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QUALIFICATION WORK

on the topic: **«DEVELOPMENT OF THE COMPOSITION OF A SYRUP WITH PAU D'ARCO EXTRACT»**

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ANNOTATION

The relevance of the development of a syrup with Pau D’arco extract is theoretically and experimentally substantiated in the qualification work. The properties of several pharmaceutical syrup formulations containing different concentrations of sorbitol were compared. The rational composition of the new medicine has been substantiated based on the results of organoleptic, physical and chemical properties studies.

The work consists of the parts: introduction, literature review, choice of research methods, experimental part, conclusions, list of reference sources, total volume of work 40 pages, contains 6 tables, 8 figures, 34 literature sources.

Key words: syrup, Pau D’arco extract, composition, sorbitol, organoleptic characteristics.

АНОТАЦІЯ

У кваліфікаційній роботі теоретично та експериментально обґрунтовано актуальність розробки сиропу з екстрактом Пау Д'Арко. Порівняно властивості кількох фармацевтичних рецептур сиропів, що містять різну концентрацію сорбітолу. Раціональний склад нового лікарського засобу обґрунтовано на основі результатів досліджень органолептичних, фізичних та хімічних властивостей.

Робота складається з таких частин: вступ, огляд літератури, вибір методів дослідження, експериментальна частина, загальні висновки, список використаних джерел літератури, загальний обсяг роботи 40 сторінок, містить 6 таблиці, 8 рисунків, 34 джерел літератури.

Ключові слова: сироп, екстракт Пау Д'Арко, склад, сорбітол, органолептичні характеристики.

CONTENT

LIST OF ABBREVIATIONS

API	–	active pharmaceutical ingredients
GIT	–	gastrointestinal tract
IUPAC	–	International Union of Pure and Applied Chemistry
LPS	–	lipopolysaccharide
mg	–	milligram
NO	–	nitric oxide
PGE_2	–	prostaglandin E_2.
sec	–	seconds
SPU	–	State Pharmacopeia of Ukraine

INTRODUCTION

The relevance of the topic. Medicines derived from plants are an important class of natural therapeutics for treating different diseases. The medical use of some plants has strongly evolved over time. About two-thirds of population prefers herbal-derived drugs for primary treatment all over the world. The selection of medicinal plants progressed into a more rational process in the traditional Arabic and Islamic medicine, Japanese Kampo, Indian Ayurveda, or traditional European medicine.

The industrial manufacture of medicines derived from plants has grown considerably over the last thirty years.

Pau D'Arco extract, also called red lapacho, is an extract from a phloem (an inner bark) of *Handroanthus impetiginosus* (Mart. ex Dc.) Mattos, (syn. *Tabebuia avellanedae* (Lorentz ex Griseb.) or *Tabebuia impetiginosa* (Mart. ex DC.) Standl.). Pau d'arco extract is traditionally used as a phytomedicine in particular in South America for its immunomodulatory, antifungal, antibacterial and anti-inflammatory properties. Despite the fact that this extract is produced in the USA, many dietary supplements contain Pau D'Arco extract on the pharmaceutical market of Ukraine. This indicates that the extract is in demand among consumers. Various studies show the efficiency and hopeful results of the extract in treating immunity disorders, such as revmatism, allergy, psoriasis and diseases such as a primary dysmenorrhea, cancer, osteoarthritis, colitis, obesity, fungal infections, and helminthiasis.

There are capsules, tablets, drops of the Pau D'Arco phloem extract and liquid extract on the domestic market, where solid dosage forms with insufficient bioavailability or medicinal forms with uncorrected organoleptic properties play a dominant role [1, 15].

The corrected medication form — syrup — is the popular and widely used pharmaceutical form due to its ease of patient compliance. Syrup is used to treat many illnesses and manage their symptoms. Syrup advantages and features are

quick relief, long-lasting results, and affordability [5, 18]. Syrups as liquid dosage forms have generally been justified on the basis of simplicity of administration to elderly and children who have difficulties in solid dosage forms swallow.

The purpose and research tasks. This research was aimed to demonstrate the possibility of the syrup composition and technology development with a Pau D'Arco extract.

The research tasks that we solved to achieve the purpose are following:

– to summarize and analyze the data of literature sources about application and active chemical compounds of *Handroanthus impetiginosus*;

– to consider syrup as a pharmaceutical form;

– to analyze the market for dietary supplements with Pau D'Arco extract;

– to justify the choice of suitable sweetener, flavor and preservative for syrup with a Pau D'Arco extract;

– theoretically and experimentally justify the composition of syrup with a Pau D'Arco extract and to study influence of pharmaceutical excipients on properties of the obtained phytopreparation;

– to develop technology of syrup with a Pau D'Arco extract.

The object of the research is the glycerol–water Pau D'Arco extract and a herbal syrup with it.

The subject of presented research is the rational composition and technology of a herbal syrup based on Pau D'Arco extract.

Research methods. The methods of researches from the State Pharmacopoeia of Ukraine were used for determining such indexes of the Pau D'Arco extract as physical, chemical, among which appearance, density, water, taste; and parameters of quality of prepared herbal syrup, such as appearance, odour, pH, density and dynamic viscosity. Experimental data that were obtained during studies of the herbal syrup with the Pau D'Arco extract were processed with methods of mathematical statistics.

The approbation of qualifying work results and scientific publications — author's participation in the XXXI International scientific and practical conference of young scientists and students «Current issues of creating new medicines» (April 23–25, 2025, Kharkiv) with oral report, and in the Interregional scientific-practical conference with international participation «Education, Science and Practice in the context of Pharmaceutical Industry Development» (May 30–31, 2025, Ivano-Frankivsk–Yaremche) with publishing abstract [24].

Structure and scope of qualification work. Qualification work consists from introduction, three chapters, conclusions, list of the references (34 sources) and annex. The content of work is presented on 40 pages of basic text and contains 6 tables and 8 pictures.

CHAPTER 1.
PROSPECTS FOR THE USE OF PAU D'ARCO EXTRACT IN MEDICINE AND CREATION OF PHARMACEUTICALS BASED ON IT (REVIEW OF LITERATURE)

1.1. Pau D'Arco extract as a promising active pharmaceutical ingredient

People have used plants to cure and assuage diseases in many countries around the world for many millennia. Therefore, knowledge about the traditional use of natural products plays an important role in drug development [22, 23].

Handroanthus impetiginosus (Mart. ex Dc.) Mattos (syn. *Tabebuia impetiginosa* (Mart. ex DC.) Standl., syn. *Tabebuia avellanedae* (Lorentz ex Griseb.)) is a tree belonging to the family Bignoniaceae, which is mainly distributed in tropical regions of Central and Latin America [26]. The species name impetiginosus is derived from the Latin word impetigo, a common and highly contagious skin infection. People believed that this plant could be used to treat impetigo. In Spain, *Handroanthus impetiginosus* is known as Lapacho negro. In Portuguese, the common name is Pau d'arco (bow tree), because the wood has been used to make strong bows for hunting by the incas for centuries.

Handroanthus impetiginosus is known due to its appearance. This deciduous species can grow to a height of 30 m with a base diameter of about 1.5-3 meters and sheds leaves in the dry season. The palmately compound and serrated leaves of a massive tree are green and arranged in opposite or subopposite pairs. The leaf shape is elliptic with pinnate venation. Dark pink or pink long-lived flowers appear in spring. The flowers calyx is campanulate to tubular with five lobes (Fig. 1.1).

Phloem (an inner layer of the bark) of the Pau D'Arco tree (Fig. 1.2) has high pharmaceutical value, has antibiotic, antinociceptive, anti-edematogenic, and antidepressant effects. That's why the Pau D'Arco tree extract has been used as a traditional medicine to treat different diseases, for example, inflammatory skin diseases. The phloem of the tree can be made into tea for these purposes. Pau

D'Arco was made into a strong decoction, which was used also topically. Modern dosages rely on tableted, incapsulated or liquid extract and drops formats [22, 25].

Fig. 1.1. The flowering Pau D'Arco tree [26]

Handroanthus impetiginosus is harvested from a rainforest as lumber and then sent off to factories to be cut up into useable pieces. It's here that *Handroanthus impetiginosus* is identified as "Pau D'arco", and the phloem is stripped off and sold on the herbal market. The heartwood is then cut into timber for various uses.

Fig. 1.2. The inner layer of the bark of the Pau D'Arco tree [26]

Some categories of phytochemicals have been identified in a Handroanthus impetiginosus inner bark, principally naphthoquinones, quinones, flavonoids, and benzoic acids. Investigations have demonstrated that compounds and extracts isolated from Pau D'Arco tree shaw an extensive range of pharmacological activities such as immunomodulatory, antifungal, anti-psoriatic, antioxidant, anti-inflammatory, ant-parasitic, anti-obesity, and anti-cancer properties. The mechanism of anti-inflammatory activity of the extract was studied through a molecular biological approach. But the clinical applications of an extract of Pau D'Arco tree have been poorly researched for today, and there is a limited information on its mechanism of action. Further investigations of its activities are conducted [22, 23, 25].

Several categories of compounds have been identified in the Pau D'Arco bark, 19 glycosides comprised of four iridoid glycosides, two isocoumarin glycosides, two lignan glycosides, eight phenolic glycosides, and three phenylethanoid glycosides were methanol-extracted. Major constituents of the tree are naphthoquinones, furanonaphthoquinones, quinones, anthraquinones, benzoic acid, cyclopentene dialdehydes, flavonoids, iridoids, coumarins, and phenolic glycosides. The presence of naphthoquinones attracted scientific attention in the medical field, with β-lapachone and lapachol especially piquing the interest of professionals. Lapachol inhibits proliferation of tumor cells, β-lapachone exhibits toxicity in human and murine cells. Lapachol can reduce the invasion of HeLa cells, which could represent an interest for the novel antimetastatic drugs [25, 26].

