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УДК 615.1

СРАВНИТЕЛЬНЫЙ АНАЛИЗ СОДЕРЖАНИЯ ФЛАВОНОИДОВ В ИЗВЛЕЧЕНИИ ИЗ КОМПЛЕКСНОГО ЛЕКАРСТВЕННОГО РАСТИТЕЛЬНОГО СЫРЬЯ ПРИ РАЗЛИЧНЫХ МЕТОДАХ ЭКСТРАКЦИИ

COMPARATIVE ANALYSIS OF FLAVONOID CONTENT IN EXTRACTION FROM COMPLEX MEDICINAL PLANT RAW MATERIALS USING VARIOUS EXTRACTION METHODS

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Аннотация. *В наше время древнейшая лекарственная категория – препараты на основе лекарственного растительного сырья (ЛРС), не потеряли актуальности, постоянно развивается и, как следствие, во многих государствах они имеют фармакопейный статус. Тенденции развития медицинской науки проявляются не только в усложнении новейших фармацевтических технологий, но и в глубоком познании механизмов воздействия средств природного происхождения, особенно при длительных и хронических заболеваниях различного генеза. В общей структуре заболеваемости патология опорно-двигательного аппарата занимает одно из лидирующих мест. Болезни позвоночника, костей и суставов одинаково свойственны и молодым, и пожилым людям. Практически каждый десятый взрослый имеет ту или иную патологию костно-мышечной системы. В процессе многочисленного подбора и исследования комбинаций разнообразного ЛРС с противовоспалительной, регенерирующей и как следствие, противоартритной и противоартрозной активностью и скрининга на Parametium caudatum, была выбрана комбинация из 13 обьектов. Все они содержат флавоноиды, которые и являются основными «носителями» фармакологической активности. Оптимальным экстрагентом, для извлечения флавоноидов (основных «носителей» интересующего фармакологического эффекта) является этанол 70%. Для выбора метода экстракции были исследованы следующие: мацерации (Метод 1), перколяции (Метод 2). Значения соизмеримы, но учитывая, что первая методика не требует длительного экстрагирования как в перколяции и является более «облегченной» в аппаратурном исполнении, мы остановили свой выбор на мацерации.*

Ключевые слова: флавоноиды, лекарственное растительное сырье, артриты, артрозы, мацерация, перколяция.

Abstract. *The ancient medicinal category-drugs based on medicinal plant raw materials (MPRM), has not lost relevance today. The production of such drugs is constantly developing and they have a pharmacopoeial status in many states. Trends in the development of medical science are manifested not only in the complexity of the latest pharmaceutical technologies, but also in a deep knowledge of the mechanisms of action of natural products, especially in long-term and chronic diseases of various genesis. In the general structure of morbidity, pathology of the musculoskeletal system occupies one of the leading places. Diseases of the spine, bones and joints are equally characteristic of both young and old people. Almost every tenth adult has one or another pathology of the musculoskeletal system. In the process of numerous selection and research of combinations of various medicinal plant raw materials with anti-inflammatory, regenerative and consequently anti-arthritic and anti-arthrotic activity and screening for Parametium caudatum, a combination of 13 objects was selected. All of them contain flavonoids, which are the main "carriers" of pharmacological activity. The optimal extractant for the flavonoids extracting is 70% ethanol. To select the extraction method, the maceration (Method 1) and percolation (Method 2) were studied. The values are comparable, but taking to account that the first method is more common and does not require a long extraction as in percolation, maceration was chosen.*

Key words: flavonoids, medicinal plant raw materials, arthritis, arthrosis, maceration, percolation.

