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Національний фармацевтичний університет
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Міжнародна internet-конференція

# Modern chemistry of medicines

25 вересня 2024 р.
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General chemistry department

# MODERN CHEMISTRY OF MEDICINES

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Збірник містить матеріали Міжнародної Internet-конференції «Modern chemistry of medicines» (25 вересня 2024 р., м. Харків) присвячені висвітленню сучасних тенденцій створення оригінальних АФІ синтетичного та рослинного походження, фармацевтичної розробки, забезпечення якості лікарських засобів.

Для широкого кола наукових та практичних фахівців у галузі фармації та медицини, магістрантів, аспірантів, докторантів, співробітників фармацевтичних підприємств, викладачів закладів вищої освіти.



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# Herb MaRS approach to quality control of *Lavandula* plant material

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**Introduction:** *Lavandula* genus (Lamiaceae family) is one of the most important medicinal and aromatic plants in the Mediterranean region and Southern Europe (1). The most commonly reported medicinal use of lavender essential oils is as an analgesic, antifungal, antidepressant, and sedative. In recent years, Bulgaria has overtaken France and become the world leader in lavender essential oil production. However, these countries are followed by Ukraine – a new country in the lavender oil market (2). The natural range of *Lavandula angustifolia* Mill. in Ukraine is located on the territory of the annexed Crimean Peninsula; it is therefore crucial to establish the cultivation and harvesting of starting plant materials. Currently, lavender is grown in different regions of the country, including Kherson, Transcarpathian, Mykolaiv, Odessa, Vinnitsa, and Ternopil. Taking into account the large biomass of *Lavandula* herb and its bioactive compounds, current research has been directed specifically at studying the potential use of lavender plant material in pharmacy/medicine. The selection of the Q-marker for *Lavandula* herb was carried out using the Herbal Chemical Marker Ranking System approach (Herb MaRS) (3), which considers bioavailability, pharmacological activity and the presence of the selected standard**.**
**Materials and methods**: Herb MaRS approach and a comparative analysis of literature data regarding the biological activity of selected Q-markers. The data on the chemical composition of the Ukrainian *Lavandula* herb was determined by HPLC as described by (4).
**Results and discussion**: According to the results of a complex phytochemical and pharmacological study, the following quality markers for lavender herbs are proposed: rosmarinic acid and chlorogenic acid based on their use for the treatment of different nervous system disorders including Alzheimer's disease, epilepsy, depression. Rosmarinic acid has significant reported antinociceptive, neuroprotective, and neurodegenerative properties (5). Among the constituents, the content of rosmarinic acids and chlorogenic acid in Ukrainian *Lavandula* herbs is high (>2 mg/g). Therefore, they can be selected as a Q-marker (ranking score 5). The linalool (content 20–45% by GC-MS method) and linalool acetate (content 25–47%) were also selected for *Lavandula* herb based on their positive influence on the Central Nervous System.
**Conclusions**: Considering the quantitative content of the selected compounds as well as their activities according to our own research and data from other authors, they can be considered as potential Q-markers of Lavandula herb and herb-based preparations for the development of standardisation parameters. **Acknowledgements**."Research of original substances for the correction of neurological deficits symptoms, prediction and assessment of factors affecting the mechanisms of action", 2023-2025; №: 0123U101751.

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# Assessment of Lavender Essential Oil Quality: Insights from Lithuanian Cultivation

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**Introduction.** Lavender is grown widely in many countries (France, Bulgaria etc.) for decoration or as essential oil (EO) source that can later be used in cosmetics or medicine. For proper lavender cultivation it is necessary to choose a location with plenty of sunlight and fast-draining soil [1]. In Lithuania there are at least 7 big lavender fields and *Lavandula angustifolia* is the only type that is widely cultivated. The main reason is that winter temperature in Lithuania can drop to -25°C and *L. angustifolia* has the best winter hardiness of all species [2]. Lavender farms are getting more and more popular in Lithuania due to their beauty and the EO healing properties. However, it is practically impossible to find pure lavender EO, that are obtained from those fields. Most of the EO are imported from other countries, for example, Bulgaria. Since environmental factors have a great influence on the qualitative composition of EO, the aim of the study was to comparatively assess the composition of lavender EO from different regions of Lithuania.

