0,01$ ; +100,0%), співвідношення 7,0 [5,3; 9,5] ( $p=0,001$ ; -72,0%; проти карведилолу  $p=0,015$ ). Отримані дані підтверджують провідну роль метаболічної дисфункції у кардіотоксичності целекоксибу та перевагу біотехнологічної корекції над стандартною фармакотерапією.

**Ключові слова:** целекоксиб, кардіотоксичність, мітохондріальна дисфункція, оксидативний стрес, лактат, піруват, співвідношення лактат/піруват, карведилол, кондиціоноване середовище мезенхімальних стовбурових клітин, міокард.

**Вступ.** Селективні інгібітори циклооксигенази-2, до яких належить целекоксиб, широко використовуються у клінічній практиці для лікування запальних і дегенеративних захворювань, зокрема остеоартрозу та ревматоїдного артриту. Їхня популярність пояснюється сприятливим гастроінтестинальним профілем, проте численні дослідження останніх років виявили суттєвий ризик розвитку серцево-судинних ускладнень при тривалому застосуванні цих препаратів. Кардіотоксичність целекоксибу пов'язують не лише з його судинними ефектами, а й із глибинними метаболічними порушеннями в міокарді, які проявляються зниженням активності мітохондріальних ферментів, посиленням утворення активних форм кисню та розвитком енергетичної недостатності серця [1, 2].

Доведено, що целекоксиб безпосередньо пригнічує активність комплексу IV дихального ланцюга мітохондрій, що порушує кінцеву ланку окисного фосфорилювання й знижує синтез аденозинтрифосфату. Унаслідок цього в кардіоміоцитах накопичується лактат і знижується рівень пірувату, що свідчить про переорієнтацію енергетичного метаболізму на анаеробний шлях і розвиток тканинної гіпоксії [1]. Паралельно посилюється утворення активних форм кисню, що ініціюють ліпопероксидацію, ушкодження білкових структур та підвищення проникності мітохондріальних мембран. Такий «порочний цикл» призводить до втрати потенціалу внутрішньої мембрани, відкриття пор мітохондріальної проникності та активації апоптозу кардіоміоцитів. Дослідження *Salimi A. та співавт.* показало, що галова кислота може інгібувати цей процес, зменшуючи перехід проникності мембран і стабілізуючи електрохімічний градієнт, що підтверджує ключову роль мітохондріального механізму токсичності целекоксибу [2].

Крім прямого впливу на мітохондрії, целекоксиб знижує експресію генів антиоксидантних ферментів (супероксиддисмутази, каталази, глутатіонпероксидази) та порушує кальцієвий гомеостаз у серцевій тканині. Це сприяє розвитку оксидативного стресу, зниженню скоротливої функції серця й

формуванню ознак міокардіальної дистрофії. Дослідження *Azizian S. та співавтор.* (2024) продемонструвало, що вітамін D значно зменшує тяжкість кардіотоксичності целекоксибу на тлі серцевої недостатності, спричиненої доксорубіцином, шляхом активації антиоксидантного захисту та нормалізації мітохондріальної функції [3]. Це доводить, що антиоксидантна модуляція може бути ефективною стратегією профілактики токсичних ефектів коксибів.

Попри наявність численних спостережень, більшість досліджень стосуються гострих моделей інтоксикації або комбінованих впливів, тоді як патогенез хронічної кардіоміопатії, індукованої целекоксибом, вивчено недостатньо. Невирішеними залишаються питання, які саме ланки енергетичного обміну найбільш уражаються при тривалому надходженні препарату, та чи можна ефективно запобігти цим змінам за допомогою сучасних фармакологічних чи біотехнологічних засобів. Особливий інтерес викликає дослідження концентрацій лактату й пірувату, а також співвідношення лактат/піруват – чутливого інтегрального маркера балансу між аеробними та анаеробними шляхами утворення енергії. Підвищення цього показника є свідченням редокс-зсуву в бік відновлення, що характерно для гіпоксичних і токсичних станів міокарда.

Серед фармакологічних засобів, здатних впливати на метаболічні порушення, найбільш перспективним є карведилол –  $\beta$ -адреноблокатор із антиоксидантними та мембраностабілізуючими властивостями. Його кардіопротекторну ефективність при доксорубіцин-індукованих ураженнях доведено на експериментальних моделях [4]. Карведилол зменшує утворення активних форм кисню, підвищує активність антиоксидантних ферментів, стабілізує ліпідні мембрани та покращує мікроциркуляцію, що сприяє частковому відновленню енергетичного балансу. Однак навіть у цих умовах препарат не завжди забезпечує повне відновлення метаболічного гомеостазу, що спонукає до пошуку нових методів біологічної корекції.

Останніми роками значну увагу привертають біотехнологічні засоби безклітинного походження, здатні модулювати клітинні сигнальні шляхи й підтримувати енергетичну рівновагу тканин. До таких належить кондиціоноване середовище мезенхімальних стовбурових клітин – комплекс біологічно активних речовин, які секретуються під час культивування клітин. Воно містить цитокіни, фактори росту, пептиди, ферменти, екзосоми та інші позаклітинні везикули, що виконують трофічну, протизапальну та антиоксидантну функції. На відміну від живих клітин, кондиціоноване середовище позбавлене імуногенності й не несе ризику трансформації, що робить його перспективним терапевтичним



інструментом.

Роботи українських авторів [5-9] засвідчили, що застосування кріоекстрактів біологічних тканин і кондиціонованого середовища МСК ефективно зменшує ступінь ушкодження серця при антрациклін-, адреналін- та автоімунно-індукованих моделях кардіоміопатії. Доведено, що плацентарний кріоекстракт у разі доксорубіцин-індукованого ураження серця знижує рівні продуктів перекисного окиснення ліпідів, зменшує вираженість дистрофічних змін і сприяє відновленню мітохондріальної ультраструктури [5]. У подальших дослідженнях доведено, що введення кондиціонованого середовища МСК тваринам з експериментальним автоімунним міокардитом покращує скоротливу здатність серця, нормалізує діастолічну функцію та знижує запальний інфільтрат [7, 8].

Експериментальні спостереження у монографії [6] підкреслили, що біокріотехнологічні агенти мають універсальний цитопротекторний потенціал, реалізований через активацію сигнальних каскадів PI3K/Akt, ERK1/2 та індукцію антиоксидантних білків. Такі засоби відновлюють функціонування мітохондрій, знижують рівень реактивних форм кисню, стимулюють експресію білків теплового шоку та факторів виживання клітини. Тому їх застосування при медикаментозно-індукованих ураженнях серця є логічним продовженням уже доведених механізмів дії.

Особливу увагу привертає те, що кондиціоноване середовище МСК виявляє метаболічну гнучкість: воно здатне як стимулювати аеробне окиснення, так і гальмувати анаеробні процеси в умовах гіпоксії. Його введення сприяє активації піруватдегідрогеназного комплексу, поліпшує транспорт субстратів у цикл трикарбонових кислот, стабілізує рівень  $\text{NAD}^+/\text{NADH}$  і нормалізує співвідношення лактат/піруват. Цей ефект є особливо цінним для умов, коли пригнічується робота мітохондріального дихального ланцюга, як це спостерігається при токсичній дії целекоксибу.

Додатковою перевагою кондиціонованого середовища є наявність позаклітинних везикул (екзосом), які переносять мікроРНК, що регулюють експресію генів антиоксидантного захисту й метаболічних ферментів. Це забезпечує довготривалу активацію внутрішньоклітинних механізмів адаптації без прямого клітинного втручання. Такий підхід відповідає сучасним концепціям регенеративної медицини, спрямованій на стимуляцію власних резервів організму замість заміщення ушкоджених структур.

Таким чином, проблема кардіотоксичності целекоксибу є надзвичайно актуальною, оскільки препарат залишається широко призначуваним у клінічній

практиці, а ризики його хронічного впливу на серце досі не мають достатнього експериментального обґрунтування. Дослідження, присвячені енергетичним аспектам ушкодження міокарда, особливо змінам співвідношення лактат/піруват, дозволяють поглибити розуміння патогенезу та визначити нові підходи до профілактики. Порівняння ефективності фармакологічного коректора карведилолу та біотехнологічного засобу – кондиціонованого середовища МСК – дає можливість оцінити їх здатність відновлювати порушений енергетичний гомеостаз і визначити потенційні переваги комбінованого застосування.

Отримані результати мають значення не лише для фундаментальної фармакології, але й для практичної кардіології, оскільки вони можуть слугувати науковим підґрунтям для створення нових патогенетично обґрунтованих стратегій лікування та профілактики медикаментозно-індукованих кардіоміопатій. Таким чином, актуальність цього дослідження зумовлена необхідністю експериментального обґрунтування механізмів ушкоджувальної дії целекоксибу на міокард і пошуку ефективних засобів їх біологічної корекції.

**Мета дослідження** – оцінити вплив тривалого введення целекоксибу на показники енергетичного обміну міокарда щурів (лактат, піруват, співвідношення лактат/піруват) та порівняти ефективність корекції виявлених порушень за умови застосування карведилолу і кондиціонованого середовища мезенхімальних стовбурових клітин, визначивши їх здатність нормалізувати метаболічний профіль у моделі хронічної кардіоміопатії, індукованої целекоксибом.

**Матеріали та методи.** Хронічну кардіоміопатію, індуковану целекоксибом, моделювали шляхом внутрішньошлункового введення целекоксибу («Целебрекс®», Р-Фарм Джермані ГмбХ, Німеччина) у дозі 100 мг/кг щоденно протягом 14 днів [10]. Дослідження проведено на 28 щурах-самцях, розподілених на 4 групи по 7 особин: інтактні, контроль без лікування, група порівняння з карведилолом 30 мг/кг («Карведилол-Зентіва», ТОВ «Зентіва», Чеська Республіка) [11], а також щури, яким вводили кондиціоноване середовище мезенхімальних стовбурових клітин у лікувально-профілактичному режимі 1 р/д з 5 по 13 дні експерименту з інтервалом в 1 день, відповідно на 5, 7, 9, 11 та 13 дні експерименту (усього 5 введень) [12]. Кондиціоноване середовище мезенхімальних стовбурових клітин отримували при культивуванні пуповинних клітин у газовому інкубаторі (37°C, 5% CO<sub>2</sub>) у безсироватковому середовищі *Dulbecco's Modified Eagle Medium/Nutrient Mixture F-12*. Супернатант збирали після третього пасажу, очищали ультрафільтрацією, заморожували й зберігали при – 20°C. Біоактивність стандартизували за галектином-1 (6,0 пг/мл). Тваринам вводили внутрішньом'язово у дозі 0,6 мл/кг. Референс-препарат карведилол

застосовували у вигляді водно-полісорбатної суспензії. На 15 день тварин виводили з експерименту шляхом декапітації, відбирали змішану венозно-артеріальну кров і серце для подальших досліджень. Вміст лактату [13] і пірувату [14] у гомогенаті міокарда визначали спектрофотометрично за допомогою дегідрогеназних реакцій, результати виражали у мкмоль/г. Статистичну обробку проводили у «Microsoft Office Excel 2016» із дотриманням принципів біостатистики: за нормального розподілу міжгрупові відмінності оцінювали t-критерієм Ст'юдента, за відхилення від нормальності – U-критерієм Манна–Вітні. Результати наводили як  $M \pm m$  ( $M \pm SE$ ) або  $Me$  [LQ; UQ].

**Результати та їх обговорення.** Встановлено, що під впливом целекоксибу в тканині міокарда формувалися виразні порушення енергетичного метаболізму, які проявлялися накопиченням лактату та зниженням рівня пірувату, що супроводжувалося різким зростанням співвідношення лактат/піруват. У щурів контрольної групи при целекоксиб-індукованій кардіоміопатії концентрація лактату збільшувалася більш ніж у півтора раза – до 5,0 [4,9;5,4] мкмоль/г тканини порівняно з інтактними тваринами, у яких цей показник становив 2,7 [2,7;3,3] мкмоль/г ( $p < 0,001$ , різниця 85,2%). Отримані дані свідчать про активацію анаеробного гліколізу, що зазвичай відбувається при гіпоксії міокарда або пригніченні мітохондріального окисного фосфорилування під впливом коксибів. Накопичення лактату може бути наслідком дефіциту кисню, зменшення активності піруватдегідрогеназного комплексу або порушення транспорту субстратів у циклі Кребса, що в сукупності призводить до зниження ефективності утворення аденозинтрифосфату та розвитку метаболічної ацидозної відповіді.

Застосування карведилолу призводило до суттєвого поліпшення показників вуглеводного обміну. У групі тварин, які отримували цей препарат, вміст лактату знижувався до 3,3 [3,0;3,5] мкмоль/г тканини ( $p < 0,01$ , різниця 34,0% щодо контролю), що свідчить про зменшення анаеробного утворення лактату та часткове відновлення аеробного шляху окиснення. Така динаміка може бути зумовлена здатністю карведилолу стабілізувати мембрани мітохондрій, зменшувати генерацію активних форм кисню та покращувати мікроциркуляцію у кардіоміоцитах. Проте повного відновлення метаболічного гомеостазу досягнуто не було, що підтверджує лише часткову корекцію порушень енергетичного обміну.

Найбільш виражений нормалізуючий ефект спостерігався у групі тварин, яким вводили кондиціоноване середовище мезенхімальних стовбурових клітин. Рівень лактату у цій групі становив 2,8 [2,5;3,1] мкмоль/г тканини, що достовірно нижче, ніж у контрольних тварин ( $p < 0,001$ , різниця 44,0%) та навіть менше, ніж

у групі карведилолу ( $p=0,02$ , різниця 15,2%). Це вказує на майже повне відновлення окисного шляху утворення енергії. Імовірно, такий ефект зумовлений наявністю у кондиціонованому середовищі комплексу біологічно активних факторів, включаючи антиоксидантні ферменти, пептиди, цитокіни та позаклітинні везикули, які забезпечують зниження оксидативного стресу та нормалізацію метаболізму глюкози.

Подібна тенденція виявлена й для рівня пірувату. У щурів контрольної групи при целекоксиб-індукованій кардіоміопатії його концентрація знижувалася в 2,5 раза – з 0,50 [0,40;0,50] мкмоль/г у інтактних тварин до 0,20 [0,15;0,25] мкмоль/г ( $p=0,002$ , різниця 60,0%). Це свідчить про пригнічення утворення пірувату з глюкози та одночасно про підвищене його відновлення в лактат. У щурів, які отримували карведилол, рівень пірувату зростав до 0,30 [0,20;0,30] мкмоль/г ( $p=0,2$ , різниця 50,0%), проте статистично достовірного відновлення не досягнуто. На відміну від цього, введення кондиціонованого середовища мезенхімальних стовбурових клітин приводило до значного підвищення пірувату – до 0,40 [0,35;0,45] мкмоль/г ( $p=0,01$ , різниця 100,0% відносно контролю;  $p=0,02$ , різниця 33,3% порівняно з карведилолом). Це вказує на відновлення аеробного етапу гліколізу та покращення функціонування піруватдегідрогеназного комплексу, що забезпечує повноцінне окиснення вуглеводів і сприяє формуванню адекватного енергетичного заряду міокарда.

Найбільш інформативним показником стану вуглеводного обміну є співвідношення лактат/піруват, яке відображає ступінь редокс-зсуву в цитоплазмі кардіоміоцитів. У інтактних тварин цей показник становив 5,4 [5,2;8,3] умовних одиниць, що характеризує збалансоване співвідношення між анаеробними та аеробними процесами утворення енергії. За умов целекоксиб-індукованої кардіоміопатії співвідношення різко зростало до 25,0 [17,9;37,0] ( $p<0,001$ , різниця 363,0%), що є маркером вираженого зсуву метаболізму у бік відновлення пірувату в лактат і, відповідно, домінування анаеробного гліколізу. Таке порушення редокс-балансу свідчить про глибокий енергетичний дефіцит у міокарді, посилення гіпоксичних процесів та розвиток метаболічної дезадаптації.

Під впливом карведилолу співвідношення лактат/піруват знижувалося до 12,0 [9,8;15,5] ( $p=0,018$ , різниця 52,0% порівняно з контролем), що свідчить про часткове відновлення редокс-стану. Однак навіть після застосування цього препарату показник залишався більш ніж удвічі вищим за норму, отже, карведилол лише частково зменшував інтенсивність анаеробних процесів, не усуваючи метаболічну гіпоксію повністю. У свою чергу, введення кондиціонованого середовища мезенхімальних стовбурових клітин призводило

до подальшого істотного зниження співвідношення до 7,0 [5,3;9,5] ( $p=0,001$  щодо контролю, різниця 72,0%;  $p=0,015$  щодо карведилолу, різниця 41,7%), що практично відповідало значенням у інтактних шурів. Це свідчить про глибоку нормалізацію редокс-гомеостазу та повноцінне відновлення окисно-відновних процесів у кардіоміоцитах.

Таким чином, результати засвідчують, що целекоксиб викликає типову метаболічну дезорганізацію у міокарді, проявом якої є лактат-ацидоз, зниження концентрації пірувату та різке підвищення співвідношення лактат/піруват. Такі зрушення свідчать про активацію анаеробного гліколізу на тлі пригнічення мітохондріального окиснення, що є характерною ланкою патогенезу кардіотоксичності коксибів. Отримані дані узгоджуються з сучасними уявленнями про роль оксидативного стресу та порушення енергетичного обміну як провідних механізмів ушкодження серця при прийомі нестероїдних протизапальних засобів, особливо тих, що селективно пригнічують циклооксигеназу-2. Застосування карведилолу забезпечувало певний кардіопротекторний ефект, зменшуючи прояви метаболічної гіпоксії та частково відновлюючи рівень пірувату, проте найвищу ефективність продемонструвало кондиціоноване середовище мезенхімальних стовбурових клітин, яке нормалізувало всі досліджувані параметри.

Фактично, за впливом кондиціонованого середовища відзначено відновлення енергетичної рівноваги до значень, близьких до фізіологічних. Концентрація лактату не перевищувала рівень інтактних тварин, а піруват та співвідношення лактат/піруват залишалися у межах адаптивного діапазону. Це дозволяє припустити, що фактори, присутні у кондиціонованому середовищі, активують внутрішньоклітинні сигнальні шляхи, які підтримують функціонування мітохондрій, посилюють експресію ферментів аеробного окиснення та знижують оксидативне навантаження. Серед таких можливих механізмів розглядають дію парокринних молекул, позаклітинних везикул та ферментів антиоксидантного каскаду, які здатні відновлювати активність ферментів циклу трикарбонових кислот, у тому числі піруватдегідрогенази та ізоцитратдегідрогенази.

Важливо, що нормалізація метаболічного профілю під впливом кондиціонованого середовища мезенхімальних стовбурових клітин супроводжується покращенням морфофункціонального стану кардіоміоцитів, про що свідчать дані попередніх досліджень: зменшення вираженості набряку, стабілізація мітохондріальних мембран, зниження вмісту продуктів перекисного окиснення ліпідів і білків. Це свідчить про системний характер коригувальної дії,



спрямований не лише на усунення симптомів енергетичного дефіциту, а й на глибинне відновлення клітинного гомеостазу. Отримані результати підтверджують, що кондиціоноване середовище мезенхімальних стовбурових клітин має потужний метаболічний потенціал, який перевищує ефективність стандартних фармакологічних кардіопротекторів, таких як карведилол, і може розглядатися як перспективний компонент патогенетичної терапії целекоксиб-індукованих ушкоджень серця.

Узагальнюючи наведені дані, можна констатувати, що під впливом целекоксибу у міокарді щурів розвивається виражена енергетична дезінтеграція, зумовлена гальмуванням аеробного окиснення та посиленням анаеробного гліколізу. Це проявляється підвищенням рівня лактату, зниженням пірувату та підвищенням співвідношення лактат/піруват, що підтверджує формування гіпоксично-дисметаболічного синдрому. Карведилол зменшує тяжкість цих порушень, однак не забезпечує повного відновлення метаболічної рівноваги. Натомість застосування кондиціонованого середовища мезенхімальних стовбурових клітин забезпечує майже повне відновлення енергетичного обміну в міокарді, що проявляється нормалізацією рівнів лактату, пірувату та редокс-показників. Такий ефект підтверджує виражений метаболічний і цитопротекторний потенціал цього біологічного засобу, який може становити основу для нових стратегій профілактики та лікування кардіотоксичності, зумовленої тривалим застосуванням нестероїдних протизапальних препаратів.

### **Висновки.**

1. Целекоксиб спричинював глибокі метаболічні порушення у міокарді щурів, що проявлялися підвищенням рівня лактату до 5,0 [4,9;5,4] мкмоль/г ( $p<0,001$ ; +85,2%), зниженням пірувату до 0,20 [0,15;0,25] мкмоль/г ( $p=0,002$ ; –60,0%) та зростанням співвідношення лактат/піруват до 25,0 [17,9;37,0] ( $p<0,001$ ; +363,0%), що вказує на активацію анаеробного гліколізу та розвиток енергетичної недостатності.
2. Карведилол частково коригував прояви метаболічного дисбалансу: знижував рівень лактату до 3,3 [3,0;3,5] мкмоль/г ( $p<0,01$ ; –34,0%) і співвідношення лактат/піруват до 12,0 [9,8;15,5] ( $p=0,018$ ; –52,0%), проте не забезпечував достовірного відновлення пірувату (0,30 [0,20;0,30] мкмоль/г;  $p=0,2$ ).
3. Кондиціоноване середовище мезенхімальних стовбурових клітин виявило найвищу коригувальну активність: зменшувало рівень лактату до 2,8 [2,5;3,1] мкмоль/г ( $p<0,001$ ; –44,0%), підвищувало піруват до 0,40 [0,35;0,45] мкмоль/г ( $p=0,01$ ; +100,0%) і нормалізувало співвідношення лактат/піруват до 7,0 [5,3;9,5] ( $p=0,001$ ; –72,0%), що свідчить про майже повне відновлення аеробного

окиснення та редокс-гомеостазу.

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## **ЗБЕРІГАННЯ СФЕРОЇДІВ З МЕЗЕНХІМАЛЬНИХ СТРОМАЛЬНИХ КЛІТИН ЗА АМБІЄНТНОЇ ТЕМПЕРАТУРИ**

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**Анотація.** Порівняно з моношаровою культурою сфероїди з мезенхімальних стромальних клітин (МСК) мають посилені протизапальні, регенеративні властивості та вищу виживаність після трансплантації. Використання сфероїдів з МСК потребує розробки ефективних методів зберігання. Перспективним є їх збереження за амбієнтною температурою, що спрощує транспортування та клінічне застосування. Метою роботи було дослідити рівень апоптозу у сфероїдах, отриманих із МСК людини, залежно від

тривалості зберігання за амбієнтної температури та кількості клітин, що входять до їхнього складу. Для отримання сфероїдів із МСК з жирової тканини людини застосовували метод «висячої краплі». Краплі об'ємом 25 мкл, що містили МСК у живильному середовищі, наносили на кришку чашки Петрі діаметром 10 см. Посівна концентрація клітин на краплю складала 3, 4 та  $5 \times 10^3$ . Через 3 доби сформовані сфероїди збирали та зберігали в герметично закритих пробірках у 1 мл культурального середовища за температури 22°C. Тривалість зберігання складала 3 та 7 діб. Для виявлення апоптозу використовували забарвлення з флуоресцентно-міченим аннексином V. Встановлено, що оптимізація посівної концентрації клітин має вирішальне значення при зберіганні сфероїдів з МСК за амбієнтних температур. На початкову добу кількість апоптотичних клітин значуще не відрізнялася від використаної посівної концентрації клітин. Однак за умов зберігання параметр клітинної кількості набував вирішального значення. У сфероїдах з посівною концентрацією МСК більше, ніж  $3 \times 10^3$  клітин/краплю, виявлялося підвищення кількості апоптотичних клітин на третю та, особливо, на сьому добу зберігання.

**Ключові слова.** Мезенхімальні стромальні клітини, апоптоз, аннексин V, зберігання, амбієнтні температури

**Вступ.** Тривимірні культури у формі сфероїдів відтворюють мікрооточення клітин в організмі та, порівняно з моношаровими культурами, точніше моделюють проліферативні, регуляторні й метаболічні процеси [1], а також реакцію клітин на вплив фізико-хімічних чинників, ліків, токсинів [2]. Встановлено, що сфероїди, сформовані з мезенхімальних стромальних клітин (МСК), характеризуються підвищеними протизапальними та регенеративними властивостями, а також вищою виживаністю після трансплантації [3]. Під час тривалого культивування у моношаровому стані МСК поступово втрачають здатність до проліферації та колонієутворення, тоді як у складі сфероїдів вони зберігають ширший спектр генетичної експресії, зокрема активацію генів, пов'язаних із окисно-відновними процесами, стійкістю до гіпоксії та стресу, ангіогенезом і запальними реакціями. Використання сфероїдів з МСК у терапевтичних цілях потребує ефективних методів їх зберігання. Традиційно для цього застосовують кріоконсервування, однак перспективним напрямом є розробка способів збереження сфероїдів за амбієнтних температур, що спрощує їх транспортування та використання без необхідності спеціальних охолоджувальних систем.

Встановлено, що життєздатність клітин у складі сфероїду залежить від багатьох факторів (складу середовища, інтенсивності перемішування середовища,

проліферативної та метаболічної активності клітин тощо) [4]. Розміри сфероїдів обмежуються ефективністю пасивної дифузії та транспорту речовин. При досягненні значного діаметра у сфероїді формується градієнт концентрації кисню з найнижчим його рівнем у центральній частині [5]. Окрім проблеми газообміну, важливим фактором є виведення продуктів метаболізму, які накопичуються у внутрішніх зонах. Внаслідок цього, в сфероїді структурна та функціональна гетерогенність клітин в залежності від локалізації. Клітини периферійного шару активно проліферують, зберігаючи нормальну морфологію та високу метаболічну/синтетичну активність. У проміжному шарі клітини перебувають у дормантному стані, не діляться, але здатні відновлювати активність за достатнього рівня поживних речовин. У центрі крупних сфероїдів знаходяться некротичні зони з мертвих клітин або клітинного детриту. Таким чином, вивчення закономірностей формування зональності сфероїдів має важливе значення для оптимізації умов їх культивування та зберігання, а першим кроком для цього є встановлення оптимальних концентрацій клітин у складі сфероїда.

**Мета дослідження.** Метою роботи було дослідити рівень апоптозу у сфероїдах, отриманих із МСК людини, залежно від тривалості зберігання за амбієнтної температури та кількості клітин, що входять до їхнього складу.

**Матеріали та методи.** Для отримання сфероїдів із МСК з жирової тканини людини застосовували метод «висячої краплі» [6]. Краплі об'ємом 25 мкл, що містили МСК у живильному середовищі, наносили на кришку чашки Петрі діаметром 10 см («SPL Life Sciences», Корея). Використовували  $3, 4$  та  $5 \times 10^3$  клітин на краплю. Культуральне середовище складалося з  $\alpha$ -MEM (Sigma-Aldrich, США), 10% фетальної сироватки телят (Biowest, Франція), 2 мМ L-глутаміну (Sigma-Aldrich, США), 50 од/мл пеніциліну (Biowest, Франція) та 50 мкг/мл стрептоміцину (Biowest, Франція). Після нанесення крапель кришку перевертали та розміщували над нижньою частиною чашки, що містила 10 мл стерильного 0,9% розчину натрію хлориду для підтримання вологості під час культивування. Чашки інкубували при  $37^\circ\text{C}$  в атмосфері з 5%  $\text{CO}_2$ . Культивування тривало 3 доби, після чого сформовані сфероїди збирали та зберігали в герметично закритих пробірках у 1 мл культурального середовища за температури  $22^\circ\text{C}$  у термостаті Alpha RA8 LAUDA (LAUDA, Німеччина). Тривалість зберігання складала 3 та 7 діб. Використовували тест-набір для виявлення раннього апоптозу з флуоресцентно-міченим аннексином V «Annexin-Cy3™ Apoptosis Detection Kit» (Sigma, США). Після зберігання сфероїди оброблювали за інструкцією, флуоресценцію виявляли за допомогою конфокального флуоресцентного мікроскопа при піках збудження 555 нм для



анексина V та 488 нм для 6-карбоксифлуоресцеїну діацетату (6-CFDA). Кількісні дані відповідали гауссовому розподілу, тому було використано параметричний тест (ANOVA). Дані представлені як середнє значення  $\pm$  стандартне відхилення; відмінності вважалися значущими при  $p < 0,05$ .

### Результати та обговорення.

Сфероїди, отримані методом висячої краплі, морфологічно не відрізнялися в залежності від кількості посіяних МСК (*рис. 1*). На 3 добу вони мали округлу чи овальну форму, компактну структуру зі щільною упаковкою клітин. Розміри сфероїдів були у межах 150-290 мкм.

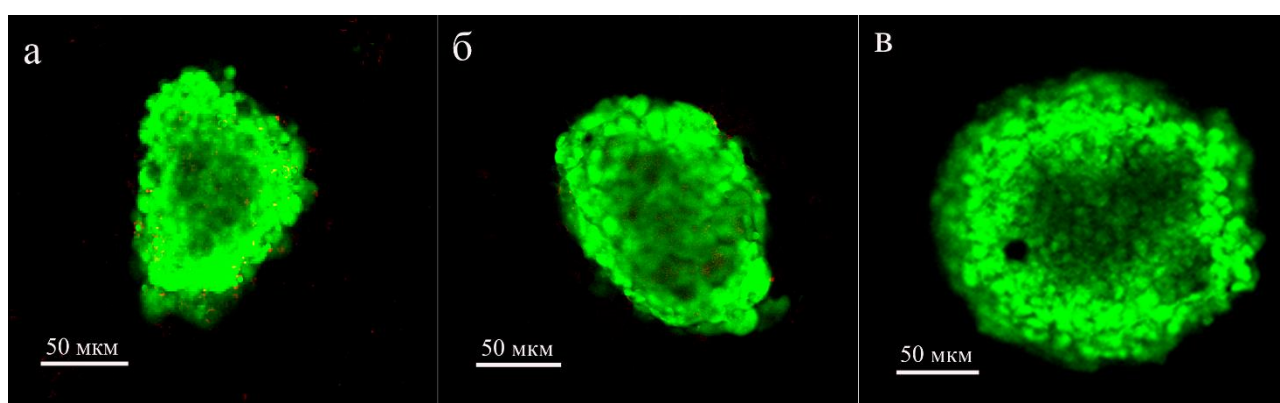


**Рисунок. 1.** Сфероїди, отримані методом висячої краплі на 3 добу культивування з МСК при посівній концентрації: а –  $3 \times 10^3$  клітин/краплю; б –  $4 \times 10^3$  клітин/краплю; в –  $5 \times 10^3$  клітин/краплю. Примітка: мічення з FDA (зелена флуоресценція)

Додатковою характеристикою функціональної активності клітин у складі сфероїдів є їх здібність адгезії, міграції та проліферації при перенесенні на адгезивну поверхню у стандартні умови культивування. Здатність сфероїдів до адгезії, отриманих з усіх вивчених посівних концентрацій клітин, складала 100%. За стандартних умов культивування з усіх сфероїдів спостерігалася міграція і проліферація клітин з формуванням моношару.

Отримані сфероїди збирали та зберігали за температури 22°C протягом 3 та 7 діб. Після цього виконували забарвлення з 6-CFDA та флуоресцентно-міченим аннексином V. Відомо, що аннексин V – це кальцій-залежний білок, який має високу спорідненість до мембранного фосфоліпиду фосфатидилсерину. Фосфатидилсерин зазвичай локалізований на внутрішньому шарі плазматичної мембрани, проте на ранніх стадіях апоптозу він переміщається на зовнішній шар, де стає доступним для аннексину V. Ця властивість дозволяє використовувати

флуоресцентно мічений аннексин V для ідентифікації та кількісного визначення апоптотичних клітин. Інший барвник, 6-CFDA, вільно проникає у клітину та гідролізується клітинними естеразами до флуоресцентної сполуки 6-карбоксифлуоресцеїну. Комбінація барвників дозволяє диференціювати ранні апоптотичні клітини (позитивні на аннексин V, позитивні на 6-CFDA), некротичні клітини (позитивні на аннексин V, негативні на 6-CFDA) та життєздатні клітини (негативні на аннексин V, позитивні на 6-CFDA).

У результаті експериментів встановлено, що у випадку, коли сфероїди було сформовано з 3 або 4 тисяч клітин, при зберіганні протягом 7 діб за амбієнтної температури значущих відмінностей між кількістю аннексин V - позитивних клітин не спостерігалось. На 3 добу зберігання показник апоптозу був на рівні 5-7%, тоді як на 7 добу – 20-24%. При збільшенні кількості клітин у сфероїді до 5 тисяч відбувалося різке підвищення апоптозу клітин вже на 3 добу (приблизно до 40%). На 7 добу кількість аннексин V-позитивних клітин у таких сфероїдах складала близько 65%.

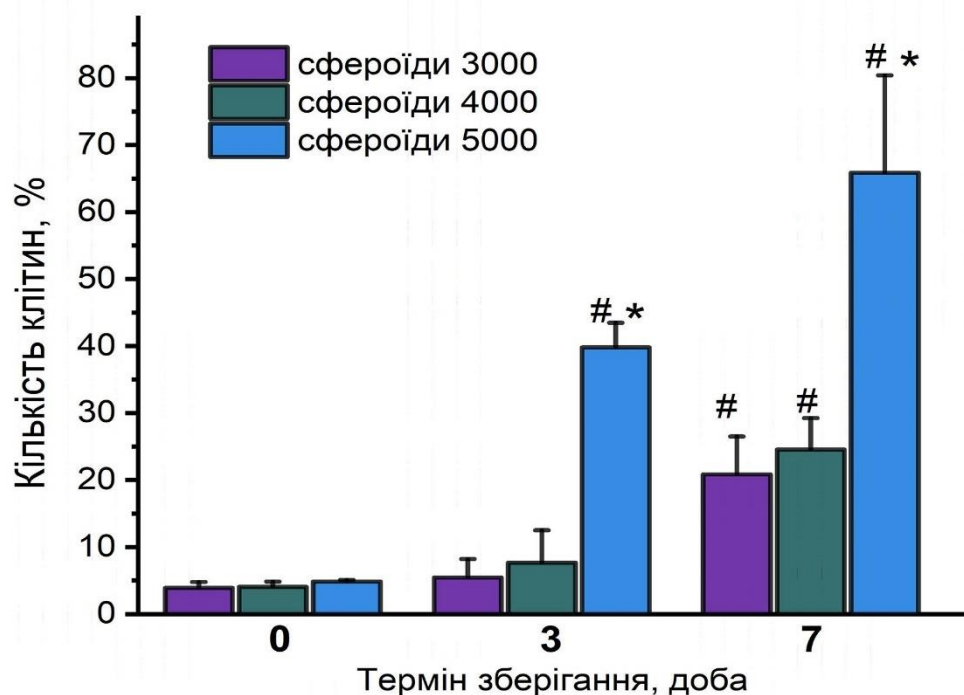


**Рисунок 2.** Кількість аннексин V-позитивних МСК у складі сфероїдів, отриманих з 3, 4 та  $5 \times 10^3$  клітин, після зберігання за температури 22°C. Примітки: # -  $p < 0,05$  порівняно з контролем (до зберігання); \* -  $p < 0,05$  порівняно зі сфероїдами 3000

Кількість апоптотичних клітин у багатоклітинному сфероїді тісно залежить від початкової концентрації клітин, використаної при його формуванні.

Збільшення посівної концентрації клітин зазвичай призводить до утворення великих сфероїдів, які, у свою чергу, демонструють більш виражені градієнти кисню, поживних речовин і продуктів метаболізму. Ці градієнти створюють просторову гетерогенність у параметрах життєздатності та метаболічної активності клітин, сприяючи розвитку у ядрі сфероїду гіпоксичних та збіднених на поживні речовини областей.

Попередні дослідження показали, що частка апоптотичних клітин у складі сфероїду збільшується, особливо коли його діаметр перевищує 300 мкм [7]. При цьому фарбування анексином V виявляє більш високу щільність апоптотичних клітин у центральних областях порівняно з периферією.

У наших дослідженнях апоптотичні клітин виявлялися у різних шарах сфероїдів, при цьому підвищення забарвлення було у середніх та центральних шарах. При відносно невеликому діаметрі отриманих нами сфероїдів на початкову добу кількість апоптотичних клітин значуще не відрізнялася від використаної посівної концентрації клітин. Однак за умов зберігання за амбієнтних температур параметр клітинної кількості набував вирішального значення. У сфероїдах з посівною концентрацією МСК більше, ніж  $3 \times 10^3$  клітин/краплю, виявлялося підвищення кількості апоптотичних клітин на третю та, особливо, на сьому добу.

**Висновки.** Виявлено залежність між посівною концентрацією МСК та кількістю апоптотичних клітин у складі сфероїду після 7 діб зберігання за амбієнтних температур. Кількість апоптотичних клітин у складі сфероїдів з МСК значуще підвищується при використанні посівної концентрації клітин більше, ніж  $3 \times 10^3$  клітин/краплю.

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### **Література.**

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## ЕНЗИМОТЕРАПІЯ НЕВИЛІКОВНИХ ПАТОЛОГІЧНИХ СТАНІВ

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**Анотація.** Ензимотерапія – один з перспективних напрямків біомедичної науки, котрий передбачає застосування ферментних препаратів або модифікацій ендогенних ферментних систем для корекції патологічних процесів. У випадках невиліковних або хронічних патологічних станів, таких як спадкові ензимні дефекти, фіброзні процеси, нейродегенеративні захворювання чи тяжкі онкологічні стани, традиційні терапевтичні підходи часто виявляються недостатніми. Метою цієї роботи є огляд сучасних досягнень ензимотерапії та аналіз потенціалу її застосування саме при таких станах, а також ідентифікація ключових проблем і перспектив подальших досліджень. Виконано аналіз літератури за останні роки з використанням баз даних *PubMed*, *Web of Science* та *Google Scholar*. Отримано дані про застосування ферментних засобів у різних патологіях, розглянуто механізми дії, обмеження (наприклад, імуногенність, нестабільність ферменту *in vivo*) та можливі шляхи подолання цих бар'єрів. У висновках підкреслено, що ензимотерапія має значний потенціал, однак потребує подальшої оптимізації доставляння ферментів, зменшення побічних реакцій та широкомасштабних клінічних досліджень.

**Ключові слова:** ензимотерапія, ферментна терапія, невиліковні патологічні стани, хронічні захворювання, ферментні препарати.

**Вступ.** В останні десятиліття у медицині зростає інтерес до терапевтичного застосування ферментів, білків-каталізаторів біохімічних реакцій. Ферменти мають високу специфічність, каталізують реакції за м'яких фізіологічних умов і можуть бути застосовані для корекції метаболічних дефектів або деградації патологічних субстратів [1-3]. У тих випадках, коли патологічні стани класифікуються як «невиліковні» за допомогою традиційної терапії (наприклад, спадкові лізосомні хвороби, прогресивні фібрози, нейродегенеративні розлади, деякі наслідки хронічного запалення), ензимотерапія може виступати як додатковий або навіть основний лікувальний підхід [4-6].

Однак, незважаючи на високий потенціал, існує низка обмежень: короткий термін дії ферментів *in vivo*, неспецифічність доставки, ризик імунної відповіді, складнощі у масштабуванні виробництва [2]. Тому доцільно здійснити системний аналіз сучасного стану ензимотерапії саме в контексті невиліковних патологічних станів – з метою виявлення реальних можливостей та бар'єрів [7-9].

У контексті України та світового досвіду важливо розглянути, яким чином ферментні препарати можуть інтегруватися до існуючих лікувальних схем, як може бути організовано їхнє клінічне впровадження та які дослідницькі питання лишаються відкритими.

**Мета дослідження.** Узагальнити сучасні дані про застосування ензимотерапії в контексті невиліковних або хронічних патологій. Проаналізувати механізми дії ферментних препаратів, їх переваги та обмеження. Виділити ключові проблеми впровадження ензимотерапії (технологічні, біологічні, клінічні) та окреслити перспективи її розвитку. Запропонувати напрямки подальших досліджень, які можуть наблизити ензимотерапію до широкого клінічного застосування при невиліковних патологічних станах.

**Матеріали та методи.** Для виконання даної статті здійснено огляд літератури з таких джерел: наукові статті, рецензовані огляди, клінічні дослідження, представлені в базах даних *PubMed*, *Web of Science*, *Google Scholar*. Відбір публікацій здійснювався за ключовими словами: «enzyme therapy», «therapeutic enzymes», «chronic disease enzyme therapy», «irreversible pathology enzyme treatment». Основна частина джерел – за останні 5 років, однак при необхідності включені й фундаментальні роботи попереднього десятиліття. Наприклад, роботи *Enzyme Therapy: Current Challenges and Future Perspectives* (2021) та *Enzymes for Disease Treatment-A Review* (2023) використовувалися як ключові огляди. Аналітичні методи: систематизація інформації за типами патологій (спадкові дефекти, фіброзні захворювання, нейродегенеративні стани, онкологія), а також класифікація за типами ферментних препаратів і



механізмами дії. Проводилась також критична оцінка переваг-недоліків та виявлення прогалин у знаннях.

**Результати та обговорення.** Згідно з оглядом, ферментні препарати вже застосовуються при спадкових лізосомних хворобах (наприклад, замісна ферментна терапія) та ряді інших станів [10-12]. У зазначеному контексті ензимотерапія може забезпечити: пряме відновлення або доповнення дефіцитної ферментної активності; деградацію патологічних субстратів (наприклад, накопичених білків, ліпідів, глікопротеїнів); модулювання запальних чи фіброзних процесів через специфічні ферменти. Це особливо актуально для тих станів, які зазвичай вважаються невиліковними або мають прогресуючий характер.

Ферменти можуть працювати через кілька основних механізмів: замісна терапія (enzyme replacement therapy, ERT) – введення функціонального ферменту замість дефектного; фермент-модифікатори – введення ферментів, які змінюють метаболізм патологічних субстратів або стимулюють ендогенну активність; таргетована доставка ферментів до певної тканини або клітини (через нанокapsули, ліганд-системи) – що дозволяє підвищити ефективність і мінімізувати побічні ефекти [3]; комбіновані підходи – ферменти+інші терапевтичні модулятори (наприклад, хіміотерапія, генно-терапія).

У спадкових лізосомних хворобах ферменти вже показали ефективність: зменшення накопичень ліпідів, покращення органних функцій [13]. При фіброзних змінах (наприклад, печінковий або легеневий фіброз) досліджуються ферменти, що можуть деградувати надмірний колаген або позаклітинний матрикс [14]. У онкології – застосування ферментів, які змінюють мікросередовище пухлини або «розм'якшують» позаклітинний матрикс для кращої доставляння препаратів [15].

Незважаючи на потенціал, є значні труднощі: коротка тривалість дії *in vivo*, ферменти швидко розщеплюються або виводяться [16]; недостатня селективна доставка: без цілеспрямованого транспорту ферменти можуть поширюватися в небажані тканини, що створює ризик побічних ефектів; імуногенність: введений фермент може викликати імунну реакцію, утворення антитіл, зниження ефективності або небезпечні побічні явища [17]; вартість виробництва: рекомбінантні ферменти, контроль якості – все це підвищує вартість терапії; дефіцит клінічних даних: багато досліджень поки що перебувають на стадії доклінічних або ранніх фаз, немає достатньо великих рандомізованих випробувань при «невиліковних» станах; регуляторні та логістичні аспекти: питання виробництва, стандартизації, дозування, маршрути введення [18, 19].

Щоб подолати зазначені виклики, у літературі запропоновано такі напрямки: вдосконалення методів доставки ферментів: нанокапсули, ліганд-мішені, інкапсуляція у клітини-переносники [1]; модифікація ферментів для покращення стабільності, зниження імуногенності (наприклад, PEG-модифікації); комбінована терапія – ферменти + інші модулятори, що можуть взаємно підсилювати ефект; персоналізований підхід – моніторинг імунної відповіді пацієнта, адаптація терапії (наприклад, мікромасиви для контролю) [4]; розширення клінічних випробувань на хронічні/невиліковні стани – щоб підтвердити безпечність і ефективність у великих групах; економічна оптимізація виробництва – масштабування, спрощення технологій [20].