Organic acids, such as oxalic acid, are found in the bark, and the fat-soluble α-tocopherol and γ-tocopherol. α-Tocopherol can decrease neurodegenerative disorders and cardiovascular disease risk. In addition, this tree has several volatile constituents, such as 4-methoxybenzaldehyde, 4-methoxyphenol, 5-allyl-1,2,3-trimethoxybenzene, 1-methoxy-4-(1E)-1-propenylbenzene, and 4-methoxybenzyl alcohol that exhibit antioxidant activity.

Cyclopentene derivatives are secondary metabolites of plants, and this compounds from the Pau D'Arco tree contained cyclopentenyl esters. These

cyclopentene derivatives may provide an anti-inflammatory activity on the lipopolysaccharide (LPS)-mediated inflammatory response by blocking the production of nitric oxide (NO) and prostaglandin E_2 (PGE_2). Then as it is known, osteoarthritis is characterized with the increased production of pro-inflammatory mediators such as PGE_2 and NO in joint tissues. Cyclopentenyl esters from *Handroanthus impetiginosus* inhibit inflammatory responses [22, 26].

Recent research has indicated the involvement of inflammation in osteoarthritis (OA, a degenerative joint disease) pathogenesis. The pharmacological effects of Pau D'Arco tree ethanol extract on OA pathogenesis induced by monoiodoacetate (MIA) and the underlying mechanisms were investigated. In the animal model, the extract significantly ameliorated OA symptoms and reduced the serum levels of inflammatory mediators and proinflammatory cytokines without any toxicity. The anti-inflammatory activity of a Pau D'Arco extract was further confirmed in a macrophage-like cell line. The anti-inflammatory and chondroprotective activities of the Pau D'Arco extract were attributed to the targeting of the nuclear factor-kappa B and activator protein-1 signaling pathways in macrophages and chondrocytes.

The antibacterial activity of Pau D'Arco has been proven, and mainly attributed to the naphthoquinone content. Some of the significant research on Pau D'Arco in recent years has been on its significant ability to reduce tumors. The quinone content, including lapachol, has shown anticancer effect when included in the extract. In isolation, these quinone compounds bring with them side effects such as severe nausea and anti vitamin K activity. However, the Pau D'Arco tree bark is used for softening side effects of chemotherapy, and has shown promise as an add-on supplement alongside cancer therapies [23, 25].

The early studies on Pau D'Arco tree bark were about anti-cancer activity throughout the 1960s. The National Cancer Institute backed more research in this area. But the National Cancer Institute was testing single plant compounds (such as lapachol), rather than the whole extract, and reported that compounds were unable to produce therapeutic effects without side effects. Unfortunately, as Taylor L,

(2005) points out, the adverse effects are very similar (nausea, vomiting, and anti-vitamin K activity) to current chemotherapy drugs side effects. The scientist points out that there have been other nature compounds discovered in the Pau D'Arco tree bark that produce positive effect on vitamin K activity, and can neutralize the side effects that lapachol may have on vitamin K [15].

Pau D'arco has provided evidence in vitro against fungi such as not only Candida albicans, but also Aspergillus fumigatus, Cryptococcus neoformans, Cryptococcus neoformans, Penicillium purpurogenum, Microsporum gypseum, and Trichophyton mentagrophytes.

Candida albicans is a commensal microorganism in vaginal cavities, and the human digestive. This microorganism can become an opportunistic pathogen, resulting in candidiasis. The common use of the Pau D'arco bark is for eliminating candida infections – for which must to be taken several times regularly for 3–4 weeks. Lapachol and β-lapachone are compounds shown to be responsible for the antifungal activity of the bark [23, 28].

The Pau D'arco extracts are used in traditional medicine for the treatment of various infections. Due to the content of high concentrations of quinones, furanonaphthoquinones, and naphthoquinones the Pau D'Arco tree bark has demonstrated broad-spectrum actions against some disease-causing microorganisms such as Staphylococcus aureus, Helicobacter pylori, Bacillus subtilis, and Brucella. These effects are suggested to be through the naphthoquinones. The mechanism of action is reported to be through an uncoupling oxidative phosphorylation reaction and inhibition of cell respiratory mechanism through interactions with the cell membranes directly. Naphthoquinones had direct inhibitory activity on the electron transport chain in fungal and bacterial cell cultures [25, 26].

Pau D'arco extract has demonstrated properties against parasites that cause malaria – protozoa of the genus Plasmodium, and also schistosoma, trypanosoma, Leishmania.

Compounds of Pau D'arco have demonstrated activity in vitro against viruses such as influenza, poliovirus, herpes I and II, and vesicular stomatitis virus. However, today there is a lack of research in this area.

The caffeic acid contained in *Handroanthus impetiginosus* produced both antidepressant and antioxidant effects. The effect on depressive states was noted to be through the modulation of N-methyl-D-aspartate receptors.

Extracts of *Handroanthus impetiginosus* exhibited unique cytokine profiles. Results verify the immunomodulatory activity of the Handroanthus impetiginosus (Mart. ex DC.) Mattos (Bignoniaceae) tree bark. Combining a lack of toxicity and potency in human immune cells supports further research of extract [28, 31, 32].

1.2. Syrups formulation with extracts

Most frequently syrups are concentrated solutions of sucrose in water. A simple syrup contains purified water and sucrose. Syrup containing pleasantly flavored substance is known as flavoring syrup such as Acacia Syrup, Cherry Syrup. Medicinal syrup is the one to which therapeutic compound has been added (e.g., Ivy Leaf Cough Syrup) [16, 17].

Although very concentrated, the sucrose solution is not saturated. Slight excess of water enhances the syrup's stability, permitting cold storage without crystallization over a range of temperatures.

The high solubility of sucrose shaws a high hydration degree or high degree of hydrogen bonding between water and sucrose. Such association limits the further association between additional solutes and water. Syrups have a not high solvent power than water and "salting out" (sugaring) may be a problem during storage [30].

Syrups are protected from microbial contamination by virtue of its high concentration. Dilute syrups are good media for bacterial growth and require the preservatives’ introduction. Such preservatives as parabens (hydroxyl-benzoic acids), benzoates, and sorbic acid are effective in acid solutions. The mixtures of two parabens are employed frequently to take advantages of the potentiating effect

[7]. Potassium sorbate and sodium benzoate were used as antimicrobial preservatives in the polyherbal syrup [8, 12].

The study of herbal syrup samples with potassium sorbate at concentrations of 0.1–0.2% showed that it was effective as an antimicrobial preservative [7].

Syrups may contain also ingredients to improve the appearance, stability, solubility or taste. Syrup USP has a specific gravity of 1.313 g/ml and a concentration of 65 % w/w solution. This 65 % by weight is the amount of sucrose which is preserve syrup. For formulation of syrup that contains less amount of sucrose, the quantity of ethanol, or preservatives, must be estimated [5, 6].

Ethanol is used in syrups to assist in dissolving some alcohol-soluble active pharmaceutical ingredients, but normally, ethanol is not present in the finished product in amounts (15% to 20%) that would be considered to be adequate for preservation.

The flavorants must be water soluble because syrups are aqueous pharmaceuticals [30].

When preparating syrups they should be produced in clean premises and equipment to prevent syrups contamination.

The methods can be used to prepare syrups: agitation without heat and solution with heat. The hot method preparating syrups is quickest, but heating must be without volatile or thermolabile active pharmaceutical ingredients. Temperature must be controlled and regulated to avoid darkening (caramelization) and decomposing a syrup [9, 10].

Syrups in pharmacy are classified according to their basic compositions:

1. Sugar based syrups are concentrated solution of sugar which can be prepared with heat.

2. Artificial syrups are formulated with purified water, artificial sweetening agents and viscosity builders.

Syrups can be produced from polyols (glycerin, sorbitol, propylene glycol, mannitol), other sugars (glucose, fructose), than sucrose, with artificial sweeteners (saccharin, aspartame), for example, when special properties is desired, as with the

diabetic patient. Artificial sweeteners do not impart the characteristic viscosity of syrup and require a viscosity adjusters' addition (methylcellulose). Polyols are less sweet than sucrose, but have advantages of providing suitable viscosity, reduce cap-locking (unlike sucrose crystallization), and some polyols may act as preservatives or cosolvents in syrups. A 70 % aqueous solution of sorbitol is available for use as a vehicle for sorbitol-base syrup [30].

Sorbitol is hexahydric alcohol ($C_6H_{14}O_6$) has led to its use as a major component of syrup formulation. Sorbitol syrup is not irritating to the membrane of the mouth and the throat. This polyol does not contribute to the formation of dental caries. Sorbitol is metabolized to glucose in the gastrointestinal tract (GIT): but it is not absorbed from GIT as rapidly as sugar. No hyperglycemia has been found. However ingestion of excessive quantities (30–40 g) of it may have laxative effect [5, 27].

Sorbitol solution about 60 % is half as viscous as simple syrup and as sweet as sugar. Sorbitol solution has excellent mouth feel qualitities and lacks the slightly acrid characteristic of other polyols such as propylene glycol. Reduce sweetness and improved flavor properties can result when sorbitol is included in sugar based compositions. This polyol is compatible with simple syrups and other polyols; as much as 10 % (v/v) of ethanol may be added to sorbitol solution. Sorbitol is practically inert and chemically stable; so many API are more stable in sorbitol. Sorbitol in common with glycerin can be added to sugar syrups to reduce the tendency to crystallize of concentrated sucrose solution and inhibits the loking or sticking of caps of bottle that occurs with syrups containing high concentrations of sugar [11, 12].