**Materials and methods.** *L. angustifolia* cultivar herbs were harvested in Babtai (lavender "Hidcote blue"), Kleboniškis (lavender "Provence blue") and Biržai (lavender mix of "Munstead", "Provence blue", and "Hidcote blue"), Lithuania in June, 2023. The essential oil was obtained by hydrodistillation. Chromatographic separation of terpenoids was conducted on the SHIMADZU GC-2010 system with FID. GC was performed while following Eur. Ph. 11.1 procedures.

**Results and discussion.** The GC method of EO samples gave the following results: in general, 10 substances were identified in each EO, with their content from 0,069 mg/ml to 35,903 mg/ml. The amount of limonene, 1,8-cineole, 3-octanone and camphor in essential oils differed not significantly between the cities. For example, quantities of limonene ranged between 0,528 mg/ml in Babtai to 0,674 mg/ml in Biržai lavender EO samples. For cineole, the values were 0,408 mg/ml in Kleboniškis to 0,803 mg/ml in Babtai. The biggest differences were spotted when analysing the quantities of linalool and linalyl acetate – two main markers used for determining the quality of lavender EO. Results of linalool differed from 14,326 mg/ml in Biržai to 35,903 mg/ml in Kleboniškis. Quantity of linalyl acetate ranged between 8,857 mg/ml in Babtai to 30,011 mg/ml in Biržai. For the other compounds, slight differences in quantities were also visible. Lithuania is a small country with no mountains, considerable differences between altitutes and even with no big differences between temperatures in cities. Hence, this leaves us with a discussion, can slight climate differences have impact on the amount of active compounds.

**Conclusions.** Regarding the Eur.Ph.11.1., the content of each of the components was determined: 7 out of 10 compounds of EO from Babtai and Kleboniškis; and 8 out of 10 compounds from Biržai were within the ranges. Overal, this information proves that it is possible to grow lavender in Lithuania and to obtain a good quality essential oil.

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# High performance thin layer chromatography (HPTLC) assessment of *Epilobii* herba

Kateryna Uminska[1], Michal Korinek[2,3], Liudas Ivanauskas[4], Mohamed El-Shazly[5], Victoriya Georgiyants[6], Zigmantas Gudžinskas[7], Olha Mykhailenko[6,8,9]*

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**Introduction.** Plants are known sources of bioactive components with potent healing effects. *Epilobium* species are widely distributed throughout the Eastern part of the European Union. They are rich in polyphenols such as oenothein B, ellagic acid, quercetin, and myricetin-3-O-*β*-D-glucuronide. The small-flowered Willow-herb or *E. parviflorum* contains high levels of *β*-sitosterol, oenothein B, and hyperoside. It is used to treat benign prostatic hyperplasia (BPH) or enlarged prostate, bladder and kidney disorders. It showed anti-bacterial, anti-inflammatory and antioxidant properties (1). However, despite the wide use of these plants, they are not included in any pharmacopeia in the world. Only the Herbal Medicines Committee (HMPC) made some conclusions and published documents (2)(2, 3) regarding the medical use of *E. parviflorum*, but not its chemical content. These documents are based on the European Union manufacturers of herbal products containing these plants. The purpose of this work is to apply the high-performance thin layer chromatography (HPTLC) method to evaluate the *E. parviflorum* quality.

**Materials and methods.** *E. parviflorum* samples collected in Ukraine and Lithuania were used for the current comparative analysis. Polyphenolics were studied using HPTLC for the methanol (50%, v/v) extracts. Reference standards including chlorogenic acid, gallic acid, isoquercitrin, and hyperoside were used. The analysis was carried out using HPTLC plates Si 60 $F_{254}$ (Merck) with a mobile phase of ethyl acetate: formic acid: acetic acid: water (67.5:7.5:7.5:17.5). The detection of compounds was performed at 365 nm after derivatization by 2-aminoethyldyphenylborinate 1% solution followed by 5% macrogol 400 in methanol.