У контексті невиліковних патологічних станів, ензимотерапія може стати важливим доповненням до класичної медицини. Проте варто підкреслити, що вона навряд чи буде «чарівною пігулкою»: успіх має залежати від інтеграції з іншими лікувальними підходами, від правильного відбору пацієнтів, від контролю безпеки та економічної доцільності. Також, якщо мова йде про країни з обмеженими ресурсами або системи охорони здоров'я, важливо враховувати фінансові та організаційні аспекти впровадження таких терапій [21, 22].

Зокрема для України важливо звернути увагу на питання доступності ферментних препаратів, налагодження виробництва або поставок, підготовку фахівців, створення мультидисциплінарних команд (генетики, біотехнологи, клініцисти). Також необхідно досліджувати місцеві клінічні умови, реєстраційні практики, страховий та державний механізми фінансування.

**Висновки.** Ензимотерапія є перспективною стратегією лікування невиліковних або хронічних патологічних станів, завдяки здатності ферментів специфічно виправляти метаболічні порушення чи змінювати патологічні субстрати. Попередні результати показують, що вона може бути ефективною в різних групах захворювань – від спадкових лізосомних захворювань до фіброзу і онкології. Однак існує низка значних бар'єрів: нестабільність ферментів *in vivo*, недостатня селективність доставки, ризик імуногенної відповіді, висока вартість, обмежені клінічні дані. Подолання цих викликів вимагає технологічних інновацій (доставка, модифікація ферментів), масштабування клінічних випробувань, економічної оптимізації та інтеграції з іншими терапевтичними підходами. Для впровадження ензимотерапії до клінічної практики, особливо в контексті України, необхідні активні зусилля щодо створення інфраструктури, забезпечення доступу до препаратів, підготовки кадрів і адаптації до місцевих умов.

Таким чином, хоча ензимотерапія ще не вийшла на широку практичну

реалізацію при всіх невиліковних патологіях, вона має потенціал стати важливою частиною майбутньої медицини – за умови подальших досліджень та впровадження.

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## ФАРМАКОЛОГІЧНА ДОЦІЛЬНІСТЬ ЗАСТОСУВАННЯ ВІТАМІНУ D З ВІТАМІНОМ K

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**Анотація.** У статті розглядається фармакологічна доцільність одночасного застосування вітаміну D та вітаміну K. Наведено сучасні уявлення про їхню синергічну дію в регуляції кальцієво-фосфорного обміну, підтриманні здоров'я кісткової, серцево-судинної та імунної систем. Проаналізовано біохімічні механізми взаємодії, особливості метаболізму, форми препаратів та клінічні аспекти комбінованої терапії. Обґрунтовано, що оптимальна комбінація D<sub>3</sub> (холекальциферол) і K<sub>2</sub> (менахінон-7) запобігає кальцифікації судин і підвищує ефективність засвоєння кальцію в кістках.

**Ключові слова:** вітамін D, вітамін K, кальцій, остеокальцин, карбоксилювання, остеопороз, кальцифікація, фармакологічна синергія.

**Вступ.** Сучасна наукова спільнота дедалі більше звертає увагу на вітамінний статус населення як важливий предиктор здоров'я та тривалості життя. Вітамін D та вітамін K є двома життєво необхідними жиророзчинними вітамінами, які відіграють ключову роль у регуляції кальцієво-фосфорного обміну, мінералізації кісткової тканини, підтриманні функцій серцево-судинної, імунної та нервової систем. Традиційно їх розглядали окремо, однак сучасні біохімічні й клінічні дослідження довели, що між цими двома мікронутрієнтами існує тісний фізіологічний і фармакологічний взаємозв'язок, що має принципове значення для забезпечення гармонійного метаболізму кальцію в організмі людини [1].

**Мета дослідження.** Обґрунтувати фармакологічну доцільність комбінованого застосування вітаміну D з вітаміном K для оптимізації кальцієвого обміну, профілактики остеопорозу та зниження ризику судинної кальцифікації.

**Матеріали та методи.** Аналіз наукових джерел (PubMed, Scopus, Web of Science, 2010–2025 рр.). Порівняльна оцінка фармакокінетичних параметрів D<sub>3</sub> і K<sub>2</sub>. Метааналіз клінічних досліджень комбінації D<sub>3</sub> + K<sub>2</sub> при остеопорозі та серцево-судинних хворобах. Огляд біохімічних механізмів (γ-карбоксилювання, експресія VDR, синтез остеокальцину). Фармакологічна інтерпретація результатів для визначення оптимальних дозувань і форм.

**Результати та обговорення.** Біохімічна взаємодія між вітамінами D та K є одним із найважливіших прикладів метаболічної синергії у живому організмі.



Вітамін D регулює експресію низки білків, відповідальних за транспорт і зв'язування кальцію, проте ці білки потребують посттрансляційної модифікації за участю вітаміну K, без якої вони залишаються неактивними.

Під впливом активної форми вітаміну D<sub>3</sub> (1,25(OH)<sub>2</sub>D<sub>3</sub>) у клітинах остеобластів активується транскрипція гену остеокальцину (BGLAP). Остеокальцин є одним із головних білків кісткової матриці, який забезпечує зв'язування кальцію та формування гідроксиапатиту, основного мінералу кісткової тканини. Однак остеокальцин у неактивній формі (ucOC, uncarboxylated osteocalcin) не може ефективно фіксувати кальцій. Для його активації необхідне γ-карбоксилювання залишків глутамінової кислоти, що здійснюється ферментом γ-глутамілкарбоксилазою за участю вітаміну K<sub>2</sub> як кофактора [1-3].

Аналогічний механізм стосується матричного Gla-білка (MGP), який є потужним інгібітором кальцифікації судин. Він синтезується клітинами судинної стінки під впливом вітаміну D, але стає активним лише після карбоксилювання за участю вітаміну K. Недостатність K<sub>2</sub> призводить до накопичення неактивної форми MGP (dp-ucMGP), що асоціюється з розвитком атеросклерозу, кальцифікації клапанів серця та зниженням еластичності судин [4].

Таким чином, вітамін D «стимулює» утворення кальційзв'язувальних білків, а вітамін K «активує» їх, забезпечуючи біологічно ефективне використання кальцію в організмі. Відсутність будь-якого з компонентів порушує фізіологічний баланс і сприяє розвитку патологічних станів [5].

Фармакокінетичні дослідження показали, що вітамін D<sub>3</sub> (холекальциферол) є більш активною формою, ніж D<sub>2</sub> (ергокальциферол), і має вищу біодоступність. Після надходження до організму він гідроксильється в печінці до 25(OH)D, а потім у нирках до 1,25(OH)<sub>2</sub>D, який є гормонально активною формою. Ця форма впливає на всмоктування кальцію в кишечнику, стимулює синтез остеокальцину та MGP, а також модулює активність імунних клітин [6].

Вітамін K існує у двох основних формах: філохінон (K<sub>1</sub>) і менахінон (K<sub>2</sub>). K<sub>1</sub> надходить переважно з рослинних джерел і бере участь у синтезі факторів згортання крові, тоді як K<sub>2</sub> (особливо МК-7) діє в позапечінкових тканинах, зокрема в кістках і судинах. МК-7 має тривалий період напіввиведення (понад 72 години), що забезпечує постійну активацію K-залежних білків при регулярному прийомі.

Синергічна дія D<sub>3</sub> і K<sub>2</sub> полягає не лише в регуляції кальцієвого обміну, але й у впливі на гени, пов'язані з проліферацією, апоптозом і запальними

процесами. Доведено, що одночасна активація рецепторів VDR (вітамін D-рецептор) і SXR (steroid and xenobiotic receptor, також відомий як вітамін K-рецептор) посилює експресію білків, які відповідають за здоров'я судинної стінки та ремоделювання кісткової тканини [7].

У низці рандомізованих клінічних випробувань доведено, що комбінація вітаміну D<sub>3</sub> і K<sub>2</sub> має виражену синергічну дію щодо підтримання здоров'я кісток та судин.

У дослідженні Iwamoto та співавт. (2019) участь взяли 120 жінок у постменопаузі. Протягом року вони отримували D<sub>3</sub> (1000 МО/день) або D<sub>3</sub> + K<sub>2</sub> (МК-7, 180 мкг/день). У групі комбінованої терапії мінеральна щільність кісткової тканини (МЩКТ) стегнової кістки збільшилася на 2,4 %, тоді як у групі лише D<sub>3</sub> лише на 0,7 %. Крім того, рівень неактивного остеокальцину (ucOC) знизився на 35 %, що свідчить про покращену карбоксилуючу активність вітаміну K<sub>2</sub>. Інше дослідження (Brandenburg, 2023) за участю осіб похилого віку з остеопенією показало, що прийом D<sub>3</sub> (2000 МО) у комбінації з K<sub>2</sub> (МК-7, 120 мкг) протягом 12 місяців приводив до зниження маркерів резорбції кісткової тканини (СТХ) і підвищення рівня остеокальцину. Це підтверджує гіпотезу про оптимізацію ремоделювання кістки за рахунок збалансованого кальцієвого метаболізму.

Клінічні дані свідчать, що ізольоване призначення високих доз вітаміну D може сприяти кальцифікації судин, якщо в організмі бракує вітаміну K. У пацієнтів із хронічною нирковою недостатністю комбінована терапія D<sub>3</sub> + K<sub>2</sub> (МК-7) знижувала рівень неактивного MGP, що є маркером судинної кальцифікації, і покращувала еластичність артерій (Fusaro, 2021).

У дослідженні на тваринах, опублікованому у *Frontiers in Cardiovascular Medicine* (2023), показано, що введення K<sub>2</sub> разом із D<sub>3</sub> зменшує відкладення кальцію у стінках артерій на 45 % порівняно з групою, яка отримувала лише D<sub>3</sub>. Це демонструє реальну захисну роль K<sub>2</sub> проти D<sub>3</sub>-індукованої кальцифікації.

Вітамін D давно відомий як потужний імуномодулятор, що підвищує активність макрофагів і Т-лімфоцитів. Вітамін K у свою чергу впливає на експресію цитокінів, знижуючи рівень запальних медіаторів IL-6 та TNF-α. Спільна дія цих вітамінів забезпечує протизапальний ефект, особливо в осіб із метаболічним синдромом, ожирінням або аутоімунними порушеннями [8, 9].

Нестача вітаміну D супроводжується зниженням абсорбції кальцію, гіпокальціємією, підвищенням секреції паратгормону, що активує резорбцію кісткової тканини. Клінічно це проявляється остеомаліцією, підвищеною ламкістю кісток, хронічною втомою [10].

Однак надмірне споживання D<sub>3</sub> (>10 000 МО/день протягом тривалого

часу) без супроводу  $K_2$  може викликати гіперкальціємію та відкладення кальцію в судинах і нирках. Саме тому вітамін D не можна розглядати ізольовано, його ефективність і безпечність значною мірою залежать від статусу вітаміну K. Дефіцит  $K_2$ , у свою чергу, проявляється збільшенням рівня неактивного остеокальцину та MGP, що веде до зниження міцності кісток і розвитку судинної кальцифікації. Особливо високий ризик спостерігається у пацієнтів, які приймають антагоністи вітаміну K (варфарин), а також у людей із порушеннями кишкової мікрофлори [11-13].

Сьогодні на фармацевтичному ринку представлені численні комбіновані препарати, що містять  $D_3$  і  $K_2$  у різних співвідношеннях. Найчастіше використовують:  $D_3$  (1000–4000 МО) +  $K_2$  (МК-7 90–180 мкг) у капсулах або краплях; олійні розчини у формі спреїв; комбіновані дитячі препарати ( $D_3$  400 МО +  $K_1$  25 мкг) [14].

Біодоступність обох вітамінів значно підвищується при прийомі з жирами, тому рекомендовано приймати їх після їжі або у формі масляних розчинів. Оптимальне співвідношення  $D_3:K_2$  становить приблизно 25 мкг: 100 мкг, що відповідає фізіологічному балансу між підвищенням рівня кальцію у крові (за дії  $D_3$ ) і його направленням до кісток (за дії  $K_2$ ) [15].

Синергічне поєднання вітаміну  $D_3$  і  $K_2$  відкриває перспективи для профілактики та лікування широкого спектра захворювань, зокрема: остеопорозу і остеомалії; атеросклерозу та кальцифікації артерій; хронічної ниркової недостатності; діабетичної ангіопатії; запальних і автоімунних патологій [5].

Крім того, останні дослідження вказують на можливу роль  $K_2$  у запобіганні віковим когнітивним розладам, а також у покращенні енергетичного обміну в мітохондріях. Вітамін D, у свою чергу, залишається ключовим гормоноподібним регулятором понад 200 генів, що пояснює широкий спектр його дії [5, 8, 12].

**Висновки.** Результати численних досліджень узгоджено свідчать, що оптимальний ефект від терапії вітаміном D можливий лише за наявності адекватного рівня вітаміну  $K_2$ . Їх поєднане застосування забезпечує: підвищення мінеральної щільності кісток; зниження ризику переломів у літніх осіб; профілактику кальцифікації артерій; поліпшення ендотеліальної функції; зменшення запальних процесів.

Таким чином, вітаміни D і K утворюють фізіологічний «кальцієвий дует», у якому D забезпечує доступ кальцію, а K визначає його «правильне місце призначення». Ця взаємодія є прикладом концепції *targeted nutrient therapy*, цілеспрямованої корекції обміну речовин через взаємодію біоактивних сполук.

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## СУЧАСНІ УЯВЛЕННЯ ЩОДО БІОХІМІЧНОЇ КОМПАРТМЕНТАЛІЗАЦІЇ

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**Анотація.** Біохімічна компартменталізація є фундаментальним принципом організації живих клітин, який забезпечує просторову й функціональну впорядкованість метаболічних процесів. Завдяки компартменталізації клітина досягає ефективності обміну речовин, регуляції енергетичних потоків, синтезу макромолекул і підтримання гомеостазу. У статті розглянуто історію формування уявлень про компартменталізацію, її молекулярні механізми, типи клітинних компартментів, взаємозв'язок між метаболічними шляхами, роль мембран, ферментних комплексів і фазових конденсатів. Особливу увагу приділено сучасним уявленням про динамічну компартменталізацію та її значення для біотехнології, фармакології й патології клітини.

**Ключові слова:** компартменталізація, клітина, метаболізм, мембрана, органела, мікродомен, фазова сепарація, біохімія.

**Вступ.** Однією з основних характеристик живої матерії є її висока структурна впорядкованість. У клітині, на відміну від неживих систем, простір не є однорідним, він поділений на спеціалізовані зони, або компартменти, у яких відбуваються строго визначені біохімічні процеси. Такий розподіл функцій і простору створює умови для одночасного протікання взаємно несумісних реакцій, ефективного використання енергії та швидкої регуляції метаболізму. Саме цей принцип отримав назву біохімічної компартменталізації [1].

Ідея просторової організації клітини почала формуватись ще в середині ХХ століття, коли електронна мікроскопія дозволила побачити внутрішню архітектуру клітинних структур. Пізніше біохімічні дослідження показали, що певні ферменти локалізуються лише в окремих органелах – мітохондріях, пероксисомах, ендоплазматичному ретикулумі тощо. Ці спостереження стали підґрунтям для формування концепції метаболічної компартменталізації, що нині розглядається як універсальна властивість живих систем.

У сучасній біології компартменталізація трактується не лише як фізичне розділення реакцій за допомогою мембран, а й як динамічний механізм, який забезпечує тимчасову, умовну або фазову сегрегацію компонентів цитоплазми. Це включає формування так званих біомолекулярних конденсатів, немембранних структур, що виникають у результаті рідинно-рідинної фазової сепарації. Прикладами таких структур є ядро, тільця Кахалі, stress-грані, Р-



тілця та інші функціональні мікродомени [2].

Біохімічна компартменталізація має виняткове значення для метаболізму, оскільки дозволяє: підтримувати концентраційні градієнти субстратів і коферментів; уникати небажаних побічних реакцій; регулювати швидкість і напрямок метаболічних шляхів; створювати мікросередовище з оптимальним рН, іонним складом або редокс-потенціалом; координувати енергетичні процеси між органелами [3].

Вивчення механізмів компартменталізації є важливим не лише для розуміння клітинної фізіології, але й для медицини, біотехнології та фармакології. Порушення просторової організації клітини лежить в основі багатьох патологій: нейродегенеративних, метаболічних, онкологічних, запальних. Отже, поглиблене розуміння сучасних уявлень про компартменталізацію є необхідним для створення нових підходів до діагностики й терапії.

**Мета дослідження.** Узагальнити сучасні наукові дані щодо біохімічної компартменталізації, її структурних та функціональних особливостей, механізмів формування і регуляції, а також визначити значення цього явища для нормальної та патологічної фізіології клітини.

**Матеріали та методи.** Під час підготовки роботи використано системний огляд сучасної літератури, включно з базами даних *PubMed*, *Scopus*, *Web of Science*. Проаналізовано результати експериментальних та теоретичних досліджень, опублікованих у 2005-2025 рр., що стосуються клітинної організації, метаболічної компартменталізації, рідинно-рідинної фазової сепарації та молекулярної динаміки. Методологічно дослідження базувалось на порівняльному аналізі механізмів компартменталізації в різних типах клітин, міжвидових аналогіях, а також на біохімічному й структурно-функціональному узагальненні отриманих даних.

**Результати та обговорення.** Компартмент у біохімічному сенсі це функціонально спеціалізована ділянка клітини, у межах якої створено певні умови для здійснення конкретних реакцій. Класично виділяють два основних типи компартментів: мембранні – органели, оточені ліпідними мембранами (ядро, мітохондрії, ЕПР, апарат Гольджі, лізосоми, пероксисоми, хлоропласти). Немембранні – тимчасові мікродомени або біомолекулярні конденсати, сформовані завдяки міжмолекулярним взаємодіям без участі мембран. Функціональна компартменталізація може також бути метаболічною (розподіл шляхів гліколізу, циклу Кребса,  $\beta$ -окиснення) та сигнальною (локалізація каскадів MAPK,  $\text{Ca}^{2+}$ -сигналізації тощо) [4].

Мембрани виконують роль бар'єрів і платформ для ферментів. У мітохондріях, наприклад, внутрішня мембрана формує кристи: ділянки інтенсивного окисного фосфорилювання. У ендоплазматичному ретикулумі локалізуються ферменти синтезу ліпідів і білків, тоді як апарат Гольджі забезпечує посттрансляційну модифікацію та сортування. Такий розподіл реакцій дозволяє клітині створювати автономні мікросистеми, де одночасно підтримуються різні хімічні режими [5].

Рідинно-рідинна фазова сепарація (LLPS) – це сучасна концепція, яка пояснює утворення динамічних немембранних структур. Її рушійною силою є слабкі мультивалентні взаємодії між білками та нуклеїновими кислотами, що спричиняють конденсацію компонентів у щільні, але рухомі краплиноподібні домени. Такі структури швидко формуються і розпадаються у відповідь на зміни умов, тому вони є ідеальними регуляторними центрами клітинної активності [6-8].

Основними факторами, що визначають локалізацію реакцій, є: транспорт білків через сигнальні пептиди; посттрансляційні модифікації (фосфорилювання, ацетилювання, убіквітінування); білок-білкові взаємодії; мембранний потенціал і локальні градієнти іонів. Завдяки цим механізмам клітина здатна швидко змінювати топологію своїх процесів, адаптуючись до зовнішніх впливів.

Відомо, що концентрація субстратів і ферментів у певному мікросередовищі може підвищувати швидкість реакцій у десятки разів. Наприклад, у гліколітичних комплексах ферменти зібрані в послідовні каскади, що мінімізує дифузійні втрати. У мітохондріях просторове зближення ферментів циклу Кребса і дихального ланцюга створює метаболічні «суперкомплекси», які підвищують продукцію АТФ [9].

Порушення компартменталізації є патогенетичним чинником багатьох хвороб. Наприклад: мітохондріальна дисфункція при нейродегенерації (альцгеймеризм, паркінсонізм); дефекти аутофагії та лізосом при ліпідозах; патологічна фазова сепарація при агрегації білків (TDP-43, FUS); зміна ядерно-цитоплазматичного транспорту при онкопроцесах. Отже, структурна цілісність компартментів є критичною для клітинного виживання [10-12].

Розуміння топології клітинних процесів відкриває нові можливості для створення таргетних лікарських засобів, спрямованих у певні компартменти, наприклад, мітохондріальні антиоксиданти, лізосомальні ферменти, нуклеарні інгібітори. У синтетичній біології на цій основі розробляють штучні мікрокомпартменти, нанокapsули та ферментні платформи для виробництва біомолекул.

**Висновки.** Біохімічна компартменталізація є ключовим принципом організації клітинного життя. Вона забезпечує просторову координацію метаболізму, підвищення ефективності реакцій та зниження енергетичних втрат. Сучасні дослідження доводять, що поряд із класичними мембранними органелами важливу роль відіграють немембранні конденсати. Порушення компартменталізації призводить до розвитку численних патологій, тому її вивчення має фундаментальне і прикладне значення. Перспективними напрямками є створення штучних компартментів і розробка препаратів, що цілеспрямовано діють у певних клітинних доменах.

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## ВИВЧЕННЯ АКТОПРОТЕКТОРНОЇ ДІЇ НОВОЇ СПОЛУКИ РЯДУ МЕТИЛКСАНТИНІВ У ЕКСПЕРИМЕНТІ

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**Анотація.** У статті представлено результати експериментального дослідження актопротекторної активності нової сполуки в ряду 7,8-дизаміщених похідних метилксантинів –  $\gamma$ -2797 (7-п-метилбензил-8-( $\alpha$ -метил)-п-метоксибензиліденгідразинотеофілін). Дослідження проводили на щурах лінії Wistar із використанням методу вимірювання тривалості плавання з вантажем. Встановлено, що курсове введення сполуки  $\gamma$ -2797 у дозі 45 мг/кг підвищує фізичну витривалість тварин на 58% порівняно з контролем. Біохімічні дослідження показали, що дія сполуки супроводжується зниженням рівня продуктів перекисного окиснення ліпідів (ТБК-реактивів), підвищенням активності каталази, збільшенням вмісту АТФ та глікогену, а також нормалізацією співвідношення лактат/піруват у тканинах. Отримані результати свідчать про активацію енергетичного метаболізму, антиоксидантного захисту та зменшення оксидативного стресу, що визначає актопротекторну дію сполуки  $\gamma$ -2797. Таким чином, нове похідне метилксантинів може бути перспективним для подальшої розробки як лікарський засіб актопротекторної дії.

**Ключові слова:** метилксантини, актопротектори, антиоксиданти, енергетичний обмін, аденозин.

**Вступ.** Актуальність пошуку та дослідження нових лікарських засобів актопротекторної дії пов'язана з потребою у вдосконаленні методів лікування та профілактики широкого спектра захворювань, що супроводжуються порушенням функціонального стану організму. Пошук безпечних засобів, які допомагають покращити фізичну та розумову активність, є важливим для спортсменів, людей з інтенсивним робочим графіком, а також для літніх людей, які прагнуть підтримувати активність у зрілому віці. Актопротектори відіграють значну роль у програмах реабілітації після серйозних захворювань, травм чи операцій, де потрібна стимуляція метаболічних процесів і покращення загального тону [4, 5, 10, 11].

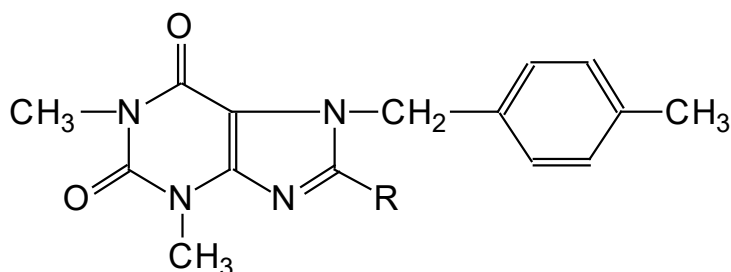
Сучасний спосіб життя, що часто включає високий рівень стресу та фізичних навантажень, вимагає засобів, які покращують адаптацію організму до

несприятливих умов. Сучасна наука дозволяє глибше вивчати механізми дії актопротекторів на клітинному та молекулярному рівнях, що дає можливість створювати більш ефективні препарати з мінімальними побічними ефектами [4, 5, 6, 9].

Похідні ксантину є важливою групою біологічно активних сполук, які виявляють широкий спектр фармакологічних ефектів, зокрема актопротекторну активність. Їх дія базується на здатності покращувати енергетичні процеси в організмі, посилювати адаптаційні можливості та стимулювати фізичну та психічну працездатність [3, 8]. Механізми дії, що забезпечують актопротекторний ефект полягають в інгібуванні фосфодіестерази (ФДЕ): Похідні ксантину пригнічують фермент ФДЕ, що призводить до накопичення циклічного аденозинмонофосфату (цАМФ) у клітинах [1]. Це сприяє підвищенню енергетичного обміну та адаптаційних можливостей організму. Наступний механізм – антагонізм до аденозинових рецепторів: Взаємодія з аденозиновими рецепторами сприяє стимуляції ЦНС, зменшенню втоми та покращенню когнітивної функції. Крім того, метилксантини підвищують кровотік у тканинах, що забезпечує краще постачання кисню та поживних речовин, особливо за умов гіпоксії. Метилксантини мають також антиоксидантну дію: захищають клітини від оксидативного стресу, що є важливим при високих фізичних та психоемоційних навантаженнях.

**Мета дослідження.** Експериментальне обґрунтування доцільності пошуку нових актопротекторних засобів, серед похідних метилксантину.

**Матеріали та методи.** Як об'єкт дослідження обрано нову сполуку в ряду 7,8-дизаміщених похідних теофіліну під шифром  $\gamma$ -2797 (7-*n*-метилбензил-8-( $\alpha$ -метил)-*n*-метоксибензиліденгідразинотеофілін). Дана речовина синтезована на кафедрі біологічної хімії та лабораторної діагностики Запорізького державного медичного університету [9].





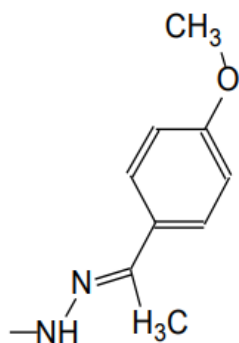


Рис. 2. Метил-п-метоксибензиліденгідразинівий радикал в структурі досліджуваної сполуки γ-2797

Сполука є білим сипучим кристалічним порошком, без запаху, розчинна у органічних розчинниках та важко розчинна у воді. Вона стабільна при зберіганні, не гігроскопічна. Досліджувану сполуку вводили лабораторним тваринам внутрішньошлунково у вигляді тонкодисперсної водної суспензії, стабілізованої твіном-80.

Експерименти проведені на 24 щурах лінії Wistar обох статей масою 180-200 г. Загальну фізичну витривалість визначали загальноприйнятим методом тривалості плавання тварин у басейні з вантажем, що становить 10 % від маси тіла [7]. Тваринам дослідної групи внутрішньошлунково вводили розчин досліджуваної речовини у дозі 45 мг/кг (1/100 LD<sub>50</sub>, визначеної у попередніх дослідженнях [9] протягом 7 днів (1 раз на добу за 30 хвилин до годування). Тварини контрольної групи отримували еквівалентний об'єм дистильованої води. Через 7 діб від початку введення досліджуваної сполуки та препарату порівняння визначали загальну фізичну витривалість шляхом плавання тварин до повної стомленості, критерієм якого служило 10-ти секундне занурення тварини під воду. В якості препарату порівняння було використано таблетки рибоксину в дозі 100 мг/кг (доза у перерахунку за Ю. Р. Риболовцевим з використанням коефіцієнта видової чутливості) [7].

Після чого у сироватці крові тварин визначали активність процесів вільнорадикального окиснення за вмістом ТБК-реактивів (ТБК-Р) та активністю каталази (КТ) [7].

З метою виявлення механізмів стійкості до інтенсивних фізичних навантажень у зразку гомогенату скелетного м'яза щурів визначали вміст АТФ, молочної кислоти (МК), піровиноградної кислоти (ПВК) з розрахунком окисно-відновного потенціалу відношенню лактатат/піруват; у зразку гомогенату печінки – глікоген [10].

Статистичну обробку отриманих даних проводили з використанням критерію Стюдента.

Під час проведення експериментів тварин утримували у віварії ЦНДЛ НФаУ, яка атестована МОЗ України на проведення вимірювань у сфері охорони здоров'я. Дослідження виконано відповідно до вимог Європейської конвенції про охорону хребетних тварин, які використовуються в експериментальних та інших наукових цілях (Страсбург, 1986 р., зі змінами 1998 р.), Закону України № 3446-IV від 21.02.2006 р. «Про захист тварин від жорстокого поводження» (Zakon Ukrainy № 3447-IV від 21.02.2006) та Директива Європейського Союзу 2010/63 ЄС «Про захист тварин, які використовуються в наукових цілях», 2010 [2]. Під час проведення досліджень тварини перебували у віварії з контрольованим температурним режимом та відносною вологістю, на дванадцятигодинному циклі день/ніч, з вільним доступом до води та їжі.

**Результати та обговорення.** Робота в екстремальних умовах потребує мобілізації всіх фізичних та психоемоційних резервів організму. Зниження працездатності може бути викликано різними факторами: висока чи низька температура навколишнього середовища, стрес, нестача кисню та ін. виснажують енергетичний потенціал та захисні сили організму, що призводить до швидкого настання втоми. Аналіз літературних джерел щодо проблеми підвищення фізичної працездатності за допомогою фармакологічних засобів у військовій та екстремальній медицині дозволив виділити п'ять принципових підходів до вирішення цієї проблеми: підвищення працездатності як негайна мобілізація функціональних резервів організму, що забезпечується застосуванням психомоторних стимуляторів центральної дії; підвищення працездатності як корекція переносимості екстремальних впливів, для чого застосовуються препарати з групи ноотропів, актопротекторів, антигіпоксантив; підвищення працездатності як корекція механізмів стомлення та зниження фізичної працездатності, рекомендується застосування попередників медіаторів ЦНС; підвищення працездатності як адаптація до фізичних навантажень анаболічні та статеві стероїди, соматотропний гормон; підвищення працездатності як припинення дії внутрішніх чинників, що сприяють її зниженню – ентеросорбенти, жовчогінні, діуретичні та лімфодинамічні засоби та відновлення неспецифічної резистентності організму з використанням вітамінів, еубіотиків, адаптогенів.

Перший і другий підхід реалізується у практиці військової та екстремальної медицини (робота рятувальників в осередку катастрофи без можливості повноцінної заміни та відпочинку).

Як свідчать дані, наведені у таблиці 1, превентивне багаторазове введення сполуки  $\gamma$ -2797 чинить виразну актопротекторну дію, про що свідчить підвищення загальної фізичної працездатності тварин дослідної групи: тривалість плавання збільшилася на 58% порівняно з даними тварин контрольної групи. Тварини з групи, якій в аналогічному режимі вводили препарат порівняння рибоксин.

*Таблиця 1*

**Вплив нового похідного ксантинів на загальну фізичну витривалість та показники інтенсивності процесів ПОЛ та АОС організму білих щурів на тлі інтенсивного фізичного навантаження**

| Показники                              | Групи тварин           |                         |                                                 |                                             |
|----------------------------------------|------------------------|-------------------------|-------------------------------------------------|---------------------------------------------|
|                                        | група 0<br>ІК<br>(n=6) | група I<br>ПК<br>(n=6)  | група II<br>$\gamma$ -2797<br>45 мг/кг<br>(n=6) | група III<br>рибоксин<br>100 мг/кг<br>(n=6) |
| Тривалість плавання, хв                | –                      | 6,8±1,92                | 10,9±1,54*                                      | 11,2±1,57*                                  |
| ТБК-Р, мкмоль/г                        | 0,60±0,11              | 0,88±0,12 <sup>#</sup>  | 0,31±0,05*                                      | 0,34±0,10*                                  |
| Активність каталази, мкмоль/(хв*100мг) | 22,82±1,45             | 19,07±0,97 <sup>#</sup> | 17,23±1,62*                                     | 16,98±1,29*                                 |

Примітка:

1. <sup>#</sup> – відмінності статистично значущі щодо інтактного контролю,  $p < 0,05$ ;
2. \* – відмінності статистично значущі щодо групи I,  $p < 0,05$ ;
3. ІК – інтактні тварини;
4. ПК – група, яка отримувала дистильовану воду.

У тварин на тлі максимального фізичного навантаження відзначається суттєве підвищення рівня ТБК-Р у крові, а також зниження активності каталази сироватки крові, що свідчить про індукції процесів перекисного окислення ліпідів і пригніченні активності ендогенної антиокисної системи організму в результаті плавання до повної втоми (*табл. 1*). На тлі превентивного введення досліджуваного засобу відзначаються менш виражені зміни у показниках вільнорадикального окислення та параметрів антиокислювальної системи. Так, концентрація ТБК-Р у сироватці крові тварин дослідної групи була на 9% менше порівняно з аналогічними показниками щурів контрольної групи. Поряд з цим, на тлі введення випробуваного засобу сироватці крові тварин дослідної групи відзначалося підвищення активності каталази на 25% порівняно з контролем, що свідчить про активації антиокислювальної системи (*табл. 1*).

Фізична активність супроводжується витратою енергії і призводить до зменшення концентрації АТФ та збільшення рівня молочної та пірвіноградної кислот у скелетних м'язах, що впливає на інтенсивність фізичної працездатності. У нашому дослідженні у групі контролю спостерігається зменшення АТФ на 50 % ( $p < 0,05$ ) та збільшення молочної та пірвіноградної кислот у 2,4 ( $p < 0,05$ ) і 1,3 ( $p < 0,05$ ) рази відповідно щодо інтактних тварин. Відношення лактат/пірват також зросла на 1,8 ( $p < 0,05$ ) рази. Дані показники обмежують інтенсивність фізичних навантажень. Посилена фізична робота також призводить до зниження вуглеводних запасів, що виявилось у зменшенні вмісту глікогену в печінці на 43% ( $p < 0,05$ ) (*табл. 2*).

*Таблиця 2*

**Вплив нового похідного ксантинів на біохімічні показники білих щурів на фоні інтенсивного фізичного навантаження**

| Показники                        | Групи тварин           |                          |                             |                                |
|----------------------------------|------------------------|--------------------------|-----------------------------|--------------------------------|
|                                  | група 0<br>ІК<br>(n=6) | група І<br>ПК<br>(n=6)   | група ІІ<br>γ-2797<br>(n=6) | група ІІІ<br>рибоксин<br>(n=6) |
| МК, мкмоль/г                     | 2,1±0,17               | 5,0±0,31 <sup>#</sup>    | 2,9±0,25*                   | 3,1±0,29*                      |
| ПВК, мкмоль/г                    | 0,50±0,051             | 0,67±0,049 <sup>#</sup>  | 0,53±0,041*                 | 0,52±0,048*                    |
| Лактат/пірват                    | 4,2±0,15               | 7,5±0,25 <sup>#</sup>    | 5,5±0,24*                   | 5,9±0,28*                      |
| Глікоген, мг %                   | 5717±133,3             | 4002 ±54,46 <sup>#</sup> | 4829±132,32*                | 4767±27,31*                    |
| АТФ у скелетному м'язі, мкмоль/г | 4,52±0,13              | 3,0±0,15 <sup>#</sup>    | 3,9±0,36*                   | 3,81±0,22*                     |

Примітка:

1. <sup>#</sup> – відмінності статистично значущі щодо інтактного контролю,  $p < 0,05$ ;
2. \* – відмінності статистично значущі щодо групи І,  $p < 0,05$ ;
3. ІК – інтактні тварини;
4. ПК – група, яка отримувала дистильовану воду.

У дослідній групі багаторазове застосування сполуки γ-2797 призвело до збільшення фізичної витривалості щурів внаслідок активації ресинтезу АТФ. Вміст АТФ у скелетному м'язі був на 30 % вище порівняно з тваринами контрольної групи. Також зазначалося зниження вмісту молочної та пірвіноградної кислот в 1,7 і 1,3 рази відповідно, що супроводжувалось зменшенням співвідношення МК/ПВК у середньому на 1,4 рази. За рахунок збільшення запасів глікогену в печінці при застосуванні γ-2797 на 20% порівняно з контрольною групою. Референтний препарат рибоксин чинив

односпрямовану дію з досліджуваною сполукою (*табл. 2*).

На підставі вищезазначених даних актопротекторна активність нової сполуки  $\gamma$ -2797 пов'язана зі збільшенням ресинтезу АТФ в м'язах, що активно працюють, за рахунок переходу з гліколітичного шляху обміну речовин на більш вигідний шлях окисного фосфорилування при ІФН. Для забезпечення достатніх резервів субстратів окислення при застосуванні  $\gamma$ -2797 спостерігалось підвищення рівня глікогену у печінці. При тяжкій фізичній роботі відзначалося зменшення метаболічного ацидозу за рахунок зниження рівня молочної кислоти та співвідношення МК/ПВК в інтенсивно працюючій скелетній мускулатурі. Курсове профілактичне введення щурам нової сполуки  $\gamma$ -2797 дозою 45 мг/кг дозволяє нормалізувати рівновагу прооксидантної та антиоксидантної систем організму. Отже, в результаті проведеного дослідження встановлено, що нова сполука в ряду 7,8-дизаміщених похідних метилксантинів  $\gamma$ -2797 при курсовому введенні в експериментально-терапевтичній дозі чинить виразну актопротекторну дію, зумовлену активацією енергетичного обміну та зниженням вираженості окислювального стресу при інтенсивному фізичному навантаженні.

**Висновки.** В результаті проведеного дослідження встановлено, що курсове введення щурам дослідної групи нової сполуки в ряду 7,8-дизаміщених метилксантинів  $\gamma$ -2797 дозою 45 мг/кг виявляє актопротекторну дію, обумовлену оптимізацією енергетичного відновлення АТФ, інгібуванням процесів вільнорадикального окислення та активацією ферментів антиоксидантного захисту. Похідні ксантину чинять широкий спектр фармакологічної дії та є перспективною групою хімічних речовин для розробки на їх основі нових препаратів з актопротекторною активністю.

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## **ОЦІНКА ВПЛИВУ ПОЛІМОРФІЗМУ ГЕНА *SIRT1* (rs2273773) НА ЕФЕКТИВНІСТЬ КОМПЛЕКСНОЇ АНТИДІАБЕТИЧНОЇ ТЕРАПІЇ У ПАЦІЄНТІВ З ЦУКРОВИМ ДІАБЕТОМ 2 ТИПУ ТА НАДЛИШКОВОЮ ВАГОЮ ЗІ СХІДНОУКРАЇНСЬКОЇ ПОПУЛЯЦІЇ**

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**Анотація.** Проведено пілотне дослідження з метою оцінки впливу поліморфних варіантів *rs2273773* (*C>T*) гена сиртуїну-1 (*SIRT1*) на ефективність комбінованої терапії метформіном та препаратом омега-3 поліненасичених жирних кислот (ПНЖК) у хворих на цукровий діабет (ЦД) 2 типу з надлишковою масою тіла зі східноукраїнської популяції. Додатково до стандартної

пероральної цукрознижувальної терапії пацієнти отримували щоденно протягом 3 місяців препарат омега-3 ПНЖК (460 мг ейкозапентаєнної кислоти + 380 мг докозагексаєнної кислоти). Клініко-біохімічні та імуноферментні вимірювання проведено на базі Національного Інституту громадського здоров'я та навколишнього середовища (м. Білтховен, Нідерланди) в межах наукового співробітництва. ДНК зі зразків крові (лейкоцитів) відібраних пацієнтів ( $n=61$ ) екстрагували за використанням іонообмінної смоли Chelex-100. Визначення одонуклеотидної заміни цитозину на тимін у екзоні 5 гена *SIRT1 rs2273773* ( $C>T$ ) здійснювали методом полімеразної ланцюгової реакції з двома парами протиставлених праймерів. Серед обстежених пацієнтів 20 осіб (32,8%) в якості антидіабетичної терапії отримували метформін та омега-3 ПНЖК. Їх було стратифіковано за дослідженням одонуклеотидним поліморфізмом ( $CC:8$ ,  $CT:9$ ,  $TT:3$ ) і проаналізовано відносно впливу терапії на біохімічні показники до та після лікування за рецесивною моделлю ( $CC$  проти  $CT+TT$ ). Визначено, що носії мінорного Т-алеля характеризувалися гіршим рівнем глікемічного контролю до лікування, однак терапія призводила до вірогідного покращення глікемії ( $P<0,05$ ). Не спостерігалось статистично значущих розбіжностей у досліджених групах щодо показників інсулінорезистентності, ліпідного обміну та адипокінів. Однак показник остеопротегерину (проатерогенний представник надсімейства рецепторів ФНП- $\alpha$ ) зазнав вірогідного зменшення під впливом терапії тільки у домінантних гомозигот ( $CC$ ) за дослідженням поліморфізмом ( $P<0,02$ ). Результат проведеного пошукового дослідження дозволяє припустити, що в східноукраїнській популяції хворих на ЦД 2 типу з надлишковою вагою домінантний генотип за поліморфізмом  $C>T$  *rs2273773* гена *SIRT1* є більш чутливим до терапії метформіном у комбінації з препаратом омега-3 ПНЖК і може носити захисний характер відносно розвитку серцево-судинних ускладнень.

**Ключові слова:** цукровий діабет 2 типу, сиртуїн-1, одонуклеотидний поліморфізм, метформін, поліненасичені жирні кислоти

**Вступ.** Відомо, що патологічний процес, пов'язаний з інсулінорезистентністю, дисфункцією панкреатичних  $\beta$ -клітин та прогресуванням предіабету до цукрового діабету (ЦД) 2 типу, залучає численні метаболічні, генетичні, епігенетичні та екологічні чинники [1]. В рамках дослідження хронічних метаболічних захворювань багато уваги приділяється вивченню сиртуїнів та, в першу чергу, продукту гену *SIRT1* – сиртуїну-1 [2, 3]. На тепер доведено, що шлях активації *SIRT1* задіяно в таких клітинних процесах, як вуглеводний / ліпідний метаболізм, біогенез мітохондрій, запалення,

аутофагія, стрес-резистентність, апоптоз, забезпечення циркадних ритмів і «мовчання» генів [2, 4]. Наявні повідомлення про пригнічення *SIRT1* у певних типах клітин і тканин за умов ІР або на тлі порушеної толерантності до глюкози і, відповідно, передбачено значний терапевтичний потенціал для сполук, здатних підвищувати експресію та активність сиртуїну-1 [5, 6]. Відомо, що частина терапевтичних ефектів антидіабетичного препарату першого вибору метформіну пов'язана з регуляторним шляхом одного з енергетичних сенсорів – АМФ-активованої протеїнкінази, однак доведено, що серед тонких сигнальних механізмів дії метформіну присутні ефекти, опосередковані активацією сиртуїну-1 [7, 8]. Ген *SIRT1* складається з 9 екзонів та 8 інтронів і розташований на хромосомі 10p37.5. Кілька ОНП у *SIRT1* були протестовані на їх зв'язок із компонентами ожиріння та метаболічного синдрому в різних популяціях [9, 10]. Однонуклеотидний поліморфізм (ОНП) *C>T* (rs2273773) гена *SIRT1* являє собою так звану «мовчазну» мутацію в екзоні 5 і може бути зчепленим з іншими мутаціями, що впливають як на рівні білка сиртуїну-1, так і на його активність.

З іншого боку, відомо, що омега-3 поліненасичені жирні кислоти (ПНЖК) є важливими регуляторами експресії генів, а саме, є природними лігандами PPAR-рецепторів (peroxisome proliferator-activated receptor, PPAR) та шляху протеїну, що зв'язує стерол-регуляторний елемент [11]. Саме з цим механізмом пов'язують здатність омега-3 ПНЖК попереджати розвиток експериментальної інсулінорезистентності за умов ожиріння завдяки утриманню нормального рівня експресії переносника глюкози GLUT4 у м'язах та жировій тканині, а також через регуляцію активності та експресії глюкозо-6-фосфатази печінки, що знижує печінкову секрецію глюкози, індуковану високожировою дієтою, та посилює синтез глікогену в скелетних м'язах.