Dextrose may be used as a substitute for sugar in syrups containing acids in order to eliminate the discoloration associated with sucrose inversion. It forms a saturated solution at 70 % w/v in water that is less viscous than sucrose syrup. But dextrose dissolves slowly than sucrose and is less sweet (0.7−0.8 sweetness of sucrose). Preservatives are also required to improve qualities of syrup. Glycerin as preservative may be added in 30 % to 45 % v/v.

Intended as substitutes for sugar syrups and to be administered to persons who must regulate their calorie and sugar intake accurately, e.g. persons suffering from diabetes mellitus, early formulae included propylene glycol or glycerin, but propylene glycol and glycerin are glycogenetic excipients, i.e. these materials are converted into glucose in the human body. As example of non–nutritive syrup — "Diabetic Simple Syrup" may contain aspartame that is about 200 times sweeter than sugar. Much research has been done to find a safe synthetic substitute for sugar. As a result, aspartame is being used in many commercial medicines as a sweetening agent [17, 18].

Viscosity builders are the components of modern syrups such as not only polyols sorbitol, glycerin, propylene glycol but also polymers (gums): natural polymers – tragacanth, acacia; semi synthetic polymers – hydroxypropylmethylcellulose (nonionic), methylcellulose (nonionic, exothermic), sodium carboxymethylcellulose (anionic), sodium alginate (anionic).

The viscosity provided by cellulose derivatives (sodium carboxymethylcellulose, hydroxypropylmethylcellulose, methylcellulose) is comparable to that of the sucrose syrup. Polymer solutions imitate texture of traditional syrup and sweeteners introduction can effectively disguise a medicine unpleasant taste [13, 14, 33].

Phytopreparations have been used since ancient times as effective prevention and treatment of illnesses. In recent years the use of herbal medicines has increased dramatically. Many formulations were oral medications which were widely used in decoction form by patients. Although traditional drugs are used now as new therapies for research, some of them have been reformulated to access pharmacopoeias standards for modern medications. Lack of profiles of the quality control for the herbal formulations drives scientists in pharmacy to explore more about herbal products. The quality control of formulations plays an important role in confirming the product efficacy and safety. Experimental syrups may contain API and required suitable components such as viscosity increasing and sweetening agents, and also preservatives [12, 19].

In order to obtain appropriate viscosity for the polyherbal syrup, wich contained aqueous extract of the roots of Glycyrrhiza glabra L., fruits of Foeniculum vulgare Mill., whole parts of Adiantum capillusveneris L., fruits of Vitis venifera L., fruits of Ficus carica L., flowers of Rosa damascena Herrm., and seeds of Onopordum acanthium L., scientists used carbomer 940, sodium carboxymethylcellulose, hydroxypropylmethylcellulose, polyvinylpyrrolidone solutions, polyethylene glycol and glycerin in prepared various experimental formulations. By adding carbomer 940, carboxymethylcellulose and hydroxypropylmethylcellulose (0.5, 1 %) in the syrup formulations, particles and turbidity were observed that indicated incompatibility between such polymers and components of the aqueous extract. Although the polymers gave suitable viscosity to the syrup at 1 % concentrations, the adding these polymers to increase the viscosity of the prepared herbal syrups was not logical. Polyvinylpyrrolidone was soluble in water and the syrup samples showed clear appearance with uniformity, however syrups did not show suitable viscosity [20, 21].

On the other hand, glycerin and polyethylene glycol improved the transparency and increased the relative viscosity of the herbal syrup samples. However solutions with various concentrations of polyethylene glycol were not acceptable due to their undesirable taste. Studies have shown that glycerin gave clear viscose syrups with sweet flavor and improved the syrup transparency and also masked the taste. Investigating the physicochemical properties of experimental samples showed that increasing the glycerin concentration improved the appearance and increased the viscosity of the syrup. But high level of glycerin (20 %) produced very sweet taste that was not desirable; formulation with 16 % of glycerin was chosen as the appropriate for the polyherbal syrup. Therefore, glycerin as viscosity-increasing agent, sweetener, transparency enhancer, stabilizer, and co-solvent was used in the prepared herbal syrup.

Ingredients like flavoring and coloring agents are not adding to syrups with plant extracts always. Additional components can be avoided to prepare a product similar to the traditional version as much as possible [12–14, 16, 29].

Conclusions to chapter 1

1. Plant products have long-standing utility toward treating the broad-spectrum of illnesses. The inner bark of *Handroanthus impetiginosus* (a tropical evergreen tree) is used in traditional medicine especially for infections, immunity disorders (allergy, revmatism, and psoriasis), and cancer. The main active compounds of Pau D'Arco phloem are quinones β-lapachon and lapachol and recent studies confirm its therapeutic effects. The most promising is their immunomodulatory and anti-tumor activity.

2. For the development of syrups with extracts from plant raw material an individual approach is necessary in each specific case.

3. According to the literature data, substances, used as excipients in syrups, were determined. It was found, that sucrose, as well as sorbitol, are most commonly used as sweeteners in herbal syrups. The commonly used viscosity-increasing agents are cellulose derivatives (carboxymethylcellulose and hydroxypropylmethylcellulose) and gums.

4. Potassium sorbate as a preservative in herbal syrups has been chosen.

CHAPTER 2
THE JUSTIFICATION OF THE RESEARCH GENERAL CONCEPT. OBJECTS AND METHODS OF RESEARCH

2.1. Methodological approaches to the development of the syrup composition with a Pau D'Arco extract

Issues of stability, bioavailability, acceptable organoleptic characteristics and creation of comfortable taking conditions are given a special role in the development of new syrups. All these issues are solved by introducing excipients into syrups that affect their physicochemical properties.

The disadvantage of traditional syrups as a dosage form is the presence of the main component – sucrose. Sucrose is a form-forming agent and flavor enhancer in syrups. The excipient is added to pharmaceutical forms in large quantities, which can decrease the bioavailability of active substances, which has been proven by many scientists, and decrease the stability of API.

Syrups with sucrose are also contraindicated in patients with diathesis, fungal infection, and diabetes mellitus. Excessive amounts of sucrose in the intestines serve as a nutrient medium for microorganisms that cause fermentation, diarrhea.

A study of the stability of ascorbic acid in vitamin syrups showed that the vitamin is prone to partial decomposition. The stability of the specified vitamin when replacing sucrose with sorbitol in syrups was significantly increased.

When developing syrups, it is necessary to take into account that the addition of a flavoring agent should not reduce the therapeutic value of API. Flavoring agents should not interact with the components of the drug, should be non-carcinogenic, non-toxic, stable at the pH of the syrup, resistant to temperatures from 10 to 110 °C, to light; resistant to oxidation, should mix well with other components of the syrup.

The physicochemical properties of the syrup depend on the concentration of sorbitol, which is used as a base in many pharmaceutical syrups [5, 30].

2.2. Characteristics of a Pau D'Arco extract and excipients

Glycerin–water liquid extract from the Pau D'Arco phloem (ARCO, Hawaii, USA) was used for the research [15]. The extract contains lapachol, β-lapachone and lapachenol, and other biologically active subsances, which have immunomodulatory, anti-inflammatory antibacterial, and antifungal effects. Lapachol is a natural phenolic compound and also effective against viral infections and parasites. Chemically, it is a derivative of vitamin K. Preferred IUPAC name of lapachol is 2-Hydroxy-3-(3-methylbut-2-en-1-yl)naphthalene-1,4-dione. Chemical formula is $C_{15}H_{14}O_3$.

The natural compound β-lapachone (2,2-Dimethyl-3,4-dihydro-2H-benzo[h]chromene-5,6-dione) which is contained in Pau D'Arco extract also in combination with various antibiotics acts against methicillin-resistant Staphylococcus aureus, also works synergistically with β-lactam antibiotics. Molecular formula of β-lapachone is $C_{15}H_{14}O_3$. Beta-lapachone is 3,4-dihydro-2H-benzo[h]chromene-5,6-dione substituted by germinal methyl groups at position 2. Isolated from *Handroanthus impetiginosus*, it exhibits antineoplastic and anti-inflammatory activities. It is a benzochromenone and a member of orthoquinones.

The lapachol, β-lapachone and lapachenol chemical structure is shown in Fig. 2.1.

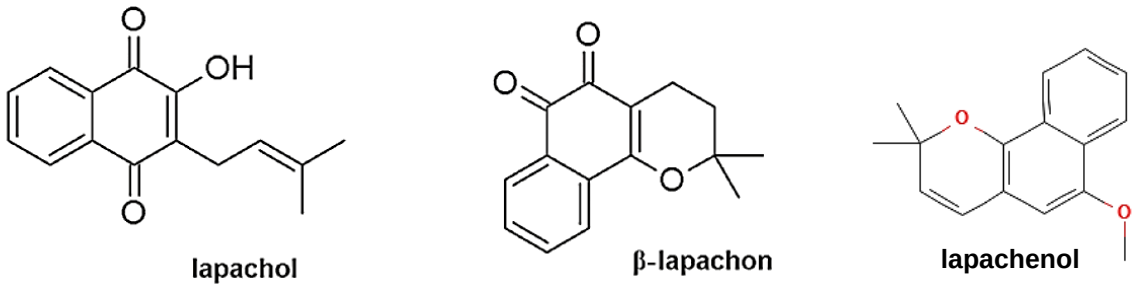

Fig. 2.1. Structure chemical formulas of lapachol, β-lapachone and lapachenol

Lapachenole is a benzochromene. IUPAC name is 6-methoxy-2,2-dimethylbenzo[h]chromene. Molecular formula of lapachenol is $C_{16}H_{16}O_2$.