**Results and discussion.** HTPLC showed the presence of all four compounds in *E. parviflorum* extracts. In the light blue fluorescent ($R_f$ = 0.54), chlorogenic acid was identified as. In the light yellow fluorescent zone ($R_f$ = 0.67), isoquercitrin was detected. In the yellow fluorescent zone ($R_f$ = 0.60) hyperoside was suggested. In the blue fluorescent zone ($R_f$ = 0.82), gallic acid was identified. The fluorescence was more intense in the sample from Ukraine.

**Conclusions.** The presented method can be further applied to assess *Epilobium* sp. chemical content.

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# *Hypochaeris* L. genus: bioactive compounds and pharmacological perspectives

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**Introduction.** The genus *Hypochaeris* is part of the Cichorieae tribe of the Asteraceae family, includes various species of flowering plants that are widely distributed across Europe, North Africa, and the Americas. Some of the best studied species within this genus include *H. radicata* L. (flatweed or cat's-ear) and *H. laevigata* L. These taxa have gained attention for their bioactive compounds and potential pharmacological benefits. This study aims to analyze the chemical composition and pharmacological activity of the main genus's species to identify the most promising species for further study.
**Materials and methods.** A systematic literature searches on the history of use, pharmacological action, and chemical composition of *Hypochaeris* genus was conducted using the following databases: NCBI-PubMed, Web of Knowledge, Science direct, Wiley online library.
**Results and discussion.** The *Hypochaeris* genus is known for its rich content of secondary metabolites, including flavonoids, sesquiterpene lactones, lignans, phenolic acids, and triterpenoids (1). *Hypochaeris* species, such as *H. radicata*, contain luteolin and quercetin derivatives, which possess antioxidant, anti-inflammatory, and cytoprotective properties. Sesquiterpene lactones are the most prevalent in *Hypochaeris* species and exhibit significant anti-inflammatory and anticancer activities. Compounds such as taraxasterol, from triterpenoids class, exhibit anti-inflammatory and anticancer properties, they also involved in the modulation of immune responses. Although the specific lignans in *Hypochaeris* species (2) have been studied less than other substances, they exhibit cytotoxic, cardioprotective effects that should be further developed. In traditional medicines plants are used to cure jaundice, dyspepsia, constipation, rheumatism, and hypoglycaemia (3). However, scientific data confirming the possibility of using the genus for medical purposes is very limited. The *Hypochaeris* genus is widely distributed across Europe, with species adapted to a range of habitats from coastal areas to mountainous regions. *H. radicata* is the most widespread species, thriving in various environments across the continent, while other species like *H. glabra* (Spain, Portugal, France, the Mediterranean basin), *H. maculata* (common in Germany, Poland, the Czech Republic, and Slovakia, the Alps and Carpathians) and *H. laevigata* (mountainous regions of the Alps, Pyrenees, and Carpathians) have more specific habitat preferences. The adaptability of these species to different climates and soil types has contributed to their broad distribution in Europe.
**Conclusions.** The *Hypochaeris* genus represents a promising source of bioactive compounds with significant pharmacological potential. Continued research into these species could lead to the development of new treatments for inflammation, oxidative stress, cancer, and microbial infections.
**Acknowledgments.** This work was supported by the Alexander von Humboldt Foundation for OM.

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# Insights on the anti-allergic constituents of *Bischofia javanica*: network pharmacology and bioactivity-guided fractionation