**Метою** дослідження було оцінити вплив поліморфних варіантів rs2273773 гена сиртуїну-1 на ефективність комбінованої терапії метформіном та препаратом омега-3 поліненасичених жирних кислот у хворих на цукровий діабет 2 типу з надлишковою масою тіла зі східноукраїнської популяції.

**Матеріали та методи.** Дослідження проведено відповідно до міжнародних та вітчизняних етичних та морально-правових вимог та ухвалено Комітетом з медичної етики при ДУ ІПЕП. Всі обстежені пацієнти проходили стаціонарне лікування в клініці інституту. Проведено ретроспективний аналіз клініко-біохімічних показників, отриманих для пацієнтів, зразки яких входять до колекції ДНК хворих на цукровий діабет (ЦД) 2 типу. Відібрано 61 хворого на ЦД 2 типу (ж/ч: 27/34) віком  $53,35 \pm 1,38$  років, з тривалістю діабету  $5,33 \pm 0,67$  років, рівнем глікозильованого гемоглобіну  $7,74 \pm 0,19$  %, з індексом маси тіла

33,28±0,89 кг/м<sup>2</sup>, зі співвідношенням обсягу талії до обсягу стегон 0,99±0,01. Додатково до стандартної пероральної цукрознижувальної терапії (сульфаніламід, бігуанід або їх поєднання) пацієнти отримували щоденно протягом 3 місяців препарат омега-3 ПНЖК (460 мг ейкозапентаєнової кислоти + 380 мг докозагексаєнової кислоти).

Клініко-біохімічні та імуноферментні вимірювання проведено на базі Національного Інституту громадського здоров'я та навколишнього середовища (м. Білтховен, Нідерланди) в межах наукового співробітництва.

Глікемію натще визначали глюкозооксидазним методом за допомогою аналізатору глюкози "Biosenc Line". Інсулінорезистентність характеризували за індексом HOMA-IR.

ДНК зі зразків крові (лейкоцитів) відібраних пацієнтів екстрагували за використанням іонообмінної смоли Chelex-100. Визначення одонуклеотидної заміни цитозину на тимін у екзоні 5 гена *SIRT1 rs2273773 (C>T)* здійснювали методом полімеразної ланцюгової реакції з двома парами протиставлених праймерів. Електрофоретичне фракціонування дозволило визначити наступні генотипи за геном *SIRT1 rs2273773 (C>T)*: *CC* – 314/228 п.н.; *CT* – 314/228/135 п.н.; *TT* – 314/135 п.н. Розраховували частоти алелей для дослідженого генотипу. Нормальність розподілу змінних визначали за допомогою критерію Колмогорова-Смірнова. Для порівняння показників, які характеризуються нормальним розподілом, застосовували непарний двобічний *t*-критерій Стюдента, для порівняння параметрів із ненормальним розподілом – критерій Манна-Уїтні. Для статистичної оцінки розбіжностей, спостережуваних між емпіричними і теоретичними частотами варіаційного ряду, застосовувався критерій  $\chi^2$  (хі-квадрат).

**Результати та обговорення.** Проведене генотипування за дослідженим поліморфізмом (*CC*:24, *CT*:29, *TT*:8) свідчить про те, що в обстеженій групі пацієнтів із ЦД 2 типу фактичний та теоретично очікуваний (відповідно до закону Харді-Вайнберга) розподіл частот співпадають, тобто немає накопичення певних генотипів за умов дослідженої патології.

Серед обстежених пацієнтів 20 осіб (32,8%) в якості антидіабетичної терапії отримували метформін та ПНЖК. Їх було стратифіковано за дослідженим ОНП (*CC*:8, *CT*:9, *TT*:3) і проаналізовано відносно впливу терапії на біохімічні показники до та після лікування. З урахуванням невеликої кількості пацієнтів з мінорним генотипом попередній аналіз було проведено за рецесивною моделлю, тобто *CC* проти *CT+TT*.

Таблиця

**Біохімічні показники у хворих на цукровий діабет 2 типу з різними генотипами за поліморфізмом  $C>T$  rs2273773 гена *SIRT1* до та після лікування, ( $\bar{x} \pm S_{\bar{x}}$ ), Me [Q<sub>25</sub>; Q<sub>75</sub>]**

| Показник                      | Генотип за <i>SIRT1</i> $C>T$ (rs2273773) |                                          |                                         |                                         |
|-------------------------------|-------------------------------------------|------------------------------------------|-----------------------------------------|-----------------------------------------|
|                               | CC (n=8)                                  |                                          | CT+TT (n=12)                            |                                         |
|                               | До лікування                              | Після лікування                          | До лікування                            | Після лікування                         |
| Глюкоза, ммоль/л              | 7,74±0,77                                 | 6,08±0,58                                | 9,82±0,85                               | 6,07±0,95*                              |
| HbA <sub>1c</sub> , %         | 7,20±0,45                                 | 6,77±0,30                                | 7,72±0,53                               | 6,63±0,47                               |
| Інсулін, пмоль/л              | 123,90±25,16                              | 123,39±25,17                             | 102,99±18,15                            | 115,38±28,98                            |
| НОМА-IR, ум. од.              | 7,00±1,90<br>5,40<br>(3,30; 10,13))       | 4,97±0,85<br>5,26<br>(3,40; 6,74)        | 6,55±0,98<br>6,20<br>(4,58; 8,63)       | 4,48±0,94<br>3,40<br>(2,63; 6,90)       |
| Адипонектин загальний, мг/л   | 5,83±1,16<br>6,81<br>(4,28; 7,47)         | 6,93±0,97<br>7,33<br>(5,68; 7,80)        | 4,42±0,81<br>4,70<br>(2,58; 5,73)       | 7,46±2,30<br>5,31<br>(3,18; 12,41)      |
| Остеопротегерин, нг/л         | 479,20±74,21<br>518,0<br>(365,0; 604,0)   | 268,83±36,28<br>248,0*<br>(223,5; 259,8) | 451,50±73,27<br>397,0<br>(325,0; 490,8) | 406,50±56,71<br>437,5<br>(312,3; 477,3) |
| Васпін, мкг/л                 | 0,24<br>(0,20; 0,79)                      | 0,25<br>(0,17; 0,39)                     | 0,35<br>(0,19; 0,51)                    | 0,44<br>(0,32; 0,49)                    |
| Вільні жирні кислоти, ммоль/л | 0,72±0,10                                 | 0,68±0,08                                | 0,95±0,11                               | 1,01±0,16                               |
| ХС ЛПВЩ, ммоль/л              | 0,97±0,04                                 | 1,02±0,07                                | 0,90±0,04                               | 1,18±0,13                               |
| ХС ЛПНЩ, ммоль/л              | 2,82±0,19                                 | 3,57±0,50                                | 3,23±0,26                               | 4,20±0,43                               |

Примітки:

\* - вірогідно порівняно з показником до лікування,  $P<0,05$ ;

ХС ЛПВЩ – холестерин ліпопротеїнів високої щільності;

ХС ЛПНЩ - холестерин ліпопротеїнів низької щільності.

Було виявлено, що носії мінорного алеля (Т) характеризувалися дещо гіршими показниками глікемічного контролю до лікування, а саме, базальна глікемія демонструвала тенденцію до більш високих рівнів ( $0,05<P<0,1$ , табл.).



Однак комплексне лікування протягом 3 місяців призводило в цій підгрупі хворих до вірогідного покращення даного показника ( $P < 0,05$ ). Не спостерігалось статистично значущих розбіжностей у досліджених групах щодо показників ІР, ліпідного метаболізму та адипокінів. В той же час привертає увагу той факт, що між групами зафіксована суттєва різниця щодо рівнів остеопротегерину, який зазнав вірогідного зменшення під впливом терапії тільки у домінантних гомозигот за дослідженим поліморфізмом ( $P < 0,02$ ). Цей глікопротеїн з надсімейства рецепторів ФНП- $\alpha$  останнім часом пов'язують із проатерогенним впливом на судини та ризиком розвитку кардіоваскулярної патології [12].

Таким чином, отриманий результат проведеного пошукового дослідження дозволяє припустити, що в східноукраїнській популяції хворих на ЦД 2 типу домінантний генотип за поліморфізмом  $C > T$  *rs2273773* гена *SIRT1* є більш чутливим до терапії метформіном у комбінації з препаратом омега-3 ПНЖК і може носити захисний характер відносно розвитку серцево-судинних ускладнень.

**Висновки.** Аналіз метаболічних показників у носіїв різних генотипів з варіантами  $C > T$  (*rs2273773*) гена сиртуїну-1 доводить більший серцево-судинний ризик у носіїв мінорного алеля за цим поліморфізмом серед хворих на цукровий діабет 2 типу з надлишковою масою тіла східноукраїнської популяції. Комбінована терапія із застосуванням метформіну та препарату омега-3 поліненасичених жирних кислот проявляє більш виразний ефект відносно гальмування показників ризику серцево-судинних ускладнень у носіїв домінантного  $CC$ -генотипу за поліморфізмом  $C > T$  (*rs2273773*) гена сиртуїну-1 серед хворих на цукровий діабет 2 типу східноукраїнської популяції. Отримані результати можуть бути використані для розробки персоніфікованої антидіабетичної терапії.

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## ВПЛИВ ДОКСИЦИКЛІНУ НА ЖИТТЄЗДАТНІСТЬ КЛІТИН ТА ОЦІНКА ЦИТОТОКСИЧНОГО ВПЛИВУ *IN VITRO* НА ЕТАПІ ДОКЛІНІЧНИХ ДОСЛІДЖЕНЬ

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**Вступ.** Загоєння ран – складний і динамічний процес, що включає послідовні стадії запалення, проліферації та ремоделювання, спрямовані на

відновлення цілісності тканин. На перебіг цього процесу впливають багато факторів, зокрема ступінь запалення, ускладнення бактеріальною інфекцією, ангіогенез (новоутворення судин), синтез позаклітинного матриксу (колагену та інших білків) і активність протеолітичних ферментів та ін.

Доксициклін – напівсинтетичний антибіотик з групи тетрациклінів, широко застосовуваний в клініці, привертає увагу дослідників як потенційний модулятор загоєння ран завдяки своїм “супутнім” властивостям. Окрім встановленої антимікробної дії доксициклін має протизапальні та протектибричні властивості. Зокрема, він пригнічує активність матриксних металопротеїназ (ММР) – ферментів, відповідальних за деградацію колагену та інших компонентів матриксу під час запалення. Це сприяє збереженню новоутвореного колагенового каркасу і попереджає надмірний розпад тканин у рані. Також доксициклін знижує продукцію прозапальних цитокінів – наприклад, інтерлейкіну-1 $\beta$  (IL-1 $\beta$ ) та фактора некрозу пухлин- $\alpha$  (TNF- $\alpha$ ) – що в сукупності пом’якшує надмірну запальну реакцію у рані. Водночас, дослідження показали, що доксициклін здатен стимулювати ангіогенез: він підвищує експресію судинного ендотеліального фактора росту (VEGF), тим самим покращуючи кровопостачання ушкодженої зони [1]. Є дані і про безпосередню дію на клітини сполучної тканини – фібробласти: під впливом доксицикліну ці клітини активніше синтезують колаген та інші компоненти позаклітинного матриксу, що сприяє швидшому утворенню грануляційної тканини. Але незважаючи на великий потенціал ранозагоючої дії відмічається відсутність комерційних лікарських форм для місцевого застосування. Отже при розробці нових форм для парентерального застосування, зокрема місцевого, актуальним напрямком є визначення цитотоксичної дії доксицикліну у місці аплікації.

**Мета дослідження.** Проаналізувати методи визначення цитотоксичності доксицикліну на процес загоєння ран на етапі доклінічних досліджень та потенціал діючої речовини для розробки антибактеріальних ранозагоювальних засобів місцевого застосування.

**Матеріали та методи.** В ході дослідження було використано методи системного підходу, бібліографічного, інформаційного пошуку, аналізу, порівняння та узагальнення, статистичної обробки отриманих даних.

**Результати та обговорення.** Важливим етапом оцінки регенеративних властивостей препаратів на етапі доклінічних досліджень є дослідження цитотоксичності – відсутність токсичного впливу на клітини. Існує кілька основних методів оцінки цитотоксичності: оцінка життєздатності клітин (MTT-тест, Alamar Blue, Trypan Blue exclusion test), оцінка пошкодження клітин

(LDH-тест (лактатдегідрогеназа), визначення апоптозу або некрозу клітин (V/PI, TUNEL-тест).

Varshosaz et al. (2020) [2] досліджували вплив доксициклін-навантаженої нанофібрильної мембрани модифікованого RGD-пептидом (PBAT) на життєздатність фібробластів L929. Цитотоксичність нанофібрів RGD-DOX-PBAT/GEL та DOX-PBAT/GEL вивчали після 1, 2, 3 та 7 діб інкубації з фібробластами миші лінії L929. PBAT/GEL нанофібри не спричиняли цитотоксичної дії на фібробласти протягом перших 24 годин. Подовжена інкубація понад 48 годин супроводжувалася збільшенням кількості життєздатних клітин. Отримані результати свідчать, що нанофібри стимулювали проліферацію клітин упродовж досліджуваного періоду та на 6,6% більш високе закриття рани.

Aldaghi et al., 2024 оцінювали вплив гідрогелю на основі карбоксиметилцелюлози/альгінату натрію/желатину (CMC/Alg/Gel), що містить доксициклін (DOX), на покращення процесу загоєння пролежнів. Додавання 1% доксицикліну в гідрогель значно покращило загоєння пролежнів у щурів: через 14 днів рани у групі з доксицикліном закрилися на ~56,7% (що було найкращим результатом). дослідження МТТ-тест продемонстрували >80% життєздатності клітин, що відповідає критеріям біосумісності [3].

Altoé et al. (2021) у своїй роботі зазначають, що доксициклін знижує рівень проапоптотичних факторів (COX-2, простагландину E2), і не тільки не викликає загибелі клітин, а навпаки – покращує клітинне виживання та активує макрофаги для підтримки загоєння, цитотоксичної дії після інкубації клітин з Dх не виявлено. Більше того, найбільш виражене підвищення проліферації клітин було зафіксовано при концентраціях 100  $\mu\text{g/mL}$  ( $182,03 \pm 6,57$ ) та 300  $\mu\text{g/mL}$  ( $253,05 \pm 30,92$ ), що свідчить про чітко виражений дозозалежний ефект. Застосування доксицикліну забезпечило збільшення швидкості загоєння рани на 21% [4].

У дослідженні Chang et al. (2023) [5] було вивчено вплив доксицикліну на життєздатність, апоптоз та молекулярні характеристики людських плюрипотентних стовбурових клітин (hPSC), включно з ембріональними (hESC) та індукованими (hiPSC), у стандартних умовах культивування. Метою роботи було оцінити потенційну цитобезпеку та підтримку самооновлення клітин під дією доксицикліну при стресових умовах *in vitro*. Обробка клітин доксицикліном у концентрації 1–2  $\mu\text{g/mL}$  призводила до зниження частки апоптотичних клітин (визначених як Annexin V<sup>+</sup>/PI<sup>+</sup>), порівняно з необробленими контролями. Метаболічна активність клітин, за результатами аналізу CellTiter-Blue

(альтернативи МТТ), залишалась високою або зростала після введення доксицикліну, що свідчить про відсутність цитотоксичності та потенційний стимулюючий вплив на проліферацію. На транскрипційному рівні спостерігалось зниження експресії апоптотичних маркерів (наприклад, CASP3, BAX) та активація генів, пов'язаних із виживанням (BCL2, NANOG, SOX2).

Під час використання системи індукованої доксицикліном експресії було випадково виявлено, що сам доксициклін (1 мг/мл) суттєво підвищує виживання hNSC. Цей ефект не був пов'язаний із активацією експресії трансгенів, що привернуло увагу до потенційної прямої біологічної дії доксицикліну на стовбурові клітини. Встановлено, що дія доксицикліну опосередковується прямою активацією сигнального шляху PI3K–АКТ, який визнаний ключовим регулятором самовідновлення плюрипотентних стовбурових клітин [6].

Загалом, доксициклін проявляє сприятливий профіль безпеки *in vitro* [7-9]. Він не індукує значної цитотоксичності чи апоптозу в клітинах шкіри та сполучної тканини при концентраціях, що використовуються для моделювання загоєння ран. Лише при значно вищих дозах спостерігалось дозозалежне зниження життєздатності клітин, що підкреслює важливість дотримання оптимальних концентрацій[10]. Таким чином, на доклінічному рівні отримано підтвердження, що доксициклін нешкідливий для клітин і придатний до подальшого вивчення як засіб для поліпшення регенерації тканин.

**Висновки.** Аналіз результатів доклінічних досліджень свідчить, що доксициклін у концентраціях, застосовуваних у моделях регенерації ран, характеризується сприятливим цитобіологічним профілем та не проявляє цитотоксичної дії на клітини шкіри та сполучної тканини. За даними різних тест-систем (МТТ, CellTiter-Blue, LDH-тест, аналіз апоптозу V/PI), доксициклін не лише не знижує життєздатність клітин, але у ряді випадків стимулює клітинну проліферацію та зменшує рівень апоптотичних маркерів. Встановлено, що його вплив може бути опосередкованим активацією сигнального шляху PI3K–АКТ, що забезпечує підтримку виживання та самооновлення клітин, включно зі стовбуровими.

Кандидати на лікарські форми на основі доксицикліну, такі як нанофібрильні мембрани та гідрогелі, виявляють високу біосумісність та сприяють прискоренню репаративних процесів, що підтверджується підвищенням швидкості закриття ран ( $\approx 21$ –56%), посиленням реепітелізації та зниженням експресії MMP2/MMP9, важливих медіаторів деструкції позаклітинного матриксу.

Таким чином, доксициклін можна розглядати не лише як



антибактеріальний агент, але і як перспективний регулятор регенерації тканин із вираженою цитопротекторною та матрикс-модулюючою дією. Отримані дані обґрунтовують доцільність подальшого його дослідження як компонента сучасних раногоюючих препаратів.

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## REGENERATIVE & ANTI-AGING POTENTIAL OF NATURAL BIOACTIVES

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**Abstract.** The intricate processes of cutaneous wound regeneration and premature skin aging involve complex molecular pathways such as inflammation, oxidative stress, and extracellular matrix (ECM) degradation. This paper elucidates the synergistic biochemical and molecular effects of a combination of propolis, *Lavandula angustifolia* (lavender), and Aloe Vera on enhancing wound healing and mitigating premature aging markers. These agents act complementarily to modulate inflammation, promote fibroblast proliferation, improve collagen synthesis, and protect against oxidative damage. The combination presents a promising multi-target therapeutic strategy for dermatological applications.

**Keywords.** *Propolis*, *Aloe Vera*, *Lavandula angustifolia*, wound healing, premature aging, synergy, molecular mechanisms, NF- $\kappa$ B, TGF- $\beta$ , oxidative stress.

**Introduction.** The skin, as the body's largest organ, serves as a primary barrier against environmental insults. Its ability to regenerate following injury and its structural integrity over time are crucial for human health. Two significant challenges in dermatology are the management of complex wounds and the prevention or reversal

of premature aging. Wound healing is a highly orchestrated physiological process involving four overlapping phases: hemostasis, inflammation, proliferation, and remodeling (Guo & DiPietro, 2010). Disruptions in this cascade, often due to persistent inflammation, infection, or oxidative stress, can lead to chronic, non-healing wounds.

Simultaneously, premature aging (photoaging and intrinsic aging) is characterized by a progressive decline in skin structure and function. At the molecular level, this is driven by an accumulation of cellular damage from reactive oxygen species (ROS), chronic low-grade inflammation (termed inflammaging), and an imbalance in the synthesis and degradation of the extracellular matrix (ECM), particularly collagen and elastin (Farage et al., 2008). Key molecular players in this process include the transcription factors Nuclear Factor-kappa B (NF- $\kappa$ B) and Activator Protein-1 (AP-1), which upregulate the expression of matrix metalloproteinases (MMPs) that degrade collagen.

Conventional treatments for wounds and aging often rely on synthetic agents that may have side effects or target only a single pathway. Consequently, there is a paradigm shift towards natural products and polyherbal formulations, which offer a multi-target approach with potentially fewer adverse effects. *Propolis*, lavender *Lavandula angustifolia*, and *Aloe Vera* are three such natural agents with well-documented, albeit largely individual, therapeutic properties in dermatology. Propolis is a resinous substance collected by honeybees, known for its potent antimicrobial, anti-inflammatory, and antioxidant properties (Kuropatnicki et al., 2013). Lavender essential oil is widely used for its antiseptic and anxiolytic effects, and recent research highlights its role in promoting collagen synthesis (Mori et al., 2016). Aloe Vera gel is a classic remedy for burns and skin irritation, attributed to its ability to stimulate fibroblast activity and moisturize the skin (Hekmatpou et al., 2019).

While the individual effects of these substances are recognized, their potential synergistic interactions at the molecular level have not been comprehensively investigated. A formulation combining these three agents practically stimulate wound healing and aging by simultaneously controlling inflammation, fighting oxidative stress, preventing infection, and stimulating tissue regeneration.

**The aim of the study.** This paper aims to elucidate the biochemical and molecular mechanisms underlying the synergistic effects of a combination of propolis, *Lavandula angustifolia*, and *Aloe Vera* (L.) on accelerating wound regeneration and mitigating the markers of premature aging.

**Materials and Methods.** This study was conducted as a comprehensive practical research elucidating the biochemical and molecular mechanisms underlying the synergistic effects of *Propolis*, *Lavandula angustifolia* (lavender), and *Aloe Vera*

on wound regeneration and premature skin aging. Analysis was performed using practical and experimental reports, and molecular studies relevant to dermatology, wound healing, and cellular aging. Some aspects are focused on studies detailing of the bioactive compounds, molecular targets, and therapeutic outcomes associated with each agent individually and in combination. Data were extracted regarding their anti-inflammatory, antioxidant, antimicrobial, and pro-regenerative activities, as well as their influence on key molecular pathways, including NF- $\kappa$ B, TGF- $\beta$ , and matrix metalloproteinases (MMPs).

**Results and Discussion.** In the present study, a comparative synthesis of experimental data and results was conducted to assess synergistic interactions throughout the wound healing continuum. The research focused on key biological processes – including inflammatory regulation, fibroblast proliferation, collagen synthesis, and extracellular matrix remodeling. Results indicated that coordinated modulation of these processes enhanced tissue regeneration efficiency and contributed to a measurable reduction in oxidative stress markers. Furthermore, the findings suggest that promoting balanced wound healing responses may mitigate inflammaging mechanisms associated with premature skin aging, highlighting potential therapeutic targets for regenerative skin care applications.

To understand the synergy, it is essential first to dissect the individual contributions of each component.

*Propolis* is a complex mixture of plant resins, beeswax, and bee enzymes, containing a large number of bioactive compounds. Its primary active constituents are polyphenols, including flavonoids (e.g., chrysin, galangin, pinocembrin) and phenolic acids, most notably caffeic acid phenethyl ester (CAPE) (Wagh, 2013).

**Anti-inflammatory mechanism.** The potent anti-inflammatory action of propolis is largely attributed to CAPE. CAPE is a highly specific inhibitor of the transcription factor NF- $\kappa$ B (Natarajan et al., 1996). NF- $\kappa$ B is a master regulator of the inflammatory response, controlling the expression of pro-inflammatory cytokines (TNF- $\alpha$ , IL-1 $\beta$ , IL-6), chemokines, and enzymes like cyclooxygenase-2 (COX-2). By blocking NF- $\kappa$ B activation, propolis effectively dampens the inflammatory cascade, which is crucial for preventing chronic inflammation in wounds and for combating inflammaging.

**Antioxidant mechanism.** The flavonoids in propolis are powerful antioxidants. They act by directly scavenging free radicals (ROS and RNS), chelating metal ions like Fe<sup>2+</sup> and Cu<sup>2+</sup> that catalyze ROS production, and upregulating endogenous antioxidant enzymes such as superoxide dismutase (SOD) and catalase (CAT) (Viuda-Martos et al., 2010). This action protects cellular structures from oxidative damage, a key factor in both wound chronicity and skin aging.

Antimicrobial and pro-regenerative effects. Propolis exhibits broad-spectrum activity against bacteria (including MRSA), fungi, and viruses. This is critical in wound care to prevent infection. Furthermore, some studies suggest propolis can increase collagen content and promote angiogenesis (the formation of new blood vessels), essential steps in the proliferative phase of wound healing (Olczyk et al., 2013).

*Lavandula angustifolia*. The Pro-collagen and remodeling agent. Lavender essential oil is primarily composed of the monoterpenes linalool and linalyl acetate. Its benefits extend beyond its well-known calming aroma.

Wound Healing Acceleration. A seminal study by Mori et al. (2016) demonstrated that topical application of lavender oil on wounds in animal models significantly increased the expression of Transforming Growth Factor-beta (TGF- $\beta$ ). TGF- $\beta$  is a pivotal growth factor that stimulates fibroblast differentiation into myofibroblasts, which are responsible for wound contraction and the synthesis of Type I and Type III collagen. This direct stimulation of the ECM-building machinery accelerates the proliferative and remodeling phases of healing.

Anti-inflammatory activity. Linalool has been shown to reduce the production of inflammatory mediators. It can inhibit the activation of inflammatory pathways and reduce edema, contributing to a more controlled inflammatory phase in wound healing (Peanu et al., 2002).

*Aloe Vera*. The Fibroblast Stimulator and Moisturizer. The gel from the leaves of Aloe Vera is a complex mixture of water, polysaccharides, vitamins, enzymes, and glycoproteins. Its most researched bioactive polysaccharide is acemannan.

Stimulation of Cellular Proliferation: Acemannan is a potent macrophage activator, leading to the release of cytokines and growth factors like Fibroblast Growth Factor (FGF) and Granulocyte-Macrophage Colony-Stimulating Factor (GM-CSF) (Zhang & Tizard, 1996). More directly, *Aloe Vera* gel has been shown to stimulate the proliferation and activity of fibroblasts and keratinocytes. This leads to increased synthesis of collagen and hyaluronic acid, improving skin elasticity and hydration (Surjushe et al., 2008).

Anti-inflammatory and moisturizing effects. *Aloe Vera* inhibits the COX pathway and reduces prostaglandin E2 production, contributing to its anti-inflammatory effects. Its high water content and muco-polysaccharides create a moist wound environment, which is known to facilitate cell migration and re-epithelialization, preventing scab formation and scarring.

Synergistic mechanisms in wound regeneration. A combination of these three agents creates a multi-target therapeutic system that addresses the entire wound healing continuum.



*Phase 1. Inflammation Control.* In the initial phase, the combination provides a powerful, multi-pathway anti-inflammatory effect. Propolis (via CAPE) blocks the central NF- $\kappa$ B pathway, lavender reduces inflammatory cytokine expression, and *Aloe Vera* inhibits the prostaglandin pathway. This rapid and comprehensive suppression of excessive inflammation prevents the wound from becoming chronic and sets the stage for efficient healing. Simultaneously, the antimicrobial properties of propolis and lavender create a sterile field, preventing infection, a common complication.

*Phase 2. Proliferation enhancement.* As inflammation subsides, the focus shifts to tissue formation. Aloe Vera stimulates the proliferation of fibroblasts, the primary cells of this phase. Lavender then upregulates TGF- $\beta$ , signaling these newly proliferated fibroblasts to produce vast amounts of collagen. Propolis may further support this phase by promoting angiogenesis, ensuring the new tissue receives adequate blood supply (Martinotti & Ranzato, 2019). The moisturizing effect of aloe provides the ideal physical environment for these processes.

*Phase 3. Optimized Remodeling.* In the final phase, the newly deposited collagen is reorganized into a strong, functional scar. Lavender's role in promoting organized collagen III to collagen I transition is crucial. By concurrently reducing Matrix metalloproteinase (MMP) activity (an effect noted for some propolis flavonoids), the formulation may prevent excessive collagen degradation, leading to minimized scarring and improved tensile strength of the healed tissue.

**Synergistic Mechanisms in Combating Premature Aging.** The same molecular pathways involved in wound healing are implicated in skin aging. The synergy of the combination is therefore equally applicable to anti-aging strategies.

**Comprehensive antioxidant defense:** the combination provides a robust defense against oxidative stress. Propolis flavonoids, lavender's terpenes, and the vitamins (C and E) in *Aloe Vera* form an antioxidant complex that can neutralize a wide spectrum of free radicals. This reduces the cumulative oxidative damage to DNA, proteins, and lipids that drives cellular senescence.

**Combating Inflammaging.** Premature aging is intrinsically linked to chronic, low-grade inflammation. The potent, multi-target anti-inflammatory action of the combination, particularly the NF- $\kappa$ B inhibition by propolis, directly counteracts this process. By keeping chronic inflammation in check, the formulation helps preserve cellular function and prevent the inflammatory-driven degradation of the ECM.

**Preservation and restoration of the extracellular matrix.** This is the base of a potent anti-aging strategy. The combination acts on the ECM in two synergistic ways:

**Inhibition of degradation.** Flavonoids in propolis have been shown to inhibit the activity of MMPs (MMP-1, MMP-3, MMP-9), the enzymes responsible for breaking

down collagen and elastin in response to UV radiation and inflammation (Chen et al., 2018).

Lavender extract, through activation of transforming growth factor beta (TGF- $\beta$ ) signaling, and *Aloe Vera*, via fibroblast stimulation, both enhance the biosynthesis of collagen and hyaluronic acid. This complementary mechanism – concurrently suppressing matrix metalloproteinase (MMP) activity and stimulating fibroblast-mediated matrix production – results in a net increase in the structural integrity and density of the dermal extracellular matrix. Consequently, these effects contribute to a reduction in wrinkle formation, improved dermal firmness, and enhanced skin hydration [17].

*Table 1.*

**Structured table summarizing the main points, mechanisms, and synergistic effects of *Propolis*, *Lavandula angustifolia* and *Aloe Vera* in wound healing and anti-aging applications**

| Component                                       | Key bioactive compounds                                           | Primary mechanisms                                                                                          | Effects on wound healing                                                                               | Effects on premature aging                                                     |
|-------------------------------------------------|-------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------|
| <b><i>Propolis</i></b>                          | Flavonoids (chrysin, galangin, pinocembrin), CAPE, phenolic acids | NF- $\kappa$ B inhibition (anti-inflammatory), antioxidant (ROS scavenging, metal chelation), antimicrobial | Reduces inflammation, prevents infection, promotes angiogenesis, increases collagen synthesis          | Reduces oxidative stress, inhibits MMP activity, protects ECM                  |
| <b><i>Lavandula angustifolia</i> (Lavender)</b> | Linalool, linalyl acetate                                         | Upregulates TGF- $\beta$ (pro-collagen), anti-inflammatory, promotes organized collagen deposition          | Stimulates fibroblast differentiation, enhances collagen synthesis, accelerates wound contraction      | Enhances ECM integrity, reduces wrinkle formation                              |
| <b><i>Aloe Vera</i></b>                         | Acemannan, polysaccharides, vitamins, glycoproteins               | Stimulates fibroblast proliferation, anti-inflammatory (COX inhibition), moisturizing                       | Promotes cell proliferation, collagen and hyaluronic acid synthesis, maintains moist wound environment | Improves dermal hydration, stimulates ECM production, enhances skin elasticity |
| <b>Synergistic Combination</b>                  | Propolis + Lavender + Aloe Vera                                   | Multi-target: anti-inflammatory, antioxidant, antimicrobial, pro-regenerative                               | Controls all wound healing phases: inflammation, proliferation, remodeling; reduces                    | Counteracts inflammaging, protects against oxidative damage, stimulates ECM    |

|  |  |  |                                               |                                     |
|--|--|--|-----------------------------------------------|-------------------------------------|
|  |  |  | scarring; promotes robust tissue regeneration | restoration, improves skin firmness |
|--|--|--|-----------------------------------------------|-------------------------------------|

*Table 2.*

**Phase-wise table showing how the combination of *Propolis*, *lavender* and *Aloe Vera* acts during each wound healing stage, including their synergistic mechanisms**

| Wound Healing Phase                        | Role of <i>Propolis</i>                                                                                                       | Role of <i>Lavender</i>                                                                             | Role of <i>Aloe Vera</i>                                                                             | Synergistic Effects                                                                                                |
|--------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------|
| <b>1. Inflammation Control</b>             | Inhibits NF- $\kappa$ B $\rightarrow$ reduces pro-inflammatory cytokines (TNF- $\alpha$ , IL-1 $\beta$ , IL-6); antimicrobial | Reduces inflammatory mediators (linalool), decreases edema                                          | Inhibits COX pathway $\rightarrow$ lowers prostaglandins; maintains moist environment                | Comprehensive suppression of inflammation, prevents chronic wounds, reduces infection risk                         |
| <b>2. Proliferation (Tissue Formation)</b> | Promotes angiogenesis, supports collagen deposition                                                                           | Upregulates TGF- $\beta$ $\rightarrow$ stimulates fibroblast differentiation and collagen synthesis | Stimulates fibroblast and keratinocyte proliferation; enhances collagen & hyaluronic acid production | Accelerated tissue formation, robust collagen synthesis, optimal cell proliferation, moist environment for healing |
| <b>3. Remodeling / Maturation</b>          | Reduces MMP activity $\rightarrow$ prevents excessive collagen degradation                                                    | Promotes organized transition from collagen III to I $\rightarrow$ improves tensile strength        | Maintains hydration $\rightarrow$ facilitates ECM remodeling                                         | Strong, functional tissue; minimized scarring; improved dermal structure and elasticity                            |
| <b>Anti-aging / ECM Preservation</b>       | Antioxidant $\rightarrow$ scavenges ROS; inhibits MMPs                                                                        | Enhances TGF- $\beta$ signaling $\rightarrow$ boosts ECM synthesis                                  | Stimulates fibroblast-mediated ECM production; improves skin hydration                               | Reduced oxidative damage, preserved ECM integrity, reduced wrinkles, improved skin firmness and elasticity         |

**Conclusions.** Combination of *Propolis*, *Lavender*, and *Aloe Vera* functions as a powerful synergistic formulation for promoting wound regeneration and mitigating the signs of premature aging. The synergy arises from the complementary, multi-target

actions of their respective bioactive compounds. This formulation effectively modulates all phases of wound healing by controlling inflammation, preventing infection, and stimulating robust tissue proliferation and remodeling. In the context of aging, it provides a comprehensive strategy to combat the root causes of skin deterioration by neutralizing oxidative stress, quelling chronic

The studies continue on optimizing the ratios of the components within a stable formulation, prolong to conducting research to quantify the synergistic effects on wound closure rates and collagen deposition, for both wound care and anti-aging dermatological applications.

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## THE EFFECT OF COFFEE DRINKS ON THE BIOCHEMICAL PROCESSES OF BLOOD CLOTTING

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**Abstract.** Coffee is one of the most widely consumed beverages worldwide, containing a complex mixture of biologically active compounds such as caffeine, polyphenols, diterpenes, and antioxidants. While numerous studies have explored its cardiovascular and metabolic effects, its influence on the biochemical mechanisms underlying blood coagulation remains an evolving field of investigation. This article aims to analyze and summarize the biochemical interactions between coffee components and the hemostatic system, focusing on platelet function, plasma coagulation factors, fibrinolysis, and oxidative stress modulation. Both experimental and clinical evidence indicate that coffee exerts dual effects on blood clotting: moderate intake may enhance endothelial function and inhibit platelet aggregation through antioxidant and nitric oxide-mediated mechanisms, whereas excessive consumption may increase pro-coagulant activity via catecholamine stimulation and dehydration. Understanding these mechanisms is crucial for evaluating the risks and benefits of coffee consumption in individuals with thrombotic or bleeding disorders.

**Key Words:** Coffee, caffeine, blood coagulation, platelets, fibrinogen, hemostasis, antioxidants, cardiovascular health, polyphenols.

**Introduction.** Coffee has been an integral part of human culture for centuries, serving not only as a social beverage but also as a potent stimulant with multiple physiological effects. The global popularity of coffee and its inclusion in various dietary patterns have prompted scientific interest in its potential health benefits and risks. Beyond its well-known impact on alertness and metabolism, coffee has been linked to several biochemical processes affecting the cardiovascular and hematologic systems [1, 2].

Blood coagulation, or hemostasis, is a finely balanced physiological process involving vascular, platelet, and plasma components. Disruptions in this system can lead to either thrombosis (excessive clot formation) or hemorrhage (inadequate clot formation). Given that cardiovascular diseases remain the leading cause of death globally, understanding how dietary factors such as coffee influence coagulation mechanisms has significant clinical implications.

Coffee contains over one thousand chemical compounds, including caffeine, chlorogenic acids, cafestol, kahweol, trigonelline, and various polyphenols. These compounds can influence endothelial function, platelet activation, oxidative stress, and inflammatory pathways – all of which are integral to coagulation dynamics. Despite numerous epidemiological studies linking coffee consumption to cardiovascular outcomes, the direct biochemical effects of coffee on blood clotting remain partially understood and occasionally contradictory [3].

This article provides an analytical review and synthesis of current knowledge on

the biochemical impact of coffee drinks on the blood clotting process, highlighting molecular mechanisms, dose-dependent effects, and clinical implications.

**The Aim of the Study.** The aim of this study is to evaluate the biochemical effects of coffee drinks on the processes of blood clotting by analyzing available literature data and experimental evidence. Specific objectives include: to identify the active coffee components that influence hemostatic mechanisms; to describe the molecular interactions of these compounds with coagulation factors and platelets; to evaluate the balance between pro-coagulant and anti-coagulant effects of coffee consumption; to discuss potential health implications of regular coffee intake concerning thrombotic and bleeding risks.

**Materials and Methods.** This article is based on a comprehensive literature analysis using data from peer-reviewed journals and databases including PubMed, Scopus, ScienceDirect, and Google Scholar. The search terms used were “coffee and blood coagulation,” “caffeine and platelet function,” “chlorogenic acid and hemostasis,” and “coffee polyphenols and thrombosis.”

Inclusion criteria comprised studies published between 2000 and 2025 that examined biochemical, molecular, or physiological effects of coffee or its constituents on coagulation parameters in humans or experimental animals. Both in vitro and in vivo investigations were considered. Exclusion criteria included articles focused solely on epidemiological associations without biochemical data.

Data were classified according to the following parameters: Platelet function: aggregation, adhesion, activation markers (P-selectin, thromboxane A<sub>2</sub>).

- Plasma coagulation factors: fibrinogen, prothrombin time (PT), activated partial thromboplastin time (aPTT), factor VII, and thrombin generation.
- Endothelial markers: nitric oxide (NO), prostacyclin, von Willebrand factor.
- Oxidative and inflammatory parameters: reactive oxygen species (ROS), cytokines, and antioxidant enzyme activity.

This methodological approach allows for a balanced evaluation of both mechanistic and clinical perspectives regarding coffee's effect on hemostasis.

## **Results and Discussion.**

### *Biochemical Composition of Coffee Relevant to Coagulation.*

Coffee contains caffeine, a methylxanthine known for its adenosine receptor antagonism and phosphodiesterase inhibition, which enhances cyclic AMP levels in platelets and vascular cells. Polyphenolic compounds, particularly chlorogenic acids, exert antioxidant and anti-inflammatory effects. Diterpenes (cafestol and kahweol), present mainly in unfiltered coffee, influence lipid metabolism and may affect coagulation indirectly by altering plasma viscosity and fibrinogen levels [4].

### *Effects on Platelet Function*

Several in vitro studies demonstrate that caffeine inhibits platelet aggregation induced by ADP and collagen. This inhibition is associated with increased intracellular cyclic AMP, leading to reduced calcium mobilization and decreased thromboxane A<sub>2</sub> synthesis. Polyphenols in coffee further contribute to platelet stabilization by scavenging reactive oxygen species that promote platelet activation.

Conversely, high caffeine doses (above 400 mg/day) can increase catecholamine release (epinephrine and norepinephrine), which enhances platelet reactivity and vascular constriction. Thus, moderate consumption (1-3 cups per day) may have anti-thrombotic effects, whereas excessive intake could shift the balance toward hypercoagulability [5].

### *Impact on Coagulation Factors.*

Human studies suggest that regular coffee consumption slightly reduces plasma fibrinogen levels and prolongs prothrombin time, indicating a mild anticoagulant effect. The underlying mechanism may involve suppression of hepatic synthesis of fibrinogen through modulation of inflammatory cytokines (e.g., IL-6). Moreover, coffee polyphenols can chelate transition metals, reducing oxidative modification of coagulation proteins.

In contrast, unfiltered coffee, which retains diterpenes, has been reported to increase serum cholesterol and factor VII activity – both associated with enhanced clotting potential. Therefore, brewing method significantly influences coffee's coagulative effects [6].

### *Endothelial and Fibrinolytic Effects.*

The vascular endothelium plays a central role in regulating coagulation through the secretion of nitric oxide and prostacyclin, both of which inhibit platelet aggregation. Coffee intake has been shown to improve endothelial-dependent vasodilation due to increased bioavailability of nitric oxide and reduced oxidative stress. Chlorogenic acids contribute by enhancing endothelial nitric oxide synthase (eNOS) activity.

Regarding fibrinolysis, caffeine may enhance tissue plasminogen activator (t-PA) activity, promoting clot breakdown. However, this effect appears transient and dependent on individual caffeine metabolism rates determined by CYP1A2 enzyme polymorphisms [7].

### *Oxidative Stress and Inflammation.*

Oxidative stress is a key modulator of coagulation, promoting platelet activation and fibrin cross-linking. Coffee's high antioxidant content – mainly from polyphenols – reduces lipid peroxidation and stabilizes redox-sensitive pathways in endothelial and platelet cells. Regular consumption of coffee has been linked with decreased C-reactive

protein (CRP) levels, lower oxidative DNA damage, and improved antioxidant enzyme activity (superoxide dismutase, glutathione peroxidase).

These anti-inflammatory and antioxidant effects collectively support an antithrombotic profile, particularly when coffee is consumed in moderation without added sugars or high-fat creamers [8].

#### *Dose-Dependent and Individual Variability.*

The influence of coffee on hemostasis exhibits significant inter-individual variability depending on genetic, metabolic, and lifestyle factors. Slow caffeine metabolizers may experience prolonged stimulant and pressor effects, potentially promoting thrombogenesis under stress conditions. Additionally, dehydration from excessive caffeine intake may transiently increase blood viscosity, influencing clot formation dynamics.

Epidemiological data suggest a U-shaped relationship between coffee consumption and thrombotic risk, with lowest risk observed at moderate intake (2-4 cups daily). Both abstinence and excessive consumption correlate with higher cardiovascular event rates, emphasizing the importance of balance [9].

#### *Clinical Implications.*

From a clinical standpoint, understanding coffee's biochemical influence on coagulation is relevant for individuals at risk of thromboembolic events, patients on anticoagulant therapy, and those with bleeding disorders. Moderate coffee intake appears safe and potentially beneficial for cardiovascular health. However, high consumption or combination with other stimulants may pose risks. Monitoring caffeine intake and considering brewing methods (filtered vs. unfiltered) should be part of dietary recommendations in patients with coagulation abnormalities [10].

**Conclusions.** Coffee contains multiple bioactive compounds that modulate blood coagulation through complex biochemical mechanisms involving platelet function, coagulation factors, and endothelial activity. Moderate coffee consumption (up to 3 cups per day) generally exerts antithrombotic effects by inhibiting platelet aggregation, enhancing endothelial nitric oxide production, and reducing oxidative stress. Excessive caffeine intake or unfiltered coffee consumption may promote pro-coagulant activity through catecholamine release, dehydration, and elevated factor VII levels. The overall impact of coffee on coagulation is dose-dependent and influenced by genetic factors, metabolic rate, and brewing methods. Coffee can be included as part of a balanced diet, but individuals with cardiovascular or hematological disorders should monitor intake carefully. Further controlled studies are required to elucidate molecular pathways and establish precise consumption guidelines for optimal vascular health.

