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QUALIFICATION WORK

on the topic

DEVELOPMENT OF THE COMPOSITION OF EXPECTORANT SYRUP FOR PEDIATRIC PRACTICE

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SUMMARY

The relevance of the development of expectorant syrup is theoretically and experimentally substantiated in the master's thesis. Based on the results of experimental studies, in particular organoleptic, physical, chemical, biopharmaceutical and microbiological the optimal composition of the new drug have been substantiated. Quality parameters of model samples were determined according to methods of SPhU. The work is presented on 43 pages, includes 7 tables, 5 figures, 55 sources of literature and 1 appendix.

Key words: syrup, composition, Viola avensis *L*, bronchitis, expectorant.

АНОТАЦІЯ

Актуальність розробки відхаркувального сиропу теоретично та експериментально обґрунтована в магістерській роботі. На основі результатів експериментальних досліджень, зокрема органолептичних, фізичних, хімічних, біофармацевтичних та мікробіологічних, обґрунтовано оптимальний склад нового препарату. Показники якості модельних зразків визначали за методиками ДФУ. Робота викладена на 43 сторінках, містить 7 таблиць, 5 малюнків, 55 джерел літератури та 1 додаток.

Ключові слова: сироп, склад, Viola avensis *L*, бронхіт, відкаркувальна дія.

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INTRODUCTION

Actuality of topic.

Despite significant advances in the development of new-generation synthetic drugs, there has been an ever-increasing interest in herbal remedies in the last decade.

Of the several thousand plants with established types of pharmacological activity, only a little more than 200 are approved for medical use. Among them, dozens of types of medicinal plant raw materials are still used only in the form of aqueous extracts - short-term in terms of storage and practically invaluable in terms of the quality of infusions and decoctions. This approach to plant raw materials, which is also burdened by outdated processing technologies, does not meet the modern requirement for its rational use, in particular, through the production of several phytochemicals under conditions of low-waste or waste-free production.

These medicinal plants include two related types of Viola tricolor and Viola field, the aerial part of which is used so far only in the form of an infusion of expectorant action with a shelf life of 3 days.

Meanwhile, viola field herb has a significant raw material base and could become an object of low-waste processing with the production of several medicines, in particular, based on the polysaccharides and flavonoids contained in it.

Simultaneously with the consideration of the issue of a more complete processing of field viola herb under industrial conditions, it seems appropriate, taking into account the pharmacological properties of this raw material, to create, in first of all, expectorants for pediatric practice. The range of this category of domestically produced drugs is extremely limited.

Field viola herb, with a time-tested sufficiently high degree of safety for a child's body, is quite a suitable object of study in this aspect as well.

At the same time, for children, syrup is considered the most preferred form of oral administration of drugs, in which it is possible to balance the necessary pharmacokinetic and organoleptic properties.

Thus, it seems relevant to study the development of a children's syrup from a

dry extract of herb viola (1:1) obtained by an industrial method.

The **purpose** and objectives of research

Theoretically and experimentally substantiate the composition of expectorant syrup of natural origin – dry extract Viola field herb (1:1) for the use in pediatric practice.

To achieve this goal it is necessary to solve the following **tasks**:

- to analyze the literature data about chemical composition and application of plants belonging to the genus Viola, in particular, Viola field *L.*;
- to consider syrup as an alternative dosage form in pediatric practice;
- to summarize the literature data on the characteristics of children's bronchitis and the place of expectorants in their therapy;
- to substantiate the choice of sweeteners and flavors of syrup based on dry extract of viola field herb;
- theoretically and experimentally substantiate the composition of expectorant syrup and the method of introduction of dry extract viola field herb;
- to study the organoleptic parameters of the developed syrup samples;
- to conduct microbiological studies of syrup samples in order to justify the need for a preservative introduction in the composition of the syrup.

Scientific novelty

The composition of an expectorant syrup with dry extract Viola field (1:1) has been developed for application in pediatric practice.

Theoretical and practical significance of the work

The theoretical and practical significance of the master's thesis is that the choice of excipients was substantiated experimentally, and the composition of new drug, which can be used in pediatric practice, was proposed.

Implementation of results

According to the results of the master's thesis, an article was published in a scientific professional journal *Annals of Mechnikov Institute* (2022. N 1.).

Structure and scope of qualification work.

Qualification work consists of an introduction, literature review (chapter 1), experimental part (chapter 2 and 3), general conclusions, references, appendices. The work is presented on 43 pages, includes 7 tables, 5 figures, 55 sources of literature.

CHAPTER I
PROSPECTS FOR THE USE OF PLANTS OF THE GENUS VIOLA IN THE TREATMENT OF BRONCHITIS IN CHILDREN

1.1. Plants of the genus Viola as an active pharmaceutical ingredients of dosage form

Of the several thousand plants with established types of pharmacological activity, only more than 200 are allowed in Ukraine for medical use. Among them, dozens of types of medicinal plant raw materials are still used only in the form of water extracts - short-term in terms of storage and practically invaluable in quality infusions and decoctions. This approach to plant raw materials, which is also burdened by outdated processing technologies, does not meet modern requirements for its rational use, in particular, due to the production of several phytochemicals under conditions of low-waste or waste-free production.

Interest in the plant of the genus Viola grew in the first half of the 19th century, thanks to horticultural breeding work with Viola tricolor. The study of Violas in the first quarter of the last century is the work of two prominent experts on the genus - the monograph of the genus W. Becker and the Baltic florist K.R. Kupfer. The works of the first are the most significant and represent the final character, as for many years large materials from Ukrainian Violas were referred to the processing and study [2].

Plants of the genus Violas are characterized by the presence of various biologically active substances. Phenolic substances (flavonoids, phenolic acids, coumarins, tannins), saponins, polysaccharides and other natural compounds were isolated and studied from them.

Analysis of data from the scientific literature on the chemical composition of field Violas allows us to conclude that among the flavonoid compounds of this plant is dominated by rutin with its inherent anti-inflammatory, capillary-strengthening, anti-edematous and other effects. Various scientists have noted the presence of ascorbic acid in almost all parts of the plant, the presence of carotenoids has been

qualitatively established. Among other classes of natural compounds that are part of the Viola, alkaloids, organic acids, fatty oil, steroid compounds, essential oil were found [3-5].

These two related types of Violas – tricolor (*Víola tricolor* L.) and field (*Viola arvensis Murr*.), the aerial part of which is used so far only in the form of an expectorant infusion. Wild pansy must contain at least 1.5 % of flavonoids, calculated with reference to the dried substance, expressed as violanthin.

Viola arvensis *Murr*.

Both types of medicinal plant materials contain two hydrophilic groups of biologically active substances - polysaccharides and flavonoids. At the same time, the pharmacognostic and technological study of Viola arvensis *Murr*., compared to the Víola tricolor *L*., has received much less attention from researchers. Meanwhile, field Viola herb has a significant raw material base and could become an object of low-waste processing with the production of several medicines, in particular, based on polysaccharides and flavonoids [1].

Respiratory tract disorders

In traditional medicine wild pansy was recommended internally, as expectorant (Hoppe 1951, Hoppe 1958; Kuźnicka and Dziak 1970; Muszyński 1954; Ożarowski 1976; Roeske 1955) for catarrhs of the respiratory tract (Hänsel et al. 1994, Rimkiene et al. 2003), coughs, whooping cough (Hänsel et al. 1994, Rimkiene et al. 2003) and in the treatment of acute bronchitis, inflammation of the throat and feverish colds (Hänsel et al. 1994; PDR 2000; 2004,Wichtl 1994; 2004).

Diuretic activity

Traditionally wild pansy is used as a diuretic (Hoppe 1951, Hoppe 1958, Bobowska et al. 1975; Kuźnicka and Dziak 1970; Muszyński 1954; Ożarowski et al. 1978; Wichtl 1994; 2004, Hänsel et al. 1994) in urinary tract disorders including cystitis and dysuria (Hoppe 1951, Hoppe 1958; Rimkiene et al. 2003).

Metabolic influence

In traditional medicine wild pansy is considered to be a "blood-purifying" remedy (Dragendorff 1898, Hoppe 1951, Hoppe 1958). It is recommended as diaphoretic (Bobowska et al. 1975; Wichtl 1994; 2004, PDR 2000; 2004) as well as for rheumatic complaints, gout, and arteriosclerosis (Hänsel et al. 1994; Hoppe 1951, Hoppe 1958; Kuźnicka and Dziak 1970; Muszyński 1954; Wichtl 1994; 2004).

Skin disorders

Wild pansy was most often recommended for cutaneous and internal use in various skin disorders (Köhler 1883, Dragendorff 1898, Schimpfky 1900; Hoppe 1951, Hoppe 1958, Martindale 2009, PDR 2000; 2004; Chevallier 1996); especially those of a seborrhoeal nature (Martindale 2009), including weeping and dry eczema (Hänsel et al. 1994, Köhler 1883, Madaus 1938, Ożarowski 1976; Roeske 1955; Schöpke et al. 1993, British Herbal Pharmacopoeia 1996), impetigo, acne, and pruritus (Braun 1974, Wichtl 1994; 2004), also in irritation and vulvular itching, skin rashes and eruptions (PDR 2000; 2004, Hänsel et al. 1994), and skin ulcers (Hoppe 1951, Hoppe 1958). Wild pansy was used in paediatric practice for treatment of various rashes and eruptions, eczema (Hoppe 1951, Hoppe 1958), and/or the treatment of seborrhea of the scalp of newborn infants (crusta lactea) (Rimkiene et al. 2003; Bundesanzeiger 1986). An ethnobotanical study indicates that the infusion of the whole plant (Viola tricolor L.) imbibed or applied externally is used in psoriasis (Amenta 2000).

Other indications

In traditional medicine wild pansy is also used in varicose ulcers, capillary fragility, haemorrhoids (Rimkiene et al. 2003; Hoppe 1951, Hoppe 1958) and gastrointestinal disorders (Hoppe 1951, Hoppe 1958). It was also proposed as a mild

laxative (Dragendorff 1898, PDR 2000; 2002; Wichtl 1994; 2004).