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**Introduction.** *Bischofia javanica* Blume, belonging to the family Phyllanthaceae, is found in Southeast Asia, such as India, Thailand, and Taiwan. Traditionally, leaf extract treats cancerous wounds, diarrhea, stomach ulcers, and eczema. We aimed to evaluate the anti-allergic activity of *B. javanica* leaf extracts and isolate major components responsible for the activity.
**Material and methods.** The 10 kg dried leaves were continuously extracted with hexane, ethyl acetate, dichloromethane, methanol, and acetone/water. The mid-polar fractions were active in *β*-hexosaminidase assay induced by calcium ionophore using RBL-2H3 cells. Cytotoxicity of the extracts was screened by MTT assay using DMSO as vehicle solvent [1]. Based on *in vitro* screening, active fractions were selected for further purification. Major compounds were isolated from the extract, and structure elucidation was performed using 1D and 2D NMR spectra and comparison with previously reported data. Furthermore, network pharmacology and KEGG pathway enrichment analysis were performed to identify hub targets and pathways.
**Results and discussion.** MTT assay revealed extracts were non-toxic at 100 µg/mL. Anti-allergic effects were expressed as inhibition of mast cell degranulation. The mid-polar fractions displayed 70% inhibition at 100 µg/mL concentration. Further purification of active fractions led to the isolation of two compounds, squalene and *β*-sitosterol. With network pharmacology, NCF1 (Neutrophil cytosolic factor 1), CYBB (Superoxide oxidase CybB), or NOX4 (NADPH oxidase 4) were identified as important targets. Enrichment results indicated that Class I MHC-mediated antigen processing and presentation and signaling events mediated by PTP1B are critical pathways for the anti-allergic properties of *B. javanica*. The identified components may play a role in the immunological disorders. For instance, *β*-sitosterol was reported to reduce cholesterol levels and treat heart diseases and rheumatoid arthritis. Squalene is used in skin care products as a moisturizer, and its anti-inflammatory properties help treat acne.
**Conclusion.** Anti-allergic effects of the *Bischofia javanica* leaves were revealed for the first time. The two major components of the active fractions were isolated and identified as squalene and *β*-sitosterol. Network pharmacology indicated potential mechanisms.

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**References**

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# Вивчення вмісту тритерпенових сапонінів у складі трави Лаванди вузьколистої

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**Вступ.** Лаванда вузьколиста – багаторічна трав'яниста рослина, яка має довгу історію використання у різних країнах завдяки широкому колу фармакологічних ефектів, що робить дану рослину дуже перспективною у застосуванні саме для потреб фармацевтичної галузі. З метою розширення знань про хімічний склад української лаванди, дуже актуальним є дослідження вмісту тритерпенових сапонінів, оскільки дані, щодо дослідження даної групи речовин відсутні у науковій літературі. Тритерпенові сапоніни мають стереоспецифічну фармакологічну активність сапонінів, тому дані дослідження є перспективними та актуальними.
**Матеріали та методи.** Об'єктом дослідження була трава лаванди, заготовлена у Ботанічному Саді Львівського Національного Університету імені Івана Франка, у 2022 році. Метод Високоефективної Рідинної Хроматографії з Діодною Детекцією (ВЕРХ-ДАД) був використаний для кількісного визначення тритерпенових сапонінів у зразку, відповідно до методики описаної у дослідженні (1).
**Результати та обговорення.** Методом ВЕРХ-ДАД було ідентифікована наявність пяти сполук у раві лаванди, що відносяться до класу тритерпенових сапонінів, а саме: масляна кислота (34,38 мкг/мл), бетулін (57,59 мкг/мл), еритродіол (15,10 мкг/мл), олеанолова кислота (132,61 мкг/мл) та урсолова кислота (995,81 мкг/мл). Визначені речовини відносяться до класу пентациклічних тритерпенових сапонінів та володіють високим рівнем доведеної фармакологічної активності, а саме противірусної, антибактеріальної, цитотоксичної, гіполіпідемічної дії тощо. Окрім того, урсолова кислота проявляє протизапальну, антиоксидантну активність (2); маслинова кислота має виражену протималярійну активність (3); бетулін здатний легко перетворюватися на бетулінову кислоту, яка проявляє також протималярійну та протизапальну активність. Бетулінова кислота та її похідні також продемонстрували анти-ВІЛ активність та цитотоксичну дію (4); еритродіол проявляє кардіопротекторну, гепатопротекторну, ранозагоювальну дії (5). Вміст олеанолової та урсолової кислот у траві лаванди були найвищі, що дозволяє розглядати лаванду, як перспективне джерело противірусної, гепатопротекторної, противиразкової активності.
**Висновки.** Тритерпенові сапоніни широко використовуються у складі лікарських засобів на рослинній основі, забезпечуючи високий рівень фармакологічної активності. Проведене дослідження показало наявність тритерпенових сапонінів в трави лаванди.