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### КЛІНІКО-МОЛЕКУЛЯРНІ ОСОБЛИВОСТІ РАКУ МОЛОЧНОЇ ЗАЛОЗИ

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**Анотація.** Рак молочної залози характеризується значною біологічною та клінічною гетерогенністю, що зумовлює потребу у використанні великих масивів даних для його вивчення. Відкриті бази даних, такі як СРТАС/OncoKB та The Cancer Genome Atlas (TCGA), містять детальну інформацію про геномні та транскриптомні зміни, а також клінічні характеристики пацієнтів, і можуть бути використані для навчальних і дослідницьких цілей без додаткового збору матеріалу.

Метою роботи було узагальнити клінічні особливості когорти пацієнтів з раком молочної залози TCGA-BRCA та описати загальні тенденції мутаційних і



експресійних змін у даних CPTAC/OncoKB. Проведено вторинний аналіз клінічних та молекулярних баз даних TCGA-BRCA та CPTAC/OncoKB. Застосовано описові статистичні методи та частотний аналіз.

Показано, що клінічна когорта TCGA-BRCA представлена переважно жінками середнього та старшого віку з локалізованими й локально поширеними формами пухлин, а молекулярні дані CPTAC/OncoKB демонструють очікувану домінуючу участь генів-драйверів контролю клітинного циклу, сигнальних шляхів та репарації ДНК. Експресійні профілі ключових генів виявляють широкий діапазон значень і суттєву міжзразкову варіабельність.

Отримані результати підтверджують можливість використання відкритих онкологічних ресурсів для побудови узагальненого клініко-молекулярного портрета раку молочної залози, водночас підкреслюючи обмеження, пов'язані з неповнотою окремих параметрів.

**Ключові слова:** рак молочної залози, TCGA-BRCA, CPTAC, OncoKB, мутації, експресія генів, відкрита база даних.

**Вступ.** Рак молочної залози є одним із найпоширеніших злоякісних новоутворень у жінок та провідною причиною онкологічної смертності у світі [1, 2]. Попри значний прогрес у діагностиці, хірургічному лікуванні, променевій, хіміо- та таргетній терапії, захворювання й надалі характеризується високою частотою рецидивів та варіабельністю індивідуальної відповіді на лікування. Особливої уваги потребують пацієнтки з біологічно агресивними формами пухлин, для яких стандартні прогностичні моделі виявляються недостатньо інформативними.

Клінічний перебіг раку молочної залози визначається складною взаємодією традиційних факторів ризику (вік, гормональний статус, супутні захворювання), морфологічних характеристик пухлини, гормон-рецепторного профілю та множинних молекулярно-генетичних змін. Уже доведено роль окремих генів-драйверів та сигнальних шляхів у формуванні чутливості до терапії та розвитку резистентності, однак для більшості пацієнток точні механізми прогресування залишаються невизначеними [3]. Гетерогенність пухлин як між різними хворими, так і в межах однієї пухлини ускладнює побудову універсальних підходів до стратифікації ризику.

Незважаючи на наявність молекулярних класифікацій та впровадження імуногістохімічних і геномних панелей у клінічну практику, залишається низка невирішених питань. Недостатньо чітко окреслені зв'язки між сукупністю геномних змін, транскриптомними профілями та реальними клінічними наслідками для пацієнток, зокрема щодо тривалості виживаності, ймовірності

рецидиву та відповіді на системне лікування. Потребують подальшого вивчення патерни поєднання мутацій у генах-драйверах, порушення експресії ключових регуляторів клітинного циклу та репарації ДНК, а також їхній внесок у формування індивідуального біологічного «портрета» пухлини. Саме ці прогалини зумовлюють необхідність системного аналізу клінічних і молекулярних даних для уточнення факторів ризику та пошуку нових орієнтирів персоналізованої терапії.

**Мета дослідження.** Встановити клініко-епідеміологічні особливості перебігу раку молочної залози та охарактеризувати основні напрями геномних і транскриптомних змін із виокремленням груп потенційно значущих молекулярних маркерів, здатних відображати біологічну гетерогенність пухлин та їхній можливий зв'язок із клінічним перебігом захворювання.

**Матеріали та методи.** Дослідження виконано як ретроспективний аналіз узагальнених клінічних та молекулярних даних пацієнтів із раком молочної залози, сформованих на основі великих міжнародних багатоцентрових когорт.

Клінічний блок включав відомості про демографічні характеристики пацієнтів (вік на момент встановлення діагнозу, стать, расово-етнічну належність), морфологічний тип пухлини, патологоанатомічну стадію та ступінь диференціювання, а також базові показники перебігу захворювання (життєвий статус, тривалість спостереження). На підставі цих даних формували узагальнений клініко-епідеміологічний профіль когорти.

Молекулярний блок ґрунтувався на даних про соматичні мутації та експресію генів у зразках пухлин молочної залози. Для аналізу відбирали гени, що належать до відомих онкогенів, генів-супресорів пухлин та ключових регуляторів сигнальних шляхів, репарації ДНК і клітинного циклу, з урахуванням їхньої потенційної клінічної значущості. Для кожного зразка оцінювали наявність мутацій у відібраних генах, а також загальний спектр мутаційних змін. Експресійні дані аналізували на рівні окремих маркерів (гени гормональних рецепторів, HER2, гени-драйвери та супресори) та їхніх сукупних транскриптомних профілів.

Статистичний аналіз включав описові показники для клінічних змінних і молекулярних параметрів, частотний аналіз мутацій, оцінку розподілу експресії вибраних генів, а за потреби – порівняння між підгрупами з використанням стандартних методів біостатистики. Структуру транскриптомних даних додатково оцінювали за допомогою методів зниження розмірності, зокрема аналізу головних компонент, з метою виявлення узагальнених патернів експресії без надмірної деталізації окремих числових значень.

## Результати та обговорення.

*Клінічні характеристики когорти.* Аналіз клінічних даних показав, що більшість пацієнтів становлять жінки, тоді як випадки раку молочної залози у чоловіків трапляються поодинокі. Віковий профіль когорти відповідає загальним епідеміологічним тенденціям: переважають пацієнти середнього та старшого віку, однак реєструються й випадки захворювання у відносно молодому віці.

Розподіл за патологоанатомічними стадіями свідчить про те, що значна частина пухлин виявляється на етапі локалізованого або локально поширеного процесу, тоді як частка дуже ранніх та віддалено метастатичних стадій є меншою. Морфологічно домінують інфільтруючі протокові карциноми, але представлено й інші гістологічні варіанти, що відображає клінічну та біологічну різноманітність захворювання.

*Молекулярні особливості.* У молекулярному наборі зосереджено відомості про соматичні мутації та експресію широкого спектра генів у зразках раку молочної залози. Аналіз мутацій у генах, віднесених до клінічно значущих, показав провідну роль змін у генах, пов'язаних із регуляцією клітинного циклу, сигнальними шляхами рецепторів та механізмами репарації ДНК. Серед них виділяються як відомі онкогени, так і гени-супресори пухлин, що відповідає сучасним уявленням про молекулярний ландшафт раку молочної залози.

Мутаційне навантаження за цими генами є істотно варіабельним: в одних зразках виявляють обмежену кількість змін, тоді як інші характеризуються множинними мутаціями, що може відображати різний ступінь геномної нестабільності. Експресія ключових генів-мішеней також демонструє широкий діапазон значень. Для маркерів гормонозалежності та HER2 спостерігається умовне розмежування зразків на групи з низькою, проміжною та підвищеною активністю, що узгоджується з концепцією молекулярних підтипів пухлин молочної залози.

Отримані нами результати загалом узгоджуються з даними багатонаціональних досліджень, які сформували сучасне уявлення про клініко-молекулярну гетерогенність раку молочної залози. Портрет когорти з переважанням жінок середнього та старшого віку, домінуванням інфільтруючих протокових карцином та локалізованих/локально поширених стадій відповідає епідеміологічним характеристикам, описаним у проєкті TCGA-BRCA та подібних реєстрах [1, 4]. Зіставлення цих даних із узагальненим спектром мутацій і профілем експресії ключових генів демонструє добре відомий, але все ще клінічно недостатньо використаний факт: навіть у межах «типової» клінічної

когорті зберігається значна біологічна варіабельність пухлин.

Молекулярні характеристики, отримані на основі даних, що відображають зміни у генах-драйверах, онкогенах і генах-супресорах, узгоджуються з висновками попередніх великих протеоеномних та геномних досліджень, де показано провідну роль порушень у генах, відповідальних за контроль клітинного циклу, сигнальні шляхи та репарацію ДНК [1-3]. Відзначена в нашому аналізі варіабельність мутаційного навантаження і спектра експресії генів, пов'язаних із гормонозалежністю та HER2-статусом, перегукується з концепцією молекулярних підтипів, запровадженою в роботах TCGA та CPTAC, і підкреслює, що лабораторна оцінка раку молочної залози не може обмежуватися лише морфологією та базовою імуногістохімією.

З практичної точки зору для лабораторної медицини ці результати мають кілька важливих наслідків. По-перше, вони підтверджують доцільність формування розширених панелей молекулярного тестування, орієнтованих не лише на поодинокі гени, а на цілі групи маркерів, що репрезентують основні сигнальні шляхи та механізми геномної нестабільності. По-друге, узгоджені клінічні й молекулярні патерни, продемонстровані в цій роботі, можуть бути використані як орієнтир для розробки алгоритмів стратифікації пацієнтів, де комбінація віку, морфології та профілю молекулярних змін допомагає обґрунтувати вибір додаткових лабораторних досліджень. По-третє, узагальнені дані можуть слугувати основою для створення стандартизованих звітів у лабораторній практиці, у яких результати генетичного та транскриптомного аналізу інтерпретуються в контексті глобально описаних патернів, що сприяє більш точному й клінічно значущому формулюванню висновків.

**Висновки.** Отриманий клінічний профіль пацієнтів із раком молочної залози та узагальнені молекулярні характеристики пухлин дозволяють цілісно представити структуру захворювання з позицій сучасної лабораторної медицини. Виявлені тенденції щодо віку, статі, морфологічних варіантів і стадій, у поєднанні зі спектром мутацій у генах-драйверах і варіабельністю експресії ключових маркерів, підтверджують гетерогенний характер раку молочної залози й підкреслюють доцільність багатокомпонентного підходу до його лабораторної діагностики.

З практичної точки зору отримані результати можуть слугувати підґрунтям для оптимізації панелей молекулярно-генетичного тестування, уточнення переліку маркерів, які доцільно включати в рутинні діагностичні алгоритми, а також для розробки комбінованих клініко-лабораторних моделей стратифікації ризику. Узгоджені клінічні й молекулярні патерни, продемонстровані в роботі,

здатні сприяти більш обґрунтованому вибору таргетних досліджень, підвищенню інформативності лабораторних висновків і формуванню єдиного підходу до інтерпретації результатів у практиці персоналізованої онкології.

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## STRATEGIC “YES” FOR GLUCOSE-BASED CHOLINESTERASES INHIBITORS

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**Introduction.** One of the most extensively studied pathways of choline metabolism is in the context of neurodegenerative pathologies. For example, the cholinergic hypothesis of Alzheimer’s disease suggests that degeneration of cholinergic neurons results in reduced acetylcholine (ACh) levels in the cortex and hippocampus, contributing to memory and cognitive decline. A primary therapeutic strategy is to inhibit enzyme acetylcholinesterase (AChE) to increase synaptic acetylcholine levels by using AChE inhibitors (AChEIs), such as donepezil. Although donepezil is relatively selective for central AChE over peripheral butyrylcholinesterase (BChE), it nevertheless distributes into peripheral tissues, and cholinergic effects in peripheral sites contribute to the known adverse-effect profile. Common cholinergic adverse effects include gastrointestinal (nausea, vomiting, diarrhoea), increased salivation, muscle cramps/fatigue, bradycardia, syncope, insomnia and vivid dreams.

From a therapeutic standpoint, awareness of this dynamic underscores the importance of meticulous patient monitoring, dose titration, and attention to comorbidities, as well as the future development of more targeted delivery systems or combination strategies to optimize benefits while minimizing side effects.



Glucose- or sugar-based AChE inhibitors and sugar-conjugated products are a credible route to reduce peripheral side effects. Sugar-conjugates, glycosides, and iminosugars have been designed firstly because they can show in vitro AChE (and sometimes multi-target) activity and may also reduce toxicity or add antioxidant/anti-aggregation properties. The first examples of cholinesterase inhibitors based on iminosugars were introduced 10 years ago [1]. To date, this field remains active and conceptually attractive [2, 3].

**The aim of this study** was to synthesize different glucose-6-esters. Lipase was used to catalyze a transesterification reaction at the primary alcohol position of glucose, which is located at the C6 position. Various vinyl esters were used as acyl group donors. After successfully synthesizing three different glucose-6-esters, their effects on acetylcholinesterase and butyrylcholinesterase were evaluated. It was found that the inhibition of these esterases depends on the length of the acyl group.

### Materials and Methods.

**Enzymes.** Immobilized recombinant lipase B *Candida antarctica* (CALB) from yeast, acetylcholinesterase from *Electrophorus electricus*, and butyrylcholinesterase from horse serum were obtained from Sigma-Aldrich.

**Vinyl esters.** Vinyl pivalate (VPi), vinyl 4-tert-butylbenzoate (VtBe), vinyl propionate (VPr), vinyl methacrylate (VMe), vinyl butyrate (VBu), vinyl laurate (VL<sub>a</sub>), and vinyl acetate (VAc) were purchased from Sigma-Aldrich, while vinyl benzoate (VBe) was purchased from Thermo Scientific.

**Reagents.** 3,5-Dinitrosalicylic acid, sodium potassium tartrate tetrahydrate, monopotassium dihydrogen phosphate (KH<sub>2</sub>PO<sub>4</sub>), 4-nitrophenyl acetate, 4-nitrophenol were purchased from Sigma-Aldrich. Molecular sieves with pore sizes of 3 Å were obtained from Alfa Aesar. 2-Methyl-2-butanol was purchased from Thermo Scientific. Dipotassium hydrogen phosphate (K<sub>2</sub>HPO<sub>4</sub>) was purchased from VWR.

**Synthesis of Glucose-6-Esters.** Glucose-6-esters were synthesized using lipase-catalyzed transesterification between D-glucose and short-chain vinyl esters in 2-methyl-2-butanol. Reaction mixtures contained 5 mM glucose, 0.02 g of 3 Å molecular sieves, and 5 mg/mL CALB. The synthesis was performed at 40°C with constant stirring for 24 h. Negative controls were prepared without the enzyme.

After synthesis, samples were filtered through 0.45 µm syringe filters and analyzed using an amperometric glucose biosensor and the DNS method to estimate conversion efficiency. The yield was calculated from the decrease in glucose concentration before and after the reaction.

**Amperometric Glucose Biosensor Measurements.** Measurements were performed using a three-electrode system (Pt working, Ag/AgCl reference,

Ti auxiliary) at 0.6 V vs Ag/AgCl in 20 mM phosphate buffer containing 100 mM KCl. The working platinum electrode was covered with a terylene membrane on which glucose oxidase was immobilized. The biosensor was calibrated with a standard 10 mM D-glucose solution. Each analysis involved 50  $\mu$ L of sample in a 1 mL cell volume at room temperature.

*Determination of Reducing Sugars.* Reducing sugars were quantified using the DNS method. Samples were mixed with DNS reagent, heated at 95°C for 7 min, cooled, and absorbance was measured at 540 nm. A 10 mM D-glucose standard was used for calibration.

*Determination of the inhibition effect.* Measurements were performed using a three-electrode system (Graphite working, Ag/AgCl reference, Ti auxiliary) at 0.3 V vs Ag/AgCl in 20 mM phosphate buffer containing 100 mM KCl. The working Pt electrode was covered with a terylene membrane on which choline oxidase was immobilized. The biosensor was calibrated with standard 20  $\mu$ L, 5 mM choline solution. The measurement procedure was as follows: a solution of acetyl- or butyrylcholine (20  $\mu$ L, 20 mM) was introduced, and the current change was recorded until a stable baseline was reached (approximately 60 s). Then, 30  $\mu$ L of 10 U/mL acetylcholinesterase or butyrylcholinesterase was added, and the current response was monitored for 70 seconds. Subsequently, 200  $\mu$ L of 2.5 mM of the corresponding glucose-6-ester was introduced. In control measurements, 200  $\mu$ L of PBS or 2.5 mM D-glucose solution was added instead. The inhibitory effect was evaluated by comparing the slopes of the current change rate after the addition of PBS and after the addition of the inhibitor. Each analysis was performed in a 1 mL cell volume at room temperature.

**Results and Discussion.** Two methods were selected to assess the efficiency of the synthesis. The first method employed an amperometric glucose biosensor. This method was chosen because it relies on the enzyme-catalyzed reaction of glucose oxidase, which is highly specific for D-glucose; therefore, successful synthesis of glucose-6-esters is reflected as a decrease in free glucose concentration. The second method was the spectrophotometric DNS assay, which detects reducing sugar groups at the C1 position. Since the glucose-6-esters retain the C1 position unreacted, no change in glucose content is observed using this method after synthesis.

Based on the data presented in Figure 1, it is evident that three different glucose-6-esters were successfully synthesized. The yield estimated using the amperometric glucose biosensor (**Fig. 1**) indicated that the reaction proceeded most efficiently with vinyl acetate, vinyl propionate, and vinyl butyrate, whereas reactions with other vinyl derivatives were significantly less efficient. In contrast, measurements using the spectrophotometric DNS method consistently showed yields close to 0%, indicating

that the transesterification reaction affected the C6 carbon of glucose while leaving the C1 carbon unaltered. These three compounds were subsequently used in further experiments as potential inhibitors of esterase activity.

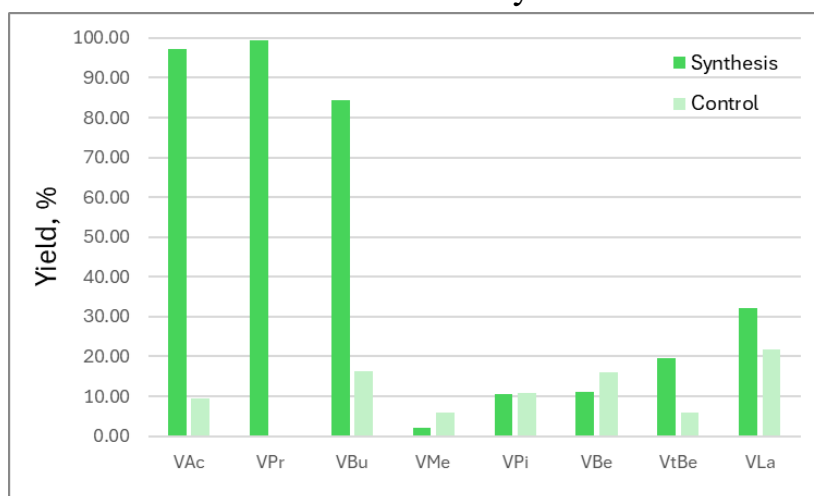


**Figure 1.** Synthesis yield using vinyl esters: VPI, VtBe, VPr, VMe, VBu, VLa, and VAc determined by amperometric glucose biosensor based on glucose consumption.

The synthesized compounds namely, glucose-6-acetate (Glu-6-Ac), glucose-6-propionate (Glu-6-Pr) and glucose-6-butyrate (Glu-6-Bu) were evaluated for their potential as esterase activity inhibitors, and the results are presented in **Figure 2**. All three compounds affected the activity of both acetylcholinesterase and butyrylcholinesterase. It was observed that inhibition increased with the length of the ester chain; the Glu-6-Ac showed the weakest effect while Glu-6-Bu the strongest. D-glucose was also tested and exhibited no inhibitory effect; in fact, it slightly enhanced enzyme activity.

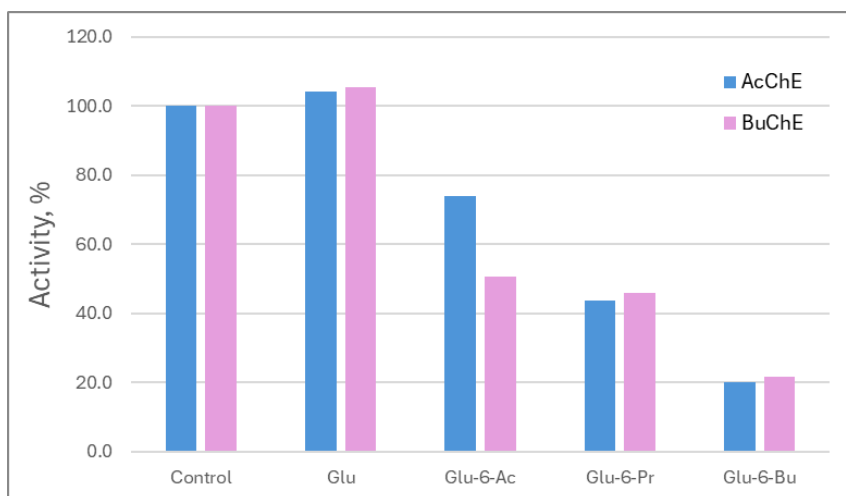


**Figure 2.** Acetylcholinesterase and butyrylcholinesterase activity with different glucose-6-esters (c = 0.4 mM).

**Conclusions.** The results demonstrate the successful synthesis of different glucose-6-esters using lipase-catalyzed transesterification between D-glucose and short-chain vinyl esters in 2-methyl-2-butanol. These glucose-6-esters, with varying efficiencies, can act as potential inhibitors for acetylcholinesterase and butyrylcholinesterase activity. The inhibition efficacy of these esterases increases with the length of the acyl group. Although the concept of using medications based on glucose derivatives is attractive, further research is needed to elucidate the exact mechanism of inhibition.

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## DEVELOPMENT OF SARCOSINE BIOSENSOR BASED ON TOLUIDINE BLUE MODIFIED ELECTRODES

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**Introduction.** Sarcosine is a biogenic amine present in various biological fluids and foods, playing a vital role in health and nutrition. High levels of sarcosine have been closely linked to the development of several diseases, including serious conditions such as prostate cancer and Alzheimer's disease. [1] Therefore, accurately measuring sarcosine levels is an essential procedure in the field of clinical chemistry.

In the food sector, sarcosine quantification is equally important for assessing product quality, freshness, and safety, as its concentration can reflect the degree of protein degradation and spoilage. Thus, accurate detection and quantification are also essential for quality control and safety assurance in the food and fermentation industries. [2]

Sarcosine detection often relies on enzymes, such as sarcosine oxidase, which catalyzes the oxidative demethylation of sarcosine, producing hydrogen peroxide. [3] While several analytical approaches, including specific biosensors utilizing this enzyme, have been developed to measure sarcosine with specificity and speed, a significant challenge remains: these methods are not yet commercially applicable. The primary limitation is the insufficient accuracy when determining the very low sarcosine concentrations often required for clinical and food safety monitoring.

**The Aim of the Study.** This work aims to develop and evaluate a sarcosine biosensor prepared with the electron transfer mediator toluidine blue and the enzymes horseradish peroxidase (HRP) and monomeric sarcosine oxidase (SOx).

**Materials and Methods.** Peroxidase from horseradish (HRP, Type II, specific activity 99 U/mg) and sarcosine oxidase from *Bacillus* sp. (SOx, specific activity 2.2 U/mg) were acquired from Sigma-Aldrich. The enzyme solutions were prepared using triple-distilled water. Toluidine blue (TB), sarcosine, glutaraldehyde solution (50%),  $\text{NaNO}_2$ , and buffer solution reagents were all sourced from Sigma-Aldrich. Hydrogen peroxide (30% solution) was obtained from Merck, and HCl (35-38 %) was from Chempur.

#### *Electrode Surface Modification with Toluidine Blue.*

Graphite rod electrodes were treated with sandpaper and washed with distilled water before modification with Toluidine Blue through covalent attachment. The electrodes were immersed in a 4 mM TB solution prepared with 10 mM HCl and 6 mM  $\text{NaNO}_2$ . Chronoamperometry (CA) was performed at -0.2 V vs. Ag/AgCl, causing TB to react with  $\text{NaNO}_2$ , forming a diazonium salt that covalently attached to the electrode surface. After modification, electrodes were washed with deionized water to remove any unbound mediator.

#### *Enzyme immobilization*

For enzyme immobilization, varying amounts of HRP and SOx were drop-cast onto the modified electrodes, which were then exposed to glutaraldehyde vapors for 30 minutes and washed with deionized water.

Cottage cheese samples were prepared by grinding 40 g of cheese with 40 mL buffer solution, resting for 1 hour at room temperature, and centrifuging at  $16,000 \times g$  for 10 minutes. To reduce interference, 20 mL of supernatant was mixed with 1 g of activated carbon and centrifuged again. The final supernatant was collected for measurement.

#### *Electrochemical measurements*

Electrochemical measurements were performed using a PalmSens4 potentiostat in a 10 mL cell with a three-electrode system. The working electrode was a TB-



modified graphite electrode, the reference electrode was an Ag/AgCl 3 M electrode, and the counter electrode was a platinum wire electrode. A potassium phosphate buffer solution (pH 7) with 100 mM KCl was used for electrochemical measurements.

**Results and discussion.** After the electrode modification with TB, the CV of the electrode in the buffer solution was registered. The CV exhibited an anodic peak at 0.15V and a cathodic peak at -0.11V; these peaks confirmed that the graphite electrodes were effectively modified with Toluidine Blue. The second pair of peaks on the CV possibly represents the adsorbed mediator.

Chronoamperometric analysis was applied to characterize the prepared sarcosine biosensors by measuring the biosensor response to the enzyme substrates hydrogen peroxide and sarcosine. The dependencies of the background current of the biosensor and its sensitivity to sarcosine on electrode potential were investigated. These dependences revealed that the developed biosensor has a low working potential (-120 mV vs Ag/AgCl), which allows for the reduction of the effects of interfering agents present in the solution.

By analyzing the dependence of the biosensor's sensitivity to sarcosine on the quantities and ratios of the enzymes used, it was found that the highest sensitivity to sarcosine ( $2.0 \pm 0.1 \mu\text{A}/\text{mM}$ ) was obtained when the highest quantities of enzymes (25 U HRP and 1.9 U SOx) were immobilized on the electrode surface. Additionally, a biosensor is well-suited for detecting low sarcosine concentrations and exhibits excellent reproducibility. However, the operational and shelf stability analyses revealed that the biosensor is unstable and is more suitable for single-use applications. The developed sarcosine biosensor has been applied to real samples for determining the sarcosine concentration in a cottage cheese sample.

**Conclusions.** Modification of the graphite electrode surface with the electron transfer mediator, Toluidine Blue, was confirmed by Cyclic Voltammetry. The observed anodic and cathodic current peaks, at 0.15 V and -0.11 V, respectively, are attributed to the redox reactions of the covalently attached TB.

The developed sarcosine biosensor exhibited a low operating potential. The best response of the biosensor to sarcosine was observed at potentials -100 mV or -120 mV.

The sensitivity of the developed sarcosine biosensor was dependent on the amounts and ratio of the immobilized HRP and SOx enzymes. The highest sensitivity to sarcosine,  $2.0 \pm 0.1 \mu\text{A}/\text{mM}$ , was achieved at a potential of -120 mV by immobilizing 25 U of HRP and 1.9 U of SOx onto the modified electrode surface.

The developed sarcosine biosensor was successfully applied to real samples. The determined sarcosine concentration in the cottage cheese sample reached 13.5 mg/L and 14.7 mg/L.

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## ТЕЗИ ABSTRACTS

### ОЦІНКА ЖИТТЄЗДАТНОСТІ КЛІТИННОЇ ЛІНІЇ L929 ПІСЛЯ ВПЛИВУ ДОКСОРУБІЦИНУ

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**Вступ.** Вплив протипухлинного препарату Доксорубіцину на живі системи залишається недостатньо вивченим, особливо з огляду на складність його багатофакторної дії на клітинному та молекулярному рівнях. Актуальним завданням сучасних досліджень є детальне вивчення цитотоксичного ефекту препарату на різні типи клітин з метою визначення дозозалежних закономірностей, механізмів ушкодження клітинних структур і метаболічних порушень. Такий підхід дозволяє не лише оптимізувати терапевтичні дози для мінімізації побічних ефектів, але й поглибити розуміння селективності дії Доксорубіцину щодо нормальних і пухлинних клітин, що є важливим для розроблення безпечніших і більш ефективних схем хіміотерапії.

**Мета дослідження.** Проаналізувати цитотоксичний вплив Доксорубіцину на клітини лінії L929 у різних дозах.

**Матеріали та методи.** Використовували препарат Доксорубіцин («Актавіс Італія С.п.А.Сіндан Фарма С.Р.Л.», Англія) 2 мг/мл, об'ємом 25 мл. Клітини висівали у 24-лункові планшети з концентрацією  $2 \times 10^5$  клітин на лунку та культивували у середовищі DMEM з 10% FBS або без нього, з додаванням 1% антибіотика-антимікотика при 37°C і 5% CO<sub>2</sub>. Після 24 годин інкубації середовище замінювали, попередньо промиваючи клітини PBS, і додавали Доксорубіцин у різних концентраціях на 24 години. Після експозиції клітини знімали 0,25% розчином трипсин-ЕТДА, здійснювали мікроскопію та визначали відсоток життєздатних клітин. Кількісний аналіз проводили за допомогою програми ImageJ, що забезпечує об'єктивну оцінку морфологічних параметрів клітин.

**Результати та обговорення.** При додаванні концентрацій Доксорубіцину 50-60 мкг/мл життєздатність клітин у середовищі без сироватки знижувалася на 80-90%, тоді як у присутності FBS – на 60-70%. Таким чином, FBS зменшував

цитотоксичність препарату приблизно на 20-30% завдяки протекторній ролі білкових і ліпідних компонентів, що зв'язують частину Доксوروبіцину і підтримують клітинну адгезію та метаболізм.

**Висновки.** На основі проведених досліджень встановлено, що Доксوروبіцин чинить виражену дозозалежну цитотоксичну дію на клітини лінії L929. Визначено, що наявність сироваткових компонентів у середовищі культивування достовірно знижує токсичний ефект препарату на 20-30% порівняно з клітинами, вирощеними у середовищі без сироватки. Такий протекторний ефект, ймовірно, зумовлений здатністю білкових і ліпідних фракцій сироватки зв'язувати частину молекул Доксوروبіцину, зменшуючи їхню біодоступність і стабілізуючи клітинні мембрани.

## **SURFACE MARKER CD44 AS AN INDICATOR OF STABILITY OF CRYOPRESERVED HUMAN RED BLOOD CELLS**

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**Introduction.** The CD44 surface marker is a transmembrane adhesion molecule that mediates cell binding to extracellular matrix components, including hyaluronic acid, laminin, fibronectin, heparin sulfate, and collagen types I and IV. In human red blood cells, CD44 is represented by the standard isoform (CD44s), also known as the hematopoietic isoform (CD44H), and carries antigens of the AnWj and In a/b (Lu) blood group systems. The adhesive properties of red blood cells, mediated by various molecules including CD44, are manifested during the development of pathophysiological processes associated with vaso-occlusive conditions arising in sickle cell anemia, hereditary spherocytosis, and other diseases. Assessing the presentation of CD44 in cryopreserved human red blood cells, intended for transfusion to a recipient, is important for understanding their ability to competently function in the bloodstream.

**The purpose** of the study was to investigate the parameters of the surface marker CD44 in red blood cells, cryopreserved under the protection of glycerol, after thawing and removal of the cryoprotective agent from the cells.

**Materials and methods.** Red blood cells, washed free of plasma and white blood cells, were mixed with a solution containing 30% glycerol, 4% mannitol, and 0.7% NaCl and frozen in liquid nitrogen ( $-196^{\circ}\text{C}$ ). Samples were thawed in a water bath at  $+44^{\circ}\text{C}$ . Glycerol was removed from thawed cells by three-step centrifugation using the following solutions: 0.6 M NaCl (first wash) and 150 mM NaCl (second and

third washes). CD44 expression on red blood cell membranes was assessed using the same-named CD44-FITC antibodies by flow cytometry on a FACS Calibur instrument (Becton Dickinson, USA). Each measurement counted 20,000 cells. Data were analyzed using WinMDI 2.8 software by plotting histograms of the CD44-FITC fluorescence intensity distribution in the red blood cell suspension.

**Results and discussion.** CD44 presentation parameters in thawed red blood cells that remained intact and available for flow cytometry analysis were assessed after short-term exposure to 37°C in the glycerol presence. A decrease in the number of cells exhibiting this marker on their surface was manifested, from  $79.25 \pm 4.93\%$  in the control to  $69.45 \pm 1.65\%$  in cryopreserved samples ( $p < 0.05$ ). In addition, a noticeable decrease in the expression of this surface marker was found in the suspension of thawed cells, as evidenced by a reduction in the values of the medians of the fluorescence intensity distribution histograms from  $13.34 \pm 1.26$  conventional units in the control to  $8.87 \pm 0.87$  conventional units in thawed red blood cells ( $p < 0.05$ ). The presentation of the CD44 marker in cryopreserved red blood cells after the glycerol removal out of the cell suspension was assessed by transferring them to physiological conditions *in vitro*, namely by incubating washed red blood cells for 1 hour at 37°C in Ringer's glucose medium. It was found that the number of CD44-positive red blood cells did not differ from control values after removal of the cryoprotective agent and the loss of unstable cells hemolyzed during the washing process. Moreover, the median distribution values of CD44-FITC fluorescence intensity in the evaluated erythrocyte suspensions also did not differ significantly from the control values. These results indicate that the decreased surface marker presentation in cryopreserved cells is stipulated by the population of unstable cells with impaired structures, which are removed during the washing process.

The factors inducing changes in the state of the surface marker may be related to the influence of physicochemical factors associated with freezing and thawing on intermolecular interactions within the membrane. As a result, certain areas of the membrane may experience conditions that promote the loss of membrane material through vesiculation with the capture of integral proteins, including the adhesion molecule CD44, into the vesicles that leads to a decrease in its expression on the membrane.

**Conclusions.** Changes in CD44 parameters in membranes of cryopreserved red blood cells indicate instability of cells with reduced CD44 expression. Removal of these cells during hemolysis, associated to washing away glycerol, eliminates the differences between the characteristics of this marker in control cells and red blood cells cryopreserved under the protection of this cryoprotective agent.



## ВПЛИВ ОБ'ЄМУ ЗРАЗКА, ЩО ЗАМОРОЖУЄТЬСЯ, НА ЗБЕРЕЖЕНІСТЬ ЕРИТРОЦИТІВ КРОЛИКА ПРИ КРІОКОНСЕРВУВАННІ

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**Вступ.** Збереження клітин крові є актуальним як для клінічної практики, так і для наукових досліджень. Завдяки уповільненню метаболічних процесів при охолодженні зразків до наднизьких температур клітини зберігають функціональність тривалий час. Під час кріоконсервації клітини піддаються негативній дії пошкоджуючих факторів різного характеру, вплив яких можна зменшити, контролюючи профілі охолодження й нагрівання, а також процедури додавання й видалення кріозахисного агента.

**Мета дослідження.** Визначення рівня пошкодження еритроцитів кролика за умов їх кріоконсервування при різних об'ємах зразка, що заморожується (2 мл і 10 мл) при використанні проникного кріопротектора диметилсульфоксид (7,5%).

**Матеріали та методи.** У роботі використовували еритроцити кролика (*Oryctolagus cuniculus*). Заготівлю крові й усі маніпуляції проводили згідно з вітчизняними та міжнародними біоетичними нормами, узгодженими із основними положеннями Закону України «Про захист тварин від жорстокого поводження» (№ 3447-IV від 21.02.2006) та «Європейської конвенції про захист хребетних тварин, які використовуються для експериментальних та інших наукових цілей» (Страсбург, 1986). До суспензії еритроцитів додавали крапельно ДМСО до кінцевої концентрації 7,5 %. Зразки заморожували прямим зануренням у рідкий азот ( $-196^{\circ}\text{C}$ ), Після розморожування кріопротектор видаляли шляхом поетапного центрифугування. На першому етапі до суспензії еритроцитів додавали в рівному обсязі розчин: NaCl 0,6 моль/л, Na-фосфатний буфер 0,01 моль/л, pH 7,4. Після цього еритроцити двічі промивали фізіологічним розчином. Вміст гемоглобіну, що вийшов у супернатант, визначали спектрофотометрично на кожному етапі Статистичну обробку отриманих числових даних проводили за допомогою програми Statistica (версія 6.0) з урахуванням t-критерію Стьюдента.

**Результати та обговорення.** Отримані дані вказують на залежність пошкодження еритроцитів кролика від об'єму зразка, що використовується. Цей ефект спостерігається на кожному етапі кріоконсервації, як при заморожуванні, так і при видаленні кріопротектора. Для об'єму зразка 2 мл пошкодження після заморожування складає  $50\pm 4\%$ . На етапах видалення кріопротектора –  $43\pm 4\%$ ,  $53\pm 5\%$ ,  $42\pm 6\%$  відповідно. Загальне пошкодження –  $92\pm 7\%$ . Для об'єму зразка

10 мл пошкодження після заморожування складає  $79 \pm 6\%$ , на етапах видалення кріопротектора –  $32 \pm 3\%$ ,  $37 \pm 3\%$ ,  $41 \pm 4\%$  відповідно. Загальне пошкодження –  $95 \pm 4\%$ . Видно, що при використанні більшого об'єму суспензії пошкодження клітин збільшується саме на етапі заморожування. Це можна пояснити тим, що зразки більшого об'єму охолоджуються повільніше, що впливає на утворення кристалів та їхні характеристики. Повільніші швидкості охолодження сприяють утворенню більших за розміром кристалів, що, в свою чергу, викликає більш виражене механічне руйнування заморожених клітин.

**Висновки.** Заморожування-відтавання еритроцитів кролика виявило залежність ступеню пошкодження цих клітин від об'єму зразка, що заморожується. Отже, при збільшенні об'єму еритроцитарної маси, що заморожується, необхідно використовувати додаткові кріозахисні речовини, які знижуватимуть вірогідність утворення кристалів, а саме змінюватимуть розподіл рідкої фази у клітинному і позаклітинному середовищі, підвищуватимуть в'язкість цитоплазми, зменшуючи цим вірогідність утворення кристалів і зменшуючи їх розмір.

## GUT MICROBIOTA COMPOSITION AND FUNCTIONAL ALTERATIONS IN OBESITY

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**Introduction.** The World Health Organization (WHO) defines obesity and being overweight as having an abnormal or excessive accumulation of body fat that poses a risk to health. It is projected that, by 2030, obesity will affect more than 40% of the global population [Kelly et al., 2008]. This condition is associated with various complications, including type 2 diabetes, cardiovascular disease, certain cancers and premature death [Scully et al., 2021]. In addition to its physical health consequences, obesity can also lead to psychological and social issues, such as depression and anxiety, and a reduced quality of life [Segal and Gunturu, 2024].

Recently, the role of the gut microbiota in the development and progression of obesity has received increasing attention [Liu et al., 2021; Enache et al., 2024]. This is a complex community comprising trillions of microorganisms, including bacteria, viruses, archaea, fungi and phages. Microbial metabolism generates a broad range of metabolites that influence host physiology, including energy extraction, lipid metabolism, intestinal permeability, immune regulation and gene expression related to

fat storage [Brown et al., 2023; Kim et al., 2024].

There is increasing evidence that obesity is accompanied by an imbalance in the composition of the gut microbiota – characterised by reduced richness and diversity – and functional alterations that promote inflammation and metabolic disturbances [Wang et al., 2024]. Notably, shifts in the *Firmicutes*-to-*Bacteroidetes* ratio, increased endotoxin production and impaired short-chain fatty acid synthesis have been implicated in the pathophysiology of obesity [Liu et al., 2021]. These findings highlight the potential of microbiota-targeted interventions, such as prebiotics, probiotics, dietary modifications and faecal microbiota transplantation, as promising strategies for the prevention and treatment of obesity [Dhanasekaran et al., 2025; Augustynowicz et al., 2025].

This paper aimed to summarise and critically evaluate the current scientific evidence on the composition and functional alterations of the gut microbiota in obesity. The article discusses key microbial taxa associated with metabolic imbalance and the mechanisms linking gut dysbiosis to obesity-related inflammation and energy metabolism. It also explores the potential of microbiota-targeted interventions in preventing and treating obesity.

**Materials and methods.** This review was conducted in accordance with the principles of narrative literature synthesis, incorporating systematic search elements. A comprehensive literature search was performed using the electronic databases PubMed, Scopus, Web of Science and Google Scholar to identify relevant articles published between 2010 and 2025. The following search terms and their combinations were used: “gut microbiota”, “intestinal microbiome”, “obesity”, “metabolic syndrome”, “*Firmicutes/Bacteroidetes* ratio”, “short-chain fatty acids”, “inflammation”, and “microbiota-targeted therapy”. Boolean operators (“AND”, “OR”) and truncation symbols were applied to refine the search.

**Results.** The gut microbiota is a highly complex ecosystem that plays a crucial role in maintaining metabolic and immune homeostasis in the host. This diverse community of bacteria, archaea, fungi and viruses inhabits the gastrointestinal tract, with bacterial cells outnumbering human cells by around 10 to 1 [Thursby and Juge, 2017; Khalil et al., 2024]. In healthy individuals, the intestinal microbiota is primarily composed of two dominant bacterial phyla: *Firmicutes* and *Bacteroidetes*. These are followed by smaller proportions of *Actinobacteria*, *Proteobacteria* and *Verrucomicrobia*. This balanced microbial composition is essential for nutrient metabolism, energy harvest, and protection against pathogens. It also supports mucosal immunity, regulates epithelial integrity and influences systemic inflammatory responses [Qin et al., 2010; Rinninella et al., 2019; Magne et al., 2020].

Numerous studies have demonstrated significant alterations in gut microbiota composition in obesity, often referred to as dysbiosis. One of the most consistent findings is an increased *Firmicutes*-to-*Bacteroidetes* ratio (F/B ratio), which is associated with enhanced energy extraction from the diet [Stojanov et al., 2020; Magne et al., 2020]. Obese individuals tend to harbour greater abundances of energy-harvesting microbes, such as *Clostridium*, *Ruminococcus* and *Lactobacillus* species, whereas lean individuals exhibit higher levels of *Bacteroides* and *Prevotella* [Davis, 2016; Gomes et al., 2018]. However, recent metagenomic analyses suggest that obesity-related dysbiosis may involve changes at genus and species levels, rather than merely a shift in phylum ratio. These shifts are often accompanied by a loss of microbial functions that are essential for regulating the host's metabolism [Patra et al., 2023; Chanda and De, 2024].

The functional capacity of the gut microbiota in obese individuals differs markedly from that in lean subjects. The microbial gene profiles of obese individuals are enriched with pathways involved in carbohydrate metabolism, lipid synthesis and the production of short-chain fatty acids (SCFAs) [Martínez-Álvaro et al., 2021; Perdigones et al., 2025]. These metabolites, particularly acetate, propionate and butyrate, play dual roles: they contribute to intestinal health but excessive production can also promote hepatic lipogenesis and adipose tissue expansion [Hernández et al., 2019; May and den Hartigh, 2021]. Therefore, the altered metabolic output of obese gut microbiota can directly affect the host's energy balance and fat storage [Cavallari and Schertzer, 2017; Heiss and Olofsson, 2018]. Furthermore, SCFA profiles may vary depending on the composition of the microbiota and the availability of dietary substrates, which complicates their role in obesity [Lange et al., 2023].

Furthermore, the gut microbiota associated with obesity is often characterised by reduced microbial diversity and a decline in beneficial bacteria such as *Akkermansia muciniphila* and *Faecalibacterium prausnitzii* [Koller et al., 2025; Shaheen et al., 2025]. These bacteria are known for their anti-inflammatory and protective properties of the gut barrier. Their depletion contributes to increased intestinal permeability and the translocation of bacterial lipopolysaccharides (LPS) into the bloodstream – a phenomenon known as metabolic endotoxemia [Effendi et al., 2022]. This activates Toll-like receptor 4 (TLR4)-mediated inflammatory pathways, promoting insulin resistance and the low-grade systemic inflammation that is characteristic of obesity. This chronic inflammation is a key driver of obesity-related comorbidities, including type 2 diabetes and cardiovascular disease [Jia et al., 2014; Mohammad and Thiernemann, 2021].