Viola tricolor is contemporary used in folk medicine in Bulgaria as antitussive, diuretic, in skin disorders against dermatitis, against atherosclerosis and in Italy against psoriasis (*Leporatti* and *Ivancheva* 2003).

Viola tricolor has been used for more than thirty years in Community, mainly as a remedy for various skin ailments, especially those of a seborrhea nature (*Bradley* 2006; *Chevallier* 1996; ESCOP 2009; *Martindale* 2009; PDR 2000; 2004).

Simultaneously with the consideration of the issue of a more complete processing of Viola arvensis *Murr*. herb under industrial conditions, it is advisable, taking into account the pharmacological properties of this raw material, to create, first of all, expectorants for pediatric practice. The range of this category of domestically produced medicines is extremely limited.

Herb of Viola arvensis *Murr*. with a time-tested sufficiently high degree of safety for a child's body is quite a suitable object of study in this aspect as well. At the same time, for children, syrup is considered the best form of oral administration of drugs, in which it is possible to balance the necessary pharmacokinetic and organoleptic properties.

Thus, research on the technological study of herb of Viola arvensis Murr., obtaining from it in conditions of low-waste production effective, convenient for use and standardized in quality medicines, is relevant.

1.2. Chemical composition and application of plants belonging to the genus Viola *L.*

In the European Pharmacopoeia it is described as the dried flowering aerial parts of Viola tricolor *L*. (wild pansy) and/or spp. Viola arvensis *Mur*. (Gaud.) and Koch (Oborny) (European field pansy). Wild pansy belongs to the family of *Violaceae*. The herb is distributed in Europe and Asia. Flowering aerial parts of wild pansy are harvested during summer.

The Viola genus Viola *L*. belongs to the Violaceae family of plants, including

900 species, which are widely distributed throughout the earth, from the Arctic in the south to the Falkland Islands, as well as in Australia, New Zealand - in the south. About 100 species of the genus grow in the CIS countries. Plants are well adapted to various environmental conditions. In particular, about 20 species are found in Ukraine, of which field Viola is one of the most common.

Flavonoids have been found in many types of violets, but they have been most fully studied only in some representatives of this city: V. tricolor, V. arvensis. This group of natural compounds is mainly represented by quercetin and its glycosides rutin (violaquercetin), quercetin-7-rhamnoside, quercetin-3,7-glucoside and kaempferol glycoside - astragalin. In addition to O-glycosides of flavonoids, many representatives of this family contain C-glucosides of luteolin: orientin (8-C-β-D-glucopyranoside of luteolin); apigenin – vitexin (8-C-β-D-glucopyranoside of apigenin) and violantin (6-C-β-glucopyranoside-8-C-α-L-rhamnopyranoside of apigenin) [3]. Researchers *A. P. Carnat et al.* a new glycoside violarvezin, which is apigenin-6-C-β-D-glucopyranosyl-8-C-β-D-6-deoxygulopyranoside, was isolated and identified from the herb V. arvensis. The data are shown in table 1.1.

The largest amount of rutin was found in the aerial part of V. tricolor. Anthocyanin glycosides were found in the flowers of V. tricolor and V. mirabilis: delphinidin, peonidin; violanin, the latter consists of delphinidin, glucose, rhamnose and p-hydroxycinnamic acid.

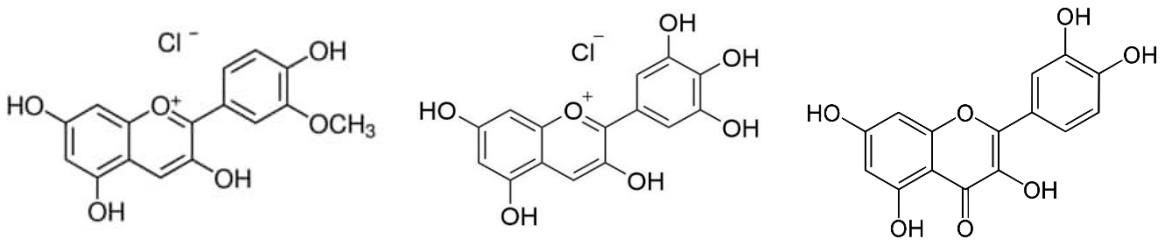


Fig. 1.1. Chemical formulas of delphinidin (a), peonidin (b) and quercetin (c).

Table 1.1

Chemical compounds identified in some species of the genus Viola

Name of BAS	***V. arvensis Murr.*** **V. field**	***V. tricolor L.*** **V. tricolor**
Flavonoids	Rutin, violarvesin	Rutin, quercetin, quercetin-7-amnoside, astragalin, Vitexin, Vicenin, Violantin, Luteolin, Orientin, Isoorientin, Luteolin-7-glucoside
Anthocyanins	Violanin	Violanin, delphinidin, cyanidin
Phenolcarboxylic acids	Coffee, protocatechuic, coumaric, gentisin, vanillin	Coffeic, chlorogenic, n-coumaric, protocatechuic, ferulic, neochlorogenic, salicylic acids
Coumarins	-	Kumarin, scopoletin
Alkaloids	Violoemitin	+
Polysaccharides	-	Water-soluble polysaccharides, pectin substances
Amino acids	Aspartic and glutamic acids, arginine, valine, glycine, histidine, serine, tyrosine, lysine	Aspartic and glutamic acids, arginine, valine, glycine, histidine, serine, tyrosine, lysine

Notes: "+" indicates the presence of a group of natural compounds qualitatively found in the plant; "-" indicates the absence of a group of natural compounds qualitatively found in the plant.

Phenolcarboxylic acids were found in most of the studied species: V. tricolor, V. uniflora, V. biflora, V. langsdorfii, and other representatives of this genus. This group is mainly represented by chlorogenic, caffeic, chicory, neochlorogenic, n-coumaric, and salicylic acids [4,9,16].

Coumarins were found in the aerial part of a number of representatives of the violet genus, but they were identified only in some species. So, in the aerial part of V. tricolor, the following were found: coumarin, scopoletin; - V. patrinii and V. biflora - o-methoxycoumarin [9,16].

The underground organs of V. arvensis contain small amounts of the alkaloid violoemetin, traces of alkaloids were found in the aboveground parts of V.

acuminata, V. acutifolia, V. altaica and other species [16].

Triterpene saponins have been found in various organs of V. acutifolia, V. ambigua, V. collina, V. arvensis, and V. tricolor. In the aboveground and underground parts of V. odorata, triterpene compounds were identified: fridelin and epifridelanol [16]. However, there are contradictory data in the literature concerning V. arvensis and V. tricolor, indicating the absence of this group of natural compounds, and the hemolytic activity that these types of violets exhibit is due to the presence of hemolytically active peptides [27].

The essential oil in the aerial parts of violets was found in small amounts (from 0.01 to 0.001%) in the herb V. arvensis, V. odorata, V. tricolor. The composition of the essential oil of these species is represented mainly by methyl ester of salicylic acid [4,16].

A fairly important class of natural compounds found in various types of violets are polysaccharides. This group of substances is represented by water-soluble polysaccharides, pectins and hemicelluloses in the aerial parts of V. tricolor, V. uniflora and V. langsdorfii. Chromatographic and other physicochemical methods of analysis in hydrolysates of polysaccharide complexes identified monosaccharides: rhamnose, xylose, arabinose, glucose, fructose. In addition, the presence of uronic acids has been established [4,6,9,10,17].

Vitamins were found in plants of the violet genus: carotenoids, ascorbic acid, vitamins K, E. Ascorbic acid was found in the leaves of V. altaica, V. odorata; in all aboveground parts of V. arvensis and V. tricolor, V. suavis [4,5,16]. Carotenoids were found in the flowers of V. biflora and V. tricolor. The composition of V. tricolor carotenoids has been studied in detail; they are represented by: violoxanthin, auroxanthin, flavoxanthin, zeaxanthin, lutein, luteoxanthin, lycopene, β-carotene and their isomers. Vitamin K1 (phylloquinone) was identified in the leaves of V. arvensis, and vitamin E (tocopherol) was identified in the inflorescences of V. tricolor [16].

The presence of tannins has been established in the aerial parts of V. tricolor, V. ambigua, but their content is low and ranges from 2 to 4.5% [4,16].

Of particular interest are amino acids, including essential ones, found in the aerial parts of V. arvensis, V. tricolor, V. langsdorfii, V. uniflora, and V. biflora. The composition is represented by aspartic and glutamic acids, arginine, valine, glycine, histidine, serine, tyrosine, lysine and other amino acids [4,8].

Macro- and microelement composition has been established in the aboveground organs of V. arvensis, V. tricolor, V. uniflora, V. biflora and V. langsdorfii [4,10,11]. Macroelements were found in them: potassium, magnesium, calcium, silicon, sodium, sulfur, phosphorus, chlorine;

- trace elements: aluminum, barium, bromine, manganese, copper, nickel, rubidium, titanium, zinc, etc. The elemental composition of plants is somewhat different from each other, however, observed some pattern of accumulation of individual elements is observed. In large quantities, plants contain potassium - over 5%, phosphorus up to 0.5%. A significant content of calcium, sulfur and magnesium was also established [3,4,7,10].

Plants of the genus Violet are widely used in medicine.

From the aerial part of V. tricolor by the Swedish scientists P. Claeson et al. cyclotides, which are short (low molecular weight) cyclic peptides, have been isolated [23]. Plant cyclotides are known to have antitumor and antiviral properties. E. Svangard et al. the cytotoxic activity of this group of compounds against tumor cells U-937 GTB (lymphoma) and RPMI-8226/s (myeloma) was established [29]. Other types of violets are being investigated for the presence of peptides and their antitumor activity [22,25,28,30]. C. Wang et al. proven anti-HIV activity of cyclotides isolated from V. yedoensis [31].

