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 This approach to plant raw materials, which is also burdened by outdated processing technologies, does not meet modern requirements for its rational use, in particular, due to the production of several phytochemicals under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 (*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. 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].

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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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.

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 6.5 g. 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 grass.

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 sweet systems. The composition of model sweetener bases of syrups is shown in table 1.

Table 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 from the meal of Viola herb had a

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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 2.

Table 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 2, the composition № 4 is corresponded optimally to all indicators. To finally confirm the choice of syrup composition, we evaluated the organoleptic properties using a rating scale (Table 3). In addition, the need to correct the flavor and aroma characteristics of the syrup was determined. In this case, peppermint oil was added for this purpose, the aroma of which is most often used for dosage forms in bronchopulmonary diseases.

Table 3. Overall scale assessment of corrected liquid dosage forms

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

The results are represented in table 4.

Table 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.

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. Studies have shown that syrups are non-sterile and populated mainly by bacterial flora. Freshly prepared syrups comply with the standards of microbiological purity of category 36, 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 6. The preservative was dissolved in the finished syrup. The finished syrup was subjected to filtration.

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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.

Table 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

Table 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

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 (42 %) and sucrose (20 %), and an acceptable technology is the dissolution of the dry extract in purified water with subsequent addition of base components.
3. 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.

Development of the composition of the base of the expectorant syrup

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Introduction. Of the several thousand plants with established types of pharmacological activity, only a little over 200 are allowed for medical use in Ukraine. Among them, dozens of types of medicinal plant raw materials are still used only in the form of aqueous extracts, which are characterized by a short shelf life. These medicinal plants include two related types of Violas - tricolor and field, the aerial part of which is used so far only in the form of an expectorant infusion. Violet herb has a powerful raw material base and can be the subject of low-waste processing to obtain a number of drugs, in particular, based on polysaccharides and flavonoids. **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.** Based on conducted research, in particular, research on the study of microbiological purity, the necessity of preservative introduction is substantiated, its choice and concentration is carried out. As the optimal preservative was sorbic acid in 0.2 % concentration. It is established that the optimal excipients for the production of syrup are sorbitol (42%) and sucrose (20%), and an acceptable technology is the dissolution of the dry extract in purified water with subsequent addition of base components. **Conclusions.** The composition of expectorant syrup containing 1.5 % of dry extract of field Viola herb in sorbitol-sugar base are developed and proposed for pediatric practice.

Keywords: *Viola arvensis*, composition, syrup, microbiological purity.

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