Microbial dysbiosis in obesity has also been linked to changes in bile acid

metabolism. The gut microbiota converts primary bile acids into secondary bile acids, which act as signalling molecules via the farnesoid X receptor (FXR) and the G-protein-coupled bile acid receptor (TGR5). Dysregulation of these pathways can impair glucose homeostasis and lipid metabolism [Li et al., 2021; Larabi et al., 2023; Mancin et al., 2023]. Obese individuals often exhibit a distinct bile acid profile reflecting microbial changes that contribute to the dysmetabolic state. These shifts in bile acids may also influence intestinal motility, nutrient absorption and enteroendocrine signaling [Fogelson et al., 2023; Romaní-Pérez et al., 2025].

In addition to compositional and metabolic shifts, obesity has been associated with changes in microbial-derived signalling molecules that affect appetite regulation. For instance, SCFAs can influence the release of satiety hormones, such as peptide YY (PYY) and glucagon-like peptide-1 (GLP-1) [Byrne et al., 2015; Pizarroso et al., 2021; Nogal et al., 2021]. Dysbiosis may therefore alter gut-brain communication, leading to dysregulated appetite and food intake [Yu et al., 2024]. Similarly, microbiota-derived metabolites can modulate endocannabinoid signalling, further linking intestinal microbial activity with energy homeostasis [Srivastava et al., 2022]. There is also emerging evidence that microbial neuroactive compounds may influence mood and behaviour, potentially contributing to obesity-related psychological symptoms [Ahmed et al., 2025].

Dietary habits play a fundamental role in shaping the gut microbiota and its function. A diet high in fat and sugar, which is typical of Western lifestyles, promotes the growth of opportunistic and pro-inflammatory bacteria [Singh et al., 2017; Rinninella et al., 2023]. In contrast, a diet high in fibre supports the growth of microbes that produce SCFAs and are beneficial to health [Fu et al., 2022]. Several studies have demonstrated that dietary interventions, probiotics and prebiotics can partially restore the balance of the microbiota and improve metabolic outcomes [Sheridan et al., 2014; Zhou et al., 2024]. For instance, supplementation with *A. muciniphila* or *Bifidobacterium* strains has been shown to enhance gut barrier integrity and reduce systemic inflammation in obese subjects [Zhao et al., 2024]. However, long-term dietary patterns appear to have the most profound and lasting impact on microbial ecology, rather than short-term interventions.

**Conclusions.** Thus, obesity is not only a disorder of excess energy storage, but also a condition characterised by microbial metabolic imbalance. Alterations in gut microbiota composition and function play a pivotal role in its pathophysiology by affecting energy harvest, inflammatory tone and host–microbe signalling networks. Understanding these complex interactions opens up new therapeutic avenues, including approaches that target the microbiota, such as dietary modulation, faecal



microbiota transplantation and precision probiotics. Integrating microbiome profiling into personalised medicine could help to identify individuals at risk and guide bespoke interventions. Future research should aim to elucidate the individualised microbial signatures of obesity and identify the specific microbial pathways that can be modulated to restore metabolic health.

## **ADVERSE TRANSFUSION REACTIONS: CLASSIFICATION, CLINICAL MANIFESTATIONS AND RISK ASSESSMENT**

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**Introduction.** Blood is a unique therapeutic substance that cannot be successfully manufactured using laboratory techniques. Its irreplaceable role in clinical medicine stems from its complex composition and biological functions, which cannot be replicated synthetically. Due to the presence of antigens and antibodies in blood components administered to patients, various reactions may occur as a result of contact between the recipient's immune system and foreign antigens or antibodies. This contact can trigger a range of reactions, from mild to severe and potentially life-threatening [Khan et al., 2020; Ray et al., 2024].

Although modern blood collection, testing and storage procedures have greatly improved safety, the risk of adverse post-transfusion events remains. These procedures include donor screening, serological testing for infectious agents and leukoreduction, all of which aim to minimise immunological and infectious complications [Green et al., 2015]. Nevertheless, adverse transfusion reactions constitute a heterogeneous group of undesirable responses that may occur during or shortly after transfusion and may even manifest months or years later [Sahu et al., 2014; Suddock and Crookston, 2023].

Accurate diagnosis and appropriate management require the recognition of the clinical signs and symptoms of transfusion reactions and their prompt reporting. An adverse transfusion reaction is defined as an unintended response in a patient during or following the transfusion of blood or its components, resulting in death, life-threatening conditions, disability, illness or prolonged hospitalization [Andrys and Korybalska, 2022]. Effective haemovigilance systems and post-transfusion monitoring protocols play a crucial role in identifying such events and improving transfusion safety [European Directorate for the Quality of Medicines (EDQM), 2021; International Society of Blood Transfusion (ISBT), 2022].

This study aimed to systematise current knowledge about adverse transfusion reactions, describe their classification and clinical manifestations, highlight potential risk factors, and emphasise the importance of preventive measures and rational blood component therapy.

**Materials and methods.** To contextualise the discussion on transfusion reactions and safety protocols, this paper provides a descriptive analysis and synthesis of clinical and haemovigilance data reported in recent scientific publications, guidelines and institutional reports. The classifications and terminology employed align with the recommendations of the International Society of Blood Transfusion (ISBT) and the World Health Organization (WHO), thereby ensuring alignment with internationally recognised standards. Furthermore, the study incorporates clinical case observations and epidemiological data from European haemovigilance systems to provide valuable insights into the frequency, nature and outcomes of transfusion-related adverse events in various healthcare settings.

**Results.** Adverse transfusion reactions can be categorised in several ways [Sahu et al., 2014; Suddock and Crookston, 2023]:

- ✓ By time of onset, they can be categorised as early (occurring within 24 hours after transfusion) or delayed (occurring beyond 24 hours).
- ✓ By mechanism of occurrence: immunological or non-immunological.
- ✓ According to the presence of haemolysis, they can be categorised as haemolytic or non-haemolytic.
- ✓ Severity: mild or severe.

This classification facilitates clinical decision-making and supports the implementation of appropriate diagnostic and therapeutic strategies [European Directorate for the Quality of Medicines (EDQM), 2021; International Society of Blood Transfusion (ISBT), 2022]. Early transfusion reactions occur within 24 hours of blood transfusion, while delayed reactions appear after more than 24 hours. Haemolytic reactions are characterised by clinical and laboratory signs of accelerated red blood cell destruction during or after transfusion. Typically, these reactions result from the recipient's alloantibodies destroying donor erythrocytes. However, in rare cases, they may be caused by other immunological or non-immunological factors, such as bacterial contamination or thermal, mechanical or osmotic damage to red blood cells [Hong et al., 2022; Rout et al., 2023].

Early immunological transfusion reactions include acute haemolytic reactions, febrile non-haemolytic reactions, transfusion-related acute lung injury (TRALI), allergic reactions and anaphylactic shock. Delayed immunological reactions include delayed haemolytic transfusion reactions, alloimmunisation, post-transfusion purpura,

transfusion-associated graft-versus-host disease (TA-GvHD) and immunomodulation [Suddock and Crookston, 2023; Rout et al., 2023].

These reactions are usually caused by antigen-antibody interactions and can result in haemolysis, fever, dyspnoea, hypotension or severe allergic symptoms. Early non-immunological transfusion reactions may include bacterial sepsis, transfusion-associated circulatory overload (TACO), transfusion pain, air embolisms, non-immune haemolysis, hypothermia, hyperkalaemia and hypocalcaemia. Delayed non-immunological complications are mainly associated with iron overload and the transmission of infectious agents, such as HBV, HCV, HIV or HTLV [Suddock and Crookston, 2023].

Despite strict donor screening and advanced pathogen testing, there is still a small risk of infectious transmission, which emphasises the need for continuous monitoring and preventive measures. Implementing hemovigilance systems and standardised reporting protocols is essential for detecting, analysing, and mitigating such risks [Buerger and Jain, 2023; Justiz Vaillant et al., 2024; Djientcheu Deugoue et al., 2025].

Any symptoms that appear during transfusion should raise suspicion of an adverse reaction, unless other causes can be clearly identified. The most common signs and symptoms include fever with or without chills, pain at the infusion site or in the chest and lumbar regions, blood pressure fluctuations, dyspnoea, skin manifestations such as urticaria, pruritus, erythema and localised oedema, nausea and vomiting, dark urine and bleeding disorders [Suddock and Crookston, 2023].

Severe reactions can progress rapidly, leading to shock, multi-organ failure or death. This requires immediate cessation of the transfusion and supportive treatment. Timely recognition and intervention are critical to improving patient outcomes and reducing morbidity [Khan et al., 2025].

The estimated frequency of immunological transfusion reactions is as follows [European Directorate for the Quality of Medicines (EDQM), 2021; International Society of Blood Transfusion (ISBT), 2022]:

- ✓ Urticaria: 1 in 50-100 transfusions;
- ✓ Alloimmunisation: 1 in 100 transfusions;
- ✓ Febrile non-haemolytic reaction: 1 in 300 transfusions;
- ✓ TRALI: 1 in 5,000 transfusions;
- ✓ Acute haemolytic reaction: 1 in 6,000-20,000 transfusions;
- ✓ Anaphylaxis: 1 in 20,000-50,000 transfusions.

The risk of TA-GvHD remains undefined. The risk of TA-GvHD remains undefined.

Non-immunological infectious risks include bacterial contamination (1 in

500,000), HTLV-1/2 (1 in 641,000), HBV (1 in 100,000-200,000), HCV (1 in 1,000,000-2,000,000) and HIV-1/2 (1 in 2,000,000-3,000,000) [Busch et al., 2000; Suddock and Crookston, 2023].

Although these risks are relatively low, they are not negligible and may not always be predictable. Many adverse effects only become apparent after years of observation. Therefore, the fundamental principle of transfusion medicine is to administer blood and its components only when medically necessary and clinically justified, in accordance with evidence-based guidelines and patient-specific risk assessments [European Directorate for the Quality of Medicines (EDQM), 2021; International Society of Blood Transfusion (ISBT), 2022; Suddock and Crookston, 2023].

**Conclusions.** Adverse transfusion reactions can present as a wide spectrum of immune and non-immune complications, ranging in severity. They can present as anything from mild, self-limiting symptoms to life-threatening emergencies requiring intensive care. The most serious of these are acute haemolytic reactions, bacterial sepsis, transfusion-related acute lung injury (TRALI), anaphylaxis, transfusion-associated graft-versus-host disease (TA-GvHD), viral infections and circulatory overload.

Given the potential severity of these complications, it is crucial to ensure transfusion safety through early recognition, proper classification, and haemovigilance. Prompt identification of symptoms and immediate intervention can significantly reduce the morbidity and mortality associated with transfusion reactions. Standardised reporting systems and continuous education of healthcare personnel can also enhance the effectiveness of haemovigilance programmes.

In light of these risks, blood and its components should only be used under strictly justified medical indications based on evidence-based guidelines and individual patient assessment. Adhering to this principle helps minimise the potential for harm and ensures that transfusion therapy remains a safe and effective intervention.

## ОСОБЛИВОСТІ ЛАБОРАТОРНОЇ ДІАГНОСТИКИ ЛЕЙКЕМОЇДНИХ РЕАКЦІЙ КРОВІ

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**Вступ.** Лейкемоїдні реакції (ЛР) – це реактивні, оборотні зміни кровотворення, що морфологічно імітують лейкози, але не мають клонального характеру. Вони виникають у відповідь на дію інфекційних, токсичних, запальних, алергічних або гіпоксичних факторів і зникають після усунення

причини. Проблема полягає у складності диференціації ЛР від хронічних мієлопроліферативних процесів, адже ці стани супроводжуються лейкоцитозом, «лівим» зсувом і морфологічними змінами лейкоцитів.

Своєчасна лабораторна діагностика лейкемоїдних реакцій має надзвичайне клінічне значення, оскільки дозволяє уникнути хибного діагнозу лейкозу та необґрунтованого призначення цитостатичної терапії.

**Мета дослідження.** Визначити діагностичну цінність основних лабораторних показників периферичної крові при різних типах лейкемоїдних реакцій та встановити критерії їх розмежування з клональними гематологічними захворюваннями.

**Матеріали та методи.** Дослідження проводилось у клініко-діагностичній лабораторії КНП «Міська студентська лікарня» Харківської міської ради. Було обстежено 3 клінічні групи пацієнтів різного профілю: 10 осіб після планових хірургічних втручань, 10 хворих на COVID-19 та групу (10 пацієнтів) здорових осіб віком 17-25 років. Критеріями включення у дослідження були: підтверджений клінічний діагноз (для основних груп), відсутність ознак тяжкої генералізованої інфекції або онкогематологічного процесу, а також добровільна згода на участь у дослідженні. Дослідження виконували із застосуванням загального аналізу крові з ручним підрахунком лейкоцитарної формули, мікроскопії мазків крові, визначення активності лейкоцитарної лужної фосфатази та концентрації вітаміну В<sub>12</sub>. Для автоматизованого підрахунку формених елементів використовувався гематологічний аналізатор H18 Light, 3-Diff. Отримані дані зіставлялися з клінічними показниками та результатами біохімічних досліджень (ШОЕ, CRP) для комплексної оцінки стану пацієнтів.

**Результати та обговорення.** Проведений аналіз дозволив виявити низку закономірностей у формуванні лейкемоїдних реакцій різних типів.

В групі пацієнтів після лапароскопічних операцій переважали нейтрофільні лейкемоїдні реакції. Лейкоцитоз сягав  $11-18 \times 10^9/\text{л}$ , кількість нейтрофілів – 78-91%, в мазку крові спостерігалися поодинокі паличкоядерні та метамієлоцити, токсична зернистість, підвищення ШОЕ було до 40-48 мм/год. Ці зміни відображали реактивну стимуляцію гранулоцитарного ростка після операційної травми, а при ускладненнях (кровотеча, гостра ниркова недостатність) реакції були більш вираженими. Нормалізація показників відбувалась на 3-5 добу, що підтверджує оборотний характер ЛР.

У пацієнтів із COVID-19 визначались нейтрофільні реакції з вираженим «лівим» зсувом, появою мієлоцитів і токсичною зернистістю нейтрофілів. Рівень лейкоцитів досягав  $20-45 \times 10^9/\text{л}$ , CRP (С-реактивний білок) – 90-150 мг/л, часто



відзначався тромбоцитоз понад  $450 \times 10^9/\text{л}$  та гіпохромна анемія. У тяжких випадках реакція була короткочасною, але різко вираженою, що відображало цитокіновий шторм і системне запалення. Після стабілізації стану кількості лейкоцитів та морфологія крові поступово нормалізувались, що підтверджує реактивний, неонкогенний характер процесу.

У здорових осіб реєструвалися показники крові в межах норми, у 2 пацієнтів був виявлен лейкоцитоз до  $11-12 \times 10^9/\text{л}$  без значного морфологічного зсуву, у 1 пацієнта – помірна еозинофілією (6-8%), що відображало реакцію організму на стрес або незначне запалення.

Визначення активності лейкоцитарної лужної фосфатази (ЛЛФ) і рівня вітаміну  $B_{12}$  мало високу діагностичну цінність: підвищена або нормальна активність ЛЛФ і відсутність клональних цитогенетичних аномалій чітко відмежовували реактивні процеси від хронічного мієлолейкозу, при якому ЛЛФ знижена, а рівень  $B_{12}$  різко підвищений. Морфологічна оцінка мазків крові з виявленням токсичної зернистості, вакуолізації цитоплазми, а також динамічне спостереження за кровотворенням підтверджували тимчасовий характер реакції.

Таким чином, комплексне застосування морфологічних, біохімічних і цитогенетичних методів забезпечує високу точність діагностики лейкемоїдних реакцій, дозволяючи диференціювати їх із клональними гематологічними процесами.

**Висновки.** Лейкемоїдні реакції є реактивними оборотними змінами кровотворення, що виникають у відповідь на інфекційні, токсичні, стресові та фізіологічні впливи. Найчастіше зустрічаються нейтрофільні реакції, які супроводжуються підвищенням кількості лейкоцитів, «лівим» зсувом формули, токсичною зернистістю нейтрофілів і підвищенням ШОЕ. Диференційно-діагностичними критеріями є підвищення активності ЛЛФ, нормальний рівень  $B_{12}$  та відсутність бластних клітин і цитогенетичних аномалій. Вчасна лабораторна діагностика ЛР запобігає хибному встановленню лейкозу й сприяє правильному веденню пацієнтів різних клінічних груп.



## ЕКСПЕРИМЕНТАЛЬНЕ ОБҐРУНТУВАННЯ МУЛЬТИМОДАЛЬНОЇ КОМБІНАЦІЇ КЕТОПРОФЕНУ З ЦЕНТРАЛЬНИМИ АД'ЮВАНТАМИ

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**Вступ.** Мультимодальна аналгезія (ММА) – цілеспрямоване поєднання препаратів із різними механізмами дії та/або регіонарних методик, що на сьогодні є стандартом опіоїд-збережувальної тактики. При цьому центральну роль займають нестероїдні протизапальні засоби (НПЗЗ), адже вони пригнічують периферичну й частково центральну простагландин-опосередковану сенситизацію та достовірно зменшують потребу у застосуванні опіоїдів (O'Neill, A., et al, 2022).

Кетопрофен – пропіоновий НПЗЗ із широким спектром пероральних та ін'єкційних форм, широко використовується як компонент ММА. Рандомізовані дослідження засвідчують, що включення кетопрофену до комбінованих режимів (зокрема з парацетамолом, нефопамом) знижує післяопераційне споживання морфіну й інтенсивність болю при абдомінальних операціях (Beloeil, H. et al, 2019).

**Мета.** дослідити й обґрунтувати ефективність мультимодальних комбінацій кетопрофену з центральними ад'ювантами (габапенти (ГАБ), прегабалін (ПРЕГ), амітриптилін (АМІ), кетамін (КТМ), дексметомедин (ДММ) для підсилення анальгезії в моделі гострого вісцерального болю в експерименті.

**Матеріали та методи.** Дослідження виконано на 56 статевозрілих самцях білих мишей (28-32 г), яких утримували у стандартизованих умовах віварію (22±2°C, цикл 12/12, харчування й вода ad libitum). Ноцицепцію моделювали тестом «оцтово-кислі корчі» (0,75% оцтова кислота, 0,1 мл/10 г, внутрішньоочеревинно, з фіксацією кількості корчів протягом 20 хв) (Mamin-Or-Rashid M. et al, 2017). Тварин рандомізовано на 8 груп (n=7) відповідно до засобу знеболення: інтактний контроль; морфін 6,2 мг/кг; кетопрофен (КЕТ) 35,1 мг/кг; комбінації КЕТ з габапентином 393,6 мг/кг, прегабалином 65,8 мг/кг, амітриптиліном 19,7 мг/кг, кетаміном 8,0 мг/кг або дексметомідіном

0,01 мг/кг. Дослідження проводились відповідно до Закону України, Директиві 2010/63/EU, Європейській конвенції (1986), наказам МОЗ/МОН та ARRIVE 2.0 (2020). Статистична обробка включала: t-критерій Ст'юдента або U-критерій Манна-Вітні (за типом розподілу), для повторних вимірювань використано Т-критерій Вілкоксона. Дані подано як  $M \pm m$  (або  $M \pm SE$ ) чи  $Me [LQ; UQ]$ , за потреби – з 95% ДІ.

**Результати та обговорення.** У групі пасивного контролю зафіксовано  $53,4 \pm 1,6$  «корчів» (95% ДІ: 50,3-6,6). КЕТ зменшив показник до  $27,9 \pm 2,3$  (23,4-32,3), тобто на 47,9 % відносно контролю ( $p < 0,001$ ). Комбінації з центральними ад'ювантами демонстрували наступні результати: КЕТ+ГАБ –  $24,7 \pm 2,5$  (95% ДІ: 19,8-29,7), ефективність вище на 53,7% у порівнянні з контролем; КЕТ+ПРЕГ –  $22,1 \pm 2,7$  (95% ДІ: 16,9-27,4) на 58,6% ефективніше за контроль; КЕТ+АМІ –  $23,3 \pm 3,7$  (95% ДІ: 16,0–30,6) на 56,4% анальгетична дія вища за контроль; КЕТ+КТМ –  $18,0 \pm 3,0$  (95% ДІ: 12,2–23,8) 66,3% різниця з контрольною групою; КЕТ+ДММ –  $16,4 \pm 2,0$  (95% ДІ: 12,5–20,4) 69,3% різниці з групою інтактного контролю. Порівняно з монотерапією КЕТ, статистично значуще посилення нальгетичної дії продемонстровано для груп КЕТ+КТМ ( $p < 0,001$ ) і КЕТ+ДММ ( $p = 0,003$ ), для комбінації з ГАБ/ПРЕГ/АМІ спостерігалась тенденція без досягнення статистичної значущості.

**Висновки.** Додавання ад'ювантів центральної дії до кетопрофену підсилює анальгезію у моделі гострого вісцерального болю. Найбільший ефект отримано при комбінації з кетаміном і дексмедетомідом. Результати експериментально підтверджують доцільність мультимодальних комбінацій «периферичний НПЗЗ + центральний ад'ювант» для подальшої трансляції та клінічної валідації.

**Ключові слова:** кетопрофен, мультимодальна анальгезія, ад'ювантні анальгетики, габапентин, прегабалін, амітриптилін, кетамін, дексмедетомідин, тест оцтових «корчів», вісцеральний біль, миші.

## МІЖВИДОВЕ ПОРІВНЯННЯ ВПЛИВУ ТРИФТОРПЕРАЗИНУ НА ЕРИТРОЦИТИ ЗА УМОВ ПОСТГІПЕРТОНІЧНОГО ШОКУ

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**Вступ.** Наразі в Україні гостро постає проблема недостатніх запасів донорської крові як для потреб цивільного населення, так і для військових. Одним із шляхів вирішення цієї проблеми є кріоконсервування еритроцитів при

низьких і наднизьких температурах під захистом гліцерину, що дає змогу зберігати їх у придатному стані до 10 років.

Однак на етапах заморожування, розморожування та видалення внутрішньоклітинного гліцерину спостерігається значне руйнування еритроцитів унаслідок дії кріопошкоджувальних факторів. Постгіпертонічний шок (ПГШ) застосовують як експериментальну модель одного з провідних факторів кріопошкодження, що імітує осмотичні зміни, які відбуваються в еритроцитах під час розморожування кріоконсервованої крові та видалення гліцерину з клітин.

Раніше було показано, що хлорпромазин – антипсихотичний препарат із групи фенотіазинових похідних, широко відомий у фармакології та клінічній медицині, – здатний знижувати ступінь ушкодження еритроцитів ссавців під впливом різноманітних стресових чинників. Зокрема, встановлено його захисну дію за умов гіпертонічного шоку, гіпертонічного кріогемолізу та постгіпертонічного шоку.

Трифторперазин (ТФП) – лікарський засіб тієї ж фармакологічної групи, що й хлорпромазин, і належить до піперазинових похідних фенотіазину. Завдяки подібності хімічної структури та потенційній мембраностабілізуючій активності, ТФП становить інтерес як можливий модулятор стійкості еритроцитарних мембран за умов осмотичного стресу. У зв'язку з цим доцільним є дослідження впливу ТФП на розвиток ПГШ еритроцитів ссавців, результати якого можуть сприяти глибшому розумінню механізмів кріопошкодження та вдосконаленню методів кріоконсервування клітин крові.

**Мета дослідження.** Провести порівняльне вивчення дії трифторперазину на еритроцити людини, кролика та щура в умовах постгіпертонічного шоку з метою оцінки міжвидових відмінностей у його ефективності.

**Матеріали та методи.** Постгіпертонічний шок еритроцитів ссавців здійснювали шляхом ізотермічного перенесення клітин з середовища дегідратації (1,65 моль/л NaCl) в середовище регідратації (0,15 моль/л NaCl) за температури 37 або 0°C. Тривалість інкубування еритроцитів в середовищах дегідратації становило 20 хв, регідратації – 5 хв. ТФП додавали до середовища регідратації безпосередньо перед внесенням еритроцитів. Рівень гемолізу визначали спектрофотометрично ( $\lambda = 543$  нм). Для оцінювання та порівняння ефективності ТФП за умов ПГШ еритроцитів з отриманих концентраційних залежностей були визначені розміри плато, обчислені ефективні концентрації і розраховані величини максимальної антигемолітичної активності.

**Результати та обговорення.** Отримані дані експериментального

дослідження вказують на видові особливості прояву постгіпертонічного гемолізу еритроцитів ссавців. За температури 0°C рівень гемолізу у еритроцитів людини, кролика та щура практично не відрізнявся і становив 60–70%. Водночас за температури 37°C були виявлені статистично значущі міжвидові відмінності рівня постгіпертонічного гемолізу: у еритроцитів людини він становив приблизно 70%, кролика – близько 40%, а щура – 80%. Отже, результати свідчать про вищу стійкість еритроцитів кролика та, відповідно, про підвищену чутливість клітин щура до дії ПГШ за температури 37 °C.

Проведення ПГШ еритроцитів ссавців за температури 37°C в присутності ТФП на етапі регідратації показало, що даний препарат проявляє літичну дію на клітини всіх досліджуваних видів ссавців. Натомість за температури 0°C ТФП, навпаки, значно знижував рівень постгіпертонічного гемолізу еритроцитів. Розрахована максимальна антигемолітична активність ТФП становила для еритроцитів людини 60%, кролика – 55%, а щура – 85%. Ймовірно, виявлені відмінності у чутливості клітин до ПГШ зумовлені структурними та біохімічними особливостями мембран еритроцитів досліджувальних видів ссавців.

**Висновки.** Таким чином, у роботі продемонстровано видові особливості прояву постгіпертонічного гемолізу еритроцитів різних видів ссавців. Порівняно з отриманими показниками рівня гемолізу за температури 37°C еритроцити щура виявились найбільш чутливими, тоді як клітини кролика – найстійкішими до дії ПГШ. Виявлено, що ТФП проявляє максимальну антигемолітичну активність за умов ПГШ еритроцитів у такій послідовності для досліджених видів: щур > людина > кролик.

Відомо, що ТФП як позитивно заряджена амфіфільна молекула переважно вбудовується в клітинну мембрану та взаємодіє з негативно зарядженими фосфоліпідами, які здебільшого локалізовані у внутрішньому моношарі мембрани. Згідно з літературними даними, еритроцитарна мембрана щура характеризується вищим вмістом аніонних фосфоліпідів (29,5%) порівняно з клітинами кролика (16,9%). Однак, за сумарним вмістом аніонних фосфоліпідів еритроцитарна мембрана щура не відрізняється від мембрани клітин людини. Отже, можна припустити, що місця зв'язування молекул ТФП у мембрані не обмежуються лише негативно зарядженими фосфоліпідами, а можуть включати інші компоненти ліпідного або білкового походження, які визначають специфіку взаємодії препарату з клітинною мембраною різних видів ссавців.



## АКТУАЛЬНІСТЬ ВИЗНАЧЕННЯ ПОКАЗНИКІВ ЛЕЙКОЦИТАРНОЇ ФОРМУЛИ В ЛАБОРАТОРНІЙ МЕДИЦИНІ

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**Вступ.** Лейкоцити – це білі кров'яні клітини, які є частиною імунної системи та захищають організм від інфекцій, знешкоджуючи бактерії, віруси та інші патогени. Вони також допомагають у боротьбі зі збудниками інфекційних процесів, раковими клітинами, усуненні мертвих клітин та регулюють інтенсивність запальних процесів та активність відповіді імунної системи. Переміщаючись по кровотоку і тканинах, лейкоцити виявляють вогнище інфекції і передають інформацію іншим клітинам імунної системи, які знищують патогени. Кількість лейкоцитів може змінюватися залежно від стану організму, і значне підвищення (лейкоцитоз) або зниження (лейкопенія) може свідчити про наявність захворювань.

Щоб вчасно помітити, що імунна система працює не так, як треба, лікарі часто призначають загальний аналіз крові з підрахунком лейкоцитарної формули. Саме він допомагає не просто виявити запальний або інфекційний процес в організмі, а й зрозуміти його характер, оцінити стан захисних клітин та навіть визначити певні серйозні патології ще до появи симптомів. При проведенні загального аналізу крові досліджують загальну кількість лейкоцитів та проводять підрахунок лейкоцитарної формули крові для кожного хворого. Аналіз тільки загальної кількості лейкоцитів дає обмежену інформацію. Набагато важливіше розуміти, які саме види цих клітин переважають в даний момент часу. Кожен тип лейкоцитів спеціалізується на певних завданнях, і зміна їх співвідношення може вказувати на конкретні патологічні процеси, саме тому важливим є підрахунок лейкоцитарної формули.

Лейкоцитарна формула – це співвідношення різних типів лейкоцитів у крові, яке дозволяє оцінити стан імунної системи та виявити запальний процес і встановити його характер. У результатах лейкоцитарної формули спочатку оцінюються дві групи лейкоцитів: гранулоцити (нейтрофіли, базофіли та еозинофіли) та агранулоцити (моноцити та лімфоцити), оцінюючи кількість всіх п'яти основних видів лейкоцитів.

**Мета дослідження.** Аналіз мікроскопічного та автоматичного методу підрахунку лейкоцитарної формули в роботі лікаря-лаборанта, які щоденно виконуються в клініко-діагностичній лабораторії.

Оцінка морфології лейкоцитів – це найважливіший результат дослідження, також дуже важливою складовою є оцінка якісних змін різних морфології різних видів лейкоцитів (поява нейтрофілів з гіперсегментованими ядрами, токсигенна зернистість, вакуолізація цитоплазми, поява бластних форм лейкоцитів). Лабораторна оцінка саме цих змін дає діагностичне та прогностичне значення про стан кровотворення у кожного пацієнта.

**Матеріали та методи.** Мікроскопічний аналіз мазка крові залишається золотим стандартом у складних діагностичних випадках. Техніка передбачає візуальну оцінку забарвленого препарату під мікроскопом з підрахунком 100-200 клітин. Лікар-лаборант може виявити тонкі зміни морфології при проведенні мікроскопічного дослідження, цей метод є незамінним при виявленні патологічних клітинних форм, при підозрі на гематологічні захворювання – лейкомії та лімфоми. При підрахунку клітин крові на гематологічному автоматичному аналізаторі визначають два види показників: процентне співвідношення різних видів лейкоцитів (відносні значення) й їх абсолютна кількість в одиниці об'єму крові (клітин/л). Сучасні апарати здатні розрізняти до 5 популяцій лейкоцитів, включаючи нейтрофіли, лімфоцити, моноцити, еозинофіли і базофіли. Деякі моделі додатково виділяють фракції незрілих гранулоцитів і атипичних лімфоцитів.

**Результати та обговорення.** Автоматичний підрахунок лейкоцитарної формули – це стандарт в роботі усіх клініко-діагностичних лабораторій. Основна перевага автоматичного підрахунку – висока швидкість обробки зразків (до 100 проб на годину) і відмінна відтворюваність результатів. Аналізатори виключають суб'єктивний фактор, неминучий при ручній мікроскопії. Однак є нюанси – необхідно додатково проводити оцінку результатів дослідження, при наявності в крові незвичайних клітинних форм або значних патологічних змін морфології клітин.

**Висновки.** Оцінка лейкоцитарної формули – це не лише підрахунок клітин, а й дослідження їхнього дозрівання. У нормі в крові переважають зрілі клітини, але іноді організм починає активно виробляти молоді форми лейкоцитів або, навпаки, припиняє. Цей процес називається зсувом лейкоцитарної формули. Він буває вліво або вправо, залежно від того, які клітини переважають – молоді чи надто зрілі. Це важливий маркер, який допомагає визначити стадію та характер запального процесу. Автоматичний і ручний методи не конкурують, а доповнюють один одного. Аналізатори забезпечують швидкий і стандартизований скринінг, в той час як мікроскопія дає можливість поглибленого вивчення складних випадків. У рутинній практиці оптимальним

підходом вважається комбінація методів – автоматичний аналіз всіх проб з подальшою мікроскопією зразків, що мають відхилення за певними критеріями (правила верифікації). Вибір методу залежить від конкретної клінічної ситуації. Для планового обстеження здорових людей зазвичай достатньо автоматичного аналізу. При наявності симптомів, підозрілих на захворювання крові, або незвичайних результатах автоматичного підрахунку мікроскопія стає обов'язковою. Оцінку результатів лабораторних досліджень проводить тільки лікуючий лікар, саме він є фахівцем в питаннях діагностики та лікування пацієнта.

## МІСЦЕ ГЕМОЛІТИЧНИХ АНЕМІЙ В ЛАБОРАТОРНІЙ МЕДИЦИНІ

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**Вступ.** До гемолітичних анемії відносять велику групу анемії, які характеризуються прискоренням швидкості руйнування червоних кров'яних тілець (гемолізом) в кровоносних судинах чи судинному просторі системи мононуклеарних фагоцитів.

Термін життя еритроцитів становить приблизно 120 днів. Після цього вони руйнуються в селезінці, печінці та кістковому мозку, а нові клітини утворюються в червоному кістковому мозку, щоб підтримувати необхідну концентрацію кисню в організмі.

При гемолітичних анеміях термін життя еритроцитів значно скорочується, зазвичай до 14-20 днів, що призводить до зниження їхньої життєздатності, при даному виді анемії руйнування еритроцитів перевищує компенсаторні можливості еритропоезу. За етіологією гемолітичні анемії поділяються на спадкові та набуті. Серед причин розвитку гемолітичної анемії слід зазначити такі чинники спадкового характеру: спадковий сфероцитоз та еліптоз мембран еритроцитів, недостатність ферментних систем, вроджені порушення синтезу гемоглобіну, аномальна структура гемоглобіну.

Серед причин появи гемолітичної анемії можуть такі неспадкові (набуті) чинники: інфекційні та аутоімунні захворювання, переливання несумісної крові, вплив токсичних та отруйних речовин, значні опіки. Спадкові форми, як правило, виявляються в молодшому віці, аутоімунні частіше зустрічаються в середньому і старшому віці (даний вид анемії зустрічається частіше). Гемолітичні анемії актуальні через високий ризик небезпечних для життя

ускладнень, таких як серцева, ниркова або печінкова недостатність, інфаркт селезінки та гемолітична кома. Під час гемолітичних кризів руйнування еритроцитів відбувається особливо інтенсивно, що може призвести до різкого загострення симптомів та ускладнень, в клінічній практиці важливе місце має гемолітична хвороба новонароджених, яка виникає через несумісність групи крові або резус-фактора матері та дитини.

**Мета дослідження.** Аналіз актуальності гемолітичних анемій в загальній структурі анемій, значення показників клінічного аналізу крові, клінічного аналізу сечі для своєчасної діагностики даного виду анемій.

**Матеріали та методи.** З метою досягнення цілей дослідження було проведено аналіз сучасних літературних наукових джерел та наведено клінічні ознаки, показники периферичної крові, дані клінічного аналізу сечі, з метою раннього виявлення патології.

**Результати та обговорення.** Першочерговими дослідженнями при даній патології є: загальний аналіз крові із кількістю тромбоцитів, ретикулоцитів, показник швидкості зсідання еритроцитів та рівень білків гострої фази запалення. В разі первинної діагностики в периферичній крові має місце різко виражена нормохромна анемія, при якій рівень гемоглобіну знижується до 50-70 г/л, при гемолітичному кризі рівень гемоглобіну – ще нижчий, високий ретикулоцитоз (при нормі – 0,5-1,5%), мікросфероцитоз, зруйновані еритроцити, лейкоцитоз. Визначають зниження осмотичної резистентності еритроцитів. В клінічному аналізі сечі виявляють уробілінурію, при кризі – протеїнурію, циліндрурію, також проводять біохімічне дослідження крові, в якому визначають високий рівень непрямого білірубіну та сироваткового заліза, високі показники тимолової проби, частіше, позитивну пряму пробу Кумбса. При даній патології показані також вивчення морфології клітин крові і дослідження кісткового мозку.

**Висновки.** Гемолітичні анемії – це велика група захворювань, що відрізняються за етіологією, патогенезом, клінічною картиною, методами лікування, головною ознакою яких є підвищений розпад еритроцитів та скорочення тривалості їх життя, необхідною є своєчасна діагностика та індивідуальний підхід до лікування, залежно від першопричини та механізму руйнування еритроцитів.



## АКТУАЛЬНІСТЬ ПАРАЗИТАРНИХ ІНВАЗІЙ В ЖИТТІ ЛЮДИНИ

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**Вступ.** За даними Всесвітньої організації охорони здоров'я (ВООЗ) за останні 10 років у світі на паразитарні інвазії захворіли більше ніж 4,5 млрд людей, згідно даних літературних джерел в Україні кількість інвазійних може досягати 5 млн. Дана статистика охоплює не тільки бідні й неблагополучні країни «третього світу», але й розвинені країни Європи, де паразитарні інвазії значно розповсюджені. Характерною особливістю збудників інвазій є специфічність. Багато паразитів трапляються лише в людини, і джерелом цих інвазій завжди є людина. Такі специфічні паразити людини спричиняють інвазійні захворювання, що називаються антропонозними. Особливість таких інвазій – здатність збудника тривалий час існувати в організмі людини й спричиняти повторне зараження. Частина збудників інвазій трапляються у тварин, але можуть уражати й людину (наприклад, печінковий сисун, блохи, воші, кліщі). Джерелом інвазії у цих випадках є зазвичай тварини. Такі захворювання називаються зоонозними. Паразити вражають практично всі органи й тканини людини. Наприклад, у кишечнику паразитують аскариди, гострики, бичачий ціп'як, широкий стьожак, лямблії, амеби, трихомонади; у жовчних шляхах – печінковий і сибірський сисуни, лямблії; у підшкірно-жировій клітковині – збудник ришти, у м'язах – личинки трихінел, у кровоносних судинах – шистосоми; у центральній нервовій системі – токсоплазми; у легенях – аскариди, пневмоцисти та інші збудники. Паразити викликають сенсibiliзацію організму з наступним розвитком алергічних реакцій, механічне ушкодження органів і тканин хазяїна, значне порушення їхніх функцій, різні запальні процеси, анемію. Вони погіршують всмоктування харчових речовин і вітамінів, виснажують імунну систему знижують резистентність організму, отруюють його продуктами своєї життєдіяльності, обтяжують плин інших захворювань. Личинкові стадії більшості гельмінтів здатні мігрувати в різні тканини, вражаючи легені, серце, головний мозок, очі, м'язи та кістки, що в свою чергу призводить до незворотних наслідків, зокрема сліпоті, епілептичних нападів, слабоумства, ураження внутрішніх органів, а іноді й до летального результату. Особливо значно паразити впливають на організм дитини. В організмі хворої дитини часто виникають неврологічні порушення: діти стають примхливими, збудливими, швидко втомлюються, погано засинають. Також характерним є



виникнення або посилення проявів алергічного діатезу, кишкового дисбактеріозу, що значно сприяє розвитку кишкових інфекцій.

**Мета дослідження.** Навести дані про актуальність паразитарних інвазій в загальній структурі захворюваності населення та навести необхідність проведення профілактичних заходів в боротьбі з ними.

**Матеріали та методи.** З метою досягнення цілей дослідження було проведено аналіз сучасних літературних наукових джерел та наведено методи профілактики паразитарних інвазій людини.

**Результати та обговорення.** Зважаючи на складну ситуацію з паразитарними хворобами у всьому світі, виникає гостра потреба якомога більше знати про збудників паразитарних захворювань, знайомитись з медичними статтями, даними Центру громадського здоров'я МОЗ України, де наведені дані про розповсюдженість паразитів на різних територіях, означені особливості їх життєвих циклів та шляхами зараження людини паразитами. Шляхи проникнення паразита в організм людини можуть бути різними. Наприклад, через рот (перорально) проникають цисти дизентерійної амеби, яйця аскариди, гострики, фіни ціп'яків, личинкові стадії сисунів, можливе зараження статевим шляхом (трихомонади), трансплацентарний шлях зараження характерний для токсоплазми.

**Висновки.** Паразитарні інвазії поширені повсюдно. Значне поширення тропічних хвороб зумовлені тим, що значно змінюється клімат. Так, значні посухи та зменшення природних водойм призводять до того, що збільшується концентрація інвазійного збудника і підвищується імовірність зараження людини, в даних регіонах під час сезону дощів змиваються нечистоти з поверхні ґрунту у водойми. Низький рівень санітарної культури населення в бідних країнах, низький рівень медичної інформованості населення, відсутність доброякісної води та їжі, забруднення територій, на яких проживає місцеве населення є чинниками, що сприяють високому рівню захворюваності на паразитарні інвазії. Профілактика інвазійних захворювань – це сукупність методів, способів та заходів, що запобігають зараженню й розвитку паразитарних захворювань. Основними напрямками захисту від інвазій є гігієнічні заходи, ветеринарно-санітарний нагляд, санітарно-просвітницька робота тощо. Також значущими є наступні методи профілактики, серед яких є біологічні, хімічні, імунологічні, соціальні та заходи особистої профілактики. Біологічні методи боротьби зі збудниками інвазій спрямовані на використання природних ворогів, речовин, що впливають на поведінку або розмноження, лікарських рослин. Хімічні методи (хіміопротекція) передбачають

використання антипаразитарних засобів, щоб запобігти захворюванням людини та позбавити організм збудників. Соціальні методи спрямовані на дотримання правил особистої та громадської гігієни. Вирішальне значення має своєчасне лікування інвазій. Найефективнішим заходом профілактики інвазій є необхідність уникнення джерел інвазії, елементарне дотримання правил особистої гігієни (миття рук перед вживанням їжі, після відвідування місць загального користування та спілкування з домашніми тваринами), стимулювання імунітету, що перешкоджає міграції паразитів в організмі хворого, знижує ймовірність аутоінвазій та виникнення повторного зараження.

## **ЛАБОРАТОРНА ОЦІНКА КЛІНІЧНОГО АНАЛІЗУ СЕЧІ**

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**Вступ.** Лабораторне дослідження стану сечовидільної системи є базовим при обстеженні організму хворих з патологією нирок і сечовивідних шляхів, оцінці ступеню тяжкості захворювання, контролю перебігу патології та ефективності лікування пацієнтів з даною патологією. Нирки – головний фільтр нашого організму. Їх надважлива функція полягає у тому, щоб забезпечити збереження максимальної кількості води, але одночасно профільтрувати всі ті речовини, які повинні бути виведені з організму. Таким чином, безперервно фільтруючи рідину, нирки рятують організм від продуктів напіврозпаду і токсинів, які отруюють його, беруть участь в регуляції водно-сольового балансу та кров'яного тиску, процесах кровоутворення, кальцієвому обміні та ендокринній регуляції.

**Мета дослідження.** Навести провідну роль клінічного аналізу сечі – як базового лабораторного для ранньої та своєчасної діагностики патологічних змін сечовидільної системи.

**Матеріали та методи.** З метою досягнення цілей дослідження надано лабораторну оцінку складових характеристик клінічного аналізу сечі, як провідного лабораторного дослідження в оцінці патології нирок.

**Результати та обговорення.** Відомо, що сеча утворюється в нирках шляхом фільтрації плазми крові з подальшою реабсорбцією води, електролітів, глюкози та інших речовин, тому саме клінічний аналіз сечі проводять з метою встановлення першочергових змін в оцінці патології нирок та сечовидільної системи, як дослідження, що призначається хворому при первинному зверненні

до сімейного лікаря. Клінічний аналіз сечі включає в себе оцінку трьох груп параметрів – фізичних, хімічних та мікроскопічних характеристик з метою оцінки функціональних змін. На початкових стадіях більшість захворювань нирок мають прогресуючий перебіг та досить часто лишаються малопомітними для пацієнта. Відсутність проявів хвороби та явного погіршення самопочуття, як правило вводить в оману пацієнта та призводить до втрати цінного часу для уповільнення прогресування незворотних змін ниркової тканини.

**Висновки.** Важливо також усвідомлювати, що ризики порушень функції нирок можуть зростати через цукровий діабет, гіпертонічну хворобу та власне захворювання нирок. Показники клінічного аналізу сечі є гарантією не лише здоров'я, а й якості життя. Інформованість хворого про стан нирок допоможе прийняти відповідальні рішення щодо способу життя і профілактики захворювань, запобігти розвитку незворотних ускладнень.