Introduction. Trends in the development of medical science are not only in the complication of the latest pharmaceutical technologies, but also in a deep understanding of the mechanisms of effect of natural products, especially in treatment of long-term and chronic diseases. Medicinal plants are in demand for the production of plant-based preparation that do not cause those side effects that are observed with the use of synthetic drugs [9]. The growing popularity of herbal medicines, which have proven their effectiveness and safety, requires constant expansion of their arsenal. Phytopreparations have advantages due to the presence of complexes of basic substances that enhance their biological activity. Herbal preparations (total preparations) – tinctures, extracts are among the oldest dosage forms of official medicine. In our time, these ancient medicinal categories have not lost their relevance, they are constantly developing and, as a result, in many countries they have a pharmacopoeial status [2, 3, 4, 6].

In practice, several plants are usually used at once (collection of medicinal herbs). This makes it possible to expand the range of applications, enhance the effect of certain medicinal herbs, introducing into the collection plant objects that affect various pathological processes in the lungs, liver, kidneys, heart, spleen, stomach, pancreas, intestines, joints and many other organs and tissues [3, 9, 11, 12].

In the general structure of morbidity, pathology of the musculoskeletal system ranks fourth after diseases of the respiratory system, blood circulation and digestion. Diseases of the spine, bones and joints are equally common in young and old people. Men suffer from them almost twice as often as women. Almost every tenth adult has one or another pathology of the musculoskeletal system. Arthritis and arthrosis is observed in every fifth patient between the ages of 30 and 40, and in every second – at the age of 50 to 60. Among people over the age of 65, the incidence of arthritis and arthrosis is 70-85%. In recent years, the proportion of diseases of the musculoskeletal system has been constantly growing: the number of new cases is increasing annually by about 25%. In addition to the threatening morbidity rates, information on the consequences are even more alarming – primary disability due to diseases of the musculoskeletal system ranks third after diseases of the circulatory system and malignant neoplasms. The constant progress of medicine provides a significant extension of life, while the percentage of chronic diseases is increasing. This tendency is most noticeable in diseases of the musculoskeletal system, and such pathologies as arthritis and arthrosis are the most urgent. An important problem of the modern approach to the treating arthrosis and arthritis is the search for external remedies based on medicinal plants that can be used for a long time, without side effects in different age groups. The objective of this study is to create a product based on medicinal plant raw materials (MPRM), which has an increased pharmacological effect, as well as to develop a method for its production [12].

In the process of numerous selection and research of combinations of various medicinal products with anti-inflammatory, regenerating and, as a consequence, antiarthritic activity and screening for Parametium caudatum, a combination of 13 objects was chosen. All of them contain flavonoids, which are the main carriers of pharmacological activity.

The optimal extractant for the extraction of flavonoids is 70% ethanol.

To select the extraction method, the maceration (Method 1) and percolation (Method 2) were studied.

Research methods

Method 1 – the technology for obtaining complex extraction by the maceration method.

Complex extraction was obtained in a maceration tank. The technological process consisted of the following main stages: preparation of medicinal plant raw materials and extractant, obtaining a complex alcohol-water extraction, packing and packaging.

The method of remaceration was used in the ratio of medicinal product: extractant – 1: 8. The crushed raw material was placed in a maceration tank and filled with a 5-fold amount of the extractant (70% ethyl alcohol + 10% methylene chloride). The addition of methylene chloride significantly increased the yield of flavonoids compared with extraction with pure 70% ethanol. The combination of polar (alcohol) and non-polar (methylene chloride) solvents made it possible not only to increase the yield of flavonoids, but also to ensure efficient extraction of lipids. This is due to the low dielectric constant of methylene chloride (about 9). Extraction was carried out at room temperature for 24 hours. Then the raw material was squeezed out, the extract was filtered, and the meal was re-poured with a 3-fold amount of the extractant, and the process was repeated for 12 hours at room temperature. Then the meal was squeezed out, and the resulting extract was filtered. Periodic change of the extractant is necessary for a more complete depletion of the raw material and to reduce the loss during diffusion. After the completion of the extraction, the resulting extracts were combined.

The combined alcohol-water extract was precipitated for 24 hours and filtered. Next, the extract was evaporated under vacuum at a temperature of 50-60. 0C and a residual pressure of 50-60 inches of mercury with water jet vacuum pump for methylene chloride removal.