Lapachenole is a member of the class of compounds known as naphthopyrans. Naphthopyrans are in turn compounds that contain a pyran ring fused to a naphthalene moiety. Naphthalene is a polycyclic aromatic hydrocarbon wich made up of two fused benzene rings [34, 35].

The recommended dose of Pau D'Arco extract is 1 ml (1156 mg) up to three–four times a day. The manufacturer of this liquid extract used classic conventional methods of extraction. Main ingredients for obtaining the extract: wild harvested Pau d'arco (*Tabebuia impetiginosa* or *Handroanthus impetiginosus*) dried bark from Brazil and solvents: vegetable glycerin, purified water. The ratio: dry plant material / solvents 1:3 w/v [15].

We filtered the Pau D'Arco extract because there was unfiltered extract and could contain some plant material inside.

In the development of composition and technology of the syrup auxiliary matters were utilized, functional characteristics and high-quality descriptions of which were confirmed with the reference documents.

Purified water is water for the preparation of the syrup. Purified water is colorless, odorless liquid which satisfies the test for endotoxins described in SPU. It is usually produced on-site from potable water. Potable water must meet also stringent quality thresholds. Purified water is a grade of pharmaceutical water that is free of sulfates, chloride, calcium, carbon dioxide, ammonia, and heavy metals.

Sorbitol (synonyms: D-Sorbitol, D-Glucitol) is a polyol (Fig. 2.2) that is naturally found in many fruits (i.e. pears, apples, peaches, ripe rowan fruits, and in apricots) and has empirical formula is $C_6H_{14}O_6$, and molecula weight — 182.17. Sorbitol is solid white powder, soluble in water (400 mg/mL), a type of sugar alcohol which widely used as a sweetening agent in pharmaceutical and food industry. The excipient has about 60 % of the sweetness of sucrose.

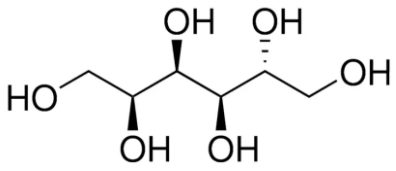

Fig. 2.2. Structure chemical formulas of sorbitol

Sucrose ($C_{12}H_{22}O_{11}$) is white odorless crystalline or powdery solid with molecular weight 342.30 g/mol. Excipient is a glycosyl glycoside formed by fructose and glucose units joined by an acetal oxygen bridges from hemiacetal of glucose to the hemiketal of the fructose. Sucrose has a role as a sweetening agent and syrup base. It has high solubility in water, dissolving about 200 g of excipient in 100 g of water at 20 °C.

Fructose ($C_6H_{12}O_6$) is a natural sweetener with a low glycemic index, making it a choice for health-conscious manufacturers. Due to its higher sweetness compared to sugar, fructose allows the developer to reduce the amount of added sweetener in pharmaceuticals, while maintaining their pleasant taste. Main advantages of fructose: low glycemic index (suitable for pharmaceuticals intended for diets with controlled sugar content), and greater sweetness of fructose compared to sugar (an opportunity to reduce the use of sweeteners in products).

Potassium sorbate (syn. potassium 2,4-hexadienoate; sorbic acid potassium salt, Fig. 2.3.) has linear formula: $CH_3CH=CHCH=CHCOOK$ and molecula weight — 150.22. Sorbates have been classified as “Generally Recognized as Safe” additives and have been reported to be less toxic than benzoates. Sorbic acid is metabolised to mainly to CO_2, while the minor amounts of thes acid are converted to trans,trans-muconic acid, which is excreted into the urine unchanged.

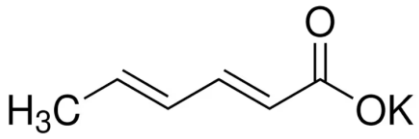

Fig. 2.3. Structure chemical formulas of potassium sorbate

Potassium sorbate is a white salt, a preservative, used for the prevention of pharmaceuticals from bacteria, molds or yeasts growth. Potassium sorbate is a antimicrobial agent, which can act effectively along a wide pH range to inhibit the growth of microorganisms. Excipient has a good solubility of 58.20 g/100 ml at 20 °C in water. Sorbate is used at concentrations of 0.025–0.3 %, it is most effective at a pH range of 3.0–4.5.

Flavors (flavoring agents) were used in the Pau D'Arco syrup also.

2.3. Methods of research

Viscosity. The viscosity coefficient η or dynamic viscosity is the tangential force per unit of surface, known as shearing stress τ and expressed in pascals, necessary to move, parallel to a sliding plane, a liquid layer of 1 square metre at a rate (v) of 1 m / sec relative to a parallel layer at a distance (x) of 1 m.

The ratio d v /d x is a speed gradient that give the rate of shear D expressed in reciprocal sec (s^{-1}), so that $\eta=\tau/D$.

The dynamic viscosity unit is the Pa·s. The commonly used submultiple is the mPa·s.

The kinematic viscosity v, expressed in square metres per sec, is obtained by dividing η by the density ρ of viscous liquid measured at the certain temperature, i.e. $v=\eta/\rho$. The kinematic viscosity is expressed in square mm per sec.

A capillary viscometer may be used for determining the viscosity of Newtonian liquids such as syrups [2–5].

Capillary viscometer method. The determination of the Pau D'Arco extract syrup viscosity using a capillary viscometer was carried out at a temperature of (20 ± 0.1) °C. The time required for the level of the syrup to drop from one mark to the other is measured to the nearest one-fifth of a second with a stop-watch. The result was valid if two consecutive readings did not differ by more than 1 %. The average of three readings gived the flow time of the Pau D'Arco extract syrup.

The dynamic viscosity η in mPa·s was calculated using the formula:

$$H = kpt,$$

where K – constant of the viscometer, expressed in mm^2/sec^2;

P – density of the syrup expressed in mg/mm^3, obtained by multiplying its relative density by 0.9982;

t – flow time of the syrup in seconds.

The viscometer constant k is determined using a suitable calibration liquid.

To calculate the kinematic viscosity ($mm^2 \cdot s^{-1}$), the such formula can be used:

$$v = kt.$$

The viscometer was filled through tube (L) with a certain quantity of the syrup, previously brought to 20 °C, then bulb (A) was filled but ensuring that the liquid level in bulb (B) is below an exit to ventilation tube (M). The viscometer was immersed in to water bath at (20±0.1) °C, it was maintained in the upright position and it standed for not less than 30 min. Tube (M) was closed and the level of the syrup in tube (N) was raised up to the level about 8 mm above mark (E). The syrup was kept at this level by closing tube (N) and then opening tube (M). Also then tube (N) was opened and, the time required for the level of the syrup to drop from mark (E) to (F) with a stop-watch to the nearest one-fifth of a second, was measured.

PH Test. Determine the pH of the Pau D'Arco syrup by suitable means; it should be 6.0 to 7.0.

Measuring the density of the Pau D'Arco extract and syrup. The measuring cylinder was taken. The samples of extract or syrup were added carefully at a specified temperature to a cylinder. The appropriate hydrometer, also at a similar temperature, was lowered into the test samples and allowed to settle. After temperature equilibrium has been reached, the hydrometer scale was read. The cylinder and its contents were placed in a constant temperature bath to avoid excessive temperature variation during the research [2–5].

Organoleptic evaluation of the extract and syrup. The organoleptic characters such as odour, colour, and taste were evaluated based on the method described in the literature. The classic approach according to methods of the "flavour map" by A. I. Tentsova and the "flavour panel" by I. A. Yegorov was used [5]. The parameters of taste and emotional feelings caused by the extract and

the syrup obtained on the basis of the Pau D'Arco glicerin-aqueous extract were studied.

The method for evaluation of flavours named the "flavour panel" is based on distribution of perception of sensations intensity and emotions in research. The evaluation of studied flavours was performed according to the five-point grading scale in the group of 20 persons. From the obtained data taste indeces were deduced as the arithmetic mean from evidence of all persons involved in research. The higher was the masking flavour potential, the greater was the numerical index.

Essences as lemon, raspberry, cherry and the combinations such as lemon/mint, raspberry/lemon, cherry/lemon were selected to determine the flavour profile of the syrup samples in research.

Conclusions to chapter 2

1. Thorough methodological approaches to the development of the syrup with the Pau D'Arco extract are suggested.

2. The characteristics of the Pau D'Arco extract and certain excipients which were used for the development of the syrup are contained in this chapter.

3. The basic methods of physico-chemical and technological research for the formulation and evaluation of the syrup with the Pau D'Arco extract are presented.

CHAPTER 3.
EXPERIMENTAL PART.
RESEARCH FOR DEVELOPMENT OF PREPARATION COMPOSITION IN FORM OF A SYRUP WITH THE PAU D'ARCO EXTRACT

3.1. Market analysis of products with Pau d'arco extract

Pau D'arco extract are mainly represented by capsules (four names from USA, one name is produced in Ukraine), tablets (one name from USA) and drops (three names from USA) on the modern market (Fig. 3.1, 3.2) [1, 15].