In folk medicine, V. arvensis and V. tricolor are used for skin diseases: eczema, allergic dermatitis, diathesis, ulcers, acne and other skin pathologies. In these cases, as a rule, the obtained extracts are administered orally and externally in the form of compresses or lotions [16].

Other species not included in the pharmacopoeia are also used in folk medicine in many countries. V. mirabilis and V. odorata are used as an antitussive and expectorant for bronchopulmonary diseases. In Tibetan and Chinese medicine,

V. brachysepala, V. dissecta, V. mandshurica, V. odorata, V. patrinii, V. variegata are recommended for pulmonary tuberculosis, lobar pneumonia, and purulent pleurisy. In European countries, some types of violets are used as expectorants in diseases of the throat, bronchitis, tracheitis [16].

Traditional medicine in many countries uses representatives of this genus, in particular: V. canina, V. disjuncta and V. odorata as a diuretic [13,16].

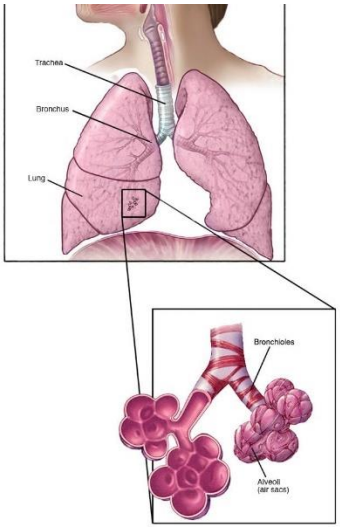
For skin diseases (boils, carbuncles, dermatitis, etc.), V. ambigua, V. brachysepala, V. palustris, V. reichenbachiana, V. stagnina, and V. uniflora are prescribed [17]. In Tibetan medicine, the aerial part of V. biflora is used as a hemostatic agent and for paralysis [16].

Since ancient times, plants of the violet genus in Tibetan and Chinese medicine and European countries have been used for various malignant tumors. For this purpose, V. arvensis, V. langsdorfii, V. mandshurica, V. odorata, V. patrinii, and V. tricolor are used [16]. It has been established that water-soluble polysaccharides of the aerial part of V. mirabilis, V. palustris, as well as the water-alcohol extract of V. reichenbachiana, exhibit antitumor activity and have immunostimulatory properties [17,22].

Thus, the analysis of literature data showed that species of the genus violet contain a complex of biologically active compounds: flavonoids, anthocyanins, phenolcarboxylic acids, coumarins, amino acids and other groups of substances with a wide range of pharmacological effects. However, this information mostly concerns pharmacopoeial species, other representatives of this genus are little studied, although they are widely used in folk medicine. Therefore, all of them are of interest for an in-depth study of their chemical composition and pharmacological properties, with a view to their further introduction into medical practice.

1.3. Bronchitis in children and the place of expectorants in their treatment

Respiratory diseases occupy a major place in the structure of morbidity. In the children's age group, this figure reaches 49.3 %.



Bronchitis describes an inflammation of child's large breathing tubes or airways, called bronchi. There are several different types of bronchitis, but the two most common are chronic, which primarily affects adults, and acute, which is an inflammation of the mucous membranes of child's bronchial tubes. Although it is often a relatively mild condition, in the earlier stages of acute bronchitis, child may experience a dry, non-productive cough. Later on, this will become an abundant, mucus-filled cough. This coughing may even cause your child to gag or vomit.Acute and chronic bronchitis is especially difficult in young children, which often occurs in the cold season alone or as a complication of respiratory infections.

Acute bronchitis comes on quickly and can cause severe symptoms. But it lasts no more than a few weeks. Viruses cause most cases of bronchitis. Many different viruses can infect the respiratory tract and attack the bronchial tubes. Infection by some bacteria can also cause acute bronchitis. Most people have acute bronchitis at some point in their lives.

Chronic bronchitis is rare in children. It can be mild to severe and lasts longer (from several months to years). The most common cause of chronic bronchitis is smoking. The bronchial tubes stay inflamed and irritated, and make lots of mucus over time. People who have chronic bronchitis have a higher risk of bacterial infections of the airway and lungs, like pneumonia.

These diseases are characterized by difficult discharge of sputum from the bronchi: it becomes viscous, clogs the small bronchi and bronchioles, disrupting their cleansing function. As a result, strains of pathogenic bacteria develop in the lungs, causing further progression of the inflammatory process and the need to use a complex of antibacterial and expectorants to treat the disease [6].

Without dwelling on the well-known negative consequences of the use of antibacterial drugs in children, such as dysbacteriosis, allergic reactions and others, it should be emphasized that even the choice of expectorant drugs should be

reasonable and substantiated. In particular, a number of adverse effects limits the use of expectorants of synthetic origin in pediatrics.

An expectorant is a substance that helps in breaking down and thinning of mucus and phlegm to make breathing easier.

Expectorants are drug used to help in the removal or expulsion of the secretion or exudate from the trachea, bronchi, or lungs and hence they are used in the treatment of cough.

Expectorant act on the respiratory tract in two ways

1. By decreasing the viscosity of bronchial secretion and facilitating their elimination from trachea.
2. By increasing the amount of respiratory tract fluid, a demulcent action is exerted on dry mucosal lining, thus relieving the unproductive cough.

It is possible to classify expectorants in according to their mechanism of action into two categories:

- sedative type
- stimulant type.

Sedative expectorants

These are stomach irritant expectorants which are able to produce their effect through stimulation of gastric reflexes. Examples of sedative expectorants include bitter drugs such as ipecac, senega, Indian squill, and compounds such as antimony potassium tartrate, ammonium chloride, sodium citrate, potassium iodide, etc.

Stimulant expectorants

These are the expectorants which bring about a stimulation of the secretory cells of the respiratory tract directly or indirectly. Since these drugs stimulate secretion, more fluid gets produced in respiratory tract and sputum is diluted.

Examples of stimulant expectorants include drugs such as eucalyptus, lemon and active constituents of oil like terpine hydrate, anethole.

Cough expectorants can be natural remedies or over the counter medications

Relief is triggered by increasing the amount of water in the mucus. You will thus have thinner mucus which is easy to clear compared to the thick mucus that

causes chest congestion when you have a cough.

In general, these natural cough remedies will soothe the respiratory tract given the clearer and lighter mucus secreted.

Expectorant herbs and other natural remedies are preferred to over the counter medications for cough due to fewer or no side effects in the remedies.

Over the counter medicine may have some chemicals which could have side effects on the user. They will often have colors, preservatives and other chemicals all of which may pose a risk to your health.

There are the following natural expectorants:

1. Licorice

Use licorice.

As an expectorant, licorice root is one of the best in this regard. With this natural cough remedy, you can do away not only with the coughing, but also with the inflamed and irritated throat.

Using licorice root is quite simple. Here's how to get rid of chest congestion and cough at home using licorice.

1. In a tea cup, mix hot water with a teaspoon of licorice root.
2. Wait for about 10 minutes before taking the tea.
3. Take the tea three times a day for the best results.

As a cautionary measure, those with high blood pressure should avoid taking licorice root for its negative effects on such.

2. Essential oils

A lot of essential oils can relieve chronic cough and congestion. You can use them to treat coughing. Most essential oils can be used in the form of a steam treatment or other form.

Among the most common essential oils are eucalyptus, rosemary, peppermint, clove and many others.

If you have the right essential oils, you can use them in several ways to do away with the coughs.

- Massage the oil on your chest when you mix it with a carrier oil.

If you do not prefer massaging the oil, here's how to use it to clear a cough fast.

1. Add essential oil to steaming hot water.
2. Cover your head and shoulders with a towel.
3. Still covered by the towel, lean over the mixture of essential oils and hot water and inhale the mixture for about 5 minutes.
4. You can then remove the towel.

Do this a few times a day for several days until you have gotten rid of the cough.

3. Honey

One of the most common types of natural expectorants is honey. Honey has many different uses which place it amongst the most useful natural products.

You can harness its delicious taste, antibacterial properties and soothing capabilities for various medical purposes at home.

Its expectorant qualities are some of the best too. Honey can be used in the following ways:

- A teaspoon of honey mixed in warm water or herbal tea
- Take the mixture daily for the best results
- It can also be mixed with milk for some incredible results.

Honey can also be used as a chest compress. To do this:

- Rub some honey on your chest then cover it with a cloth for an hour.
- Wash it off afterwards. You can repeat the exercise daily until you see results.

4. Steam treatment

Steam soothes your throat and makes coughing less painful besides moisturizing the mucus making it less thick. It can be used in the following ways:

- Simply cover yourself with a towel in a steam-filled environment to do away with the thick mucus.

5. Herbal tea

Most warm fluids are very helpful when it comes to doing away with the

coughing and thick mucus in the breathing system.

Most types of herbal teas have expectorant qualities which will be instrumental in doing away with the coughing and the general symptoms of be disease.

For the best results:

- Add a teaspoon of your favorite herbal tea to warm water.
- Steep the mixture for about ten minutes before straining and taking it.

Instead of using sugar, herbal teas go well with honey which is an expectorant on its own. You will be okay soon enough with this mixture.

6. Garlic for cough

Garlic has many qualities as a medicinal plant. As time goes by, a lot of uses for this herb are being discovered.

Among its growing list of medicinal roles is its use as an expectorant. It is used to treat coughs and in clearing the respiratory system with ease.

You can use garlic in different ways including:

- Eating it raw among many other ways. It is preferable to take it raw to have all its benefits.
- Adding it to food.

7. Salt water gargle

Using salt water is a simple procedure which has the following stages:

- In a glass of warm water, add a teaspoon of salt and stir until the salt is wholly dissolved.
- Gargle the mixture for about 3 minutes about 3 times a day.

The salt provides an environment that is not conducive for the cough virus while the steam in the warm water helps in making the mucus in the breathing system lighter.

8. Onions

Unknown to many, onions have medicinal qualities which can be easily harnessed for some relief. The high amounts of quercetin and Sulphur in onions makes them a great expectorant.