In the selected complex of medicinal products, terpene compounds are also contained in addition to flavonoids. Volatile compounds – essential oils are having been lost during storage and processing. Significant losses also occur during the roll milling of crushed plant materials. In this connection, impregnation of a blended mixture of raw materials with a solution of castor oil and ethanol was tested. It has been determined that the optimal is the addition of a 7-8 wt.% alcohol solution per unit mass of raw material.The studies have shown that the impregnation of the raw material

before roll milling allows to increase the content of essential oils in the product (phytoconcentrate) by 5-7% compared to the control process without impregnation. The yield of essential oils without impregnation is 4-8%.

The combination of solvents also allows additional extraction of such a valuable product as chlorophyll from medicinal plant raw materials. Chlorophyll is the "green blood" of the plant world, which acts as a protein. Being the basis of the entire plant world, it is the very first product of sunlight, carries out photosynthesis. Regular consumption of chlorophyll can improve the body's resistance to many diseases, such as arthritis, rheumatoid arthritis, rhinitis, diabetes mellitus, high blood pressure, etc. Thus, the maintenance of chlorophyll in the extract is an important link in obtaining the extract.

Method 2 – extract preparation by percolation method. The extraction of complex raw materials was carried out in a battery of six diffusers according to the counterflow principle, in which the extract obtained from the first diffuser is sent to the second, the extract obtained from the second diffuser is sent to the third, etc. All six doses of the extractant with this extraction method are supplied into the first diffuser. After putting into operation all the diffusers of the battery, all six portions of the extract are taken from the head, sixth diffuser, and the tail diffusers are taken out alternately, with the start of the selection of finished products.

Quantification of the amount of flavonoids in the extract. Alcohol-water extraction was obtained from standardized raw materials [7].

The quantitative determination of flavonoids in terms of narutin was carried out traditionally. The optical density of the resulting solution was measured on a spectrophotometer at a wavelength of 415 ± 2 nm in a cuvette with a layer thickness of 10 mm. In parallel, the optical density of the rutin working standard solution was measured.

Research results. The final combination of MPRs was matched by studying the increase in the lifespan of Paramecia with the addition of extracts (pre-thickened to remove ethanol). Among all the variety of microorganisms, paramecia are one of the most convenient test objects for medico-ecological, pharmacokinetic and toxicological studies, as they are well studied, have large sizes that allow working with individual organisms [1, 5, 8, 10]. Cultivation methods have been developed for them that provide the necessary culture standardization with relatively inexpensive methods. There are no pathogenic forms among them. Paramecia in pharmacology, as a biological model, is used to screen antioxidant (regulating lipid peroxidation) and membrane-stabilizing drugs. Paramecia, as living self-regulating structures, are characterized by a high degree of adaptability, that is, they are able to develop protective reactions aimed at weakening the damaging effects of various stimulant, and resistance to stimulant remains for some time after its removal. There are various modifications of microscopic counting in medical and microbiological research. To conduct an experiment, a few drops are taken from a suspension with organisms and the number of ciliates is counted under a microscope [1, 10]. The microscopical method allows visual observation of changes in the functional and structural parameters of Paramecia under the influence of substances of various natures in both acute and long-term experiments. As a pharmacological indicator (toxicant), predominantly damaging the lipid part of the membrane, hydrogen peroxide 1% is used, which is broken down to peroxide radicals in vivo, initiating the process of lipid peroxidation (LPO) of membranes; a pharmacological indicator that predominantly damages the structure of the protein biomembrane is 14% ethyl alcohol, leading to denaturation of both enzymatic and membrane proteins [1, 8, 10].