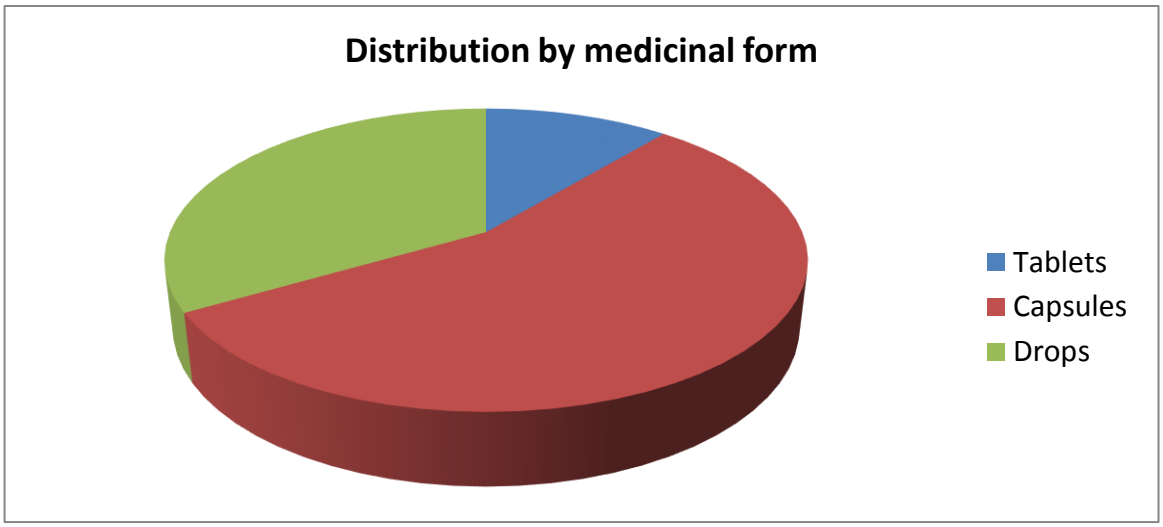

Fig. 3.1. Distribution of dietary supplements by medicinal form

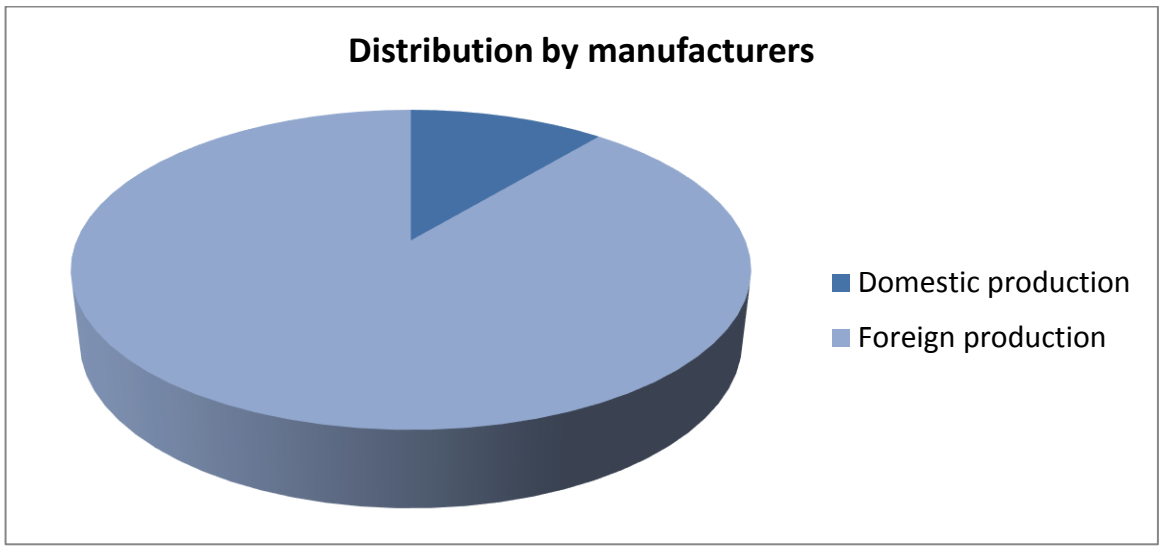

Fig. 3.2. Distribution of dietary supplements by manufacturers

As can be seen only one dietary supplement is represented on the market that produced in Ukraine, and these are capsules.

3.2. Research of characteristics of Pau d'arco extract, choice of excipients and development of the syrup composition

At the first stage of the research the Pau D'Arco liquid extract was analyzed for indicators such as appearance, dry residue, and density necessary to justify the further technological research of a syrup. Certain characteristics of the Pau D'Arco liquid extract are given in the table 3.1.

Table 3.1

The Pau D'Arco glycerin–aqueous extract indicators

Index	Characteristics
Appearance	Transparent brown liquid of slightly thick consistency with a characteristic odor and bitterish taste
The water content, %	49.1
Density	1.156 g/ml

It can be seen from the table 3.1 that the Pau D'Arco extract had a bitterish taste, which is unacceptable for syrup and confirms the need for corrected pharmceutical form of this extract. Glycerin is liquid with sweet tastes but in the Pau D'Arco extract can not masked the taste.

Further research on the rational flavor in the composition and the sweetener basis for a syrup with the Pau D'Arco extract were carried out. Sucrose, sorbitol and fructose solutions were used as sweetener systems in such proportions: sucrose and purified water – 64 : 36; sorbitol and water purified – 64 : 30, 45 : 55, 55 : 45; fructose and also purified water – 64 : 30. The compositions of model syrup bases are shown in table 3.2.

Model concentrated sweetener solutions (sucrose, sorbitol and fructose) were obtained with heating to 100 °C. The Pau D'Arco extract was added to the

cooled syrup samples. Corrective agents for a more pleasant smell (flavor: lemon, raspberry, cherry and the combinations such as lemon/mint, raspberry/lemon, cherry/lemon) were added to the syrup base samples.

Table 3.2

The compositions of samples of model syrup bases

Ingredients	Number of sample / g				
	1	2	3	4	5
Sucrose	64				
Sorbitol			45	55	64
Fructose	36	64			
Water purified		36	55	45	36

High compliance of therapy with the using of different oral dosage forms largely depends on their taste, i.e. sensations in the mouth. API molecules interact with the tongue taste receptors to give salty, sweet or bitter taste, when substances dissolve in saliva. These taste sensations are results of transduction of signal from the receptor organs, nown as taste buds. There are numbers of pharmaceuticals available in which API with bitter taste on the pharmaceutical market. For the improved palatability and acceptability of these pharmaceuticals the development of numerous formulations was carried out. Many methods have been developed to mask the bitter taste of drugs to overcome the problem of imperfect taste. Such developed methods not only mask the bitter taste of medicines but increase also the pharmaceutical form bioavailability. They include sugars, flavors, sweeteners replenishment, lipoproteins and adsorbates using, a temporary numbing taste buds, granulation and coating particles with polymers or microencapsulation, multiple emulsions, modifier of viscosity, creation of liposomes and vesicles, formation of salts, prodrugs, inclusions, solid dispersion, molecular complexes, and Ion Exchange Resins (IERs).

Organoleptic parameters are very important for an oral drug form especially for pediatric and geriatric patients. The elderly and children show difficulties in

swallow of solid dosage forms. Liquid dosage forms or small sized particulates are superior to common tablets or capsules. The one of problems with using medicines in liquids is the palatability, especially when considering that sensation of taste differs interindividually and age-dependently. Recent technological developments promise improvements.

The sense of taste is mediated by special taste bud, that is group of receptor cell (60–100 cells). Such receptor cells bundled together in clusters and gives definite taste sensation via neurons to the central nervous system in a brainstem. Taste buds are chemoreceptors that stimulated by chemicals from medicines dissolved in saliva. Chemicals enter via the special taste pore and then cause electrical changes by interaction with surface proteins, causing a transmission of signals to a brain.

Four taste sensations have been described in the scientific literature. The salty taste is one of four tastes tongue receptors that located on a tongue edge and upper front portion.

The sweet taste is also one among the four tongue taste receptors. They are found on the tongue tip.

The sour taste is also tongue taste receptor that occurs at tongue sides and is stimulated by acids mainly.

The bitter taste, which is the last of the four taste tongue receptors, located toward the tongue back. It is stimulated by organic chemical substances. Several inorganic substances, for example, calcium and magnesium salts can produce bitter taste.

Taste transduction begins with the medicine interaction with taste receptor cells. The medicine molecules binds with G-Protein coupled receptors in the cells triggering the releasing G-Protein called Gustducin. The taste sensation process begins when G-Protein Gustducin activates the effector enzymes phosphodiesterase IA or phospholipase C beta-2. The enzyme then changes in the intracellular level of second messengers (cyclic adenosine monophosphate, inositol, diacylglycerol and 1, 4, 5-triphosphate). Second messengers activate ion

channel inside cells and on extra cellular membrane. The ionization depolarizes cells causing the releasing neurotransmitters wich send nerve impulse to a brain. The brain carries a signal of the bitter taste. Special taste blockers work by interfering with the transduction of taste.

Age affects taste buds. Researchers have been proved that the taste buds' cells wear out with age. Taste buds begin to disappear on sides of a mouth except taste buds located over tongue. Taste buds become less sensitive. Eating of scalding food and smocking may damage to taste buds. This lacking of taste can lead to poor nutrition and loss of appetite. In addition, taste is a type of medium to experience the world for children, wich are more sensitive to tastes than adults, and however taste can be subjective. The taste sensitivity mechanism in youngsters may be very difficult to analyze.

Depending on individuals, the perceived taste can vary to different degrees because taste is a very subjective perception. When we have well controlled experimental set up, it is possible to reproducibly and accurately measure taste thresholds. To evaluate taste sensation, several methods have been reported by researchers. The first one is panel testing, that a psychophysical rating of gustatory stimuli. About 5-10 human volunteers are trained for the taste evaluation by the use of reference solution ranging in taste from tasteless to bitter in this method. Subsequently, values are assigned to levels (e. g. 0-5) of bitterness. Then test solutions are rated to assess its bitterness. The test results for all taste-masked drugs can be seen in the reports.