These compounds combine to break down the mucus and ease the breathing.

- You can directly eat onions or squeeze their juice and take it for the same benefits.

9. Ginger

The anti-inflammatory properties of ginger give you relief from the mucosal inflammation brought about by the cough.

Besides that, ginger has a high amount of polyphenols which will restrict the production of mucus. This will decongest the chest and ease up on your breathing.

10. Lemon

The presence of citric acid in lemons makes it a great expectorant for your coughs. For one, the citric acid will break down the thick mucus to make it easy to expel and breath easily. The high amount of vitamins in lemons helps in fighting the cough germs. Unless you have an allergy to any these remedies, they will provide quick relief to coughing.

The main active ingredients with an expectorant effect of synthetic origin are presented in Fig. 1.2.

GENERIC NAME	TRADE NAME*	USES	ADVERSE REACTIONS	DOSAGE RANGES
Expectorants				
guaifenesin (glyceryl guaiacolate) *gwye-fen'-e-sin*	Fenesin, Humibid LA, Liquibid Muco-Fen-LA, Tussin, *generic*	Relief of dry, nonproductive cough, and in the presence of mucus in the respiratory tract	Nausea, vomiting, dizziness, headache, rash	Adults and children 12 years and older: 100–400 mg PO q4h; children 6–12 years: 100–200 mg q4h PO; children 2–6 years: 50–100 mg q4h
potassium iodide *poe-tass'-ee-um-eye-o-dide*	Pima, SSKI, *generic*	Symptomatic relief of chronic pulmonary diseases for which tenacious mucus complicates the problem	Iodine sensitivity or iodinism (sore mouth, metallic taste, increased salivation, nausea, vomiting, epigastric pain, parotid swelling, and pain)	300–1000 mg PO after meals BID or TID, up to 1.5 g PO TID
terpin hydrate *ter'-pin-high'-drate*	*generic*	Symptomatic relief of dry, nonproductive cough	Drowsiness, nausea, vomiting or abdominal pain	85–170 mg TID or QID PO

Representatives of this pharmacological group of plant origin are a worthy alternative to synthetic expectorants. The effectiveness and safety of their use in the treatment of diseases of the bronchopulmonary system in children has been confirmed by many years of experience in folk and official medicine and is due to the undeniable, well-known benefits of herbal medicines. The special value of herbal

medicines used in pediatric practice, including in the treatment of acute and chronic bronchitis, is the complex symptomatic and etiopathogenetic effects on the course of the disease.

Analysis of the nomenclature of expectorant phytopreparations presented on the Ukrainian pharmaceutical market allows us to conclude that the largest part of them, especially for children, is produced in the form of syrups.

1.4. Syrups as an alternative dosage form in pediatric practice

Syrup is a concentrated solution of sugar in water or other aqueous solutions. Medicinal syrup is a nearly saturated aqueous solution in which the medicinal substance or drug is dissolved. Basically, it is an oral suspension in liquid form. Medical syrup or medicinal syrup is actually used as a carrier for drugs. It is often used as a flavoring agent for medicines. The syrup should be kept tightly in a cool and dry place after use for preservation. Medicinal syrups are widely used as medicines for children, but there are also pharmaceutical syrups for adults.

Adavantages of syrups are:

- Appropriate for any patient of different ages
- The most natural and easiest route of administration
- Economical and safe to the patient
- No nursing is required, which means the patient can take it with no help
- The liquid dosage form is expected for certain types of products like cough medicines

Components of syrups are:

- Sweetening agent- the sugar, usually sucrose, or sugar substitute used to provide sweetness and viscosity
- Antimicrobial preservatives
- Viscosity modifier
- Flavorants
- Colorants

The Process of Developing Syrups

Pharmaceutical syrups are produced by mixing purified water, sweeteners, active ingredients (API), aromas, flavors and other ingredients (thickeners).

Syrup may contain preservatives. Glycerin, methylparaben, benzoic acid, and sodium benzoate may be used to prevent bacterial and mold growth. Glycine, benzoic acid (0.1%–0.2%), sodium benzoate (0.1%– 0.2%), and various combinations of methylparaben, propylparaben, and butylparaben or alcohol are commonly used as antimicrobial preservatives.

There are four methods of preparing syrups. Based on the physical and chemical properties on the ingredients, the choice of the method is selected.

1. **Solution with heat**
    - This method is a suitable preparation method, if the constituents are not volatile or degraded by heat. Purified water is heated to 80–85°C, and then removed from its heat source. Sucrose is added with vigorous agitation. Then, other required heat-stable components are added to the hot syrup, the mixture is allowed to cool, and its volume is adjusted to the proper level by the addition of purified water. In instances in which heat-labile agents or volatile substances, such as flavors and alcohol, are added, they are incorporated into the syrup after cooling to room temperature.
    - **Invert sugar:** When heat is used in the preparation of syrups, inversion of a slight portion of the sucrose (a disaccharide) into monosaccharides, dextrose (glucose), and fructose (levulose) by hydrolyzation process. This hydrolytic reaction is referred to as “inversion”, and the combination of the two monosaccharide products is “invert sugar.” Sucrose solutions are dextrorotary, but, as hydrolysis proceeds, the optical rotation decreases and becomes negative when the reaction is complete. The rate of inversion is increased greatly by the presence of acids; the hydrogen ion acts as a catalyst in this hydrolytic reaction. Fructose is responsible for the darkening of syrup. Invert sugar is more

readily fermentable than sucrose and tends to be darker in color. But, its two reducing sugars prevent the oxidation of other substances.

$$C_{12}H_{24}O_6 \longrightarrow C6H12O6\ (\text{Glucose}) + C6H12O6\ (\text{Fructose})$$

2. **Agitation without heat**
    - This method is used for substances that degradation on heating or volatilize formulation constituents.
3. **Addition of Sucrose to a Liquid Medication or Flavored Liquid:-**
    - This method is often used with fluidextracts or tinctures.
4. **Percolation**
    - In the percolation method, either purified water or the source of the medicinal component is passed slowly through a bed of crystalline sucrose, thus, dissolving it and forming a syrup. Example Ipecac syrup

The manufacturing process must achieve the following factors (fig. 1.3):

- Dissolving of the sugars to form a syrup
- Hydration of powdered ingredients
- Blending ingredients of widely different viscosity
- Suspension or dissolving of active ingredients
- The end product must be smooth, agglomerate-free and homogeneous
- Equipment should conform to GMP standards

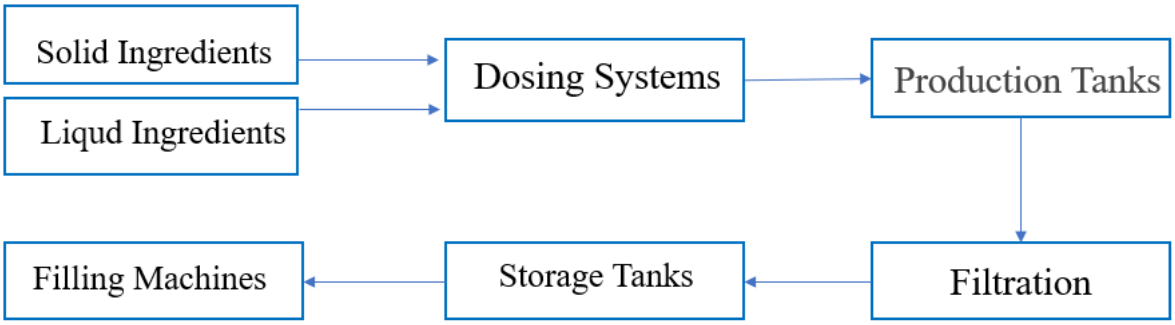


Fig. 1.3. Preparation of syrup.

There are 3 types of syrup (fig 1.4.).

1. **Simple Syrup:** When purified water alone is used in making the solution of sucrose, the preparation is known as “syrup,” or “simple syrup.

2. **Medicated syrup:** When syrup contains medicinal substance is known as medicated syrup – cough syrup.

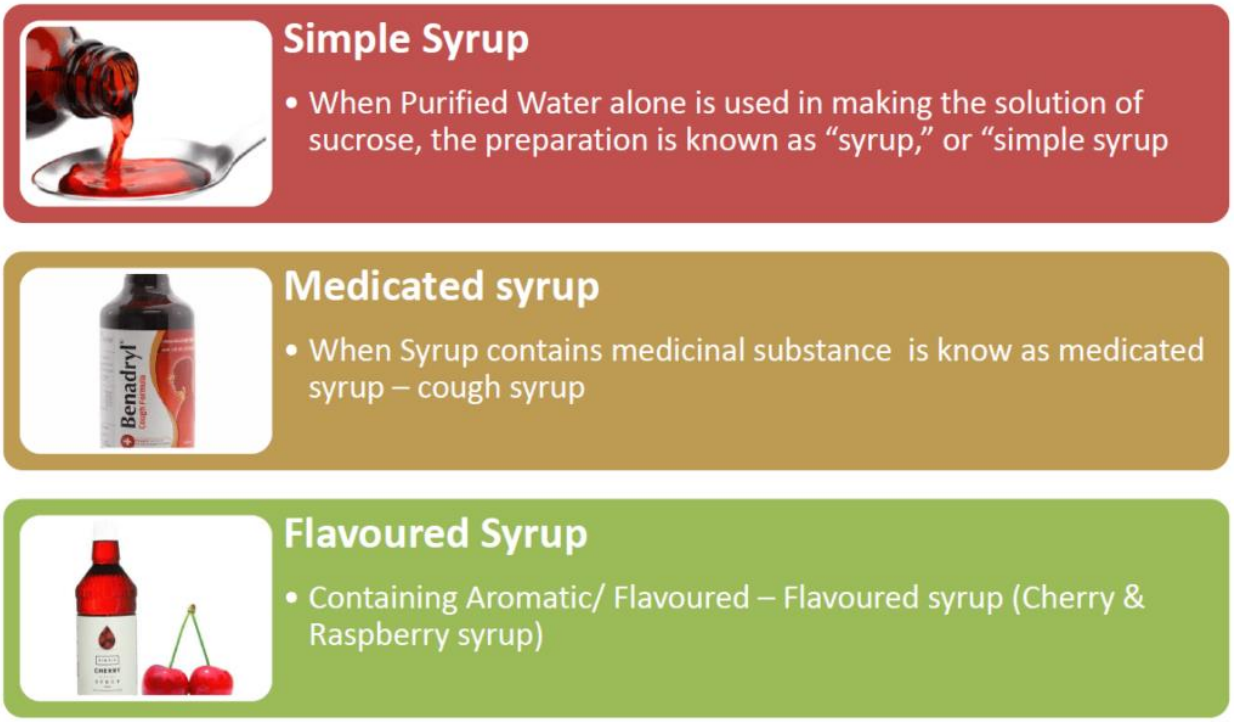


Fig. 1.4. Types of syrup.