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# Electrospun Nanofibres Loaded with *Lavandula angustifolia* Mill. Extract for Potential Use in Cutaneous Wound Healing

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**Introduction.** Many medicinal plants have a long history of therapeutic properties in wound healing. They have excellent antimicrobial, anti-inflammatory, and antioxidant activities owing to various bioactive components in their structure (1). Electrospun nanofibres provide high solubility and bioavailability of active compounds and also increase the medicinal potential of these extracts (2). Electrospinning makes it possible to combine the advantages of using plant extracts in the form of nanofibre mats for use as skin graft substitutes. In this study, we investigated the potential of electrospinning of *Lavandula angustifolia* Mill. herb dry water extract with polyvinylpyrrolidone (PVP) as a potential drug in skin wound healing.
**Materials and methods.** Lavender herb was air-dried and ground prior to analysis. The dry extract was prepared through triple extraction in a water bath, followed by filtration, combining the extracts, and evaporation to obtain a dry extract. Anhydrous ethanol was selected as the solvent. The electrospinning solutions contained 10% w/v PVP and different concentrations of lavender extract (1%, 2%, and 3.33% w/v), which were stirred overnight to ensure complete dissolution. The resulting fibres incorporated different ratios of lavender extract and PVP, with fibre compositions ranging from 0% w/w lavender extract for the control sample to 24.98% w/w lavender extract in the highest concentration sample. The morphology, physical form, and chemical analysis of polymeric nanofibres were carried out by scanning electron microscopy (SEM), X-ray diffraction (XRD), thermogravimetric analysis (TGA), differential scanning calorimetry (DSC), nuclear magnetic resonance (NMR), and FTIR-ATR spectroscopy. Disintegration and dissolution tests were also conducted.
**Results and discussion.** Optical microscopy showed that fibres produced at 10 kV had good quality, with uniform and smooth morphology. SEM analysis revealed that fibres containing 9.09%, 16.67%, and 24.98% w/w lavender extract had smooth surfaces, with the 9.09% w/w formulation exhibiting the best morphology. The average diameters were 0.70 µm for 9.09%, 0.77 µm for 16.67%, and 1.49 µm for thick fibres of 24.98% and 0.73 µm for think ones of 24.98%. XRD and DSC confirmed all formulations were amorphous, and TGA demonstrated good thermal stability. FTIR-ATR showed hydrogen bonding between PVP and lavender extract, stabilising the drug's distribution and enhancing solubility. All fibres disintegrated quickly, improving lavender extract's dissolution in PBS.
**Conclusions.** During fabrication, electrospun fibres containing PVP and lavender extract were successfully produced. By adjusting the voltage from 5 to 12.5 kV and maintaining a constant flow rate of 0.5 mL/h and a spinneret-to-collector distance of 15 cm, the optimal voltage for the electrospinning process was determined to be 10 kV. All fibre formulations displayed smooth surfaces, with the 9.09% w/w formulation showing the best morphology. It was concluded that all fibre of different formulations were amorphous, demonstrated good thermal stability, and dissolved more rapidly than the lavender extract alone. While higher lavender extract concentrations showed a slight increase in dissolution speed, overall differences were minimal, indicating that lower PVP content could still maintain rapid dissolution rates.

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# Фітофотодерматити, викликані рутою запашною

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**Вступ.** Поняття «фітофотодематит» складається з двох частин: «фіто» - рослина та «фотодерматит» - запальна хвороба шкіри, що викликана дією світла. Дана патологія виникає в разі контакту шкіри з певними видами рослин та подальшим перебуванням під УФ-випромінюванням. Даний напрям набув розвитку у медичній літературі тільки у XX ст. Перші описані випадки хвороби пов'язані з народною медициною, при застосуванні рослин у ритуалах та спостереженням за їх впливом на шкіру під дією сонця. Найчастіше фітофотодерматит виникає при контакті з рослинами з родини Селерові (борщовик, фенхель, укроп) та Рутові (рута, бергамот, лайм). Рута запашна - рослина, що є недостатньо вивчена з даного приводу, тому дослідження даного напряму є актуальними.