Electronic tongue is a taste sensing device for detecting the magnitude of API bitterness. The automated device has a transducer which is composed of lipid / polymer membranes with such parameters that may detect taste in similar manner to the human gustatory sensation. A response of taste is transferred into a pattern composed with electrical signal of definite membrane potentials of a receptor part. The response electrical potential pattern may be obtained for drugs with definite taste qualities. The technique has been applied for evaluation of the bitterness of several medicines. The standard for bitterness was quinine hydrochloride. Basic

compound with amino groups in the molecules shows a good correlation between the relative response electrical potential of taste sensor channels, which contain membranes with negative charges.

The electric potential of channels did not increase, for API with both a cationic (amino) groups and an anionic (carboxylic acid) group in the molecule, such as caffeine and theophylline, even though bitterness was observed in the human gustatory sensation test. So, different types of membrane component must be for the evaluation of the bitterness of API.

Another method is spectrophotometric. A known quantity of the tastemasked composition is mixed with 10 ml of purified water in 10 ml syringe by revolving the syringe. Then the test solution is filtered through a membrane, followed consistently by spectrophotometric determination of the API concentration in a filtrate. If API concentration is below a threshold concentration, developer may conclude that a bitter taste would be masked by such composition. This technique has been applied by scientists to evaluate sparfloxacin granules with a taste masking. The threshold concentration was 105 μg/ml in this case.

The results of testing organoleptic characteristics of the Pau D'Arco syrup samples are shown in Table 3.3. The taste is shown in the table on a five-point scale (column 2): very pleasant – 5, pleasant – 4, not bad – 3, bad – 2, very bad – 1. Also, from the point of view of assessing the main taste, the assessment was carried out using the following terms: smooth, not bitter – 5; little astringent or bitter – 4; slightly astringent or bitter – 3; astringent or bitter – 2; very astringent or bitter – 1. The higher the numerical index of the taste, the higher the masking potential of the correcting agent.

Taste sensations were conventionally indicated by letters (column 3): (Sw – sweet, B – bitter, Sa – salty, So – sour) and numerical indices: 1 – not sweet, not bitter, not salty, not sour; 2 – slightly sweet, slightly bitter, slightly salty, slightly sour; 3 – sweet, bitter, salty, sour; 4 – very sweet, very bitter, very salty, very sour.

Table 3.3.

The results of evaluation of Pau D'Arco syrups organoleptic characteristics

Number of sample	Numerical index value (by A. I. Tentsova method)	Flavour panel (by I. A.Yegorov method)	
	Taste sensation (score) / basic taste sensation (score)	Flavor formula (with changes in letters to English)	General taste
1	2	3	4
1 – sucrose 64 %	4.0 / 5	Sw4	Very sweet
2 – fructose 64 %	3.9 / 5	Sw4	Very sweet
3 – sorbitol 45 %	3.8 / 4.1	B2Sw2	Slightly bitter, slightly sweet
4 – sorbitol 55 %	4.0 / 4.4	B2Sw3	Slightly bitter, sweet
5 – sorbitol 64 %	4.6 / 5	Sw3	Sweet

According to the table 3.3 data sorbitol syrup 64 % with Pau D'Arco extract received the highest organoleptic characteristics rating – 4.6 / 5. Sucrose and fructose syrups with Pau D'Arco extract were very sweet. Fructose is the sweetest of natural sugars. Crystalline fructose is 1.8 times sweeter than crystalline sucrose.

It was this concentration of sorbitol 64 % that allowed masking the bitter taste of the extract. This choice of the taste effect is consistent with the results obtained by two methods (column 2–4 in the table 3.3). Investigating the properties of model compositions showed that increasing the sorbitol ratio improved the taste and increased the viscosity of the syrup. While sorbitol syrups 45 % and 55 % did not have a pleasant taste.

To give the Pau D'Arco extract syrup a more pleasant fruity smell, corrective agents flavors were added to it – food flavors lemon, raspberry, cherry and the

combinations such as lemon/mint, raspberry/lemon, cherry/lemon produced by the company "Symrise" (Austria). The choice of flavoring agents and its concentration was carried out experimentally and the organoleptic properties were evaluated using a rating scale: very pleasant (5), pleasant, good (4), not bad (3), bad (2) [5, 6, 18]. The results are represented in table 3.4.

Table 3.4.

Evaluation of organoleptic properties of sorbitol syrup samples with extract and flavoring agents

Flavoring agents		Average rating of objective sensations
Name	Concentration, %	
Lemon	0.03	4,3
	0.05	4,4
Raspberry	0.03	4,5
	0.05	4,7
Cherry	0.03	4,5
	0.05	4,6
Lemon/mint 1:1	0.03	4,9
	0.05	5,0
Raspberry/lemon 1:1	0.03	4,5
	0.05	4,6
Cherry/lemon 1:1	0.03	4,3
	0.05	4,4

The results of the syrup evaluation showed that best composition was with Lemon/mint flavoring combinations in 0.05 % concentration. This was transparent viscous solution; light brown, sweet with a lemon/mint flavor. The syrup gives a feeling of a slight cold effect in the oral cavity due to the presence of sorbitol.

The finished the Pau D'Arco syrup may be contaminated by saprophytic bacteria or yeasts that are resistant to the osmotic pressure in the solution. They can

cause decomposition of the extract by high enzymatic activity even in small quantities that meet the limits regulated by the SPhU.

A preservative – potassium sorbate – was added at a concentration of 0.2 % to prevent the growth of microorganisms in the syrup during storage because potassium sorbate is typically used at a concentration of 0.1–0.2 % in oral pharmaceuticals. Potassium sorbate was chosen as a preservative, which included in many formulations of liquid dosage forms, according to the literature [6, 7].

Potassium sorbate is used at approximately twice sorbic acid in pharmaceuticals (it is more soluble and stable in water). The effectiveness of this preservative increases with growth of concentration and temperature.

Thus, theoretically and experimentally substantiated composition of the Pau D'Arco syrup. The composition of the syrup with extract of Pau D'Arco bark was offered (Table 3.5).

Table 3.5

Composition of the syrup with extract of Pau D'Arco bark

Components, g	Content, g	Function
Pau D'Arco bark extract (extracting agents – glycerin, water, the ratio: dry plant material / solvents 1:3 w/v)	23.12	API
Sorbitol	64.0	Sweetener
Lemon flavor	0.025	Flavoring agent
Mint flavor	0.025	Flavoring agent
Potassium sorbate	0.2	Preservative
Purified water up to	100.0	Solvent

The flowshart of the Pau D’Arco syrup obtaining is presented in Fig. 3.3 and consists from several stages.

The syrup production technology at the factory was proposed. The technology includes such technological stages as preparation of a solution of excipients, mixing and filtration, filling the bottles, capping, labeling and packaging.

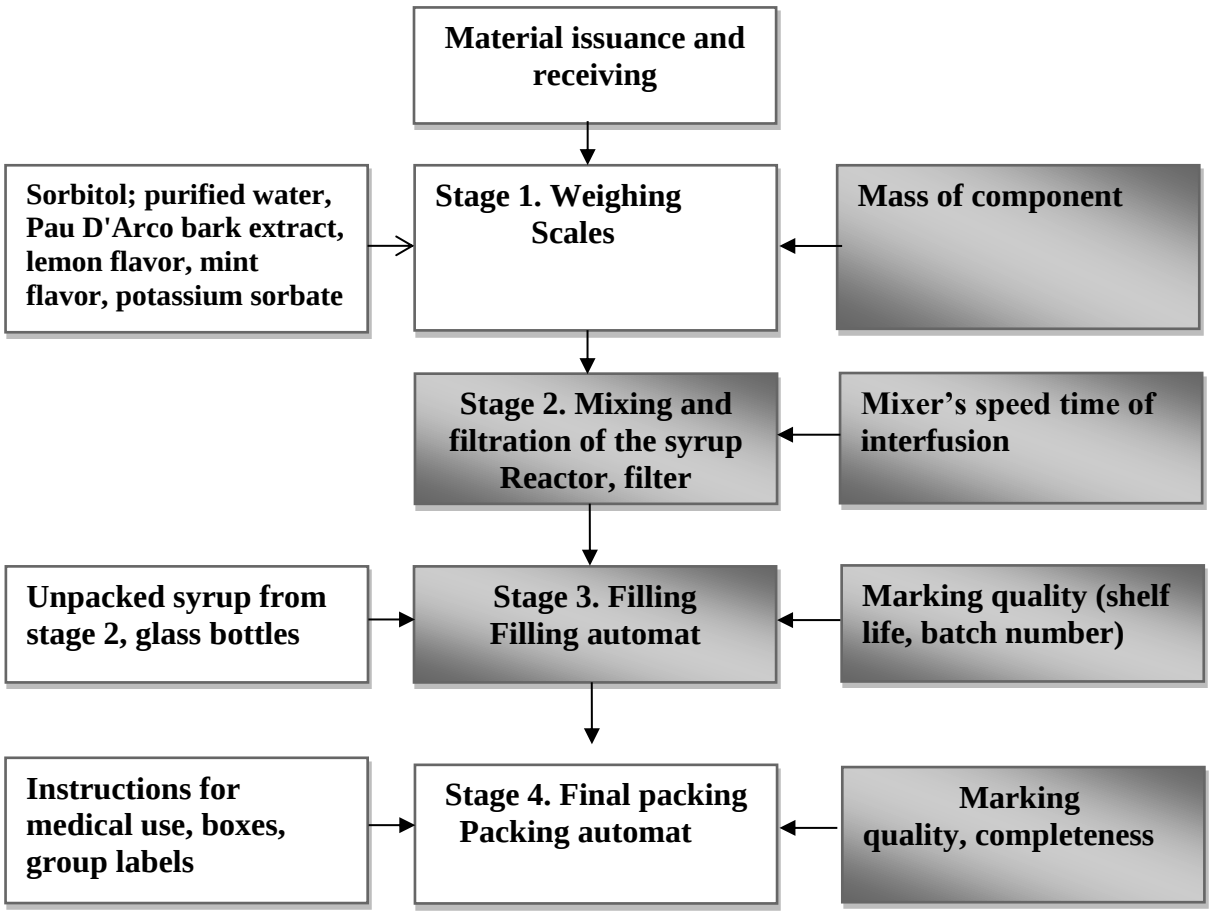

Fig. 3.3.The flow-chart of technological process of production of Pau d'arco extract syrup

Stage 1. Weighing.