3. Flavoured Syrup: syrups containing flavoring agents but not medicinal substances are called flavored vehicles; Containing Aromatic/ Flavoured – Flavoured syrup (Cherry & Raspberry syrup).

CONCLUSIONS

1. Information on the use of plants of the genus Viola, such as tricolor violet L. and field violet L. in medicine, namely in the form of their extracts as promising APIs in the composition of syrup, is summarized.
2. The main groups of BAS in the composition of plants of genus Viola have been analyzed in detail and the place of Viola field as an expectorant in pediatric practice is considered.
3. The expediency and prospects of developing a new drug in the form of syrup with API of natural origin and high expectorant action for pediatric practice have been proved.

CHAPTER II
EXPERIMENTAL PART
OBJECTS AND METHODS OF RESEARCH

While developing an liquid dosage form - an syrup for the pediatric practice, dry extract of Viola field herb (1:1) with expectorant activity was used as a medicinal substance.

2.1. Objects of researches

Objects of research were the active pharmaceutical ingredient (dry extract of Viola field herb) and model samples of syrups with different concentration of excipients.

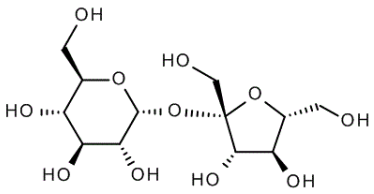
2.1.1. Characteristics of active substances

Dry extract of Viola field herb (1:1) is a hygroscopic amorphous powder of light brown color with a specific odour and taste. Soluble in aqueous-alcoholic solutions, hot water.

2.1.2. Characteristics of excipients

As an excipients for the preparation of syrup were used: sorbitol food; sucrose and fructose.

Sucrose (CAS 57-50-1) – a disaccharide, is a sugar composed of glucose and fructose subunits. It is produced naturally in plants and is the main constituent of white sugar. It has the molecular formula $C_{12}H_{22}O_{11}$.

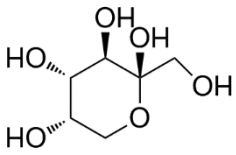


For human consumption, sucrose is extracted and refined from either sugarcane or sugar beet. Sugar mills – typically located in tropical regions near where sugarcane is grown – crush the cane and produce raw sugar which is shipped to

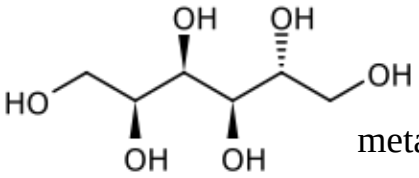
other factories for refining into pure sucrose. Sugar beet factories are located in temperate climates where the beet is grown, and process the beets directly into refined sugar. The sugar-refining process involves washing the raw sugar crystals before dissolving them into a sugar syrup which is filtered and then passed over carbon to remove any residual colour.

The sugar syrup is then concentrated by boiling under a vacuum and crystallized as the final purification process to produce crystals of pure sucrose that are clear, odorless, and sweet. Molar mass 342.30 g/mol. Density 1.59 g/cm3 (25°C). Melting Point 185.5°C. pH value 5.5 - 7.5.

Fructose (CAS 7660-25-5) or fruit sugar, is a ketonic simple sugar found in many plants, where it is often bonded to glucose to form the disaccharide sucrose. It is one of the three dietary monosaccharides, along with glucose and galactose, that are absorbed directly into blood during digestion. Pure, dry fructose is a sweet, white, odorless, crystalline solid, and is the most water-soluble of all the sugars. It has the molecular formula $C_6H_{12}O_6$. Molar mass 180.156 g/mol. Density 1.694 g/cm^3. Melting Point 103°C.



Sorbitol (CAS 50-70-4) is a white crystalline powder with a sweet taste which the human body metabolizes slowly. It can be obtained by reduction of glucose, which changes the converted aldehyde group (−CHO) to a primary alcohol group (−CH_2OH). Most sorbitol is made from potato starch, but it is also found in nature, for example in apples, pears, peaches, and prunes. It is converted to fructose by sorbitol-6-phosphate 2-dehydrogenase. Sorbitol is an isomer of mannitol, another sugar alcohol; the two differ only in the orientation of the hydroxyl group on carbon 2. It has the chemical formula $C_6H_{14}O_6$. Molar mass 182.17 g/mol. Density 1.49 g/cm^3. Melting point 94-96°C.



Purified water (SPhU 1.1, p. 308-309) is a colorless, transparent liquid, odorless and tasteless, pH 5.0-7.0 (potentiometrically).

Peppermint oil (CAS 8006-90-4**) -** colorless to amber yellow clear liquid, similar to the special aroma of menthol, no visible impurities. Density 0.890~0.908.

Refraction index 1.4570~1.4650. Storage conditions: To be stored in Cool, dry and ventilated location and protected from light. Shelf life: two year with proper storage.

Sorbic acid (CAS 110-44-1) – is a white crystalline odorless powder. Slightly

soluble in water, soluble in ethanol. Melting point 134.5°C. Slightly acidic and astringent taste with a faint odor. Molecular weight 112.13.

2.2. Methods of researches

In the process of creating and studying of syrup with dry extract of Viola field herb, a complex of physical, chemical, microbiological and biopharmaceutical research methods based on the qualitative and quantitative indicators of API and excipients were used.

Organoleptic control was performed visually, assessing the color, particle size, homogeneity (absence of inclusions, sequins or pieces of sucrose).

The average weight of the syrup was determined according to SPhU weighing 50.0 g to the nearest 0.01. Deviations in mass should not exceed ± 5 %.

pH determination.

The pH of the syrup was determined potentiometrically (SPhU 1 ed., supl. 2.2.3) using a glass electrode ESL-43-07 with silver chloride-saturated electrode EVL-1-M3.1 and ionomer laboratory "Ionometer I-130" with accuracy ± 0.05 pH.

The syrup was placed in a beaker and determined.

Determination of viscosity of the syrup.

The study of the viscosity of syrup was performed according to SPhU 1 ed. (Section 2.2.10) using a rotary viscometer with coaxial cylinders of the device "Reotest-2" (Germany).

Biopharmaceutical research. An important criterion for the manifestation of the pharmacological action of API is the bioavailability under study. But these studies are more expensive, so we used biopharmaceutical studies to judge the bioavailability and so-called "pharmaceutical availability" of API by its specific amount released from the syrup. Thus, the quality of dosage form can be judged by the degree of release of API from the syrup. Evaluation of the degree of release of API from the syrup was performed using the method of diffusion into agar gel.

The method of diffusion into agar gel is based on the formation reaction with the formation of a colored product between the flavonoids of the API (dry extract of Viola field herb) and iron (III) chloride, previously introduced into the agar gel.

Method of preparation of 2 % agar gel:

agar was placed in a pre-weighed glass vessel, filled with purified water for 30 minutes to swell. Then the agar was heated to boiling, brought to the desired mass and to the warm gel was added 2 ml of iron (III) chloride. The agar gel prepared in this way was poured into Petri's dishes (diameter 98-100 mm, height 20 mm) on a table with a horizontal surface. The agar was poured into cups in two portions of 10 and 15 ml.

After solidification of the agar (first portion) in each cup at equal distances from each other and from the edge of the cup was placed 3 metal cylinders of the same size and weight (10 mm high and 8 mm outer diameter). Then poured a second portion of agar gel.

After solidification of the agar, the cylinders were carefully removed and samples (2.0 g) of the tested ointment samples were placed in the wells (wells) formed.

Samples of syrup in the wells of the cups were placed with a glass rod, achieving good contact with agar. Petri dishes were numbered and placed in a thermostat at 37 ° C. After 1, 2, 4, 6, 8, and 24 hours, the plates were removed and the diameter of the colored zones formed by API in agar gel with iron (III) chloride was measured with a ruler. The observation time was 24 hours.

Study of microbiological purity. Tests of the syrup for microbiological purity were performed according to SPhU 1 ed. (chapters 2.6.12; 2, 6, 13).

CONCLUSIONS

1. Dry extract of Viola field herb (1:1) and model samples of syrup with different quantity of excipients were used as the objects of research.

2. Organoleptic, biopharmaceutical, microbiological and physical, chemical research methods were used in the development of expectorant syrup.

CHAPTER III
DEVELOPMENT OF THE COMPOSITION OF EXPECTORANT SYRUP FOR PEDIATRIC PRACTICE

3.1. The selection of sweeteners in the development of syrup composition for children

Syrups are thick, transparent concentrated aqueous solutions of sucrose, which may contain medicinal substances, fruit food extracts, which, depending on the composition, have a characteristic taste and smell.

Syrups according to the traditional scheme are prepared by dissolving sugar when heated in water or in extracts from vegetable raw materials, and, in addition, by adding to the sugar syrup tinctures, extracts.

An important aspect of the technology of medicinal syrups in general, and intended for pediatric practice, in particular, is the selection of auxiliary components (sweeteners, flavors etc.) that provide optimal organoleptic properties of this dosage form [7].