Table 1

The composition of the optimal combination of medicinal products

№ п/п	Optimal combination of alcohol-water extraction from medicinal plant raw materials	The optimal ratio of medicinal products
1.	Chamomile (flowers)	0,04
2.	Calendula (flowers)	0,05
3.	Cumin (fruit)	0,03
4.	Pine (buds)	0,50
5.	Yarrow (herb)	0,05
6.	Mint (leaf)	0,10
7.	Rosehip (fruit)	0,06
8.	Fennel (fruit)	0,30
9.	Licorice (root)	0,25
10.	Wormwood (herb)	0,40
11.	Thyme (herb)	0,15
12.	St. John's wort (herb)	0,05
13.	Celandine (herb)	0,02
Итого:	13 ingredients	2,00

The choice of the medicinal plant was based on the analysis of researches on raw materials that have anti-inflammatory, regenerating effects and indirectly affect pathological links in degenerative-inflammatory processes of the musculoskeletal system.

The results of determining the degree of protection of the paramecia cell wall when the developed combination is added to them in relation to cell poisons (14% ethanol and 1% hydrogen peroxide solution) are shown in Table 2.

Table 2

Study of the degree of protection of paramecium from the action of toxicants by the time of stopping (acute experience)

Object name	Stop time of paramecium in 14% ethanol, min	Stopping time of paramecium in 1% hydrogen peroxide solution, min
Control	0,2 ± 0,01	0,09 ± 0,01
Medicinal product combination	11,0 ± 0,30	5,9 ± 0,20

The developed combination significantly extended the stopping time of paramecium by a factor of 55 and 65 under the influence of cellular poisons – ethyl alcohol and hydrogen peroxide, respectively. The lengthening of the stopping time of the movement of paramecium under the influence of ethyl alcohol, characterizes the membrane-stabilizing activity of the developed combination, selected components, which in a qualitative and quantitative ratio prevent damage to the protein part of the biomembrane. Antioxidant activity was tested by extending the time of movement of paramecium under the influence of a solution of hydrogen peroxide, which is associated with the ability of the components of the developed combination to inhibit membrane lipid peroxidation.

Quantification of the amount of flavonoids in the extract

Method 1 (maceration)

The metrological characteristics of the developed methodology are shown in Table 3.

Table 3 – Metrological characteristics of the method for determining the content of the sum of flavonoids in the complex extract (Method 1)

n	$X_{ср}$	ΔX	S	S^2	S_x	t (p,f)	ε,%
10	2,850	0,025	0,035	0,0013	0,011	2,26	0.90

Thus, in the extract obtained by Method 1, the content of flavonoids in terms of rutin is 2,850±0,025 ($X_{ср}$± ΔX).

To confirm the correctness of the method, a calibration curve was plotted, the dependence of the optical density of the solution on the concentration of rutin and is shown in Figure 1.