## **АКТУАЛЬНІ ПИТАННЯ ПОТОВОЇ ПРОБИ ЯК «ЗОЛОТОГО СТАНДАРТУ» ДІАГНОСТИКИ ПРИ МУКОВІСЦИДОЗУ**

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**Вступ.** Потова проба на муковісцидоз є актуальним, необхідним і невід'ємним етапом діагностики в сучасній медицині 2025 року, особливо у поєднанні з іншими методами дослідження для однозначного встановлення діагнозу. Муковісцидоз належить до найпоширеніших генетичних патологій, що зумовлює порушення секреції екзокринних залоз і призводить до ураження дихальної, травної та репродуктивної систем. Своєчасне виявлення захворювання є вирішальним чинником для підвищення ефективності лікування та поліпшення прогнозу життя. Попри розвиток молекулярно-генетичних технологій, потова проба і надалі вважається провідним («золотим») методом підтвердження діагнозу завдяки своїй доступності, достовірності та стандартизованій методиці.

**Мета дослідження.** Визначити значення потової проби у сучасній діагностиці муковісцидозу, проаналізувати її діагностичну точність і доцільність застосування у клінічній практиці. Оцінка потової проби як основного методу діагностики муковісцидозу.

**Матеріали і методи.** Для виконання дослідження було проведено аналітичний огляд сучасних наукових джерел, клінічних настанов Європейського товариства муковісцидозу та досвіду українських лабораторій.

Основою аналізу слугували результати проведення пілокарпін-іонофорезу (метод Гібсона-Кука) та автоматизованих систем збору поту, які нині активно впроваджуються у медичних закладах.

**Результати і висновки.** Результати аналізу свідчать, що потова проба має високі показники діагностичної точності: чутливість понад 95% і специфічність близько 98%, що дозволяє вважати її надійним еталоном діагностики.

У більшості лабораторій концентрація хлоридів у поті понад 60 ммоль/л підтверджує наявність муковісцидозу, показники у межах 40-59 ммоль/л розцінюються як прикордонні та потребують подальших досліджень.

Використання автоматизованих систем збору поту дозволяє зменшити ймовірність технічних похибок і полегшує діагностику у новонароджених.

Додатково встановлено, що результати потової проби корелюють із клінічними проявами захворювання – частотою легеневих інфекцій, рівнем маси тіла та функціональними показниками зовнішнього дихання. Це підкреслює не лише її діагностичну, а й прогностичну цінність. Серед переваг методу – відносна простота виконання, невисока вартість, відсутність інвазивного втручання та можливість повторного контролю ефективності лікування.

**Висновки.** Таким чином, потова проба залишається незамінним компонентом діагностичного алгоритму муковісцидозу, забезпечуючи точне, швидке й економічно обґрунтоване підтвердження хвороби. Вона зберігає статус «золотого стандарту» навіть за умов впровадження нових генетичних технологій.

## ПЕРСПЕКТИВИ ЗАСТОСУВАННЯ БІОХІМІЧНИХ МЕТОДІВ В ДІАГНОСТИЦІ ТОКСОКАРОЗУ

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**Вступ.** Токсокароз – зоонозне гельмінтозне захворювання, спричинене личинками нематод роду *Toxocara* (*T. canis*, *T. cati*), яке становить серйозну загрозу для здоров'я людини, особливо дітей. За даними ВООЗ, серопревалентність у світі коливається від 5% у розвинених країнах до 80% у тропічних регіонах. Клінічна картина варіабельна (вісцеральна, окулярна, неврологічна, прихована форми), що ускладнює діагностику. Традиційні методи (мікроскопія фекалій, біопсія) малоефективні через міграцію личинок і відсутність статевозрілих форм у людини. Імунологічні тести (ІФА з

екскреторно-секреторним антигеном TES) мають високу чутливість (78-90%), але низьку специфічність через перехресні реакції з іншими гельмінтами (*Ascaris*, *Trichinella*). Біохімічні методи діагностики відкривають нові перспективи завдяки прямому виявленню метаболітів паразита, ферментів або ДНК/РНК у біологічних рідинах.

**Метою** досліджень стало провести аналіз сучасних і перспективних біохімічних підходів до діагностики токсокарозу.

**Матеріали та методи.** Під час дослідження були використані системний та контент-аналіз (вивчення вітчизняних та іноземних публікацій щодо впливу стресу на функції організму), а також метод узагальнення (формулювання висновків).

**Результати та обговорення.** Серед сучасних біохімічних методів слід звернути увагу на:

1. Імуноферментний аналіз (ІФА) з рекомбінантними антигенами. Використання рекомбінантних білків TES-30, TES-32, TES-120 підвищує специфічність до 95 % (дослідження Fan C.-K. et al., 2015). Серед переваг слід зазначити: стандартизацію та зниження перехресних реакцій. До недоліків: потребував дорогого обладнання, неможливість диференціації активної/минулої інфекції.

2. Вестерн-блот (WB). Дозволяє ідентифікувати специфічні смуги (24-35 кДа) у сироватці. До переваг можна віднести чутливість 91%, специфічність 86% (Mohamad S. et al., 2009). Використовується як підтверджувальний тест після ІФА.

3. Молекулярно-біологічні методи (ПЛР). Реал-тайм ПЛР на основі ITS-1, ITS-2 або гена COI виявляє ДНК *Toxocara* у крові, СМР, тканинах. Чутливість 1-10 копій ДНК/реакція (Durán-Palacios J. et al., 2020). Переваги: рання діагностика, диференціація видів. Обмеження: висока вартість, потреба в лабораторіях рівня BSL-2.

Необхідність удосконалення методів діагностики токсокарозу сприяє пошуку нових можливостей використання біохімічних підходів за цією метою. Серед перспективних методів слід вказати наступні: метаболоміка та мас-спектрометрія LC-MS/MS, що надає можливість ідентифікувати специфічні метаболіти личинок (N-ацетилтирозин, таурин) у сечі та сироватці. Згідно результатів пілотних досліджень, що були проведені групою вчених під керівництвом Wu X. Встановлено, що чутливість цього методу становила 88%, а специфічність – 92%. Однією з переваг є можливість моніторингу терапії. Ще один перспективний метод дослідження – це біосенсиори та нанотехнології. В



основі цього методу є використання імуносенсорів на основі золотих наночастинок з моноклональними антитілами до TES-антигенів, що дозволяють провести експрес-діагностику (LOD 0,1 нг/мл). Дані результатів досліджень демонструють отримання результатів протягом 15 хв. Крім того, слід звернути увагу ще на протеомний аналіз 2D-PAGE + MALDI-TOF, що дозволяє виявити циркулюючі паразитарні протеази (катепсини). Дослідження на мишачій моделі (2024) показали 14 унікальних пептидів. Перспектива: створення мультиплексних панелей.

МікроРНК-профайл – це метод, що дозволяє визначити miR-21, miR-122 у плазмі як маркерів запалення та міграції личинок. Кореляція з рівнем еозинофілії ( $r=0,78$ ;  $p<0,01$ ).

Таким чином, проведений аналіз щодо застосування перспективних біохімічних методів в діагностиці токсокарозу, показав напрямки пошуку ефективної діагностики.

*Таблиця*

**Порівняльна характеристика методів**

| Метод                | Чутливість | Специфічність | Час аналізу | Вартість | Неінвазивність |
|----------------------|------------|---------------|-------------|----------|----------------|
| ІФА (TES)            | 78-90%     | 70-85%        | 3-4 год     | середня  | так            |
| WB                   | 91%        | 86%           | 6-8 год     | висока   | так            |
| ПЛР                  | 95-98%     | 99%           | 2-3 год     | висока   | частково       |
| Метаболоміка (LC-MS) | 88%        | 92%           | 24 год      | висока   | так            |
| Біосенсор            | 96%        | 94%           | <15 хв      | низька*  | так            |

Примітка: \* – при масовому виробництві

**Висновки.** Біохімічні методи діагностики токсокарозу еволюціонують від імунологічних до молекулярно-біохімічних та нанотехнологічних. Найперспективнішими є:

- комбіновані панелі (ІФА + ПЛР + метаболоміка);
- портативні біосенсори для скринінгу в ендемічних регіонах;
- неінвазивні метаболічні маркери для моніторингу.

Подальші дослідження повинні фокусуватися на стандартизації рекомбінантних антигенів, зниженні вартості ПЛР та валідації метаболічних біомаркерів у великих когортах. Інтеграція ІІІ для інтерпретації мультиомікних даних дозволить досягти діагностичної точності >98 %.

## MODIFYING EFFECT OF ZINC SUCCINATE ON HEPATOTOXICITY OF CADMIUM CHLORIDE IN EXPERIMENT ON PREGNANT RATS.

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**Introduction.** Cadmium (Cd) is a widespread toxic pollutant. It has an extremely long biological half-life (approximately 20-30 years in humans) and is stored mainly in soft tissues (primarily the liver and kidneys). Cadmium is absorbed in significant quantities from cigarette smoke, food, water and air and is known to have numerous undesirable effects for both humans and animals. An important role in the mechanism of cadmium activity is associated with its strong prooxidant properties and the ability to generate reactive oxygen species through direct action, i.e. by disrupting the electron transport chain, or indirectly, by weakening the enzymatic and non-enzymatic antioxidant barrier. Zinc (Zn) is an essential metal that plays a key role in protein structure, catalysis and regulation of their function. Moreover, zinc is a well-known inhibitor of apoptosis and cell necrosis, as zinc prevents the production of reactive oxygen species (ROS), which are described as mediators of apoptosis. Numerous studies have shown that Zn can reduce Cd toxicity.

**Aim of the study.** To experimentally determine the modifying effect of zinc succinate on the hepatotoxicity of cadmium chloride after chronic intragastric administration throughout the entire gestation period in rats.

**Materials and methods.** For embryonic research, female Wistar rats with a dated gestation period were obtained using the vaginal swab method. The test substances were administered from the first day of pregnancy. To assess the effect and determine the toxic effect of cadmium chloride, we administered a solution of cadmium chloride (at a dose of 2.0 mg/kg) to females per os daily throughout pregnancy. In the second experimental group, a combined administration of cadmium chloride (at a dose of 2.0 mg/kg) and zinc succinate (at a dose of 5.0 mg/kg) was performed. On the 13th and 19th days of pregnancy, surgical slaughter was performed. The enzymatic activity of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) was determined according to the method for determining the specified enzymes according to Reitman-Frenkel. The reliability of statistical studies was assessed using the Student's t-test.

**Results and discussion.** In pregnant female rats, which were administered cadmium chloride for 13 days, a hepatotoxic effect was observed, a sign of which was a significant increase in the activity of ALT (by 34%) and AST (by 16%) in the blood serum. In the group of combined administration of cadmium chloride and zinc

succinate, a significant decrease in the activity of these enzymes was observed almost to the control level. When cadmium chloride was administered for 19 days of the experiment, the activity of ALT significantly increased by 22% compared to the control. When combined administration of cadmium chloride and zinc succinate, a decrease in ALT activity by 19% was observed in the blood plasma of rats. When cadmium chloride was administered, we also observed an increase in the activity of AST in the blood plasma by 20%. With the combined administration of cadmium chloride and zinc succinate, we observe a decrease in AST activity in the blood plasma of rats compared to the group of individual administration of cadmium chloride and an approach of this indicator to the control.

**Conclusions.** The hepatotoxic effect of cadmium chloride was revealed, which is confirmed by an increase in the activity of the liver enzymes ALT and AST compared to the control. With the administration of the complex of cadmium chloride and zinc succinate, a decrease in the activity of ALT and AST to the control values is observed in almost all groups. Therefore, zinc succinate may have a modifying effect on the hepatotoxicity of cadmium chloride

## БІОХІМІЧНІ МЕХАНІЗМИ РЕАЛІЗАЦІЇ ПРОТИПУХЛИННОЇ ДІЇ КОРЕНЯ ІМБИРУ

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**Вступ.** Корінь імбиру (*Zingiber officinale*) вже століттями використовується в традиційній медицині як пряно-лікарська рослина. Сучасні дослідження дедалі частіше звертають увагу на його потенціал у профілактиці та лікуванні онкологічних захворювань. Так, виявлено, що активні компоненти імбиру, зокрема фенольні сполуки, такі як 6-gingerol, 6-shogaol, здатні впливати на різні сигнальні шляхи пухлинних клітин. Біохімічні механізми протипухлинної дії імбиру включають гальмування проліферації, індукцію апоптозу, автографії, зміни оксидантного статусу, інгібування ангиогенезу, метастазування тощо. Однак попри значний обсяг досліджень, остаточно не визначено всі механізми дії, їх взаємозв'язки, а також клінічну ефективність у різних типах пухлин. Тому доцільно системно викласти сучасні дані про біохімічні механізми дії імбиру в контексті пухлинної патології.

**Мета дослідження.** Узагальнити сучасні наукові дані щодо біохімічних механізмів протипухлинної дії кореня імбиру та його активних компонентів. Виділити ключові сигнальні шляхи, ферментні та молекулярні мішені, на які

впливає імбир. Оцінити перспективи застосування імбиру як допоміжного засобу в онкологічній терапії та визначити існуючі прогалини у знаннях.

**Матеріали та методи.** Для підготовки тез проведено огляд літератури в міжнародних рецензованих виданнях та базах даних (наприклад, PubMed, PMC) за ключовими словами: «ginger anticancer mechanisms», «6-gingerol apoptosis cancer cells», «ginger extract cell cycle arrest cancer», «Zingiber officinale signaling pathways cancer». Відібрані джерела переважно охоплюють останні 5–10 років і включають як *in vitro*, так і *in vivo* дослідження. Наприклад, систематичний огляд присвячений дії імбиру при колоректальному раку.

**Результати та обговорення.** Дослідження демонструють, що активні сполуки імбиру здатні викликати блокування клітинного циклу пухлинних клітин. Наприклад, 10-gingerol затримує клітини раку шийки матки у фазі G0/G1. Інше дослідження показало, що 6-gingerol і 6-shogaol знижують проліферацію колонних ракових клітин HCT116 шляхом пригнічення лейкотрієну A4 гідролази. Отже, один із механізмів є інгібування сигнальних шляхів, що забезпечують перехід клітин через контрольні точки циклу.

Імбир та його компоненти в численних дослідженнях здатні індукувати апоптоз пухлинних клітин, що підтверджується активацією каспаз, зниженням експресії антиапоптотичних білків (Bcl-2, XIAP) та активацією прозапальних/проапоптотичних сигнальних каскадів. Наприклад, екстракт імбиру викликав ROS-опосередковану форму клітинної загибелі (аутозис) у клітинах раку підшлункової залози. Це означає, що імбир може активувати як класичні апоптотичні механізми, так і менш типові механізми клітинної загибелі у пухлинах.

Імбирні феноли мають антиоксидантні та протизапальні властивості, які можуть опосередковувати протипухлинний ефект. Наприклад, імбир пригнічує експресію NF- $\kappa$ B та TNF- $\alpha$  у моделі раку печінки у щурів. Додатково, щоденне застосування екстракту імбиру у пацієнток із пухлинами під час хіміотерапії підвищувало активність антиоксидантних ферментів (SOD, CAT, GPx) та знижувало рівень маркерів окисного стресу (MDA, NO<sub>2</sub><sup>-</sup>/NO<sub>3</sub><sup>-</sup>). Зменшення оксидативного стресу та запалення створює несприятливе середовище для пухлинного росту і метастазування.

Імбирні компоненти також впливають на процеси ангіогенезу та метастазування: вони знижують активність MMP-2/-9, інгібують сигнальні шляхи PI3K/Akt, MAPK, STAT3, що беруть участь у інвазії пухлин. Наприклад, 6-shogaol гальмує інвазію і метастазування раку печінки через пригнічення MMP-2/-9 та uPA. Таким чином, імбир має потенціал не лише гальмувати ріст

первинної пухлини, а й стримувати її поширення.

Накопичена база даних свідчить про багатоаспектну дію кореня імбиру та його складових у контексті протипухлинної терапії. Проте слід звернути увагу на кілька обмежень: більшість досліджень проведено *in vitro* або на тваринах; клінічні дані щодо пухлинної терапії обмежені; дозування, біодоступність, метаболізм активних сполук ще недостатньо вивчені. Наприклад, використання наноемульсій імбирної олії значно покращило ефект. Взаємодія імбиру із стандартними онкологічними препаратами потребує додаткового вивчення: синергізм чи потенційні протилежні ефекти. Хоча ефекти демонструються в різних типах пухлин, конкретна ефективність може варіювати залежно від гістології, стадії, мікрооточення пухлини. Отже, корінь імбиру, перспективний природний засіб із багатьма біохімічними мішенями, але його трансформація в клінічну онкологічну практику потребує подальших досліджень

**Висновки.** Корінь імбиру (*Zingiber officinale*) містить активні компоненти (6-gingerol, 6-shogaol та інші), які мають протипухлинну дію через багаторівневе модулювання біохімічних та сигнальних процесів. Основні біохімічні механізми включають: блокування клітинного циклу (проліферації), індукцію апоптозу/автофагії/аутолізу, зниження запалення та окисного стресу, інгібування ангіогенезу, інвазії та метастазування. Ключовими сигнальними мішенями є NF- $\kappa$ B, PI3K/Akt, MAPK, STAT3, MMPs, цикліни/CDK та інші. Хоча експериментальні дані багатообіцяючі, клінічна реалізація поки що обмежена: необхідні дослідження на людях, оптимізація формулювання (наприклад, наноемульсії) та вивчення взаємодії з існуючими терапіями.

У перспективі корінь імбиру може виступати як допоміжний або ад'ювантний засіб у онкології, особливо за умови належного наукового обґрунтування та стандартизації.

## KEY MECHANISMS OF CARCINOGENESIS

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**Introduction.** The main characteristics of a malignant tumor are uncontrolled growth, cellular atypia, invasion, and metastasis. Autonomous, or uncontrolled, growth is the primary characteristic of tumors. However, tumor autonomy does not mean complete independence from the host organism. Tumor cells require nutrients and oxygen to grow, proliferate, and invade. If the tumor's blood supply is impaired, areas



of necrosis develop, accompanied by tissue breakdown. Furthermore, tumor cells are constantly exposed to the influence of normal cells, elements of the endocrine microenvironment, the immune system, and various cytokines. Tumor cells themselves also constantly produce various metabolites, toxic substances, oncoproteins, growth factors, and hormones that affect the host organism.

Tumor cell autonomy is based on disruption of intercellular interactions due to the auto-, para-, and endocrine effects of oncoproteins and cytokines (growth factors, tumor necrosis factors, interferons). One of the main causes of disruption of intercellular interactions during tumor growth is genomic and/or epigenomic rearrangements in the tumor cell, leading to changes in the cell's structure and function. The nature of disruption of intercellular interactions in a tumor constantly changes during tumor progression. Tumor autonomy reaches its maximum at the metastatic stage.

**Aim of the study.** To analyze modern research in the field of etiology and pathogenesis of tumor growth, and also to study the main mechanisms of the stage of transformation of a normal cell into a tumor cell.

**Materials and methods.** Analysis of modern scientific research and literary sources in the field of pathophysiology, genetics, oncology.

**Results and discussion.** Activation of proto-oncogenes and their transformation into active cellular oncogenes under the influence of various carcinogenic factors is a key variant of cell genome damage during its malignant transformation. The following basic mechanisms of activation of proto-oncogenes are described:

1. Activation with the participation of retroviruses and less often DNA-containing viruses (papovaviruses), integrating their genes into the DNA of the host cell and modulating the activity of nearby proto-oncogenes of the host.
2. Translocation of sections of chromosomes carrying proto-oncogenes, which leads to contact of proto-oncogenes with strong modulators of gene expression.
3. Gene amplification. The multiplication of copies of proto-oncogenes will lead to an increase in the probability of their activation into oncogenes.
4. Point mutations. They can be accompanied by activation of proto-oncogenes.

After the activation of oncogenes, the synthesis of proteins, which are called oncoproteins, increases or begins. All known oncoproteins participate in the transmission of mitogenic signals to cells with the only difference that they can act at various stages of growth signal transmission.

According to their functional activity and similarity to elements of the mitotic signal chain, all oncoproteins can be divided into: 1) oncoproteins – growth factor homologues (c-sis; int-r; k-fgt; c-erbB; c-neu); 2) oncoproteins – homologues of

receptors for growth factors (ras family); 3) oncoproteins associated with the work of receptors – analogues of G-proteins (src; fps; fes; abl; met); 4) oncoproteins that transmit growth signals to DNA (fos; jun; myc families).

Oncoproteins are able to stimulate the proliferation of tumor cells, including in the mitotic cycle. The transition from G<sub>0</sub> to G<sub>1</sub> is controlled by "immediately responsive" oncogenes - families of fos, jun. C-myc also acts on this transition, but later, and c-ras – on the transition from G<sub>1</sub> to S and requires the additional action of growth factors or activation of the genes of the first two families. The transition from G<sub>2</sub> to M is controlled by the mitosis-promoting factor (MPF), which is represented by several proteins that are not oncoproteins. However, one of the FPM proteins, Ca<sup>2+</sup>-dependent protein kinase (eds 2), is activated through phosphorylation with the participation of the oncoprotein c-src.

In addition, during tumor growth, changes occur in the system: the growth factor is a sensitive tumor cell, an increase in the production of growth factors and the synthesis of the corresponding receptors are recorded, which leads to the stimulation of tumor growth by an autocrine mechanism. The production of growth factors by tumor cells can cause the activation of proto-oncogenes and the proliferation of non-neoplastic nearby cells via the paracrine pathway.

Cells contain genes that suppress cell division (anti-oncogenes). This is first of all the gene encoding protein (phosphoprotein) p53. When the p53 gene is mutated or the p53 protein is chemically modified, it binds to the cell and stimulates cell growth. Proteins with a high degree of homology with p53 - p63 and p73 are also found in cells, which, unlike p53, are expressed only in selected tissues and in certain periods of development. The second anti-oncogene is the Rb-1 gene, one of its products is the p105 Rb protein, which forms a complex with the T-antigen of the SV-40 oncogenic virus and the E1A oncoprotein. Consequently, not only the loss of the anti-oncogene, but also its suppression lead to cell transformation. Inactivation of p105 Rb occurs under the action of many DNA-containing viruses: adenoviruses; polyoma and papilloma viruses, SV-40.

Chemical carcinogens mainly cause point mutations and contribute to the activation of promoters, which leads to the transformation of proto-oncogenes into active oncogenes.

Classic carcinogens include N-acetylaminofluorene, nitroquinoline-1-oxide, polycyclic hydrocarbons such as 3,4-benzapyrene, and vinyl chloride. Dimethyl sulfate, β-propiolactone, methyl methanesulfonate, nitrogen mustard, dialkylnitrosamine, cycasine, ethionite, urethane, and carbon tetrachloride are among procarcinogens that turn into carcinogens in the body.

The process of chemical transformation is quite long, the transformation occurs due to multiple effects on the DNA structure.

Among the physical factors, the impact of which leads to malignant cell regeneration, the most important are ultraviolet, X-ray and gamma radiation, foreign bodies, and hyperthermia. The primary cause of transformation under the action of ultraviolet radiation and ionizing radiation is their mutagenic effect.

The variety of causes leading to the development of tumors is the main obstacle to the creation of effective methods of treatment of oncological diseases. At the molecular level, this diversity is observed even among tumors belonging to the same histological type.

The only change common to the vast majority of malignant neoplasms is the activation of the telomerase enzyme. Stimulation of uncontrolled division due to the activation of oncogenes is directly related to the replication factor E2F. The action of E2F is controlled by the Rb protein. This protein exists in two forms: phosphorylated and non-phosphorylated. In its unphosphorylated form, it is able to bind to E2F and block its activity. In turn, Rb is under the control of cyclin-dependent kinases (Cdk). Inhibitors of these kinases are proteins INK4, Kip 1, WAF1. Oncoprotein from the myc family interferes with the action of inhibitors of cyclin-dependent kinases and is able to activate the E2F gene.

Ionizing radiation or chemical carcinogens activate the p53 protein, which, with the help of WAF1, delays the initiation of replication until repair enzymes complete the removal of DNA damage. Preventing mutagenesis in general, p53 reduces the risk of such mutations that contribute to the transformation of a normal cell into a cancerous one. Absence of functioning p53 is observed in approximately 50% of human cancer cases. The body's natural defense against tumor cells is their recognition and destruction by apoptosis. However, it is known that transformed cells acquire significant resistance to apoptotic death, in particular, due to the high level of expression of the protein bcl-2, which stops apoptosis, or due to the loss of functional activity of p53.

The activity of telomerase, apparently, is under the control of nodal components of the cell division system - cyclin-dependent kinases, proteins Rb, E2F. Some signaling molecules: myc oncoproteins, estrogens can act directly on the promoter of the hTERT gene, as well as indirectly through the action on p53 or the TER1 gene.

Probably, there are several levels of regulation of telomerase activity, which can be implemented in different conditions and tissues. However, the fact that telomerase activation is a key moment in the transformation of a normal cell into a malignant tumor cell is indisputable.

**Conclusions.** Thus, carcinogenesis is a multi-stage process of accumulation of genetic defects in the cell, causing its constant mitogenic stimulation, insensitivity to anti-growth and pro-apoptotic signals, unlimited proliferative potential, angiogenesis, invasion and metastasis.

## СЕЛЕКТИВНІ ІНГІБІТОРИ ЗВОРОТНОГО ЗАХОПЛЕННЯ СЕРОТОНІНУ ТА ПЕРЕДМЕНСТРУАЛЬНИЙ СИНДРОМ

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**Вступ.** Передменструальний синдром (ПМС) – це поєднання фізичних, психологічних та соціальних симптомів у жінок репродуктивного віку, а передменструальний дисфоричний розлад (ПМДР) – це важкий тип синдрому, що уражає близько 3-5% жінок, раніше відомий як дисфоричний розлад пізньої лютеїнової фази (ДРЛФ). Обидва синдроми викликають симптоми протягом двох тижнів до менструації (лютеїнова фаза). Селективні інгібітори зворотного захоплення серотоніну (СІЗЗС) все частіше використовуються як терапія першої лінії для лікування ПМС, оскільки вони вважаються ефективними для зменшення симптомів, до яких можемо віднести: емоційні зміни (подрозливість, тривожність, плаксивість, перепади настрою), фізичні прояви (біль у грудях та животі, головний біль, здуття живота, набряки), а також інші ознаки, як-от втома, порушення сну, підвищений апетит, або висипання.

**Метою** багатьох досліджень на цю тему є оцінка та вивчення ефективності та безпеки СІЗЗС у зменшенні симптомів передменструального синдрому у жінок з діагнозом тяжкого передменструального синдрому.

**Результати та обговорення.** Говорячи про основний механізм дії, то СІЗЗС збільшують позаклітинний рівень нейротрансмітера серотоніну, завдяки обмеженню його реабсорбції пресинаптичною клітиною та підвищенню таким чином в синаптичній щілині рівня серотоніну, доступного для зв'язування з постсинаптичним рецептором. Іншими словами, антидепресивна дія СІЗЗС полягає у блокуванні зворотного захоплення (реаптейка) серотоніну нейронами, які його виділяють, що призводить до збільшення кількості серотоніну в синаптичній щілині. З впливом на серотонінові рецептори пов'язують такі ефекти, як корекція зниженого настрою, зниження вітальної туги, тривоги, фобій, апетиту, легкий анагетичний ефект.

Науковцями було здійснено електронний пошук відповідних рандомізованих контрольованих досліджень у спеціалізованому реєстрі

контрольованих досліджень Кокрейнівської групи з питань менструальних розладів та субфертильності, Кокрейнівському реєстрі контрольованих досліджень, MEDLINE, EMBASE та PsychLit. Пошук посилань проводився інтерактивно для виявлення пропущених досліджень. Були розглянуті всі дослідження, в яких жінки з проспективним діагнозом ПМС/ПМДР були рандомізовані для отримання СІЗЗС або плацебо у подвійному сліпому дослідженні для лікування передменструального синдрому.

До огляду було включено тридцять одне РКД. В цих роботах був проведений порівнювальний аналіз флуоксетину, пароксетину, сертраліну, есциталопраму та циталопраму з плацебо. СІЗЗС зменшували загальні симптоми, оцінені самотійно, значно ефективніше, ніж плацебо. Первинний аналіз зниження загальної симптоматики включав дані 844 жінок з передменструальним синдромом. Було виявлено, що СІЗЗС є високоефективними в лікуванні передменструальних симптомів. Вторинний аналіз показав, що вони були однаково ефективними в лікуванні як фізичних, так і поведінкових симптомів. Не було суттєвої різниці між випробуваннями, що фінансувалися фармацевтичними компаніями, та тими, що фінансувалися незалежно. Випадки припинення участі через побічні ефекти були в 2,5 рази частішими в групі лікування, особливо при застосуванні вищих доз. Побічними ефектами, пов'язаними з СІЗЗС, були нудота, безсоння, сексуальна дисфункція або зниження лібідо, втома або седативний ефект, запаморочення або вертиго тремор, сонливість та зниження концентрації уваги, пітливість, сухість у роті, астенія або зниження енергії, та запор. Існували докази помірної достовірності для всіх побічних ефектів, окрім сонливості/зниження концентрації, що було доказом низької достовірності. Загалом, достовірність доказів була помірною.

**Висновки.** СІЗЗС, ймовірно, зменшують передменструальні симптоми у жінок з ПМС та ПМДР і, ймовірно, є більш ефективними при безперервному прийомі порівняно з прийомом у лютеїнову фазу. Лікування СІЗЗС, ймовірно, збільшує ризик побічних ефектів, найпоширенішими з яких є нудота, астенія та сонливість.





## ДИСРЕГУЛЯЦІЯ МЕТАБОЛІЗМУ ТРИПТОФАНУ: АКТИВАЦІЯ КІНУРЕНІНОВОГО ШЛЯХУ ТА ДЕФІЦИТ СЕРОТОНІНУ ЯК КЛЮЧОВІ БІОХІМІЧНІ МЕХАНІЗМИ НЕЙРОКОГНІТИВНИХ ДИСФУНКЦІЙ ПРИ LONG COVID-19

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**Вступ.** Long COVID-19 – персистуючий або хронічний постінфекційний синдром, для якого характерне збереження симптомів понад 3 або 12 місяців відповідно після завершення гострої фази SARS-CoV-2-інфекції. Серед найбільш поширених проявів є нейрокогнітивні дисфункції (зокрема, «мозковий туман», порушення пам'яті та уваги), що суттєво знижують якість життя. Етіологія постковідного синдрому є багатофакторною (хронічне запалення, автономна дисфункція, гіперкоагуляція), проте більшість досліджень вказують на молекулярні та метаболічні порушення у ролі центральної ланки патогенезу.

Ключовим біохімічним посередником між імунною та нервовою системами є незамінна амінокислота триптофан, яка є субстратом для двох метаболічних шляхів – серотонінового та кінуренінового. Перший ініціюється ферментом триптофангідроксилазою і призводить до синтезу серотоніну (5-гідрокситриптамін або 5-НТ), в свою чергу, другий шлях ініціюється ферментом індоламін-2,3-діоксигеназою (IDO1) або триптофан-2,3-діоксигеназою (TDO) і відповідає за катаболізм понад 90% вільного триптофану, утворюючи нейроактивні метаболіти. Хронічна імунозапальна відповідь при Long COVID-19, опосередкована IFN-γ та іншими прозапальними цитокінами, призводить до гіперактивації IDO1. Це перенаправляє метаболізм триптофану з серотонінового шляху на кінуреніновий, спричиняючи дефіцит гормону серотоніну.

**Мета дослідження.** Проаналізувати сучасні дані щодо біохімічних механізмів порушення метаболізму триптофану при Long COVID-19 і визначити роль активації кінуренінового шляху та дефіциту серотоніну у розвитку нейрокогнітивних дисфункцій.

**Матеріали та методи.** Аналіз наукових публікацій, присвячених порушенням метаболізму триптофану та серотоніну у пацієнтів з Long COVID-19.

**Результати та обговорення.** Аналіз сучасних наукових даних підтверджує тісний зв'язок між розвитком нейрокогнітивних порушень при постковідному синдромі та дисрегуляцією метаболізму триптофану.

Ключовим патогенетичним компонентом є накопичення нейротоксичних продуктів кінуренінового шляху. Хінолінова кислота (QA), надлишок якої формується у ЦНС під впливом активованої мікроглії, є агоністом NMDA-рецепторів і спричиняє ексайтотоксичність, порушення кальцієвого гомеостазу, мітохондріальну дисфункцію та апоптоз нейронів, особливо в гіпокампі – структурі, критичній для процесів пам'яті. QA-індукована ексайтотоксичність вважається провідним молекулярним механізмом «мозкового туману».

Паралельно, дефіцит серотоніну посилюється через багатofакторну дисфункцію вісі «кишківник-мозок». По-перше, персистенція SARS-CoV-2 та локальне запалення пошкоджують ентероцити, порушуючи всмоктування триптофану з їжі. По-друге, зниження рівня 5-гідрокситриптаміну через дисбіоз: зменшується кількість бактерій, що виробляють коротколанцюгові жирні кислоти (КЛЖК/SCFA). Ці кислоти є біохімічними модуляторами, котрі стимулюють ентерохромафінні клітини кишечника до синтезу 5-гідрокситриптаміну. Зниження цієї стимуляції, разом із конкуренцією за IDO1, поглиблює системний дефіцит серотоніну. Додатковими факторами є дисфункція тромбоцитів (порушення зберігання 5-НТ) та посилений катаболізм серотоніну через активацію моноаміноксидази А (МАО-А). Системне зниження периферичного 5-НТ порушує сигнальну активність блукаючого нерва й погіршує нейропластичність гіпокампу та когнітивні процеси.

З огляду на встановлені механізми обґрунтовуються потенційні терапевтичні стратегії: застосування 5-гідрокситриптофану для поповнення дефіциту серотоніну, інгібіторів IDO1 для блокування надмірної активації кінуренінового шляху, пробіотиків і пребіотиків для відновлення синтезу серотоніну в кишечнику за участю КЛЖК. Мультицільовий вплив на всі зазначені ланки патогенезу є перспективним напрямом лікування нейрокогнітивних порушень при Long COVID-19.

**Висновки.** Нейрокогнітивні порушення при Long COVID-19 значною мірою зумовлені дисбалансом метаболізму триптофану. Формування нестачі серотоніну відбувається паралельно з надлишком нейротоксичної хінолінової кислоти внаслідок зміщення перетворення триптофану у бік кінуренінового шляху. Отримані дані підкреслюють необхідність терапевтичних стратегій, спрямованих на зниження патологічної активації кінуренінового шляху та відновлення серотонінового балансу.

## ВПЛИВ ПАЛІННЯ НА ЦИТОГЕНЕТИЧНИЙ СТАТУС СЛИЗОВОЇ ОБОЛОНКИ РОТОВОЇ ПОРОЖНИНИ В ЖІНОК ЮНАЦЬКОГО ВІКУ

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**Вступ.** Сьогодні активно проводяться дослідження щодо вивчення ролі спадкових чинників у розвитку захворювань, в тому числі хвороб ротової порожнини. Завдяки цитогенетичному моніторингу можна отримати інформацію як про стан здоров'я населення обстежуваної популяції, так і про вплив генотоксичних факторів, тобто цитогенетичний статус людини може служити біомаркером рівня впливу генотоксикантів, в тому числі різних видів паління. Так як слизова оболонка ротової порожнини віддзеркалює стан всього організму, стає актуальним вивчення впливу різних видів паління на цитогенетичний статус букальних епітеліоцитів із метою виявлення цитогенетичних порушень і визначення цитогенетичних маркерів (Нейко Є.М. та ін. 2007; Федоров С.В., Ковальчук Л.Є., 2015; Хомик М.І. та ін., 2019; Лісецька І.С., 2024).

Отже, науковий інтерес представляє вивчення токсичного впливу та мутагенного ефекту різних видів паління в жінок юнацького віку на цитогенетичний статус, а саме каріологічні показники букального епітелію, так як саме ці клітини виступають первинними мішенями впливу токсичних речовин і можуть бути використані як цитогенетичні маркери.

Отже, **мета дослідження** – вивчити вплив різних видів паління на цитогенетичний статус шляхом проведення аналізу каріологічних показників букальних епітеліоцитів слизової оболонки ротової порожнини в жінок юнацького віку.

**Матеріали та методи.** Для досягнення поставленої мети було проведено вивчення цитогенетичного статусу шляхом проведення аналізу каріологічних показників букальних епітеліоцитів слизової оболонки ротової порожнини у 72 жінок юнацького віку від 18 до 24 років (класифікація вікової періодизації запропонована ООН 1982 року – Provisional Guidelines on Standard International Age Classifications), яких було розділено на групи: у I групу включили 16 осіб, що регулярно палять традиційні сигарети; у II групу – 14 осіб, що регулярно палять електронні сигарети (Вейпи); у III групу – 16 осіб, що регулярно палять пристрої для нагрівання тютюну (IQOSи); у IV групу – 26 осіб, без шкідливої звички паління. Цитогенетичному дослідженню підлягали клітини і ядра букальних епітеліоцитів слизової оболонки ротової порожнини, а саме клітини

розташовані по середній лінії внутрішньої поверхні щок. Вивчали міжнародно визнані дванадцять варіантів ядерних порушень, які об'єднані в чотири підгрупи. Для статистичної обробки матеріалу під час дослідження застосовано комп'ютерні програми на основі «Microsoft Excel» та «Statistica 12.0».

**Результати досліджень та їх обговорення.** Отже, було проаналізовано частоту клітин із мікроядрами. В учасниць спостереження, що палять, кількість епітеліальних клітин букального епітелію з ядерцями (мікроядрами) достовірно переважала відповідний показник в учасниць без шкідливої звички, причому в осіб, що палять традиційні цигарки, кількість таких клітин було в 2 рази більше порівняно із особами, що не палять, ( $p<0,05$ ). В жінок II та III груп також було виявлено більшу кількість епітеліальних клітин із ядерцями, відповідно в 1,6 рази більше порівняно із особами IV групи, ( $p<0,05$ ). Другим цитогенетичним показником є частота клітин із протрузіями. Клітини із протрузіями в осіб, що не палять не виявлено. В осіб, що палять традиційні цигарки, клітини із протрузіями діагностовано в 1,7 та 1,9 рази частіше ніж в осіб, що використовують сучасні альтернативні види паління, відповідно в осіб II та III групи, ( $p<0,05$ ). Наступний цитогенетичний показник, що вивчали – це частота виявлення атипових ядер. Частота атипових ядер також виявилась вищою в осіб, що палять традиційні цигарки, а саме, в 2,6 рази більше порівняно з особами, що не палять, ( $p<0,05$ ). У осіб підліткового та юнацького віку що використовують альтернативні види паління – особи II та III груп значення показника також зростає, але дещо менше, а саме в 2,3 рази, порівняно з особами, що не палять, ( $p<0,05$ ). В учасниць спостереження, що палять традиційні цигарки, кількість епітеліальних клітин букального епітелію з двома ізольованими ядрами достовірно переважала відповідний показник в учасників II та III групи – кількість таких клітин було в 1,6 та 2 рази більше відповідно, ( $p<0,05$ ). Кількість епітеліальних клітин із здвоєними ядрами в учасниць спостереження I групи також виявлено незначно більше, ніж в учасниць спостереження II та III груп, відповідно в 1,3 та 1,5 рази, ( $p<0,05$ ). У групі осіб, що не палять маркерів проліферації не було виявлено. Показники ранньої деструкції ядра – перинуклеарна вакуоля та вакуолізація ядра в мазках учасників дослідження, що не палять не було виявлено. В осіб I групи показник ранньої деструкції ядра – перинуклеарна вакуоля було виявлено частіше в 1,4 рази ніж в осіб II групи та в 1,8 рази ніж в осіб III групи, ( $p<0,05$ ). Вакуалізацію ядра в осіб I групи виявляли в 1,4 та 1,5 рази, ( $p<0,05$ ) частіше порівняно із учасницями спостереження, що палять альтернативні види паління, відповідно – осіб II та III груп. Кількість клітин із каріопікнозом у осіб I групи було більше порівняно із особами II та III груп відповідно в 1,2 та 1,5 рази,

( $p > 0,05$ ). В осіб, що палять традиційні цигарки каріорексис було виявлено частіше в 1,4 та 1,5 рази ніж в осіб, що палять альтернативні види паління відповідно - в осіб II та III груп, ( $p > 0,05$ ). Каріолізис в учасниць дослідження, що палять традиційні цигарки даний показник виявився вищим в 1,3 та 1,6 рази ніж в учасниць дослідження, що палять альтернативні види паління відповідно в II та III групах, ( $p > 0,05$ ).

**Висновки.** Таким чином, було вивчено вплив різних видів паління на цитогенетичний статус, шляхом проведення аналізу каріологічних показників букальних епітеліоцитів слизової оболонки ротової порожнини в жінок юнацького віку. В ході дослідження було встановлено чутливість букальних епітеліоцитів до дії різних видів паління, що позначається на змінах каріологічних показників. Отримані результати дослідження цитогенетичного статусу в жінок юнацького віку вказують на наявність цитогенетичних порушень в осіб, що палять. Причому дані показники були більш виражені в учасниць дослідної групи, що палять традиційні цигарки. В осіб дослідних груп, що використовують альтернативні види паління, також показники цитогенетичного статусу збільшені порівняно із особами без шкідливої звички паління, але дещо нижчі порівняно із жінками, що палять традиційні цигарки. Каріологічні показники букальних епітеліоцитів можуть служити цитогенетичними маркерами токсичного і мутагенного впливу різних видів паління та застосовані з метою виявлення цитогенетичних порушень.

## **ПОРІВНЯЛЬНА ХАРАКТЕРИСТИКА МОРФОМЕТРИЧНИХ ПОКАЗНИКІВ ПЕРЕДМІХУРОВОЇ ЗАЛОЗИ ЩУРІВ НА МОДЕЛІ СУЛЬПРИД-ІНДУКОВАНОЇ ДОБРОЯКІСНОЇ ГІПЕРПЛАЗІЇ ПІСЛЯ ПРОФІЛАКТИЧНОГО ЗАСТОСУВАННЯ ЕКСТРАКТУ ПЛОДІВ ПАЛЬМИ САБАЛЬ ТА ВІТАМІНУ D.**

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**Вступ.** Стресові фактори сучасного життя в умовах воєнного стану в Україні, є потужними тригерами ендокринних порушень, що призводять до



гормонального дисбалансу. У чоловіків це проявляється зниженням секреції тестостерону, підвищенням рівнів пролактину, кортикостероїдів і гонадотропінів, а також порушенням андроген-естрогенного співвідношення. Сукупність цих змін впливає на функціональний стан органів репродуктивної системи, зокрема передміхурової залози (ПЗ).

Доброякісна гіперплазія передміхурової залози (ДГПЗ) є одним із найпоширеніших урологічних захворювань у чоловіків віком 50–65 років, однак останніми роками спостерігається тенденція до її появи у більш молодих вікових групах. Патологічний процес супроводжується збільшенням об'єму передміхурової залози, порушенням відтоку сечі та зниженням якості життя пацієнтів. Патогенез ДГПЗ має поліетіологічний характер і включає гормональні, запальні, вікові та метаболічні чинники.

Відомо, що підвищення рівня пролактину стимулює проліферацію епітеліальних клітин ПЗ через активацію рецепторів ростових факторів, що часто використовується для відтворення ДГПЗ в експериментальних умовах (наприклад, сульпірид-індукована модель).

Значну популярність у світі має фітотерапія ДГПЗ. Широко використовується екстракт плодів *Serenoa repens* для лікування та профілактики ДГПЗ, хоча дані літературних джерел неоднозначні та зазвичай ще не мають великої кількості спостережень.

У контексті як профілактики так і лікування ДГПЗ велика кількість літературних джерел свідчить також, що вітамін D має антипроліферативні, протизапальні та імуномодулювальні властивості.

Отже, пошук ефективних засобів впливу на гіперплазовану ПЗ шляхом нормалізації її гормонального, структурного та функціонального стану залишається актуальним напрямом сучасної експериментальної морфології та фармакології.

**Метою дослідження** було проведено вивчення морфометричних показників передміхурової залози щурів зі змодельованою сульпірид-індукованою гіперплазією після профілактичного застосування екстракту плодів пальми Сабаль та вітаміну D.