When creating medicines for children, mostly natural, only harmless excipients allowed for medical practice should be used. The amount of excipients should optimally ensure the desired therapeutic effect and stability of the drug, without reducing its therapeutic activity.

An aspect such as the microbiological purity of the dosage form cannot be ignored. Syrups belong to the category of non-sterile dosage forms. The presence of water in syrups creates favorable conditions for the growth and reproduction of microorganisms, so it is necessary to use preservatives.

In the pharmaceutical industry for canning are used: derivatives of p-oxybenzoic acid (methyl, butyl ether); sorbic and benzoic acids, sodium benzoate and ethyl alcohol. It should be noted at once that preservatives have a number of restrictions on use in dosage forms. With this in mind, it is necessary to identify and use the natural antibacterial properties of drugs and excipients, so that the ratio of all substances in pediatric dosage form was generally unfavorable for the

development of microflora, as well as exclude other conditions that promote the growth of microorganisms [8].

The primary issue of dosage form technology is the choice of drug concentration. This was based on the recommended for children the average therapeutic dose of Viola infusion, the concentration of polysaccharides in it, as well as the feasibility of using a minimum volume of syrup per dose and day.

The solution of this problem began with the development of the composition of the syrup and, above all, to determine the content of dry extract from the meal of Viola grass. It was found that at a dosage of one teaspoon (5 ml) per reception should be included in the syrup about 3% of the dry extract.

However, to create such a concentration of dry extract containing polysaccharides in this dosage form was technologically difficult due to the high viscosity of the syrup created by it. In this regard, the concentration of the main component in the syrup was determined at 1.5 %.

Dosing of syrups is carried out by volume, while preparation - by weight. When calculating the dosage was based on the fact that 5 ml of syrup have a weight of 6.5g. Per 100 g of finished syrup it should be 1.5 g of extract to provide a therapeutic dose per dose provided by dosing with teaspoons. Children's dose is 2 teaspoons 2 times a day, morning and evening. The basis for calculating the dosage was the instructions for use of infusion of Viola herb.

The next stage of research was the choice of sweet composition.

Currently, sucrose is used as the main sweet component in the compositions in a mixture with other sweeteners, usually with sorbitol or fructose. Valuable in combined sorbitol systems is the lack of recrystallization, in contrast to sucrose solutions, when exceeding 65 % of the concentration leads to saccharification. In addition, sucrose solutions are invertible and unstable. Fructose solutions differ favorably from sucrose in the absence of side effects in diabetes.

Therefore, the replacement of traditionally used sucrose solutions with combined systems based on sorbitol in adjusted dosage forms is reasonable and promising.

Simple sugar syrup, sorbitol solution, fructose solution and their combinations have been studied as sweetsystems.

The composition of model sweetener bases of syrups is shown in table 3.1.

Table 3.1

The composition of model sweetener base of syrups

Ingredients	Number of sample/g				
	1	**2**	**3**	**4**	**5**
Sucrose	64	-	-	20	-
Fructose	-	-	70	-	20
Sorbitol	-	70	-	40	50
Purified water	36	30	30	40	30

The syrup was prepared as follows.

Initially, at a temperature of about 60 °C in purified water used in syrup technology, dissolved dry extract of Viola field herb (1: 1). Then the flavor base components (samples 1–5) were added to the resulting solution.

This sequence of dissolving the ingredients avoided the caramelization of sucrose and other sweeteners and to obtain a transparent system with less prolonged heating. Obtained at the first stage, a solution of dry extract of Viola herb had a certain viscosity, in this regard, when using the traditional concentration of sugar in the syrup technology, the finished product becomes thick, crystallizes.

Reducing the sugar concentration allowed to obtain a syrup of optimal consistency.

At the next stage of the study we determined the main indicators and quality standards of model syrups, the results of the definitions are shown in table 3.2.

As we can see, model samples 2 and 4 were represented as viscous transparent liquids with a brown color with barely noticeable, caramel-herbal odour and sweet taste. The pH values were within the norms for samples 1-4.

Table 3.2

Main quality indicators of model samples of syrup with dry extract of Viola

field herb (1:1)

Quality indicator	Model samples					Quality standard
	1	2	3	4	5	
Appearance	-	+	-	+	-	Viscous transparent liquid with brown color
Odour	+	-	-	+	+	Barely noticeable, caramel-herbal
Taste	+	+	+	+	+	Sweet taste
pH	+	+	+	+	-	5.5-5.6

According to the results shown in table 3.2, the composition № 4 is corresponded optimally to all indicators. The good results is represented for composition № 1.

Thus, syrup model samples № 1 and № 4 were chosen for further researches.

3.2. Biopharmaceutical studies of syrup samples with dry extract of Viola field herb

For biopharmaceutical research, samples of syrup of compositions 1 and 4 have been selected. Method of “agar’s plates” was used. This method is often used for a comparative study of the biopharmaceutical parameters of the studied compositions quite simple and affordable.

Samples of syrup in the wells of the cups were placed with a glass rod, achieving good contact with agar. Petri dishes were numbered and placed in a thermostat at 37 ° C. After 1, 2, 4, 6, 8, and 24 hours, the plates were removed and the diameter of the colored zones (yellow) formed by API in agar gel with iron (III) chloride was measured with a ruler. The observation time was 24 hours.

The results are presented in figure 3.1.

As can be seen from the diagram data, the release of flavonoids occurred from all studied syrup compositions. At the same time, the completeness of the release of flavonoids from composition No. 1 turned out to be rather low, and

therefore this composition was deemed inappropriate for subsequent tests.

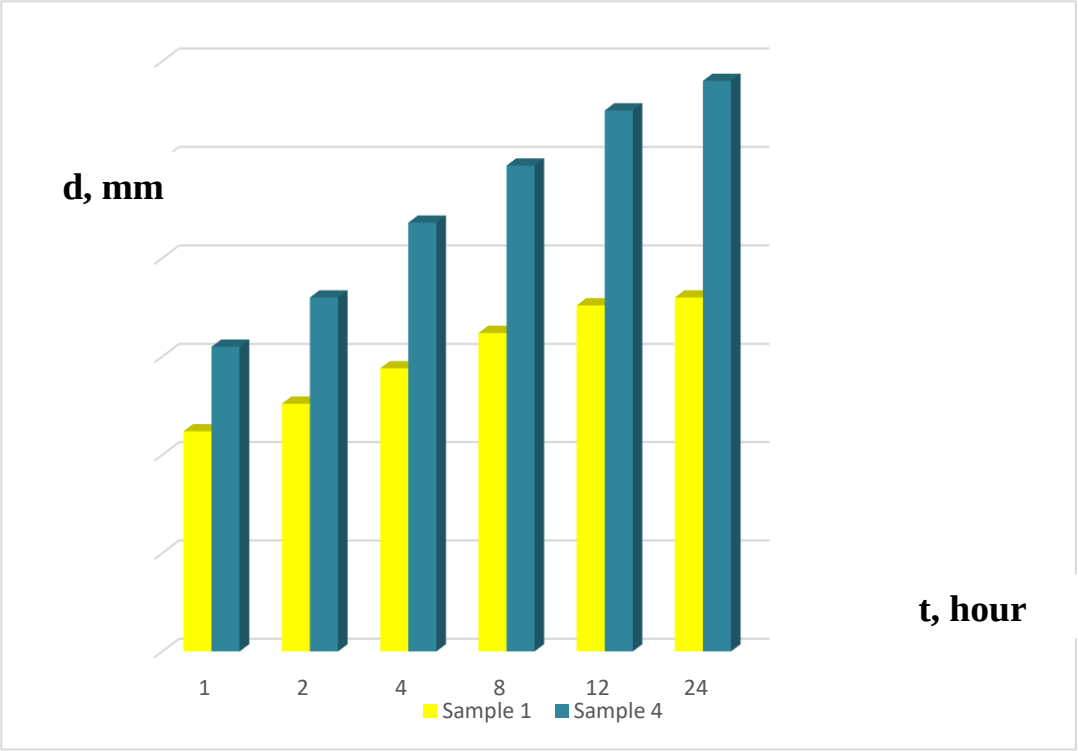


Fig. 3.1. Dynamics of flavonoids release from syrup samples

From syrup sample № 4 (on sucrose and sorbitol) the release of flavonoids was higher. Therefore, this sample was selected for further research.

Thus, based on the complex of physical, chemical and biopharmaceutical researches (agar diffusion method), we determined that sample 4 and is recommended for further study.

3.3. Studying the taste characteristics of syrup

To finally confirm the choice of syrup composition, we evaluated the organoleptic properties using a rating scale (table 3.3.).

Table 3.3

Overall scale assessment of corrected liquid dosage forms

Rating	Total score
Perfectly	23-26
Good	19-22
Satisfactorily	15-18
Unsatisfactorily	Less 15

In addition, the need to correct the flavor and aroma characteristics of the

syrup was determined. In this case, peppermint oil was added (0.04 %) for this purpose, the aroma of which is most often used for dosage forms in bronchopulmonary diseases. The results are represented in table 3.4.

Table 3. 4.

Evaluation of organoleptic properties of syrup samples with dry extract of field Viola herb (1:1)

Name of sample with composition	**Evaluation of organoleptic properties**						**General assessment of perception**
	Appearance		**Color**		**Taste and odour**		
	description	rating	description	rating	description	rating	
Field Viola syrup (sucrose)	viscous transparent liquid	7	Brown or greenish-brown	7	sweet taste with a faint caramel-herbal odor	8	22 good
Field Viola syrup (sucrose, peppermint oil)	thick clear liquid	6	Greenish-brown color	5	sweet taste with mint aroma	10	21 good
Field Viola syrup (sorbitol + sucrose)	viscous transparent liquid	7	Brown or greenish-brown	7	sweet taste with a faint caramel-herbal odor	12	26 perfectly
Field Viola syrup (sorbitol + sucrose, peppermint oil)	viscous transparent liquid	7	Brown or greenish-brown	7	sweet taste with mint aroma	12	26 perfectly

The results of the evaluation showed that there is no need for adjustment, as the overall assessment of perception for both, syrup without sweetener and with it was

similar.