Weigh the amount of sorbitol and potassium sorbate specified in the production recipe, calculated for the production of a products batch of a certain volume. All substances must be accompanied by a quality certificate and a permit for use from the Quality Control Agency.

The amount of Pau d'arco extract specified in the production recipe is measured, and the required amount of lemon liquid flavor and mint liquid flavor is weighed.

The weighed components are transferred to the reactor in closed containers.

Stage 2. Mixing and filtration of the syrup.

The required amount of purified water is measured into a reactor equipped with an anchor mixer and heated to a temperature of (65 ± 2) °C. Then sorbitol and preservative are loaded into the reactor, mixed for (20 ± 3) min. The solution is brought to the boiling temperature (105 ± 1.5) °C, boiled for (5 ± 0.5) min. Then the solution is gradually cooled to the temperature (25 ± 2) °C.

To the prepared sorbitol solution 64 % with preservative obtained in stage 1, a measured amount of a Pau D'Arco liquid extract and flavoring agents are added while stirring. Mixing is carried out for (10 ± 1.5) minutes.

Unfiltered syrup from the reactor is transferred through a cartridge filter to the tank using compressed air.

Intermediate control of the Pau D'Arco syrup is carried out. Filtered syrup samples are taken for intermediate quality control according to the parameters: identification, density, viscosity, and pH. After receiving positive results of the syrup analysis it is transferred to stage 3.

Stage 3. Filling.

The Pau D'Arco syrup is dosed into bottles and capped with caps filled bottles by a filling and capping machine. The dosage of syrup (104 ml) is measured before starting the dosing by machine. The mass of Pau D'Arco syrup in one bottle is controlled during the dosing process. Self-adhesive labels are applied to the bottles by a labeling machine.

Stage 4. Final packing.

Bottles and instructions for medical use are placed in cardboard packs using a cartoning machine. The boxes are placed in corrugated cardboard boxes on the packing table. Group labels are glued to these cardboard boxes.

Packaged products (the Pau D'Arco syrup), identified with the "Quarantine" label, are transferred to a quarantine warehouse. Control of packaged products is carried out in accordance with the reference documents.

3.3. Research of the quality of a syrup with Pau d'arco extract

The evaluation of syrup quality control with Pau d'arco extract has shown that it has the optimum visual properties without crystallization and any indications of cap locking. There was no indication of physical changes were observed during short term stability tests. Researches on a stability of the Pau D'Arco bark extract syrup are presented in table 3.6 showed that main characteristics of developed syrup remained stable during 6 months (observation time).

The quality parameters of the syrup with the Pau D'Arco bark extract determined in accordance with the SPhU, 2.0. Appearance, density, viscosity, pH were the criteria of estimation of syrup quality in storage conditions 15–25 °C.

Table 3.6

Appearance and physicochemical characteristics and researches on a stability of the syrup with the Pau D'Arco bark extract

Characteristics	Freshly made	Storage time, month		
		1	3	6
1. Appearance	Transparent viscous solution, light brown, sweet with a lemon/mint flavor. Feeling a slight cold effect in the mouth			
2. Density, g/ml	1.2567± ±0.004	1.2568± ±0.004	1.2564± ±0.004	1.2565± ±0.004
3. Viscosity, mm^2/sec	111.0 ± ±0.003	110 ± ±0.004	110.0 ± ±0.005	111.0 ± ±0.003
4. pH	6,7	6,7	6,7	6,7

Note: table data are average values from five measurings

Studies on the stability of the syrup with the Pau D'Arco bark extract are ongoing. Additional research into its qualitative and quantitative formulation is proposed to prove the quality of the obtained syrup.

Thus, it is possible to conclude on the basis of the complex of research, that the developed syrup of the Pau D'Arco bark extract by many measures of quality correspond to the SPhU, 2 edition [24].

Conclusions to chapter 3

1. The composition and technology of phytopreparation with the Pau D'Arco bark extract are developed in the medicinal form of a syrup as a result of theoretical and experimental research.
2. As a result of technological research, a sweetener was selected for the developed syrup based on Pau D'Arco bark extract (sorbitol syrup 64 %), combination of lemon flavor and mint flavor, and a syrup preservative was proposed — potassium sorbate.
3. Influence of excipients is studied on the indexes of syrup bases and indexes of quality of the obtained Pau D'Arco syrup.
4. The studied quality indicators of the syrup with Pau D'Arco bark extract such as appearance, density, viscosity, and pH remain stable during storage at the temperature of 15–25 °C for 6 months (observation period). The study of the shelf life of the developed syrup is ongoing.

CONCLUSIONS

1. The data of scientific literature on the main characteristics of the Pau D'Arco bark as plant raw materials were analyzed and summarized, the immunomodulatory, antifungal, antibacterial and anti-inflammatory properties of the Pau D'Arco bark were identified. The possibility of developing a new liquid medicinal product in the medicinal form of syrup with Pau D'Arco extract using modern excipients has been established.

2. The range of medicines and dietary supplements, which include the Pau D'Arco extract, presented on the Ukrainian market has been analyzed. A phased analysis of the dietary supplements by dosage forms and manufacturing countries has been made.

3. The complex of different theoretical and experimental researches is carried out to develop composition with the Pau D'Arco extract in the syrups form. The chosen base for the syrup is sorbitol solution 64 %.

4. Organoleptic and physicochemical indicators of syrup with Pau D'Arco extract (appearance, viscosity, density, pH) have been determined, which can be included to the reference documentation.

5. Research has been carried out on stability of phytopreparation of the Pau D'Arco extract in the form of syrup.

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ANNEX

Annex A

МІНІСТЕРСТВО ОХОРОНИ ЗДОРОВ'Я УКРАЇНИ
НАЦІОНАЛЬНИЙ ФАРМАЦЕВТИЧНИЙ УНІВЕРСИТЕТ

ГРАМОТА

нагороджується

OUAKRIM Safae

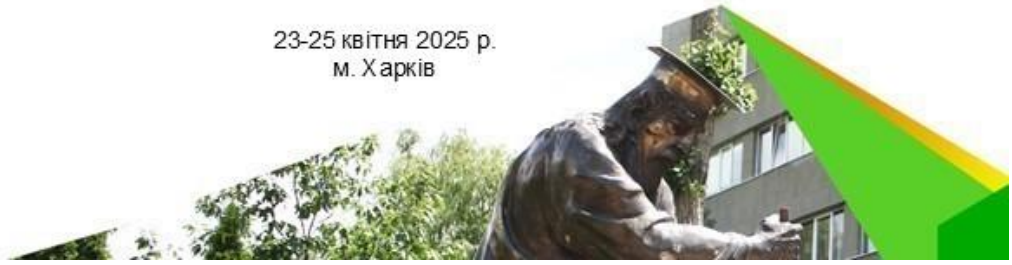
у секційному засіданні студентського наукового товариства кафедри
промислової технології ліків та косметичних засобів

XXXI Міжнародна науково-практична конференція
молодих вчених та студентів
«Актуальні питання створення нових лікарських засобів»

В.о. ректора
Національного фармацевтичного
університету

Алла КОТВІЦЬКА

23-25 квітня 2025 р.
м. Харків



Ф А 2.2.1–32-366

National University of Pharmacy

Faculty pharmaceutical
Department of industrial technology of medicines and cosmetics

Level of higher education master

Specialty 226 Pharmacy, industrial pharmacy
Educational- professional program Pharmacy

APPROVED
The Head of Department
of Industrial Technology
of Medicines and
Cosmetics

_____

Olena RUBAN
" 26 " of September 2024

ASSIGNMENT
FOR QUALIFICATION WORK
OF AN APPLICANT FOR HIGHER EDUCATION

Safae OUAKRIM

1. Topic of qualification work: «Development of the composition of a syrup with Pau D'arco extract», supervisor of qualification work: Antonina SICHKAR, PhD, assoc. prof.

approved by order of NUPh from "27th" of September 2024 № 237

2. Deadline for submission of qualification work by the applicant for higher education: May 2025.

3. Outgoing data for qualification work: to analyze the market for dietary supplements with Pau D'Arco extract, theoretically and experimentally justify the composition of syrup with a Pau D'Arco extract and to study influence of pharmaceutical excipients on properties of the obtained phytopreparation

4. Contents of the settlement and explanatory note (list of questions that need to be developed): literature review, objects and methods, experimental part, references

5. List of graphic material (with exact indication of the required drawings):
Tables – 6, pictures –8

6. Consultants of chapters of qualification work

Chapters	Name, SURNAME, position of consultant	Signature, date	
		assignment was issued	assignment was received
1	Antonina SICHKAR, professor of higher education institution of department of industrial technology of medicines and cosmetics	26.09.2024	26.09.2024
2	Antonina SICHKAR, professor of higher education institution of department of Industrial Technology of Medicines and Cosmetics	22.11.2024	22.11.2024
3	Antonina SICHKAR, professor of higher education institution of department of Industrial Technology of Medicines and Cosmetics	22.12.2024	22.12.2024

7. Date of issue of the assignment: «_26___» ___ September _____2024.

CALENDAR PLAN

№ з/п	Name of stages of qualification work	Deadline for the stages of qualification work	Notes
1.	Literature review	September	**done**
2.	Experiment planning	October	**done**
3.	Experiment execution	November-February	**done**
4.	Processing of results	March-April	**done**
5.	Submission to EC	April	**done**

An applicant of higher education _____ Safae OUAKRIM

Supervisor of qualification work _____ Antonina SICHKAR

ВИТЯГ З НАКАЗУ № 237

По Національному фармацевтичному університету

від 27 вересня 2024 року

Затвердити теми кваліфікаційних робіт здобувачам вищої освіти 5-го курсу Фм20(4,10д) 2024-2025 навчального року, освітньо-професійної програми – Фармація, другого (магістерського) рівня вищої освіти, спеціальності 226 – Фармація, промислова фармація, галузь знань 22 Охорона здоров'я, денна форма здобуття освіти (термін навчання 4 роки 10 місяців), які навчаються за контрактом (мова навчання англійська та українська) згідно з додатком № 1.