**Матеріали та методи.** Досліджено 54 біоптати тканини ПЗ від 12-місячних статевих активних самців щурів, масою 330-380г (n=9). Профілактично щурам I групи вводили 14 діб екстракт плодів пальми Сабаль, 35 мг/кг; II групі – вітамін D<sub>3</sub> per os у дозі 4000 МО. Потім на тлі введення досліджуваних речовин у тварин моделювали ДГПЗ шляхом введення самцям щурів розчину сульпіриду у дозі 40 мг/кг м.т. протягом 30 діб, а далі аналогічно

по групах продовжили введення препаратів ще 7 діб з профілактичною метою.

Для мікроскопічного дослідження з тканини ПЗ вирізали по три шматочки з двох зон – дорзальної та вентральної (54 шматочків ПЗ загалом). Шматочки фіксували в 10 % розчині нейтрального формаліну, а згодом матеріал підлягав стандартній проводці, після чого заливали парафіном, із блоків виготовляли зрізи завтовшки 3-5 мкм на мікротомі Microm HM-340.

Мікроскопічно досліджено за допомогою оптичного мікроскопа Primo Star Zeiss із цифровою камерою MICROmed MDC-500 5,0 Mpix (Німеччина) біоптати тканини дорзальної та вентральної зони ПЗ. На зрізах, які фарбували гематоксилін-еозином, оцінювали зміни стромального, паренхіматозного й судинного компонентів, наявність або відсутність вторинних змін та проводили морфометричну оцінку рівня гіперплазії (висоту залозистого епітелію, стромального та паренхіматозного компонентів (%), стромально-паренхіматозний індекс (СПІ, ум. од.). Розраховували U-критерій Манна-Уїтні (МУ).

**Результати та обговорення.** Аналізуючи морфометричні показники біоптатів тканини вентральної частини ПЗ I та II груп установили, що не відмічалось статистично вірогідної різниці між показниками висоти епітелію,  $(71,62 \pm 1,29)$  мкм та  $(72,33 \pm 1,17)$  мкм; питомою вагою стромального компоненту  $(51,89 \pm 1,56)\%$  та  $(50,33 \pm 0,33)\%$ ; питомою вагою паренхіматозного компонента  $(48,11 \pm 1,56)\%$  та  $(49,67 \pm 1,43)\%$ ; та стромально-паренхіматозного індексу  $(1,08 \pm 0,07)$  ум.од. та  $(1,01 \pm 0,01)$  ум.од, відповідно ( $p > 0,05$ ).

У морфометричних показниках біоптатів тканини дорзальної частини ПЗ була виявлена статистично вірогідна різниця між морфометричними показниками I та II групи, ( $p < 0,05$ ): висота епітелію була зменшена  $(63,13 \pm 2,73)$  мкм та  $(68,17 \pm 1,50)$  мкм; збільшена питома вага стромального компоненту  $(40,33 \pm 0,44)\%$  та  $(30,78 \pm 2,67)\%$ ; питома вага паренхіматозного компонента зменшена,  $(59,67 \pm 0,44)\%$  та  $(69,22 \pm 2,67)\%$ ; та збільшено стромально-паренхіматозний індекс  $(0,74 \pm 0,02)$  ум.од.) та  $(0,45 \pm 0,02)$  ум.од., відповідно.

**Висновки.** Таким чином встановлено, що морфометричні показники дорзальної частини передміхурової залози щурів I групи з ДГПЗ дещо покращилися на тлі профілактичної корекції екстрактом плодів пальми Сабаль ( $p < 0,05$ ), при цьому морфометричні показники вентральної частини передміхурової залози щурів із ДГПЗ залишилися без статистично вірогідних змін. Такі зміни можуть вказувати на більшу чутливість саме клітин дорзальної частини передміхурової залози до профілактичної корекції екстрактом плодів пальми Сабаль.

## ГЛЮКОЗО-6-ФОСФАТ ЯК КЛЮЧОВИЙ МЕТАБОЛІТ

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**Вступ.** Глюкозо-6-фосфат (Г6Ф) є одним із найважливіших проміжних метаболітів клітинного обміну речовин. Його утворення відбувається в результаті фосфорилування глюкози під дією ферменту гексокінази або глюкокінази. Ця реакція є першим етапом гліколізу, пентозофосфатного шляху та глікогенезу, що визначає Г6Ф як вузлову сполуку, через яку перехрещуються основні метаболічні потоки.

Регуляція рівня Г6Ф має вирішальне значення для підтримання енергетичного гомеостазу, біосинтезу нуклеотидів, жирних кислот та антиоксидантного захисту клітини. Порушення метаболізму Г6Ф лежить в основі багатьох патологій, включно з цукровим діабетом, глікогенозами, ожирінням, пухлинними процесами та нейродегенеративними захворюваннями. Отже, дослідження біохімічних властивостей, регуляторних механізмів та функціональних ролей Г6Ф має важливе теоретичне і практичне значення.

**Мета дослідження.** Метою роботи є узагальнення сучасних даних про біохімічну роль глюкозо-6-фосфату як ключового метаболіту, визначення його участі у головних енергетичних і пластичних шляхах метаболізму, а також аналіз його регуляторних функцій та клінічного значення при патологічних станах.

**Матеріали та методи.** Для проведення теоретичного аналізу використано дані сучасної наукової літератури, результати експериментальних і клінічних досліджень, опублікованих у базах PubMed, Scopus, SpringerLink та ResearchGate. Методологічну основу роботи становили: порівняльний біохімічний аналіз шляхів утворення та перетворення Г6Ф у клітині; енергетичний баланс реакцій за участю Г6Ф; структурно-функціональний підхід для оцінки ролі ферментів гексокінази, глюкозо-6-фосфатдегідрогенази, фосфоглюкомутази; патобіохімічний аналіз метаболічних порушень, пов'язаних із дефектами обміну Г6Ф.

**Результати та обговорення.** Глюкозо-6-фосфат – це ефір фосфорної кислоти і глюкози, що утворюється під дією АТФ-залежного фосфорилування. Його структура дозволяє одночасно брати участь у декількох метаболічних шляхах, зокрема гліколіз, окиснення Г6Ф до пірувату з утворенням АТФ; глікогенез, перетворення Г6Ф у глюкозо-1-фосфат і подальший синтез глікогену; пентозофосфатний шлях, дегідрогенізація Г6Ф із утворенням НАДФН і рибозо-5-фосфату; глюконеогенез – реверсивне перетворення вільної глюкози з Г6Ф у

печінці. Це свідчить, що Г6Ф є своєрідним «метаболічним вузлом», який координує обмін енергії та біосинтетичні процеси.

Г6Ф виконує роль алостеричного ефектора для багатьох ферментів: інгібує гексокіназу за принципом зворотного зв'язку; активує фосфофруктокіназу-2, стимулюючи утворення фруктозо-2,6-бісфосфату; контролює рівень глікогенфосфорилази і, відповідно, швидкість глікогенолізу. Таким чином, Г6Ф виступає інтегратором сигналів про енергетичний стан клітини, забезпечуючи баланс між анаболізмом і катаболізмом.

Окиснення Г6Ф глюкозо-6-фосфатдегідрогеназою є першим і лімітуючим етапом пентозофосфатного шляху. Цей процес генерує НАДФН, необхідний для синтезу жирних кислот і відновлення глутатіону, головного антиоксиданту клітини. Дефіцит Г6ФДГ (глюкозо-6-фосфатдегідрогенази) призводить до підвищеної чутливості еритроцитів до окисного стресу і гемолітичної анемії.

Порушення метаболізму Г6Ф спостерігаються при таких патологіях: цукровий діабет, гіперглікемія змінює розподіл потоків Г6Ф між гліколізом і пентозофосфатним шляхом; глікогенози I типу (хвороба фон Гірке), дефіцит ферменту глюкозо-6-фосфатази призводить до накопичення Г6Ф у печінці; пухлинні процеси, клітини з високою проліферативною активністю демонструють підвищений рівень Г6Ф та активацію пентозофосфатного шляху, що забезпечує синтез нуклеотидів і антиоксидантний захист.

Рівень Г6Ф використовується як діагностичний маркер при метаболічних синдромах, а фермент глюкозо-6-фосфатдегідрогеназа, як мішень у терапії оксидативного стресу. Крім того, інгібітори шляхів утилізації Г6Ф досліджуються як потенційні протипухлинні агенти.

**Висновки.** Глюкозо-6-фосфат є центральним метаболітом, що визначає напрямок енергетичного та пластичного обміну клітини. Його участь у гліколізі, глікогенезі, пентозофосфатному шляху і глюконеогенезі забезпечує інтеграцію метаболічних процесів. Порушення обміну Г6Ф веде до розвитку ряду патологій: від діабету до онкозахворювань. Г6Ф і ферменти, що його метаболізують, можуть виступати потенційними терапевтичними мішенями для метаболічної та протипухлинної терапії.

Подальші дослідження регуляції Г6Ф на молекулярному рівні відкривають перспективи у створенні нових біохімічних маркерів та лікувальних стратегій.



## АНАЛІЗ ПОКАЗНИКІВ ЗАПАЛЕННЯ НА МОДЕЛЯХ ГОСТРОГО ЗАПАЛЕННЯ У ЩУРІВ

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**Вступ.** Запалення є універсальною захисною реакцією організму на ушкодження, інфекційні або неінфекційні чинники, спрямованою на локалізацію патологічного процесу, усунення ушкоджувального агента та відновлення гомеостазу. Гостра запальна реакція характеризується швидким розвитком, короткотривалістю та участю клітинних і гуморальних факторів імунної системи. Серед них ключову роль відіграють цитокіни (інтерлейкіни, фактор некрозу пухлин  $\alpha$ ), простагландини, оксид азоту, білки гострої фази, а також ферментні системи, зокрема мієлопероксидаза, циклооксигеназа і ліпооксигеназа. Вивчення біохімічних та морфологічних показників запалення на експериментальних моделях у лабораторних тварин є важливою ланкою в розумінні механізмів розвитку патологічних процесів та оцінці ефективності протизапальних засобів. Моделювання гострого запалення у щурів дозволяє отримати репрезентативні дані про зміни гомеостатичних систем, активність ферментів, концентрацію прозапальних медіаторів та ступінь окисного стресу.

**Мета дослідження.** Метою роботи було провести комплексний аналіз біохімічних показників запальної відповіді у щурів на різних моделях гострого запалення для визначення характерних змін у системі запалення та оцінки можливості їх використання як маркерів патологічного процесу.

**Матеріали та методи** Дослідження проводили на білих лабораторних щурах-самцях масою 180-220 г, яких утримували у стандартних умовах віварію при постійному доступі до води та корму. Експериментальні моделі гострого запалення включали: модель карагенінового набряку лапи (індукцію запалення здійснювали підшкірним введенням 1% розчину карагеніну у підшову задньої лапи; модель формалінового запалення (застосовували 2,5% розчин формаліну, який викликає асептичну запальну реакцію з чіткими фазами гострої ексудації та проліферації; модель турпентинового запалення (вводили підшкірно 0,1 мл скипидару у стегнову ділянку для імітації стерильного запалення). Через 6, 24 і 48 годин після індукції запалення проводили забір крові та тканин (печінки, селезінки, запаленої ділянки). У сироватці крові визначали: активність ферментів антиоксидантної системи (каталази, супероксиддисмутази, глутатіонпероксидази); вміст малонового діальдегіду (МДА) як маркера ліпопероксидації; рівень загального білка, альбуміну, С-реактивного білка



(СРБ). Отримані результати опрацьовували статистично з використанням критерію Стюдента ( $p < 0,05$  вважали достовірним).

**Результати та обговорення.** У результаті досліджень виявлено, що на всіх моделях гострого запалення спостерігалось достовірне підвищення вмісту прозапальних цитокінів, інтенсифікація процесів пероксидного окиснення ліпідів та зміни у системі антиоксидантного захисту.

На моделі карагінінового набряку вже через 6 годин після індукції фіксували збільшення концентрації  $\text{TNF-}\alpha$  у 2,3 рази ( $p < 0,05$ ), що супроводжувалося підвищенням МДА на 60% порівняно з контролем. Активність каталази знижувалась на 25%, що вказує на розвиток оксидативного стресу.

На формаліновій моделі запалення зміни були більш тривалими: максимальні показники МДА і СРБ спостерігали через 24 години, що свідчить про активацію гуморальної ланки запальної реакції. У тканинах відзначали інфільтрацію нейтрофілами, дегенеративні зміни клітин та судинну гіперемію.

Терпентинова модель супроводжувалася вираженою системною відповіддю: підвищення рівня  $\text{TNF-}\alpha$  у 2,5 рази що свідчить про інтенсивну активацію нейтрофільного запалення.

Загалом встановлено, що всі моделі характеризуються типовими фазами запалення – альтерацією, ексудацією та проліферацією. Найбільш чутливими маркерами гострого запалення є рівні  $\text{TNF-}\alpha$ , С-реактивного білка. Показники антиоксидантної системи (каталаза, супероксиддисмутаза, глутатіонпероксидаза) відображають інтенсивність окисного стресу та можуть бути використані для оцінки ефективності протизапальних агентів.

Важливим спостереженням стало те, що динаміка цитокінів і ферментів залежить від природи запального агента: хімічні подразники (формалін, скипидар) викликають більш пролонговану системну реакцію, тоді як карагенін – більш локалізовану, але інтенсивну на ранніх стадіях.

**Висновки.** На моделях гострого запалення у щурів встановлено достовірні зміни біохімічних показників, що характеризують розвиток запальної відповіді. Найбільш інформативними маркерами гострого запалення є підвищення рівнів  $\text{TNF-}\alpha$ , СРБ, а також зростання продуктів пероксидного окиснення ліпідів. Зниження активності ферментів антиоксидантного захисту (каталази, супероксиддисмутази, глутатіонпероксидази) свідчить про посилення окисного стресу в тканинах.

Порівняння різних моделей показало, що карагенінова модель є зручною для оцінки локальних запальних реакцій, тоді як формалінова і терпентинова –

для аналізу системних ефектів. Отримані результати можуть бути використані для апробації протизапальних препаратів, дослідження патогенезу гострих запалень та розробки біохімічних маркерів запального процесу.

## **БІОХІМІЯ СТРЕСУ У НАСЕЛЕННЯ ПІД ЧАС ТРИВАЛИХ КРИЗОВИХ СИТУАЦІЙ**

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**Вступ.** На сьогоднішній час найголовнішим чинником що впливає на здоров'я став хронічний стрес. Тривалі кризові ситуації такі як війна, економічна та матеріальна нестабільність, географічні катастрофи, все це сприяє хронічному впливу стрес-факторів, що сприяє порушенню біохімічної рівноваги. Стрес – це складна адаптивна реакція організму, спрямована на підтримку виживання в умовах загрози або тривалого психоемоційного напруження. Коли стресові фактори стають надмірними або тривалими, захисні механізми переходять у фазу виснаження, що викликає системні біохімічні та фізіологічні зміни. У відповідь на стрес активується гіпоталамо-гіпофізарно-надниркова (ГГН) вісь, яка регулює секрецію кортизолу – основного гормону стресу. Одночасно стимулюється симпатично-надниркова система, що підвищує рівень адреналіну та норадреналіну. Тривала активація цих систем призводить до зниження адаптивних можливостей організму, розвитку запалення, порушень обміну речовин та ослаблення імунітету. В умовах тривалої соціальної та військової кризи, з якою зараз стикається населення України, хронічний стрес набуває поширення, впливаючи не лише на здоров'я людини, але й на загальну працездатність, соціальну стабільність та демографічну ситуацію.

**Мета дослідження.** Встановити біохімічні показники стресу у людей, які перебувають під впливом тривалих кризових факторів, та оцінити зміни в гормональному, метаболічному та імунному гомеостазі.

Особливу увагу приділено населенню України, яке протягом останніх років зазнає тривалого психоемоційного навантаження внаслідок війни та соціально-економічних потрясінь.

**Матеріали та методи.** Збір та аналіз інформації здійснювалися на основі матеріалів, взятих із мережі Інтернет, наукових публікацій, електронних баз даних (*PubMed, ResearchGate, Google Scholar*) та актуальних звітів ВООЗ.

**Результати дослідження.** Аналіз численних наукових публікацій та статистичних даних показує, що стрес, спричинений тривалими кризовими

ситуаціями, має системний вплив на організм людини. Його біохімічна картина включає зміни в ендокринній, нервовій, імунній та метаболічній системах. Найбільш суттєві зміни спостерігалися в гормональному балансі. Тривалий психоемоційний стрес активує гіпоталамо-гіпофізарно-надниркову вісь, що призводить до підвищення рівня кортизолу – основного гормону стресу. Короткочасний вплив допомагає організму мобілізувати енергію, підвищує рівень глюкози в крові та активує розщеплення білків і жирів, забезпечуючи задоволення енергетичних потреб організму в екстремальних умовах.

Проте при тривалому стресі надмірна секреція кортизолу призводить до низки негативних наслідків: пригнічення синтезу білків; порушення регенерації тканин; інгібування імунної відповіді; посилення катаболізму м'язової тканини; підвищення ризику інсулінорезистентності.

Дослідження, проведені в повоєнних регіонах України, відзначили стійке підвищення рівня кортизолу у 65-70% учасників, що свідчить про хронічний стан стресу. Також було виявлено підвищення концентрації адреналіну та норадреналіну, що вказує на постійну активацію симпатично-надниркової системи.

На біохімічному рівні це проявляється у зниженні рівня серотоніну та дофаміну, що обумовлює емоційне виснаження; підвищенні вільних радикалів у плазмі крові, що спричиняє оксидативний стрес; зниженні антиоксидантного захисту.

Цікаво, що біохімічний стрес має також епігенетичний ефект. Дослідження показують, що тривале підвищення рівня кортизолу може викликати зміни у метилюванні ДНК, які впливають на експресію генів, пов'язаних із реакціями на стрес, і навіть передаватися наступним поколінням.

Сучасні українські вчені також відзначають підвищення рівня маркерів запалення (IL-6, TNF- $\alpha$ , С-реактивний білок) у людей, які пережили війну або тривалі кризи. Такий стан отримав назву «біохімічного запалення стресу», яке поєднує фізіологічну активацію імунної системи з психологічними порушеннями. Одним з найважливіших показників цього процесу є інтерлейкін-6 (IL-6). За нормальних умов він виконує захисну функцію, активуючи імунну систему у відповідь на пошкодження або інфекцію. Однак у випадках хронічного психоемоційного стресу рівень IL-6 підвищується навіть за відсутності зовнішніх загроз. Надмірний рівень сприяє розвитку хронічного запалення, яке з часом може призвести до серцево-судинних, метаболічних та нейродегенеративних розладів. Іншим важливим запальним цитокином є фактор некрозу пухлини альфа (TNF- $\alpha$ ). Його основна роль полягає в запуску запальних

реакцій та активації імунних клітин. При тривалому стресі TNF- $\alpha$  виділяється надмірно, що спричиняє розвиток хронічного запалення і навіть ушкодження нервових клітин. Підвищений рівень цього маркера асоціюється з появою симптомів депресії, тривоги, інсулінорезистентності та передчасного старіння клітин.

Ще одним важливим показником запалення є С-реактивний білок (СРБ), білок гострої фази, що синтезується печінкою у відповідь на підвищений рівень IL-6. Це простий та надійний лабораторний маркер для оцінки системного запалення. Не менш важливим є вплив стресу на кишковий мікробіом – «другий мозок» організму. Тривалий або інтенсивний стрес викликає значні зміни у складі кишкової мікробіоти. Постійне підвищення рівня кортизолу, адреналіну та норадреналіну створює несприятливе середовище для росту корисних бактерій, таких як лактобактерії та біфідобактерії, а також сприяє проліферації умовно-патогенних мікроорганізмів (клостридії, кишкова паличка та ентерокок). Цей стан відомий як дисбактеріоз.

Таким чином, біохімічні наслідки хронічного стресу включають гормональні зміни (підвищення кортизолу); оксидативні процеси (накопичення вільних радикалів); імунні порушення (зростання рівня запальних цитокінів); метаболічні зрушення (гіперглікемія, дисліпідемія); зниження адаптаційного потенціалу організму.

Поєднання цих процесів сприяє розвитку синдрому хронічної втоми, зниженню стійкості організму до інфекцій та, в довгостроковій перспективі, передчасному старінню клітин.

**Висновок.** Аналіз показує, що тривалий стрес, спричинений кризовими ситуаціями, має глибокий системний вплив на організм людини, порушуючи його біохімічний баланс. Хронічний психоемоційний стрес активує гіпоталамо-гіпофізарно-надниркову вісь, що супроводжується надмірною секрецією кортизолу, адреналіну та норадреналіну. Це призводить до гормональних, імунологічних, метаболічних і навіть епігенетичних змін, що створюють стан хронічного біохімічного стресу. Високий рівень прозапальних цитокінів (IL-6, TNF- $\alpha$ , С-реактивний білок) вказує на активацію системного запалення, яке поєднує фізіологічні та психологічні реакції на довгострокові негативні фактори. Особливої уваги заслуговує порушення кишкового мікробіома – «другого мозку» людини, що посилює емоційне виснаження, порушує баланс нейромедіаторів та підвищує ризик розвитку депресії.

Отримані дані підтверджують, що біохімічні зміни при хронічному стресі мають не лише тимчасовий, а й довготривалий ефект, який впливає на здоров'я,

адаптаційні можливості та навіть спадкові механізми регуляції. В умовах сучасних викликів, зокрема тривалих кризових подій і війни в Україні, вивчення біохімії стресу набуває стратегічного значення – як для охорони психофізичного здоров'я населення, так і для розробки нових профілактичних підходів, спрямованих на підтримання стійкості організму до дії хронічних стресорів.

## **СИСТЕМНІ РЕГУЛЯТОРНІ КЛІТИНИ (SRC) ЯК ПОТЕНЦІЙНИЙ ФАКТОР УПОВІЛЬНЕННЯ СТАРІННЯ У ПРИМАТІВ: ДОКАЗИ ТА ПЕРСПЕКТИВИ ТРАНСЛЯЦІЇ НА ЛЮДИНУ**

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**Вступ.** Старіння – це складний багаторівневий процес, який охоплює все: від клітин до систем організму. Воно супроводжується поступовою деградацією тканин, зниженням функції стовбурових клітин та накопиченням пошкоджених макромолекул. Як наслідок, зростає ризик хронічних захворювань – серцево-судинних, нейродегенеративних, метаболічних порушень, а також ослаблення імунної системи. Ключовими факторами, що прискорюють старіння, є хронічне запалення та окисний стрес, які руйнують клітини та порушують гомеостаз організму.

Серед перспективних підходів до уповільнення старіння особливе місце займають системні регуляторні клітини (SRC). Це генетично модифіковані мезенхімальні клітини-попередники, стійкі до стресу та старіння, здатні модулювати імунну відповідь, знижувати рівень запальних цитокінів і стимулювати відновлення тканин. Вони демонструють мультисистемний ефект, одночасно підтримуючи когнітивну, репродуктивну, опорно-рухову та імунну функції.

Експерименти на старіючих маках показали, що введення SRC може уповільнювати біологічне старіння, покращуючи фізіологічні та біохімічні показники. Ці дослідження відкривають перспективу створення нових фармакологічних стратегій для підтримки здоров'я та профілактики вікових захворювань у людей. Оцінка безпеки, ефективності та молекулярних механізмів дії SRC у приматів створює критичну основу для майбутніх клінічних випробувань, наближаючи нас до епохи персоналізованих терапій старіння.

**Мета дослідження.** Оцінити вплив системних регуляторних клітин (SRC) на фізіологічні та біохімічні показники приматів, визначити механізми, за допомогою яких ці клітини можуть уповільнювати старіння, а також оцінити



перспективи застосування SRC у людини для потенційних терапевтичних стратегій.

**Матеріали та методи.** У роботі проведено системний аналіз опублікованих досліджень щодо впливу системних регуляторних клітин (SRC) на старіння приматів. Основою для аналізу стали дослідження, проведені в Китаї та підтверджені 13 червня 2025 року, із використанням приматів віком від 10 до 25 років, що дозволяє оцінити ефекти SRC у різні періоди дорослого життя. Для аналізу застосовували порівняння фізіологічних і біохімічних показників, структуроване виділення результатів за органами системами та узагальнення ефектів SRC з акцентом на мультисистемний вплив і перспективи трансляції отриманих даних на людину. Такий підхід дозволив систематизувати інформацію та виділити ключові механізми дії SRC.

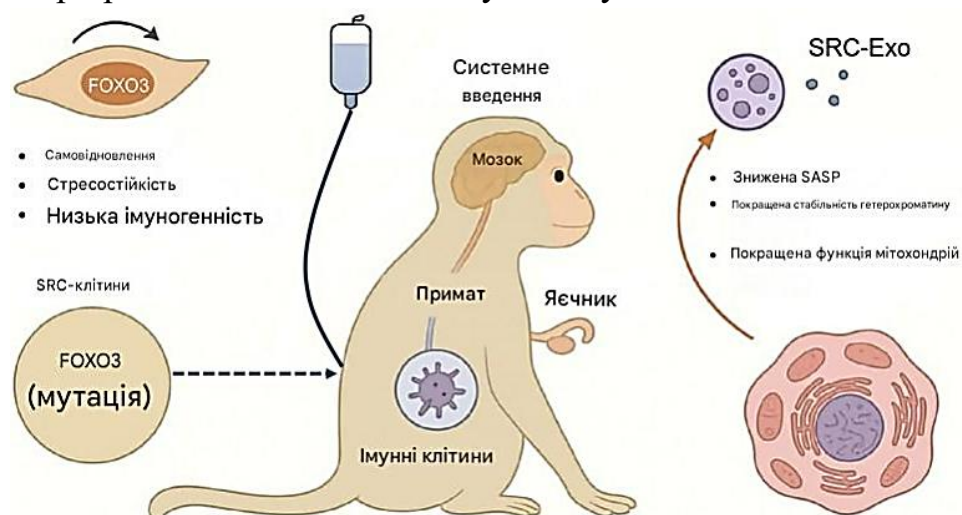
**Результати та обговорення.** З віком здатність організму до самовідновлення та регенерації поступово знижується через виснаження популяцій стовбурових клітин, зменшення їхньої проліферативної активності та підвищену сенесценцію. Сенесценція - це стан клітин, при якому вони втрачають здатність ділитися, але залишаються життєздатними. Такі клітини перестають виконувати свої нормальні функції і часто виділяють молекули, що спричиняють запалення та пошкодження сусідніх тканин.

Можна уявити місто, де будівельники постійно ремонтують і зводять споруди, але з часом їхня кількість зменшується, і інфраструктура починає руйнуватися. У біологічному контексті це проявляється погіршенням відновлення тканин, накопиченням пошкоджених клітин і прогресуванням вікових дегенеративних процесів, таких як остеопороз, атрофія мозку та фіброз органів. Протягом багатьох років науковці вивчали можливість використання трансплантації стовбурових клітин для уповільнення старіння, проте складність інтеграції, ризик пухлиногенності та імунні реакції ускладнювали їх практичне застосування.

У дослідженні, опублікованому 13 червня 2025 року в Cell, група Китайської академії наук та Столичного медичного університету продемонструвала прорив у терапії старіння за допомогою стійких до старіння мезенхімальних клітин-попередників (SRC), генетично перепрограмованих для підвищеної стійкості до стресів і сенесценції. Ці клітини, подібні до «надзаряджених будівельників», зберігають високу проліферативну активність, не утворюють пухлин і здатні тривало інтегруватися в тканини.

Протягом 44-тижневого дослідження літнім макакам, біологічно еквівалентним людям 60-70 років, внутрішньовенно вводили SRC у дозі

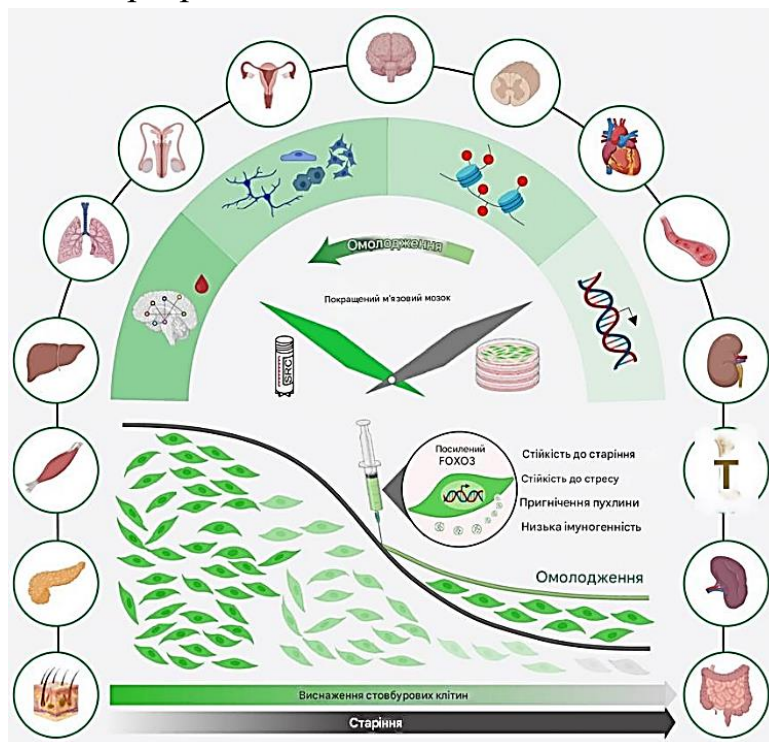
$2 \times 10^6$  клітин/кг кожні два тижні. Жодних клінічно значущих побічних ефектів не зафіксовано: ні лихоманки, ні надмірних імунних реакцій, ні втрати ваги. Гістопатологія підтвердила відсутність ушкодження тканин, запалення та пухлиногенності, що свідчить про високий профіль безпеки SRC та долає ключовий бар'єр для можливого застосування у людей.



Ефекти SRC охоплювали декілька систем організму. У нервовій системі терапія сприяла значному покращенню когнітивних функцій, навчальної здатності та просторової пам'яті. Гістологія показала зменшення атрофії гіпокампа, збільшення кількості нейронних попередників та зниження накопичення вікових маркерів дегенерації, таких як бета-амілоїд і фосфорильований тау. Ці молекули є ключовими показниками нейродегенерації та старіння мозку, особливо при хворобі Альцгеймера. Зменшення їх накопичення, що спостерігалось під час SRC-терапії, асоціюється з покращенням когнітивних функцій і пам'яті. Одноклітинний аналіз продемонстрував зменшення старіючих клітин у периферичній крові на 33%, регрес вікових змін у гіпокампі на 42% і омолодження тканини яєчників на 45%. Ці зміни супроводжувалися підвищенням геномної стабільності, відновленням протеостазу та зниженням хронічного запалення, що підтверджує системний омолоджувальний ефект SRC.

У скелетно-м'язовій системі SRC сприяли відновленню щільності кісткової тканини, покращенню мікроархітектури кісток і підвищенню їхньої стійкості до переломів, демонструючи потенціал клітинної терапії для боротьби з віковими змінами опорно-рухового апарату. Репродуктивна система також реагувала на терапію: відновлювалася чисельність ооцитів та сперматозоїдів, зменшувалася дегенерація тканин, що підтверджує здатність SRC підтримувати гормональний гомеостаз та репродуктивне здоров'я.

Основним механізмом омолоджувальної дії SRC є виділення екзосом - малих везикул, що переносять білки, мРНК та мікроРНК, які регулюють запалення, стабільність геному та протеостаз. Екзосомы омолоджують нейрони, ендотеліальні клітини, гепатоцити та клітини яєчників, пригнічують хронічне запалення і активують програми клітинного відновлення. Дослідження *in vitro* та на мишах показали, що екзосомы SRC зменшують дегенерацію органів і стимулюють клітинні програми відновлення.



Поєднання SRC із геропротекторами, зокрема метформіном, може посилювати системний омолоджувальний ефект, підвищувати нейропротекцію та підтримувати метаболічний гомеостаз. Для трансляції на людину важливо забезпечити стандартизацію клітинних продуктів, контроль інтеграції у тканини, довготривалу безпеку та розробку біомаркерів для оцінки ефективності терапії.

**Висновки.** Системні регуляторні клітини (SRC) демонструють здатність одночасно впливати на кілька фізіологічних систем, відновлювати функціональні резерви організму та омолоджувати клітинні й тканинні структури у приматів, близьких до людини за біологічними характеристиками. Тривале внутрішньовенне введення SRC показало їхню безпечність: не спостерігалось імуногенних реакцій, або пухлиногенності.

Мультисистемний омолоджувальний ефект включав значне покращення когнітивних, репродуктивних, опорно-рухових та імунних функцій. Молекулярні механізми дії, зокрема через екзосомы, сприяли підвищенню стабільності геному, пригніченню хронічного запалення та стимуляції популяцій

клітин-попередників у різних тканинах.

Отримані дані підтверджують високий потенціал SRC як геропротекторної терапії, відкриваючи нові можливості для регенеративної медицини та майбутніх клінічних випробувань у людей. Для успішної трансляції на людину необхідно додатково опрацювати стандарти виробництва клітин, оптимізацію умов культивування та оцінку довготривалої безпеки, що створює основу для протидії віковій мультиморбідності - одночасній наявності у людини декількох хронічних захворювань, або патологічних станів (наприклад, остеопороз, серцево-судинні хвороби, цукровий діабет, когнітивні розлади) та підвищення якості життя в старшому віці.

### **НАСЛІДКИ ВПЛИВУ ПЕРОКСИДУ ВОДНЮ НА ЕРИТРОЦИТИ, КРІОКОНСЕРВОВАНІ У МОДИФІКОВАНОМУ ЗА СКЛАДОМ КРІОКОНСЕРВАНТІ З ГЛІЦЕРИНОМ.**

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**Вступ.** При гіпотермічному зберіганні еритроцитів розвивається окислювальний стрес, при якому окислення гемоглобіну (Hb) призводить до утворення метгемоглобіну (metHb) та супероксид-аніонів ( $O_2^-$ ). Супероксид нейтралізується супероксиддисмутазою з утворенням пероксиду водню, який може розкладатися за допомогою  $Fe^{2+}$  або гемоглобіну- $Fe^{2+}$  з утворенням гідроксильного радикалу (OH). •OH реагує з поліненасиченими жирними кислотами мембран та ініціює процес перекисного окислення ліпідів (ПОЛ), що призводить до утворення гідроперекисів жирних кислот та руйнування клітинних мембран.

**Мета дослідження.** Підвищення стійкості кріоконсервованих еритроцитів до дії пероксиду водню при зміні складу кріоконсерванту з гліцерином.

**Матеріали та методи.** В роботі досліджували осмотичні, морфологічні та окисдантні характеристики еритроцитів після заморожування у кріоконсервантах, що містять: 1) 38% гліцерину, 2,9% сорбітолу, 0,63% NaCl (стандартний склад); 2) 38% гліцерину, 6,8% сорбітолу, 0,27% NaCl (модифікований склад).

**Результати та обговорення.** Показано, що при використанні 1-го кріоконсерванту ступінь втрати клітин після відтавання та відмивання еритроцитів становив 13-17%, тоді як при використанні 2-го кріоконсерванту –

8-12%. Після відтавання та відмивання кріоконсервованих еритроцитів відзначаються незначні зміни у вмісті антиоксиданту глутатіону та малонового діальдегіду як у 1-му, так і у 2-му варіантах складу кріоконсерванту. Дослідження осмотичного гемолізу показало, що осмотична крихкість еритроцитів після кріоконсервування у 2-х зазначених кріоконсервантах не суттєво відрізняється від такої для інтактних клітин. Еритроцити, відмиті після кріоконсервування у 2-х варіантах кріоконсерванту морфологічно представлені дискоехіноцитами з невисоким ступенем дискоцитів (нормоцитів). Включення до експериментального середовища стабілізатора дискоїдних форм еритроцитів альбуміну викликає трансформацію клітин у дискоцити на 75-85%. Разом з тим, вплив на суспензію еритроцитів (0,7% гематокрит) пероксиду водню призводить до зниження оптичної щільності (ОЩ) суспензії на довжині хвилі 543нм і підвищення ОЩ при 632нм. Ці зміни свідчать про окислення гемоглобіну з утворенням метгемоглобіну. Зміни ОЩ більш виражені для інтактних клітин та клітин, кріоконсервованих у стандартному кріоконсерванті, порівняно з еритроцитами, кріоконсервованими у модифікованому кріоконсерванті. Подальше центрифугування та ресуспендування осадів не викликає порушення характеру змін ОЩ клітинних суспензій. У той же час, при впливі пероксиду водню на гемолізати досліджених зразків, не виявлено відмінностей у ОЩ гемолізатів інтактних та кріоконсервованих клітин у 2-х використаних кріоконсервантах. Крім того, дія пероксиду водню на інтактні клітини у фізрозчині та клітини у кріоконсервантах без заморожування не виявляє описаних відмінностей ОЩ. Морфологічно інтактні еритроцити та еритроцити, заморожені в стандартному кріоконсерванті при дії пероксиду водню, більшою мірою представлені ехіноцитами (~30%) порівняно з клітинами, замороженими в модифікованому кріоконсерванті (~10%). Отримані результати вказують на те, що модифікація структури мембран при заморожуванні в зміненому за складом кріоконсерванті, є причиною ослаблення ушкоджуючої дії пероксиду водню.

#### **Висновки.**

1. Ослаблення інтенсивності наростання гіпертонічного сольового (NaCl) стресу на клітинні мембрани при заморожуванні еритроцитів у модифікованому за складом кріоконсерванті забезпечує менший ступінь втрати клітин.
2. Менша вираженість змін ОЩ суспензії еритроцитів, кріоконсервованих у модифікованому кріоконсерванті при дії пероксиду водню, ймовірно, визначається послабленням гіпертонічного стресу і підвищенням у кріоконсерванті сорбітолу.
3. Зміна складу кріоконсерванту може бути фактором модифікації



структури клітинної мембрани при заморожуванні, оскільки без заморожування різниці дії пероксиду водню на ОЩ суспензій інтактних клітин та клітин у кріоконсервантах не виявляється.

4. Підвищення стійкості еритроцитів, кріоконсервованих у модифікованому кріоконсерванті, до шкідливої дії окислювального стресу, може забезпечити підвищену стійкість до гіпотермічного зберігання. Крім того, еритроцити, кріоконсервовані у зазначеному кріоконсерванті можуть мати стійкість до окислювального стресу в руслі крові при переливанні пацієнтам, які страждають на гематологічні захворювання, а також на злоякісні новоутворення.

## **LORATEDINE IN COMBINATION WITH *BUPLEURUM AUREUM* PHYTOCOMPONENT: A NEW APPROACH TO THE TREATMENT OF ALLERGIC DISEASES IN CHILDREN**

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**Introduction.** Modern pharmacotherapy of allergic diseases requires the development of safe, effective and hepatoprotective agents, especially for pediatric practice. The combination of the synthetic antihistamine loratadine with the extract of *Bupleurum aureum* opens new possibilities in the direction of combining antiallergic, anti-inflammatory and antioxidant effects.

**The aim of the research.** Prospects for the use of a combined preparation of loratadine with *Bupleurum aureum* extract.

**Materials and methods.** A literature review was conducted in international peer-reviewed journals and databases (PubMed, PMC). Selected sources cover the last 5-10 years and include *in vitro* and *in vivo* studies.

**Results and discussion.** Loratadine is a second-generation selective histamine H1 receptor antagonist. Its main action is associated with blocking histamine receptors without penetrating the blood-brain barrier, which ensures the absence of a sedative effect. In biochemical terms, loratadine also exhibits antioxidant activity, reducing the level of malondialdehyde and increasing the activity of superoxide dismutase in hepatocytes. It is metabolized mainly by the CYP3A4 and CYP2D6 systems in the liver with the formation of the active metabolite desloratadine. *Bupleurum aureum* extract contains flavonoids (quercetin, rutin, isorhamnetin), saponins, phenolic acids and terpenoids, which cause antioxidant, anti-inflammatory, diuretic and immunomodulatory effects. Biochemically, *Bupleurum aureum* flavonoids inhibit cyclooxygenase-2 (COX-2) activity and reduce the expression of TNF- $\alpha$ , IL-6, and

other pro-inflammatory cytokines. *Bupleurum aureum* extract has been shown to exhibit hepatoprotective properties, reducing ALT, AST, and bilirubin levels in experimental models of toxic liver injury.

The combined use of loratadine and *Bupleurum aureum* extract can provide a synergistic effect: flavonoids enhance the antioxidant protection of liver cells and stabilize cell membranes, loratadine reduces histamine-mediated vascular permeability, which in total reduces systemic inflammation, allergic reactions and oxidative stress. Such a combination is promising for use in children with allergic diseases that are accompanied by impaired liver function or require long-term use of antihistamines. Further studies will be aimed at creating a dosage form in the form of a syrup with a mild hepatoprotective effect.

**Conclusions.** The biochemical interaction between loratadine and *Bupleurum aureum* extract forms the basis for the creation of a new generation of combined antihistamines with additional antioxidant and anti-inflammatory properties. This opens prospects for their implementation in pediatric allergology and pharmacotherapy, taking into account the hepatoprotective potential of the phytocomponent.

### **EFFECT OF *BUPLEURUM AUREUM* EXTRACT AND ITS COMBINED USE WITH LORATADINE ON LIPID PEROXIDATION INDICATORS UNDER THE ACTION OF CADMIUM CHLORIDE *IN VITRO***

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**Introduction.** Today, pharmaceutical sciences and medicine are faced with the urgent problems of studying the negative impact of xenobiotics and finding ways to correct these pathologies. Data is rapidly accumulating, indicating that many stress factors, xenobiotic poisoning, including the negative impact of drugs, cause a shift in the balance in the pro-oxidant-antioxidant system and the development of oxidative stress. Therefore, an urgent problem is to study the impact of various substances that may have antioxidant properties on the studied indicators.

**The aim of the work** – to investigate the effect of dry extract of *Bupleurum aureum* (DEBA) and its combined use with the drug loratadine on lipid peroxidation indices *in vitro* under the influence of cadmium chloride.

**Materials and methods.** *In vitro* experiments were carried out to determine the antioxidant properties of dry DEBA and the combination of loratadine with DEBA. For this purpose, blood serum and liver cytosol of male white rats weighing

180-220 g, which were kept under standard conditions of the NUPh vivarium, were used. Blood serum and liver cytosol were incubated for 30 minutes at 37°C in three variants: without any additives, with the addition of cadmium chloride solution (at the rate of 280 µg/ml serum or 2.8 mg/ml cytosol) and with the addition of cadmium chloride (the same dose) and DEBA and the combination of loratadine with DEBA (at the rate of 1 mg/ml serum or 10 mg/ml cytosol).

**Results and discussion.** As a result of the study, it was found that incubation of blood serum and liver cytosol in the presence of cadmium chloride causes the accumulation of lipid peroxidation products. The obtained results indicate that under conditions of oxidative stress, the preliminary administration of both the goldenseal extract and its combination with loratadine significantly improves the oxidative state of the studied objects. The level of lipid peroxidation products is significantly reduced; the content of isolated double bonds increases compared to the effect of cadmium chloride. It was found that *in vitro* DEBA and its combined use with the drug loratadine also protects lipoproteins of blood serum and liver cytosol from peroxidative damage.

**Conclusions.** The results of the conducted studies indicate a high level of antioxidant activity of DEBA and its combination with loratadine *in vitro*, which indicates the feasibility of further studying their combined use *in vivo*.

## EFFECT OF THE PHYTOEXTRACT FROM *BUPLEURUM AUREUM* AND ITS COMBINED USE WITH LORATADINE ON THE PARAMETERS OF LIPID PEROXIDATION UNDER THE ACTION OF CADMIUM CHLORIDE *IN VIVO*

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**Introduction.** This work is a continuation of the cycle of works on the pharmacological study of dry extract of *Bupleurum aureum* (DEBA), which contains phenolic compounds, flavonoids, saikosaponins, tannins, phytosterols, amino acids, micro- and macroelements and has long been used in folk medicine for the treatment of liver diseases, exhibits choleretic, anti-inflammatory, detoxifying, wound-healing effects. Among the substances that make up this extract, there is a significant number of various flavonoids, in particular, quercetin, the antioxidant effect of which is well known.