3.3. Microbiological researches of syrup

An important point for children's dosage forms is their microbiological purity, which corresponds to class 3 B (not more than 500 aerobic bacteria and 50 yeasts and molds per 1 g). Therefore, the microbiological purity of the obtained Viola syrups was determined (table 3.5).

Table 3.5

Microbiological purity of syrup samples with dry extract of Viola field herb

Sample	The number of viable microorganisms in 1 g of syrup				The presence of bacteria *Enterobacteriaceae*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*	
	bacteria		fungus			
	1 hour after preparation	after 5 days of storage at 30°C	1 hour after preparation	after 5 days of storage at 30°C	1 hour after preparation	after 5 days of storage at 30°C
1	40	650	less than 10	less than 10	there is not	there is not
2	90	180	less than 10	less than 10	there is not	there is not
3	20	450	less than 10	less than 10	there is not	there is not
4	75	890	less than 10	less than 10	there is not	there is not
5	60	820	less than 10	less than 10	there is not	there is not

Studies have shown that syrup is non-sterile and populated mainly by bacterial flora. Freshly prepared syrup comply with the standards of microbiological purity of category 3B, but when stored at elevated temperatures, favorable for the

development of the microflora, the base has no bacteriostatic effect.

Given this fact, the composition of the syrup was a preservative - sorbic acid, which is the most acceptable for children's dosage form.

The results of determining the microbiological purity of syrups depending on the concentration of the preservative are presented in table 3.6.

The preservative was dissolved in the finished syrup. The finished syrup was subjected to filtration.

Table 3.6.

Microbiological purity of syrup with different concentration of preservative

Concentration of sorbic acid in the composition of syrup	The number of viable microorganisms in 1.0 g of base		The presence of bacteria *Enterobacteriaceae*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*
	bacteria	fungus	
0.1 %	40	less than 10	not found
0.2 %	20	less than 10	not found

Based on the data obtained, the concentration of sorbic acid 0.2 % was selected for the composition of syrup with dry extract of Viola field herb.

Thus, the proposed composition of a children's syrup of expectorant action:

Components, g	**Functional role**
Dry extract of Viola field herb (1:1) – 1.5	API
Sucrose – 20.0	Sweetener
Sorbitol – 40.0	Sweetener
Sorbic acid – 0.2	Preservative
Aqua purificata up to 100.0	Solvent

CONCLUSIONS

1. The composition of expectorant children's syrup containing 1.5 % of dry extract of Viola field herb in sorbitol-sugar base are developed and proposed.
2. It is established that the optimal excipients for the production of syrup with the extract are sorbitol (40 %) and sucrose (20 %), and an acceptable technology is the dissolution of the dry extract in purified water with subsequent addition of base components.
3. Studies have shown that syrup is non-sterile and populated mainly by bacterial flora. Freshly prepared syrup comply with the standards of microbiological purity of category 3B, but when stored at elevated temperatures, favorable for the development of the microflora, the base has no bacteriostatic effect.
4. The necessity of preservative introduction is substantiated, its choice and concentration is carried out. As the optimal preservative sorbic acid was chosen in 0.2 % concentration, the most acceptable for children's dosage form.

GENERAL CONCLUSIONS

1. Based on the analysis of literature data, the use of plants of the genus Viola, such as V. field *L*. in medicine, namely in the form of extract as promising APIs in the composition of syrup, is summarized.
2. The main groups of BAS in the composition of plants of genus Viola have been analyzed in detail and the place of Viola field as an expectorant in pediatric practice is considered
3. Based on the study of the physical, chemical and biopharmaceutical properties of the samples, the rational composition of the syrup with 1.5 % of dry extract of Viola field herb in sorbitol-sugar base are developed and proposed.
4. Sorbitol (40 %) and sucrose (20 %) are the optimal excipients for the production of syrup with the extract and an acceptable technology is the dissolution of the dry extract in purified water with subsequent addition of base components.
5. The necessity of preservative substantiation is substantiated and the research on the choice of its concentration is carried out. It was found that sorbic acid in a concentration of 0.2% is the most acceptable for children's dosage form that ensures its quality.
6. Based on the results of the master's work, an article was published in a scientific professional journal *Annals of Mechnikov Institute* (2022, N 1.).

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APPENDIX

Annals of Mechnikov Institute, N 1, 2022
www.immun.org.ua /journal.htm

DEVELOPMENT OF THE COMPOSITION OF EXPECTORANT SYRUP FOR PEDIATRIC PRACTICE

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Introduction

Of the several thousand plants with established types of pharmacological activity, only more than 200 are allowed in Ukraine for medical use. Among them, dozens of types of medicinal plant raw materials are still used only in the form of water extracts - short-term in terms of storage and practically invaluable in quality infusions and decoctions. This approach to plant raw materials, which is also burdened by outdated processing technologies, does not meet modern requirements for its rational use, in particular, due to the production of several phytochemicals under conditions of low-waste or waste-free production. These medicinal plants include two related types of Violas – tricolor (*Viola tricolor* L.) and field (*Viola arvensis* Murr.), the aerial part of which is used so far only in the form of an expectorant infusion. Both types of medicinal plant materials contain two hydrophilic groups of biologically active substances - polysaccharides and flavonoids. At the same time, the pharmacognostic and technological study of *Viola arvensis* Murr., compared to the *Viola tricolor* L., has received much less attention from researchers. Meanwhile, field Viola herb has a significant raw material base and could become an object of low-waste processing with the production of several medicines, in particular, based on polysaccharides and flavonoids [1].

Simultaneously with the consideration of the issue of a more complete processing of *Viola arvensis* Murr. herb under industrial conditions, it is advisable, taking into account the pharmacological properties of this raw material, to create, first of all, expectorants for pediatric practice. The range of this category of domestically produced medicines is extremely limited. Herb of *Viola arvensis* Murr. with a time-tested sufficiently high degree of safety for a child's body is quite a suitable object of study in this aspect as well. At the same time, for children, syrup is considered the best form of oral administration of drugs, in which it is possible to balance the necessary pharmacokinetic and organoleptic properties.

Thus, research on the technological study of herb of *Viola arvensis* Murr., obtaining from it in conditions of low-waste production effective, convenient for use and standardized in quality medicines, is relevant.

The Viola genus *Viola* L. belongs to the *Violaceae* family of plants, including 900 species, which are widely distributed throughout the earth, from the Arctic in the south to the Falkland Islands, as well as in Australia, New Zealand - in the south. About 100 species of the genus grow in the CIS countries. Plants are well adapted to various environmental conditions. In particular, about 20 species are found in Ukraine, of which field Viola is one of the most common.

Interest in the plant of the genus Viola grew in the first half of the 19th century, thanks to horticultural breeding work with Viola tricolor. The study of Violas in the first quarter of the last century is the work of two prominent experts on the genus - the monograph of the genus W. Becker and the Baltic florist K.R. Kupfer. The works of the first are the most significant and represent the final character, as for many years large materials from Ukrainian Violas were referred to the processing and study [2].

Plants of the genus Violas are characterized by the presence of various biologically active substances. Phenolic substances (flavonoids, phenolic acids, coumarins, tannins), saponins, polysaccharides and other natural compounds were isolated and studied from them. Analysis of data from the scientific literature on the chemical composition of field Violas allows us to conclude that among the flavonoid compounds of this plant is dominated by rutin with its inherent anti-inflammatory, capillary-strengthening, anti-edematous and other effects. Various scientists have noted the presence of ascorbic acid in almost all parts of the plant, the presence of carotenoids has been qualitatively established. Among other classes of natural compounds that are part of the Viola, alkaloids, organic acids, fatty oil, steroid compounds, essential oil were found [3-5].

The aim of the work is to develop the composition of expectorant syrup with dry extract of field Viola herb for the application in pediatric practice.

Materials and Methods

Dry extract of Viola field herb (1:1) is a hygroscopic amorphous powder of light brown color with a specific odour and taste. Soluble in aqueous-alcoholic solutions, hot water. As an excipients for the preparation of syrup were used: sorbitol food; sucrose and fructose.

During development of the composition of expectorant syrup, an organoleptic, physical-chemical and microbiological studies were carried out.

Results and discussion

Respiratory diseases occupy a major place in the structure of morbidity. In the children's age group, this figure reaches 49.3 %. Acute and chronic bronchitis is especially difficult in young children, which often occurs in the cold season alone or as a complication of respiratory infections. These diseases are characterized by difficult discharge of sputum from the bronchi: it becomes viscous, clogs the small bronchi and bronchioles, disrupting their cleansing function. As a result, strains of pathogenic bacteria develop in the lungs, causing further progression of the inflammatory process and the need to use a complex of antibacterial and expectorants to treat the disease [6].

Without dwelling on the well-known negative consequences of the use of antibacterial drugs in children, such as dysbacteriosis, allergic reactions and others, it should be emphasized that even the choice of expectorant drugs should be reasonable and substantiated. In particular, a number of adverse effects limits the use of expectorants of synthetic origin in pediatrics.

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National University of Pharmacy

Faculty for foreign citizens' education
Department Technology of Drugs

Level of higher education master

Specialty 226 Pharmacy, industrial pharmacy
Educational program Pharmacy

APPROVED
The Head of Department
Technology of Drugs
Tatyana YARNYKH

" 18 " of June 2021

ASSIGNMENT
FOR QUALIFICATION WORK
OF AN APPLICANT FOR HIGHER EDUCATION

Ahmad JUNBLAT

1. Topic of qualification work: «Development of the composition of expectorant syrup for pediatric practice», supervisor of qualification work: Yuliia LEVACHKOVA, DSc, prof.,

approved by order of NUPh from "17th" of February 2022 № 76.