**Матеріали та методи.** Аналіз літературних джерел з PubMed, ScienceDirect; ключові слова: «Рута запашна», «фототоксичність», «фітофотодерматит».

**Результати та обговорення.** Рута запашна – трав'яниста рослина із яскраво-жовтими квітками та блакитно-зеленими листочками, що розповсюджена у дикому та культивованому вигляді в країнах Європейського Союзу й Південній Америці. З давних часів рослина використовувалась при лікуванні різних захворювань. Але слід враховувати небезпечність при контакті з рослиною, вона здатна викликати сильні нашкірні опіки. У літературі описано лише декілька випадків фітофототоксичності, але при цьому всі вони мають досить важку клінічну картину. [1]

Хімічний склад рослини є досить широким та містить у собі фурокумарини (псоралени), алкалоїди, терпеноїди, фенольні сполуки. Саме фурокумарини рути (5-метоксипсорален, 8-метоксипсорален) відповідають за фототоксичність рослинної сировини. Найбільш небезпечною речовиною, особливо під час цвітіння, визнано 8-метоксипсорален. [2] Так, при контактні з фурокумаринами та подальшим перебуванням під УФ-випромінюванням виникають опіки, подразнення, свербіж, біль. У подальшому з'являються пігментні плями. Слід зауважити, що наслідки контакту з рутою є індивідуальними. Лікування фітофотодерматиту є симптоматичним та підтримуючим.

Варто зауважити, існує безліч позитивних аспектів використання фурокумаринів у медицині для хіміотерапії, при лікуванні вітіліго, псоріазу й лімфоми. [2] До того ж, з екстракту рути виділено 16 алкалоїдів та досліджено, що один з них сприяє виробленню меланіну й захищає меланоцити від окиснення. Завдяки цьому можна використовувати сировину для розробки ліків проти вітіліго.[3]

**Висновки.** Таким чином, рута запашна здатна викликати важкі клінічні картини фітофотодерматиту, лікування якого є досить важким. Не дивлячись на це, при правильному використанні, заготівлі сировини та фракціонуванні її екстрактів є велика кількість досліджень, які підтверджують позитивну активність фітофотоксичних сполук при терапії хвороб шкіри. У висновку, рута має великий потенціал у лікуванні вітліго, псоріазу та раку шкіри.

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# Development of new dual antiviral/anti-inflammatory inhibitors in silico for the treatment of COVID-19

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One of the most promising directions in modern pharmacy is the development of dual-purpose drugs. Such drugs include dual inhibitors. In the present work, a number of promising structures are considered that are potentially capable of exerting both anti-inflammatory and antiviral (anti-COVID-19) effects. Receptor-oriented docking was performed using the most likely macromolecular targets aimed at both inhibiting the main pathways of viral replication and reducing the inflammatory process in damaged tissues. The hit molecules were shown to have the potential to inhibit SARS-CoV-2 Mpro and PLpro proteases involved in the mechanisms of viral replication, as well as the potential to inhibition of Janus kinase, which mediates signaling responsible for inflammation processes.
Nine key hub genes (ACE2, STAT1, SRC, PIK3R1, HIF1A, ESR1, ERBB2, CDC42 and BCL2L1) were selected for molecular modelling. In the present work, we performed docking of a home library to the hub targets described above, which were previously identified as potential targets of the pharmacological mechanisms of action of cepharanthine against COVID-19. The docking was performed using AutoDock Vina.
Molecular docking results of the investigated molecules show a good potential to inhibit the target 2AJF, the spike receptor binding domain of the SARS coronavirus in complex with its receptor, as well as the pool of targets responsible for modulating the immune response.
**Conclusion**. Virtual in silico screening and receptor-based docking in three-dimensional structural models of active sites of biological molecules involved in the mechanisms of SARS-CoV-2 virus exposure to the organism was performed using cepharanthine as a representative structure. A number of hits were identified that were characterised by binding energies to target active sites at or above the level of the representative structure of cepharanthine. Receptor-based docking showed that the hit molecules had the potential to inhibit Mpro and PLpro SARS-COV-2 proteases, which are involved in viral replication mechanisms, as well as Janus kinase, which mediates intracellular signaling and is responsible for inflammatory processes.

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