**The aim of the work.** This series of experiments investigated the effect of DEBA and its combined use with the drug loratadine on lipid peroxidation (LPO) indices *in vivo* under the influence of cadmium chloride.

**Materials and methods.** *In vivo* experiments were used outbred white mice of both sexes weighing 20-25 g. The object of the study was the liver cytosol and blood serum. Cadmium chloride was injected intraperitoneally to mice once at a dose of 1.96 mg per 100 g of body weight. 3 days before the injection of CdCb, some animals (some animals) were injected intragastrically with dry DEBA and its combination with the drug loratadine in effective doses, which were previously selected. The remaining animals were administered orally with DEBA and a combination of the drug loratadine with DEBA in effective doses 2 hours before the injection of cadmium chloride. The oxidative state of the liver cytosol and blood serum was studied.

**Results and discussion.** According to the results of the studies, it was found that the administration of sublethal doses of cadmium chloride to mice causes a picture typical of oxidative stress: 2 hours after injection, the level of isolated double bonds decreases by more than 4 times, the content of POL products increases by 2 times. At the same time, the administration of DEBA and its combination with the drug loratadine to animals did not affect the POL indicators. Prophylactic administration of DEBA and its combination with loratadine to animals under the influence of cadmium chloride significantly reduced the number of POL products, although not to the norm. It should be noted that the administration of sublethal doses of cadmium chloride is too strong a stress that animals (like humans) almost never encounter in natural conditions, except for acute poisoning. Even with such extreme exposure, DEBA and its combined use with loratadine proved to be a powerful antioxidant complex, which makes it a valuable object for further research.

**Conclusions.** The results of the conducted studies indicate a high level of antioxidant activity of DEBA and its combined use with the drug loratadine, which indicates the feasibility of further pharmacological study of this combination.

## РОЛЬ ФЕРМЕНТІВ У ФОРМУВАННІ ТА РУЙНУВАННІ БІОПЛІВОК

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**Вступ.** Утворення біоплівки є однією з найсерйозніших проблем сучасної медицини, оскільки вони відіграють ключову роль у розвитку хронічних та рецидивуючих інфекцій. Сучасні антибіотики та антисептики продемонстрували обмежену здатність повністю видаляти біоплівки. Здатність біоплівок до тривалого існування в організмі та високий рівень антибіотикорезистентності

створюють потребу в нових терапевтичних підходах. Одним із перспективних напрямів є використання ферментів, здатних руйнувати матрикс біоплівки та підвищувати ефективність антимікробної терапії. Таким чином, дослідження механізмів формування та деструкції біоплівок, зокрема за участю мікробних ферментів, є надзвичайно актуальним завданням сучасної медицини.

**Мета дослідження.** Аналіз функціональної ролі мікробних ферментів у процесах формування, стабілізації та деструкції біоплівок, а також оцінка їхнього потенціалу як біологічних агентів для контролю та усунення біоплівкових структур у медичних і біотехнологічних системах.

**Матеріали та методи.** В роботі проведено аналіз сучасних науково-дослідних матеріалів з використанням медичної бази даних Medscape, PubMed, публікацій фахових видань за темою дослідження.

**Результати та обговорення.** Біоплівки є мікробними спільнотами, які живуть в асоціації з біотичними/абіотичними поверхнями і укладені в позаклітинний матрикс (полімерну речовину). Біоплівка може складатися з одного або кількох видів мікроорганізмів. Мікробні ферменти відіграють ключову роль у формуванні, структурі та стійкості біоплівок, сприяючи міжклітинній взаємодії, захисту та адаптації мікроорганізмів. Так, у формуванні білкових і ліпідних компонентів матриці беруть участь протеази та ліпази; глікозилтрансферази беруть участь у синтезі полісахаридів, які є основою матриці біоплівки; наявні ферменти, що регулюють синтез сигнальних молекул, які координують поведінку клітин у біоплівці, що дозволяє мікроорганізмам адаптуватися до змін середовища та регулювати щільність популяції. Низка ферментів мікроорганізмів біоплівок беруть участь у перебудові їх структури, дозволяючи їй рости, змінювати форму або відокремлювати частини для колонізації нових поверхонь. Здатність мікроорганізмів прикріплюватись завдяки адгезинам активованих ферментами до поверхонь та створювати біоплівки є найважливішим механізмом виживання у природі. Мікроорганізми кворум-системи здатні підвищувати свою вірулентність і резистентність, зокрема до антимікробних агентів, захищають біоплівку від імунної відповіді (каталаза та супероксиддисмутаза). Інфекції, пов'язані з біоплівкою становлять близько 80% бактеріальних інфекцій у людини. Біоплівки, що утворюються на тканинах людини та поверхнях медичних пристроїв (імпланти, катетери), беруть участь у патогенезі хронічних бактеріальних інфекцій (наприклад, інфекції сечовивідних шляхів, ортопедичні інфекції, інфекції порожнини рота, ранові інфекції, пневмонія), сприяють тривалому перебуванню у лікарні, здатні призвести до смерті та збільшенню витрат на охорону здоров'я.



Видалення біоплівки становить серйозну проблему в медичній практиці, особливо коли йдеться про живі системи, де застосування хімічних засобів і високих температур є неприйнятним. Традиційні антимікробні методи ефективно знищують планктонні мікроорганізми, але не здатні знищити мікроколонії організовані у біоплівки через обмеження проникнення антибіотиків у її глибокі шари і втрату препарату через активність пошкоджуючих ферментів. Тому вважається, що необхідність видалення біоплівки потребує альтернативних, інноваційних підходів, зокрема застосування ферментів, які володіють високою специфічністю та здатні ефективно руйнувати структурну цілісність матриксу біоплівки.

Порушення цілісності біоплівки можна здійснити за допомогою деградуючих ферментів. Для успішного видалення складних біоплівок пропонується використання складної асоціації ферментів, яка містить ДНКазу (для деградації позаклітинної ДНК), CDH (для гідролізу позаклітинних полісахаридів), протеази (для гідролізу білків) та антикворумні ферменти (для запобігання утворенню біоплівки). Ферменти можуть регулювати процес біообростання, видаляючи різні види конгломератів мікроорганізмів та білків з різних біотичних/абіотичних поверхонь. Наприклад, мананази можуть порушувати адгезію *P. aeruginosa* і *S. aureus*, можуть перешкоджати бактеріальній комунікації, знижуючи вірулентність та здатність утворювати біоплівку таких патогенів, як *P. aeruginosa*.

Крім того, численні ферменти, що продукуються бактеріями, грибами та водоростями, мають здатність змінювати структуру біоплівок, руйнуючи екзополісахарид, позаклітинну ДНК і білок, що міститься в EPS (слизоподібних речовинах, які бактерії виділяють назовні), або перешкоджаючи почуттю кворуму. Вони також вивчаються як потенційні антибіоплівкові агенти для клінічного застосування. Наприклад, фермент Dispersin B (глікозидгідролаза), що володіє широким спектром дії є продуктом життєдіяльності бактерії *Aggregatibacter actinomycetemcomitans*. Dispersin B продемонстрував здатність інгібувати утворення біоплівок і плівок, відшаровувати вже існуючі біоплівки, руйнувати бактеріальні кластери і підвищувати сприйнятливість вже сформованих біоплівок до відшарування ферментами, до руйнування антисептиками та антибіотиками. В даний час Dispersin B представляє інтерес як комерційний антибіоплівковий агент, який можна комбінувати з антибіотиками для лікування бактеріальних інфекцій. Вибір одного ферменту чи його комбінації залежить від хімічної природи матриксу біоплівки.

Ферментативні методи продемонстрували значний потенціал для

руйнування бактеріальних біоплівки та покращення лікування інфекцій, пов'язаних з біоплівками, які часто стійкі до традиційної антимікробної терапії. Не зважаючи на значні ефекти у диспергуванні біоплівки ферментативні методи мають ряд недоліків, які можуть обмежувати їх ефективність. Наприклад, демонструють різну ефективність проти різних складів біоплівки, що може призводити до неповного видалення біоплівки, у деяких випадках спостерігається відсутність синергії, що обмежує їхню загальну ефективність, необхідність врахування негативного впливу рН і температури, які не завжди можуть бути оптимальними для функції ферменту. Тим не менше, ферментативні методи залишаються цінною областю досліджень, особливо у поєднанні з іншими антимікробними стратегіями. На сучасному етапі завдяки методам синтетичної біології, дослідники розробили генетично модифіковані бактерії, здатні продукувати ферменти з підвищеною активністю проти біоплівки. Кім з групою дослідників розробили новий клас химерних літичних ферментів, використовуючи технологію модульної збірки. Технологія включає в себе розробку конструкцій ферментів з поліпшеними антимікробними властивостями шляхом поєднання різних функціональних доменів з підвищеною активністю і специфічністю проти біоплівки MRSA.

**Висновки.** Мікробні ферменти відіграють ключову роль на всіх етапах життєвого циклу біоплівки – від їх формування до деструкції. Водночас, певні ферментативні системи здатні порушувати структурну стабільність біоплівки, що відкриває перспективи для їх використання у боротьбі з хронічними інфекціями та біоплівковою резистентністю. Зважаючи на високу специфічність, біосумісність та ефективність ферментів, їх застосування є особливо актуальним у живих системах, де недопустиме використання агресивних хімічних агентів. Подальші дослідження у цьому напрямі можуть сприяти розробці нових терапевтичних стратегій для контролю біоплівки у медицині та біотехнології.

## ПЕРЕБІГ АВТОІМУННОГО ТИРЕОЇДИТУ В УМОВАХ ХРОНІЧНОГО ПСИХО-ЕМОЦІЙНОГО СТРЕСУ (ЕКСПЕРИМЕНТАЛЬНІ ДОСЛІДЖЕННЯ)

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**Вступ.** Поширеність аутоімунного тиреоїдиту (АІТ) в Україні складає від 3 до 11% населення. Це захворювання призводить до хронічного порушення

роботи щитоподібної залози (ЩЗ) та виникненню в подальшому гіпотиреозу. Основні виклики цього захворювання включають прихований перебіг хвороби, вплив на якість життя, ускладнення з боку серцево-судинної та репродуктивної систем, необхідність довічного контролю.

Відомо, що стрес, ушкодження імунної та ендокринної системи тісно пов'язані одне з одним. За умов війни на тлі стресів різного походження спостерігається розбалансування усіх ланок гомеостазу внаслідок чого не тільки зростають ризики виникнення нових випадків захворюваності, а й загострюється перебіг хронічних захворювань, в тому числі і тиреопатій.

**Метою** нашого дослідження стало вивчення перебігу експериментального автоімунного тиреоїдиту за умов впливу психоемоційного стресу.

**Матеріали та методи.** Дослідження проведено на 60 статевозрілих самцях щурів. Експериментальний автоімунний тиреоїдит у щурів викликали шляхом імунізації тварин антигеном екзогенної ЩЗ, в комбінації з повним ад'ювантом Фрейнда. Для вивчення впливу психоемоційного стресу на функціональну активність ЩЗ використовували модель хронічного психологічного стресу, викликаного звуковим навантаженням (крик щура з яким проводять лабораторні маніпуляції), гучністю від 45 до 60 дБ, по 3 години вранці та 3 годин ввечері впродовж 21 дня. Вивчалися моделі окремого та поєданого впливу.

Верифікацію індукції АІТ проводили за гормональними показниками, вплив стресу – за тестами та рівня кортикостерону. Вивчалися функціональні показники щитоподібної залози в динаміці 1 та 3 місяці.

**Результати та обговорення.** Аналіз стану тиреоїдної системи щурів в динаміці створення моделі АІТ в комбінації з психоемоційним стресом та окреме психоемоційне навантаження показав наступне. Через 1 місяць після моделювання АІТ відбувалося розбалансування функціонального стану залози. На цьому терміні спостерігалася тенденція до зростання відносної маси ЩЗ, значне підвищення обох форм тиреоїдних гормонів (Т3 та Т4) та двократним збільшенням рівня антитіл до тиреоглобуліну (АТ ТГ) у сироватці крові. Такі дані вказували на гострий розвиток автоімунного процесу, так звану першу стадію (гіпертрофічну форму), яка характеризується «гормональною бурєю» та розбалансуванням ланки гуморального імунітету.

В групі інтактних щурів (без моделювання АІТ) що піддавалися психоемоційному стресу щурів на цьому терміні дослідження спостерігалася гальмування функціональної активності ЩЗ, яке супроводжувалося зростанням титру АТ ТГ майже вдвічі (дещо в меншій мірі порівняно з групою АІГ), відмічалася значуще, практично двократне зменшення вмісту Т3 загального (на

45%,  $P < 0,05$ ) та тенденція до зниження концентрації Т4 загального в циркулюючій крові (на 19%,  $0,05 \leq P \leq 0,02$ ). При цьому значуще, порівняно з групою інтактного контролю та групою АІГ, зростає індекс співвідношення Т3/Т4 у бік превалювання саме Т4. Така невідповідність зміни динаміки обох форм йодованих тиронінів може бути обумовлена тим, що на фоні гальмування утворення Т4 в самій ЩЗ, відбувається порушення його конверсії у Т3 у нирках та печінці, оскільки ці органи значною мірою першочергово реагують на стрес.

У відповідь на падіння вмісту тиреоїдних гормонів у крові стресованих тварин концентрація ТТГ зростала на 62% ( $p < 0,05$ ), що свідчило про збереження нормальних регуляторних взаємин у системі гіпофіз-щитовидна залоза. Таким чином, психоемоційний стрес, протягом 21 доби, призводив до гіпофункції ЩЗ.

Комбінована експериментальна патологія (стрес на тлі АІГ) призводила до значного розбалансування гуморального імунітету. У щурів цієї групи відмічається найбільше зростання титру АТ ТГ. І хоча через місяць рівень тиреоїдних гормонів у групі комбінованої патології були вищими ніж у групі з психоемоційним стресом, через три місяці спостереження ці показники вірогідно знижувалися, на відміну від групи яка піддавалася лише психоемоційному навантаженню.

Спостерігалася «рефракція» обох патологій: імунізація, що сприяла руйнуванню ЩЗ, та психоемоційне навантаження що виснажувало функціональну активність залози. Гіпотиреоз який виник в результаті комбінованої дії мав стійкий та незворотній ефект.

**Висновки.** Таким чином, в умовах автоімунного ураження ЩЗ психоемоційне навантаження призводить до стрімкого зниження функції залози та поглибленню автоімунної агресії, що призводить до незворотних змін у залозі. Психоемоційний стрес, як самостійний фактор впливу, сприяє гіпофункції залози та порушує периферичну конверсію йодованих тиронінів.



## АВТОРСЬКИЙ ПОКАЗЧИК AUTHOR'S INDEX

- Abuladze N. 57, 166, 276, 312  
Abzianidze E. 57, 166, 276, 312  
Alavidze N. 57, 166, 276, 312  
Butkevičiūtė M. 372, 454  
Chichoyan N. 57, 166, 276, 312  
Davitashvili M. 57, 144, 166, 276, 312  
Dubinina N.V. 494  
Filimonova N.I. 494  
Gabunia K. 57, 166, 276, 312  
Gabunia L. 25, 57, 166, 225, 276, 312  
Galuzinska L.V. 436  
Gerzmava O. 57, 166, 276, 312  
Giorgobiani M. 25, 57, 166, 225, 276, 312  
Gorgaslidze N. 25, 57, 166, 225, 276, 312  
Gradziuk M. 470  
Grigolia L. 57, 166, 276, 312  
Gurevičienė V. 372  
Kamuta R. 444  
Kantaria Temur 144  
Kantaria Tengiz 144  
Katsarava R. 144  
Kavaliauskaitė G. 458  
Kravchenko V. 57, 166, 276, 312  
Kukhtenko O.S. 436  
Kurhaluk Natalia 466, 470  
Kvizhinadze N. 57, 166, 276, 312  
Lartsuliani K. 25  
Makharadze D. 144  
Manskiy O.A. 436  
Misiurova S.V. 494  
Naboka O.I. 520, 521, 522  
Pasynchuk I.I. 520, 521, 522  
Patsia L. 25, 57, 144, 166, 276, 312  
Plantus V.M. 436  
Ratkevičiūtė K. 458  
Razumienė J. 372, 454  
Robakidze K. 57, 166, 276, 312  
Šakinytė-Urbikienė I. 372, 454  
Seniuk I. 57, 144, 166, 225, 276, 312, 444  
Serapinas S. 458  
Shamelashvili K. L. 491  
Sukackienė D. 372  
Sulashvili M. 25, 57, 166, 276, 312  
Sulashvili N. 25, 57, 144, 166, 225, 276, 312, 444  
Tadevosyan A. 57, 166, 276, 312  
Tarapata M.O. 436  
Tetianec L. 458  
Tishchenko I.Yu. 494  
Tkaczenko Halina 466, 470  
Tsintsadze T. 57, 166, 276, 312  
Zarnadze I. 25, 57, 166, 276, 312  
Zarnadze S. 25, 57, 166, 276, 312  
Zavradashvili N. 144  
Zbigniew M. 466  
Zemlianskykh N.G. 463  
Авідзба Ю.Н. 480  
Баранова Д.С. 500  
Березнякова М.Є. 482  
Белкіна І.О. 504  
Божок Г.А. 397  
Бойко М.О. 504  
Бондаренко В.О. 504  
Бречка Н.М. 504  
Галузінська Л.В. 403, 487, 509



- Гладких Ф.В. 364, 387, 476  
Гладченко О.М. 418  
Гойдіна В.С. 462  
Гончаров О.В. 409, 492  
Горшунська М.Ю. 425  
Горюнова І.О. 514  
Гуріна О.Е. 504  
Дробнер І.Г. 387  
Дубініна Н.В. 523  
Єршов С.С. 465  
Єршова Н.А. 465, 477  
Залюбовська О.І. 480  
Іванова С.В. 502  
Канколонго К.Д.Д. 507  
Карабут Л.В. 418, 480, 482, 484, 486  
Козар В.В. 380  
Козіна А.С. 473  
Колеснікова А.О. 425  
Комарова І.В. 526  
Коренєва Є.М. 504  
Кравченко В.М. 403, 409, 414, 492, 507  
Красова Н.С. 425  
Кустова С.П. 504  
Литвинова О.М. 473  
Лісецька І.С. 502  
Лядова Т.І. 364, 387, 476  
Ляшок А.Л. 476  
Макарова В.Д. 511  
Малашенко Н.І. 488  
Малова Н.Г. 526  
Мамонтова В.Д. 449  
Мамонтова Т.В. 449  
Мараховський І.О. 504  
Матвеєнко М.С. 364, 387, 476  
Матвійчук А.В. 418, 484  
Матвійчук О.П. 418, 418, 486  
Ніпот О.Є. 465  
Орлова К.Ю. 487  
Павлюк О.Д. 502  
Пахомов О.В. 397  
Петренко О.Ю. 397  
Підгайна В.В. 418, 480, 482  
Плохотніченко О.О. 425  
Попова М.Е. 431  
Проценко О.С. 504  
Рамазанов В.В. 518  
Ревенко О.Б. 397  
Ремньова Н.О. 504  
Рибачук О.А. 431  
Рогоза О.Є. 498  
Руденко С.В. 518  
Салій О.О. 431  
Сенюк І.В. 403, 409, 414, 492, 507, 509, 511  
Сиротенко Л.А. 526  
Смоленко Н.П. 504  
Студент В.О. 364  
Тижненко Т.В. 425  
Тіщенко І.Ю. 488, 523  
Ткаченко Н.О. 504  
Труфанова Н.А. 397  
Тюпка Т.І. 484  
Філімонова Н.І. 488  
Чабаненко О.О. 477  
Черкашина Д.В. 397  
Чиж М.О. 476  
Чумак Л.І. 504  
Шаповалова О.В. 380  
Шпакова Н.М. 465, 477  
Щербак О.А. 414, 523

## ЗМІСТ CONTENT

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |    |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----|
| ПРИВІТАННЯ ВІД ОРГАНІЗАТОРІВ КОНФЕРЕНЦІЇ<br>GREETINGS FROM THE CONFERENCE ORGANIZERS                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | 4  |
| ПОСВІДЧЕННЯ ПРО РЕЄСТРАЦІЮ ПРОВЕДЕННЯ ЗАХОДУ<br>CERTIFICATE OF REGISTRATION OF THE EVENT                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | 19 |
| ІНОЗЕМНІ КРАЇНИ-УЧАСНИКИ КОНФЕРЕНЦІЇ<br>FOREIGN COUNTRIES PARTICIPATING IN THE CONFERENCE                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | 20 |
| ЗАКЛАДИ ТА УСТАНОВИ МЕДИЧНОГО, ФАРМАЦЕВТИЧНОГО І<br>БІОЛОГІЧНОГО СПРЯМУВАННЯ, УЧАСНИКИ ЯКИХ<br>ПРЕДСТАВЛЕНІ НА КОНФЕРЕНЦІЇ<br>PARTICIPANTS OF THE CONFERENCE REPRESENT THE<br>FOLLOWING MEDICAL, PHARMACEUTICAL AND BIOLOGICAL<br>INSTITUTIONS                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | 21 |
| <b>СТАТТІ<br/>ARTICLES</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |    |
| <b>THE SCIENTIFIC DISCOURSE OF KEY ISSUE ASPECTS OF<br/>TRANSFORMING CARDIAC CARE: A CASE STUDY OF<br/>INNOVATION IN WEARABLE TECHNOLOGY FOR DETECTING<br/>AND MANAGING RAPID HEART RHYTHMS</b><br>Lali Patsia, Ketevan Lartsuliani, Nodar Sulashvili, Luiza Gabunia, Nana<br>Gorgaslidze, Marika Sulashvili, Marina Giorgobiani, Irine Zarnadze, Shalva<br>(Davit) Zarnadze                                                                                                                                                                                                                                                                                                                                              | 25 |
| <b>COMPREHENSIVE ANALYSIS AND CRITICAL EVALUATION OF<br/>THE DISTINGUISHING QUALITIES, FUTURE DIRECTIONS,<br/>CHALLENGES, OPPORTUNITIES, OBSTACLES, AND<br/>PROFESSIONAL DEVELOPMENT PROSPECTS OF THE<br/>PHARMACIST ROLE AND OCCUPATION IN CONTEMPORARY<br/>LOCAL AND GLOBAL CONTEXTS IN GENERAL</b><br>Nodar Sulashvili, Otar Gerzmava, Ada (Adel) Tadevosyan, Vira<br>Kravchenko, Elene Abzianidze, Naira Chichoyan, Luiza Gabunia, Nana<br>Gorgaslidze, Tamar Tsintsadze, Natia Kvizhinadze, Nato Alavidze, Nino<br>Abuladze, Ketevani Gabunia, Igor Seniuk, Lali Patsia, Marika Sulashvili,<br>Lela Grigolia, Kakhaber Robakidze, Magda Davitashvili, Marina<br>Giorgobiani, Irine Zarnadze, Shalva (Davit) Zarnadze | 57 |

**FUNDAMENTAL INSIGHTS INTO ADVANCING THE FUNCTIONALITY AND ADAPTABILITY OF BIODEGRADABLE TRIAZOLE-BASED 'CLICK' POLYMER LIBRARIES FOR DIVERSE BIOMEDICAL USES: CURRENT ACHIEVEMENTS, CHALLENGES, STRATEGIC DIRECTIONS, AND NOVEL PRACTICAL APPROACHES** 144

Tengiz Kantaria, Temur Kantaria, David Makharadze, Nino Zavrashvili, Nodar Sulashvili, Ramaz Katsarava, Magda Davitashvili, Lali Patsia, Igor Seniuk

**COMPREHENSIVE INVESTIGATION OF GENETIC INFLUENCES AND INDIVIDUALIZED THERAPEUTIC APPROACHES IN MANAGING MEDICATION-INDUCED TOXICITIES, SAFETY OVERSIGHT CHALLENGES, CAUSATIVE AGENTS, RISK FACTORS, AND EVIDENCE-BASED PHARMACOTHERAPY OPTIMIZATION** 166

Nodar Sulashvili, Otar Gerzmava, Ada (Adel) Tadevosyan, Vira Kravchenko, Elene Abzianidze, Naira Chichoyan, Luiza Gabunia, Nana Gorgaslidze, Tamar Tsintsadze, Natia Kvizhinadze, Nato Alavidze, Nino Abuladze, Ketevani Gabunia, Igor Seniuk, Lali Patsia, Marika Sulashvili, Lela Grigolia, Kakhaber Robakidze, Magda Davitashvili, Marina Giorgobiani, Irine Zarnadze, Shalva (Davit) Zarnadze

**THE MANIFESTATION OF COMPREHENSIVE ANALYSIS OF KEY ISSUES ASPECTS OF PHARMACEUTICAL WASTE IN THE ENVIRONMENT: ECOLOGICAL CONSEQUENCES, PUBLIC HEALTH RISKS, COMPLEX INTERACTIONS, RISK ASSESSMENT, AND STRATEGIC MITIGATION APPROACHES** 225

Nodar Sulashvili, Nana Gorgaslidze, Luiza Gabunia, Marina Giorgobiani, Igor Seniuk

**THE MANIFESTATION OF KEY ISSUES ASPECTS OF INTEGRATIVE PERSPECTIVES ON STEM CELL HETEROGENEITY, TRANSCRIPTIONAL REGULATION, HOMEOSTASIS, AND REGENERATIVE MEDICINE** 276

Nodar Sulashvili, Otar Gerzmava, Ada (Adel) Tadevosyan, Vira Kravchenko, Elene Abzianidze, Naira Chichoyan, Luiza Gabunia, Nana Gorgaslidze, Tamar Tsintsadze, Natia Kvizhinadze, Nato Alavidze, Nino Abuladze, Ketevani Gabunia, Igor Seniuk, Lali Patsia, Marika Sulashvili, Lela Grigolia, Kakhaber Robakidze, Magda Davitashvili, Marina Giorgobiani, Irine Zarnadze, Shalva (Davit) Zarnadze

**THE SCIENTIFIC DISCOURSE OF EXPLORING THE APPLICATION OF CONTEMPORARY EDUCATIONAL PRACTICES IN UNIVERSITY LEVEL MEDICAL-PHARMACEUTICAL TRAINING AROUND THE WORLD**

Nodar Sulashvili, Otar Gerzmava, Ada (Adel) Tadevosyan, Vira Kravchenko, Elene Abzianidze, Naira Chichoya, Luiza Gabunia, Nana Gorgaslidze, Tamar Tsintsadze, Natia Kvizhinadze, Nato Alavidze, Nino Abuladze, Ketevani Gabunia, Igor Seniuk, Lali Patsia, Marika Sulashvili, Lela Grigolia, Kakhaber Robakidze, Magda Davitashvili, Marina Giorgobiani, Irine Zarnadze, Shalva (Davit) Zarnadze **312**

**КРІОЕКСТРАКТ СЕЛЕЗІНКИ ЯК ПОТЕНЦІЙНИЙ ЗАСІБ КОРЕКЦІЇ ПОРУШЕНЬ АЗОТИСТОГО ОБМІНУ ПРИ ЕКСПЕРИМЕНТАЛЬНІЙ НЕФРОПАТІЇ ІНДУКОВАНИЙ КЕТОРОЛАКОМ**

Студент В.О., Гладких Ф.В., Лядова Т.І., Матвєєнко М.С. **364**

**MONITORING OF ARGINASE ACTIVITY VIA UREA BIOSENSOR**

Butkevičiūtė M., Gurevičienė V., Šakinytė-Urbikienė I., Sukackienė D., Razumienė J. **372**

**ВИКЛИКИ АНТИМІКРОБНОЇ РЕЗИСТЕНТНОСТІ В УКРАЇНІ**

Шаповалова О.В., Козар В.В. **380**

**РЕДОКС-РЕАБІЛІТАЦІЯ СЕРЦЯ: ПОТЕНЦІАЛ КОНДИЦІОНОВАНОГО СЕРЕДОВИЩА СТОVBУРОВИХ КЛІТИН У ПОДОЛАННІ МЕТАБОЛІЧНОЇ ДЕЗОРГАНІЗАЦІЇ, ІНДУКОВАНОЇ ЦЕЛЕКОКСИБОМ**

Дробнер І.Г., Гладких Ф.В., Лядова Т.І., Матвєєнко М.С. **387**

**ЗБЕРІГАННЯ СФЕРОЇДІВ З МЕЗЕНХІМАЛЬНИХ СТРОМАЛЬНИХ КЛІТИН ЗА АМБІЄНТНОЇ ТЕМПЕРАТУРИ**

Божок Г.А., Труфанова Н.А., Ревенко О.Б., Пахомов О.В., Черкашина Д.В., Петренко О.Ю. **397**

**ЕНЗИМОТЕРАПІЯ НЕВИЛІКОВНИХ ПАТОЛОГІЧНИХ СТАНІВ**

Сенюк І.В., Кравченко В.М., Галузінська Л.В. **403**

**ФАРМАКОЛОГІЧНА ДОЦІЛЬНІСТЬ ЗАСТОСУВАННЯ ВІТАМІНУ D З ВІТАМІНОМ К**

Сенюк І.В., Кравченко В.М., Гончаров О.В. **409**

|                                                                                                                                                                                                                |            |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------|
| <b>СУЧАСНІ УЯВЛЕННЯ ЩОДО БІОХІМІЧНОЇ КОМПАРТМЕНТАЛІЗАЦІЇ</b>                                                                                                                                                   | <b>414</b> |
| Сенюк І.В., Кравченко В.М., Щербак О.А.                                                                                                                                                                        |            |
| <b>ВИВЧЕННЯ АКТОПРОТЕКТОРНОЇ ДІЇ НОВОЇ СПОЛУКИ РЯДУ МЕТИЛКСАНТИНІВ У ЕКСПЕРИМЕНТІ</b>                                                                                                                          | <b>418</b> |
| Матвійчук А.В., Матвійчук О.П., Підгайна В.В., Карабут Л.В., Гладченко О.М.                                                                                                                                    |            |
| <b>ОЦІНКА ВПЛИВУ ПОЛІМОРФІЗМУ ГЕНА <i>SIRT1</i> (rs2273773) НА ЕФЕКТИВНІСТЬ КОМПЛЕКСНОЇ АНТИДІАБЕТИЧНОЇ ТЕРАПІЇ У ПАЦІЄНТІВ З ЦУКРОВИМ ДІАБЕТОМ 2 ТИПУ ТА НАДЛИШКОВОЮ ВАГОЮ ЗІ СХІДНОУКРАЇНСЬКОЇ ПОПУЛЯЦІЇ</b> | <b>425</b> |
| Красова Н.С., Колеснікова А.О., Горшунська М.Ю., Плохотніченко О.О., Тижненко Т.В.                                                                                                                             |            |
| <b>ВПЛИВ ДОКСИЦИКЛІНУ НА ЖИТТЄЗДАТНІСТЬ КЛІТИН ТА ОЦІНКА ЦИТОТОКСИЧНОГО ВПЛИВУ <i>IN VITRO</i> НА ЕТАПІ ДОКЛІНІЧНИХ ДОСЛІДЖЕНЬ</b>                                                                             | <b>431</b> |
| Попова М.Е., Салій О.О., Рибачук О.А.                                                                                                                                                                          |            |
| <b>REGENERATIVE &amp; ANTI-AGING POTENTIAL OF NATURAL BIOACTIVES</b>                                                                                                                                           | <b>436</b> |
| Tarapata M.O., Kukhtenko O.S., Galuzinska L.V., Manskiy O.A., Plantus V.M.                                                                                                                                     |            |
| <b>THE EFFECT OF COFFEE DRINKS ON THE BIOCHEMICAL PROCESSES OF BLOOD CLOTTING</b>                                                                                                                              | <b>444</b> |
| Igor Seniuk, Nodar Sulashvili, Riad Kamuta                                                                                                                                                                     |            |
| <b>КЛІНІКО-МОЛЕКУЛЯРНІ ОСОБЛИВОСТІ РАКУ МОЛОЧНОЇ ЗАЛОЗИ</b>                                                                                                                                                    | <b>449</b> |
| Мамонтова Т.В., Мамонтова В.Д.                                                                                                                                                                                 |            |
| <b>STRATEGIC “YES” FOR GLUCOSE-BASED CHOLINESTERASES INHIBITORS</b>                                                                                                                                            | <b>454</b> |
| Butkevičius M., Šakinytė-Urbikienė I., Razumienė J.                                                                                                                                                            |            |
| <b>DEVELOPMENT OF SARCOSE BIOCSENSOR BASED ON TOLUIDINE BLUE MODIFIED ELECTRODES</b>                                                                                                                           | <b>458</b> |
| Ratkevičiūtė K., Kavaliauskaitė G., Serapinas S., Tetianec L.                                                                                                                                                  |            |



| <b>ТЕЗИ<br/>ABSTRACTS</b>                                                                                       |            |
|-----------------------------------------------------------------------------------------------------------------|------------|
| <b>ОЦІНКА ЖИТТЄЗДАТНОСТІ КЛІТИННОЇ ЛІНІЇ L929 ПІСЛЯ<br/>ВПЛИВУ ДОКСОРУБІЦИНУ</b>                                | <b>462</b> |
| Гойдіна В.С.                                                                                                    |            |
| <b>SURFACE MARKER CD44 AS AN INDICATOR OF STABILITY OF<br/>CRYOPRESERVED HUMAN RED BLOOD CELLS</b>              | <b>463</b> |
| Zemlianskykh N.G.                                                                                               |            |
| <b>ВПЛИВ ОБ'ЄМУ ЗРАЗКА, ЩО ЗАМОРОЖУЄТЬСЯ, НА<br/>ЗБЕРЕЖЕНІСТЬ ЕРИТРОЦИТІВ КРОЛИКА ПРИ<br/>КРІОКОНСЕРВУВАННІ</b> | <b>465</b> |
| Єршова, Н.А., Ніпот О.Є., Єршов С.С., Шпакова Н.М.                                                              |            |
| <b>GUT MICROBIOTA COMPOSITION AND FUNCTIONAL<br/>ALTERATIONS IN OBESITY</b>                                     | <b>466</b> |
| Zbigniew Mazur, Halina Tkaczenko, Natalia Kurhaluk                                                              |            |
| <b>ADVERSE TRANSFUSION REACTIONS: CLASSIFICATION,<br/>CLINICAL MANIFESTATIONS AND RISK ASSESSMENT</b>           | <b>470</b> |
| Małgorzata Gradziuk, Halina Tkaczenko, Natalia Kurhaluk                                                         |            |
| <b>ОСОБЛИВОСТІ ЛАБОРАТОРНОЇ ДІАГНОСТИКИ<br/>ЛЕЙКЕМОЇДНИХ РЕАКЦІЙ КРОВІ</b>                                      | <b>473</b> |
| Козіна А.С., Литвинова О.М.                                                                                     |            |
| <b>ЕКСПЕРИМЕНТАЛЬНЕ ОБҐРУНТУВАННЯ<br/>МУЛЬТИМОДАЛЬНОЇ КОМБІНАЦІЇ КЕТОПРОФЕНУ З<br/>ЦЕНТРАЛЬНИМИ АД'ЮВАНТАМИ</b> | <b>476</b> |
| Матвєєнко М.С., Гладких Ф.В., Чиж М.О., Лядова Т.І., Ляшок А.Л.                                                 |            |
| <b>МІЖВИДОВЕ ПОРІВНЯННЯ ВПЛИВУ ТРИФТОРПЕРАЗИНУ НА<br/>ЕРИТРОЦИТИ ЗА УМОВ ПОСТГІПЕРТОНІЧНОГО ШОКУ</b>            | <b>477</b> |
| Чабаненко О.О., Єршова Н.А., Шпакова Н.М.                                                                       |            |
| <b>АКТУАЛЬНІСТЬ ВИЗНАЧЕННЯ ПОКАЗНИКІВ<br/>ЛЕЙКОЦИТАРНОЇ ФОРМУЛИ В ЛАБОРАТОРНІЙ МЕДИЦИНІ</b>                     | <b>480</b> |
| Карабут Л.В., Залюбовська О.І., Авідзба Ю.Н., Підгайна В.В.                                                     |            |
| <b>МІСЦЕ ГЕМОЛІТИЧНИХ АНЕМІЙ В ЛАБОРАТОРНІЙ<br/>МЕДИЦИНІ</b>                                                    | <b>482</b> |
| Карабут Л.В., Березнякова М.Є., Матвійчук О.П., Підгайна В.В.                                                   |            |

|                                                                                                                                                                                |            |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------|
| <b>АКТУАЛЬНІСТЬ ПАРАЗИТАРНИХ ІНВАЗІЙ В ЖИТТІ ЛЮДИНИ</b>                                                                                                                        | <b>484</b> |
| Карабут Л.В., Тюпка Т.І., Матвійчук А.В.                                                                                                                                       |            |
| <b>ЛАБОРАТОРНА ОЦІНКА КЛІНІЧНОГО АНАЛІЗУ СЕЧІ</b>                                                                                                                              | <b>486</b> |
| Карабут Л.В., Матвійчук О.П.                                                                                                                                                   |            |
| <b>АКТУАЛЬНІ ПИТАННЯ ПОТОВОЙ ПРОБИ ЯК «ЗОЛОТОГО СТАНДАРТУ» ДІАГНОСТИКИ ПРИ МУКОВІСЦИДОЗУ</b>                                                                                   | <b>487</b> |
| Орлова К.Ю., Галузінська Л.В.                                                                                                                                                  |            |
| <b>ПЕРСПЕКТИВИ ЗАСТОСУВУВАННЯ БІОХІМІЧНИХ МЕТОДІВ В ДІАГНОСТИЦІ ТОКСОКАРОЗУ</b>                                                                                                | <b>488</b> |
| Малашенко Н.І., Філімонова Н.І., Тіщенко І.Ю.                                                                                                                                  |            |
| <b>MODIFYING EFFECT OF ZINC SUCCINATE ON HEPATOTOXICITY OF CADMIUM CHLORIDE IN EXPERIMENT ON PREGNANT RATS</b>                                                                 | <b>491</b> |
| Shamelashvili K.L.                                                                                                                                                             |            |
| <b>БІОХІМІЧНІ МЕХАНІЗМИ РЕАЛІЗАЦІЇ ПРОТИПУХЛИННОЇ ДІЇ КОРЕНЯ ІМБИРУ</b>                                                                                                        | <b>492</b> |
| Сенюк І.В., Кравченко В.М., Гончаров О.В.                                                                                                                                      |            |
| <b>KEY MECHANISMS OF CARCINOGENESIS</b>                                                                                                                                        | <b>494</b> |
| Tishchenko I.Yu., Dubinina N.V., Filimonova N.I., Misiurova S.V.                                                                                                               |            |
| <b>СЕЛЕКТИВНІ ІНГІБІТОРИ ЗВОРОТНОГО ЗАХОПЛЕННЯ СЕРОТОНІНУ ТА ПЕРЕДМЕНСТРУАЛЬНИЙ СИНДРОМ</b>                                                                                    | <b>498</b> |
| Рогоза О.Є.                                                                                                                                                                    |            |
| <b>ДИСРЕГУЛЯЦІЯ МЕТАБОЛІЗМУ ТРИПТОФАНУ: АКТИВАЦІЯ КІНУРЕНИНОВОГО ШЛЯХУ ТА ДЕФІЦИТ СЕРОТОНІНУ ЯК КЛЮЧОВІ БІОХІМІЧНІ МЕХАНІЗМИ НЕЙРОКОГНІТИВНИХ ДИСФУНКЦІЙ ПРИ LONG COVID-19</b> | <b>500</b> |
| Баранова Д.С.                                                                                                                                                                  |            |
| <b>ВПЛИВ ПАЛІННЯ НА ЦИТОГЕНЕТИЧНИЙ СТАТУС СЛИЗОВОЇ ОБОЛОНКИ РОТОВОЇ ПОРОЖНИНИ В ЖІНОК ЮНАЦЬКОГО ВІКУ</b>                                                                       | <b>502</b> |
| Лісецька І.С., Павлюк О.Д., Іванова С.В.                                                                                                                                       |            |

**ПОРІВНЯЛЬНА ХАРАКТЕРИСТИКА МОРФОМЕТРИЧНИХ ПОКАЗНИКІВ ПЕРЕДМІХУРОВОЇ ЗАЛОЗИ ЩУРІВ НА МОДЕЛІ СУЛЬПРИД-ІНДУКОВАНОЇ ДОБРОЯКІСНОЇ ГІПЕРПЛАЗІЇ ПІСЛЯ ПРОФІЛАКТИЧНОГО ЗАСТОСУВАННЯ ЕКСТРАКТУ ПЛОДІВ ПАЛЬМИ САБАЛЬ ТА ВІТАМІНУ D.** 504

Ткаченко Н.О., Проценко О.С., Ремньова Н.О., Чумак Л.І., Коренєва Є.М., Смоленко Н.П., Мараховський І.О., Белкіна І.О., Гуріна О.Е., Кустова С.П., Бойко М.О., Бречка Н.М., Бондаренко В.О.

**ГЛЮКОЗО-6-ФОСФАТ ЯК КЛЮЧОВИЙ МЕТАБОЛІТ** 507

Сенюк І.В., Кравченко В.М., Канколонго Кабея Джан Джакуес

**АНАЛІЗ ПОКАЗНИКІВ ЗАПАЛЕННЯ НА МОДЕЛЯХ ГОСТРОГО ЗАПАЛЕННЯ У ЩУРІВ** 509

Галузінська Л.В., Сенюк І.В.

**БІОХІМІЯ СТРЕСУ У НАСЕЛЕННЯ ПІД ЧАС ТРИВАЛИХ КРИЗОВИХ СИТУАЦІЙ** 511

Макарова В.Д., Сенюк І.В.

**СИСТЕМНІ РЕГУЛЯТОРНІ КЛІТИНИ (SRC) ЯК ПОТЕНЦІЙНИЙ ФАКТОР УПОВІЛЬНЕННЯ СТАРІННЯ У ПРИМАТІВ: ДОКАЗИ ТА ПЕРСПЕКТИВИ ТРАНСЛЯЦІЇ НА ЛЮДИНУ** 514

Горюнова І.О.

**НАСЛІДКИ ВПЛИВУ ПЕРОКСИДУ ВОДНЮ НА ЕРИТРОЦИТИ, КРІОКОНСЕРВОВАНІ У МОДИФІКОВАНОМУ ЗА СКЛАДОМ КРІОКОНСЕРВАНТІ З ГЛІЦЕРИНОМ.** 518

Рамазанов В.В., Руденко С.В.

**LORATEDINE IN COMBINATION WITH *BUPLEURUM AUREUM* PHYTOCOMPONENT: A NEW APPROACH TO THE TREATMENT OF ALLERGIC DISEASES IN CHILDREN** 520

Pasynchuk I. I., Naboka O. I.

**EFFECT OF *BUPLEURUM AUREUM* EXTRACT AND ITS COMBINED USE WITH LORATADINE ON LIPID PEROXIDATION INDICATORS UNDER THE ACTION OF CADMIUM CHLORIDE *IN VITRO*** 521

Pasynchuk I. I., Naboka O. I.

**EFFECT OF THE PHYTOEXTRACT FROM *BUPLEURUM AUREUM*  
AND ITS COMBINED USE WITH LORATADINE ON THE  
PARAMETERS OF LIPID PEROXIDATION UNDER THE ACTION  
OF CADMIUM CHLORIDE *IN VIVO*** **522**

Pasynchuk I. I., Naboka O. I.

**РОЛЬ ФЕРМЕНТІВ У ФОРМУВАННІ ТА РУЙНУВАННІ  
БІОПЛІВОК** **523**

Дубініна Н.В., Тіщенко І.Ю., Щербак О.А.

**ХРОНІЧНОГО ПСИХО-ЕМОЦІЙНОГО СТРЕСУ  
(ЕКСПЕРИМЕНТАЛЬНІ ДОСЛІДЖЕННЯ)** **526**

Сиротенко Л.А., Малова Н.Г., Комарова І.В.

**АВТОРСЬКИЙ ПОКАЗЧИК** **529**  
**AUTHOR'S INDEX**

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Наукове видання  
Scientific publication

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