2. Deadline for submission of qualification work by the applicant for higher education: April 2022.

3. Outgoing data for qualification work: Objects of researches: dry extract of viola field herb (1:1), syrup samples. The purpose is theoretically and experimentally substantiate the composition of expectorant syrup for pediatric practice.

4. Contents of the settlement and explanatory note (list of questions that need to be developed):
- to analyze the literature data about chemical composition and application of plants belonging to the genus Viola, in particular, Viola field *L.*; - to consider syrup as an alternative dosage form in pediatric practice; - to summarize the literature data on the characteristics of children's bronchitis and the place of expectorants in their therapy; - to substantiate the choice of sweeteners and flavors of syrup based on dry extract of viola field herb; - theoretically and experimentally substantiate the composition of expectorant syrup and the method of introduction of dry extract viola field herb; - to study the organoleptic parameters of the developed syrup samples; - to conduct microbiological studies of syrup samples in order to justify the need for a preservative introduction in the composition of the syrup.

5. List of graphic material (with exact indication of the required drawings):
tables – 7
figures – 5

6. Consultants of chapters of qualification work

Chapters	Name, SURNAME, position of consultant	Signature, date	
		assignment was issued	assignment was received
I Chapter	Yuliia LEVACHKOVA, professor of higher education institution of department Technology of Drugs	18 June 2021	18 June 2021
II Chapter	Yuliia LEVACHKOVA, professor of higher education institution of department Technology of Drugs	10 September 2021	10 September 2021
III Chapter	Yuliia LEVACHKOVA, professor of higher education institution of department Technology of Drugs	5 December 2021	5 December 2021

7. Date of issue of the assignment: ____18 of June 2021_____

CALENDAR PLAN

№ з/п	Name of stages of qualification work	Deadline for the stages of qualification work	Notes
1.	Analysis of literature data. Treatment of nervous system diseases, analyze of pharmaceutical market of homeopathic drugs and their dosage forms.	September – November 2021	**done**
2.	Researches of active substances and excipients	December 2021 – February 2022	**done**
3.	Justification of the results	March 2022	**done**
4.	Registration of qualification work	April 2022	**done**

An applicant of higher education _____ Ahmad JUNBLAT

Supervisor of qualification work _____ Yuliia LEVACHKOVA

ВИТЯГ З НАКАЗУ № 76

По Національному фармацевтичному університету
від 17 лютого 2022 року

1. нижченаведеним студентам 5-го курсу 2021-2022 навчального року, навчання за освітньо-кваліфікаційним рівнем «магістр», галузь знань 22 охорона здоров'я, спеціальності 226 – фармація, промислова фармація освітня програма – фармація, денна форма навчання (термін навчання 4 роки 10 місяців), які навчаються за контрактом, затвердити теми магістерських робіт:

№ з/п	Прізвище студента	Тема магістерської роботи	Посада, прізвище та ініціали керівника	Рецензент магістерської роботи
по кафедрі технології ліків				
1.	Джунблат Ахмад	Розробка складу відхаркувального сиропу для педіатричної практики Development of the composition of expectorant syrup for pediatric practice	проф. Левачкова Ю.В.	доц. Гербіна Н.А.

Підстава: подання декана, згода ректора.

Ректор

Вірно. Секретар

Національний фармацевтичний університет * УКРАЇНА * Факультет з підготовки іноземних громадян №02010936 місто Харків

F A 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

Ahmad JUNBLAT

on the topic: «Development of the composition of expectorant syrup for pediatric practice»

Relevance of the topic. Expectorants - even though they are a class of medicine used to treat cough - don't prevent coughing, but they help stop mucus from building up in your respiratory system. This is important because coughing up mucus is your body's way of removing microorganisms, foreign bodies, and excess mucus from your airways. Natural expectorants and cough remedies include various herbs and other natural substances that help clear airways. Other natural treatments help soothe symptoms caused by inflammation of the upper airways. When infected or irritated by a cough or sore throat, the cells in throat or upper airway triggers immune system to help fight back. There are plenty of cough medicines available at pharmacy but they are full of chemicals that may have adverse side effects. Fortunately, nature has plenty of answers to a wide variety of medical complaints and coughing is no exception. In fact, there are myriad natural expectorants that can help treat cough, in particular, in children. Among the expectorants of plant origin, special attention is drawn to the field viola, namely the dry extract (1:1).

Practical value of conclusions, recommendations and their validity. The obtained experimental results became the basis for the development of the composition of a new expectorant syrup, which will expand the range of drugs for children in the treatment of bronchitis.

Assessment of work. Qualification work in terms of theoretical and practical research fully meets the requirements for qualification work.

General conclusion and recommendations on admission to defend. The qualification work of Ahmad JUNBLAT can be submitted for defense to the Examination Commission of the National University of Pharmacy for the assignment of the educational qualification of the master’s level.

Scientific supervisor _____ prof. Yuliia LEVACHKOVA

«12» of April 2022

F A 2.2.1-32-356

REVIEW

for qualification work of the master's level of higher education, specialty 226 Pharmacy, industrial pharmacy
Ahmad JUNBLAT
on the topic: «Development of the composition of expectorant syrup for pediatric practice»

Relevance of the topic. Expectorants are prescribed for the treatment of cough, which occurs with the formation of viscous mucus in the bronchi. Preparations with expectorant properties are intended to facilitate the separation and excretion of sputum in adults and children from an early age. When coughing with sputum, expectorants containing marshmallow root, licorice root extract, anise seed, thyme extract, viola herb are used. All of these plants are distinguished by an expectorant effect, they are approved for use in the treatment of children with a wet cough, taking into account compliance with the dosage. A fairly high degree of safety for the child's body is characterized by field viola herb, as an active pharmaceutical ingredient with a high content of polysaccharides that have an expectorant effect. It should also be noted that for children, syrup is considered the most preferred form of oral administration of drugs, in which it is possible to balance the necessary pharmacokinetic and organoleptic properties.

Theoretical level of work. The work analyzes the literature on the modern assortment of expectants, as well as analyzes information on the prospects for the use of syrup in pediatrics.

Author's suggestions on the research topic. The author selected the concentrations of active pharmaceutical ingredients, flavors, sweeteners and preservative in the development of the composition of syrup.

Practical value of conclusions, recommendations and their validity. Based on the research conducted, the author substantiated viola field herb as an API in the development of expectorant syrup and selected the optimal excipients for good organoleptic and microbiological quality indicators. Results are of practical interest for the purpose to expand the range of herbal medicines for children.

Disadvantages of work. There are spelling mistakes, technical errors in the work.

General conclusion and assessment of the work. Qualification work of Ahmad JUNBLAT can be submitted for defense to the Examination Commission for the assignment of the educational and qualification level of the master.

Reviewer _____ assoc. prof. Natalia GERBINA

«19» of April 2022

МІНІСТЕРСТВО ОХОРОНИ ЗДОРОВ'Я УКРАЇНИ
НАЦІОНАЛЬНИЙ ФАРМАЦЕВТИЧНИЙ УНІВЕРСИТЕТ

ВИТЯГ З ПРОТОКОЛУ № 10
«28» квітня 2022 року
м. Харків

засідання кафедри
технології ліків

Голова: завідувачка кафедри, доктор фарм. наук, професор Тетяна ЯРНИХ
Секретар: канд. фарм. наук, доцент Володимир КОВАЛЬОВ

ПРИСУТНІ: професор Олександр КОТЕНКО, професор Юлія ЛЕВАЧКОВА, доцент Марина БУРЯК, доцент Оксана Данькевич, доцент Ганна ЮР'ЄВА, доцент Вікторія ПУЛЬ-ЛУЗАН, асистент Світлана ОЛІЙНИК

ПОРЯДОК ДЕННИЙ

1. **Про представлення до захисту до Екзаменаційної комісії кваліфікаційних робіт другого (магістерського) рівня вищої освіти**

СЛУХАЛИ:
Здобувача вищої освіти 5 курсу групи Фм18(3.10д)англ- 01 спеціальності 226 Фармація, промислова фармація Ахмада ДЖУНБЛАТА з доповіддю на тему «Розробка складу відкаркувального сиропу для педіатричної практики» (науковий керівник: професор Юлія ЛЕВАЧКОВА).
УХВАЛИЛИ:
Рекомендувати до захисту кваліфікаційну роботу.

Голова засідання **Тетяна ЯРНИХ**

Секретар **Володимир КОВАЛЬОВ**

Ф А2.2.1-32-042

НАЦІОНАЛЬНИЙ ФАРМАЦЕВТИЧНИЙ УНІВЕРСИТЕТ

ПОДАННЯ
ГОЛОВІ ЕКЗАМЕНАЦІЙНОЇ КОМІСІЇ
ЩОДО ЗАХИСТУ КВАЛІФІКАЦІЙНОЇ РОБОТИ

Направляється здобувач вищої освіти Ахмад ДЖУНБЛАТ до захисту кваліфікаційної роботи за галуззю знань 22 Охорона здоров'я
спеціальністю 226 Фармація, промислова фармація
освітньою програмою Фармація
на тему: «Розробка складу відкаркувального сиропу для педіатричної практики».

Кваліфікаційна робота і рецензія додаються.

Декан факультету _____ / Світлана КАЛАЙЧЕВА /

Висновок керівника кваліфікаційної роботи

Здобувач вищої освіти Ахмад ДЖУНБЛАТ представив магістерську роботу, яка за об'ємом теоретичних та практичних досліджень повністю відповідає вимогам до оформлення магістерських робіт.

Керівник кваліфікаційної роботи

_____ Юлія ЛЕВАЧКОВА

«12» квітня 2022 року

Висновок кафедри про кваліфікаційну роботу

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

Завідувачка кафедри технології ліків

_____ Тетяна ЯРНИХ

«23» квітня 2022 року

Qualification work was defended
of Examination commission on
« ___ » of June 2022
With the grade _____
Head of the State Examination commission,
DPharmSc, Professor
_____ / Oleh SHPYCHAK /