Прізвище, ім'я здобувача вищої освіти	Тема кваліфікаційної роботи		Посада, прізвище та ініціали керівника	Рецензент кваліфікаційної роботи
по кафедрі промислової технології ліків та косметичних засобів				
Укрім Сафа	Розробка складу сиропу з екстрактом Пау Д'Арко	Development of the composition of a syrup with Pau D'Arco extract	доц. Січкар А.А.	доц. Буряк М. В.

Ректор

Вірно Секретар

ФА2.8-03-317

ВИСНОВОК

експертної комісії про проведену експертизу
щодо академічного плагіату у кваліфікаційній роботі

здобувача вищої освіти

«21» травня 2025 р. № 331302192

Проаналізувавши кваліфікаційну роботу здобувача вищої освіти Укрім Сафа, групи Фм20(4,10д.)англ-01, спеціальності 226 Фармація, промислова фармація, освітньої програми «Фармація» навчання на тему: «Розробка складу сиропу з екстрактом Пау Д'Арко / Development of the composition of a syrup with Pau D'Arco extract», експертна комісія дійшла висновку, що робота, представлена до Екзаменаційної комісії для захисту, виконана самостійно і не містить елементів академічного плагіату (компіляції).

Голова комісії,
проректор ЗВО з НПР,
професор **Інна ВЛАДИМИРОВА**

Ф А 2.2.1-32-353

REVIEW

of scientific supervisor for the qualification work of the master's level of higher education of the specialty 226 Pharmacy, industrial pharmacy

Safae OUAKRIM

on the topic: «Development of the composition of a syrup with Pau D'arco extract»

Relevance of the topic. Plant preparations have a long history of use in traditional medicine and are increasingly being explored for their potential therapeutic applications. Taking into account the current state of medicines production with Pau D'arco extract, development and introduction into the manufacture of a medicine on the basis of this extract in the form of a syrup is relevant.

Practical value of conclusions, recommendations and their validity is the possibility of using the results of research for the further introduction into the industrial production of composition for obtaining syrup based on the Pau D'arco extract.

Assessment of work. According to the form and content of the qualification work of the student corresponds to the current requirements, is an independent study, in which the student showed knowledge about a particular subject of her research, the ability to receive information using modern scientific methods, the ability to comprehend the information received and submit it in an acceptable form.

General conclusion and recommendations on admission to defend. In general, the qualification work on the topic «Development of the composition of a syrup with Pau D'arco extract» deserves a positive assessment, and its author Safae Ouakrim — admission to the defense of the qualification work.

Scientific supervisor _____ Antonina SICHKAR

«_22_» of May 2025

Ф А 2.2.1-32-356

REVIEW

for qualification work of the master's level of higher education, specialty 226 Pharmacy, industrial pharmacy

Safae OUAKRIM

on the topic: «Development of the composition of a syrup with Pau D'arco extract»

Relevance of the topic. Given the current state of production of medicines in syrup form, advantages of the Pau D'arco extract, the development of a new drug based on the Pau D'arco extract is relevant.

Theoretical level of work. The student of higher education independently conducted an analysis of the current state of syrups manufacture, carried out the extract analysis, developed the composition of syrup of the Pau D'arco extract based on the results of physico-chemical and technological studies.

Author's suggestions on the research topic. The author developed suggestions for solving the problem of obtaining syrup with the Pau D'arco extract.

Practical value of conclusions, recommendations and their validity is the possibility of using the research results for the further introduction into the industrial production of technology of syrup with the Pau D'arco extract.

Disadvantages of work. Minor, namely, disproportionate placement of material, presented in separate sections, were revealed. However, these disadvantages are not important and should not affect the overall assessment of work.

General conclusion and assessment of the work. The qualification work is executed on an urgent topic, because it covers the issues of developing the

composition of the new syrup with the Pau D’arco extract. The work as a whole meets the requirements of the qualification level and deserves an excellent assessment.

Reviewer _____assoc. prof. Marina BURYAK

«_23__» of _May___ 2025

Ф А2.2.1-91-287

МІНІСТЕРСТВО ОХОРОНИ ЗДОРОВ'Я УКРАЇНИ
НАЦІОНАЛЬНИЙ ФАРМАЦЕВТИЧНИЙ УНІВЕРСИТЕТ

Витяг з протоколу
засідання кафедри промислової технології ліків та косметичних засобів НФаУ
№ 13 від 23 травня 2025 року

Голова: завідувачка кафедри, докторка фарм. наук, проф. Рубан О. А.

Секретар: к. фарм. н., доц. Січкар А. А.

ПРИСУТНІ: зав. каф., проф. Рубан О.А., проф. Бобрицька Л.О., проф. Гриценко В.І., проф. Ковалевська І.В., проф. Кухтенко О.С., проф. Сліпченко Г.Д., доц. Безрукавий Є.А., доц. Криклива І.О, доц. Кутова О.В., доц. Кухтенко Г.П., доц. Ніколайчук Н.О., доц. Манський О.А., доц. Петровська Л.С., доц. Пуляєв Д.С., доц. Січкар А.А., доц. Солдатов Д.С., доц. Трутаєв С.І., ас. Пономаренко Т.О. та аспіранти.

ПОРЯДОК ДЕННИЙ:
1. Про представлення до захисту в Екзаменаційну комісію кваліфікаційних робіт здобувачів вищої освіти випускного курсу НФаУ 2025 року випуску

СЛУХАЛИ: Про представлення до захисту в Екзаменаційній комісії кваліфікаційної роботи на тему: «Розробка складу сиропу з екстрактом Пау Д'Арко»

здобувача вищої освіти випускного курсу Фм19(4,10д.)англ-05 групи НФаУ 2024 року випуску _____Сафа УКРІМ_____
(ім'я, прізвище)
Науковий (-ві) керівник (-ки)_к.фарм.н., доц. Антоніна СІЧКАР_____
Рецензент_____к.фарм.н., доц. Марина БУРЯК_____

УХВАЛИЛИ: Рекомендувати до захисту кваліфікаційну роботу здобувача вищої освіти _5_ курсу Фм20(4,10д.)англ-01 групи Сафа УКРІМ_____
(ім'я, прізвище)
на тему: «Розробка складу сиропу з екстрактом Пау Д'Арко»

Голова
завідувачка кафедри,
докторка фарм. наук, проф. _____ Олена РУБАН
(підпис)

Секретар
к. фарм. н., доцент _____ Антоніна СІЧКАР
(підпис)

Ф А2.2.1-32-042

НАЦІОНАЛЬНИЙ ФАРМАЦЕВТИЧНИЙ УНІВЕРСИТЕТ

ПОДАННЯ
ГОЛОВІ ЕКЗАМЕНАЦІЙНОЇ КОМІСІЇ
ЩОДО ЗАХИСТУ КВАЛІФІКАЦІЙНОЇ РОБОТИ

Направляється здобувач вищої освіти Укрім Сафа до захисту кваліфікаційної роботи
за галуззю знань 22 Охорона здоров'я
спеціальністю 226 Фармація, промислова фармація
освітньо-професійною програмою Фармація
на тему: «Розробка складу сиропу з екстрактом Пау Д'Арко».

Кваліфікаційна робота і рецензія додаються.

Декан факультету _____ / Микола ГОЛІК /

Висновок керівника кваліфікаційної роботи

Здобувач вищої освіти Укрім Сафа виконала кваліфікаційну роботу на високому рівні, з логічним викладенням матеріалу та обговоренням, оформлення роботи відповідає вимогам НФаУ до випускних кваліфікаційних робіт та може бути рекомендований до захисту в Екзаменаційній комісії НФаУ.

Керівник кваліфікаційної роботи

_____ Антоніна СІЧКАР

«_22__» __травня_____ 2025 року

Висновок кафедри про кваліфікаційну роботу

Кваліфікаційну роботу розглянуто. Здобувач вищої освіти Укрім Сафа допускається до захисту даної кваліфікаційної роботи в Екзаменаційній комісії.

Завідувач кафедри
технологій фармацевтичних препаратів

_____ Олена РУБАН

« _23_» _травня____ 2025 року

Qualification work was defended

of Examination commission on

« _____ » _____ 2025

With the grade _____

Head of the State Examination commission,

DPharmSc, Professor

_____ / Volodymyr YAKOVENKO /