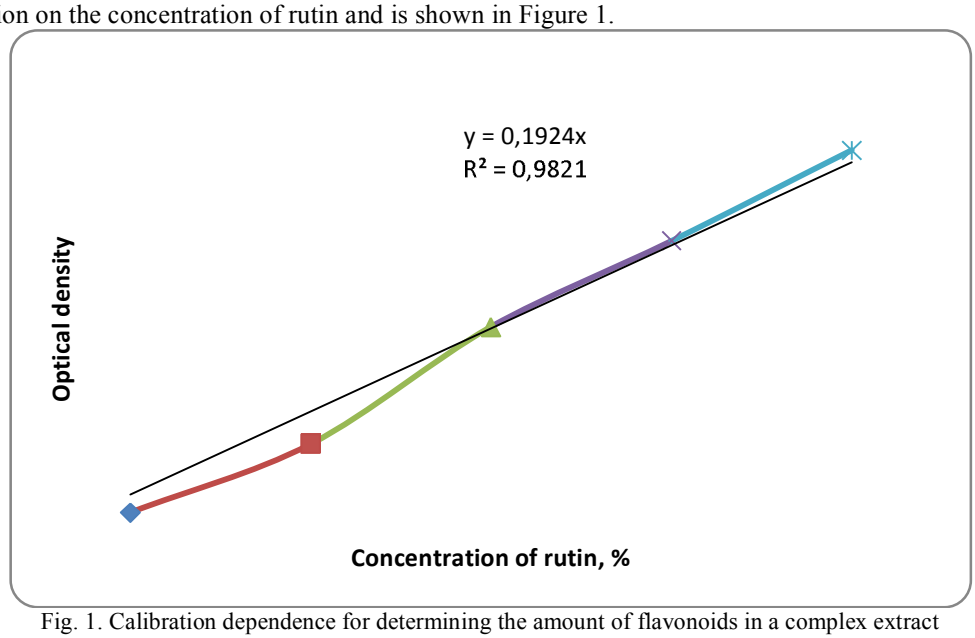

Fig. 1. Calibration dependence for determining the amount of flavonoids in a complex extract

The graph shows a direct dependence of the increase in optical density on the concentration of rutin.

Method 2 (percolation)

The metrological characteristics of the developed methodology are shown in Table 4.

Table 4

Metrological characteristics of the method for determining the content of the sum of flavonoids in the complex extract (Method 2)

n	$X_{ср}$	ΔX	S	S^2	S_x	t (p,f)	ε,%
10	2,950	0,035	0,035	0,0013	0,011	2,26	0,75

Thus, in the extract obtained according to Method 2, the flavonoid content in terms of rutin is 2,950±0,035 ($X_{ср}$±ΔX).

Conclusions. Flavonoids – substances of a polyphenolic nature that protect plants from adverse environmental factors, perform similar functions in animals, whose body does not produce these substances, but consumes them with food. Although the concentration of flavonoids in the body of animals is significantly lower than that of plants, these substances retain their protective functions and are normally constantly present in the blood, lymph and intercellular

fluids, acting on the receptors of the signaling system of cells. Flavonoids also enter the cytoplasm, having a direct effect on the work of some enzymes. Currently, there is a lot of evidence of changes in the expression and functioning of various proteins in the cytoplasm and nucleus, although the molecular mechanisms explaining the mechanisms of the effect of flavonoids on the functioning of proteins are poorly understood. In addition, in the body of animals, flavonoids undergo a variety of chemical modifications. Flavonoid metabolism products also have biological activity. However, the pharmacokinetics of flavonoids is still in its infancy and there is still relatively few research in this area [12, 13, 14, 15].

Medicinal plant preparations containing flavonoids, the release and quantitative analysis of flavonoids are of particular interest. Studies of the action of flavonoids show their ability to influence various vital processes, both of individual cells and the body as a whole. Epidemiological studies of the relationship between the spread of various diseases (cardiovascular, oncological, neurological, diseases of the musculoskeletal system) with the consumption of flavonoids under experimental conditions on animals convincingly indicate the prospects of using some flavonoids in the prevention and even in the treatment of various diseases. Flavonoids are powerful antioxidants that prevent the development of oxidative stress in cells where metabolism is impaired by toxic prooxidants, UV radiation, and other damaging factors. The antioxidant properties of flavonoids are determined both by the ability of these molecules to capture free radicals and by the ability to chelate cations of variable valence metals involved in oxidation processes. The antioxidant effect of flavonoids is not limited to the direct effect of these substances on the processes of peroxidation. Flavonoids are sometimes a subtle, but necessary link in the assembly and functioning of proteins, in the formation of biological membranes, in the transmission of information in the cell. Always available, they serve as helpers in many processes. This is a kind of "lubricant" in the complex mechanism of the cell. It can be hoped that further research of flavonoids will make it possible to make many interesting discoveries, and the creation of artificial derivatives of flavonoids will make it possible to obtain new effective medicinal substances [12, 13, 14, 15].

Comparative analysis of the methods of extraction – maceration and percolation, based on the analysis of the transition of flavonoids, in terms of rutin, in alcohol-water extraction showed that in the extract obtained by Method 1, the content of flavonoids was 2.850 ± 0.025, according to Method 2, the content of flavonoids was 2.950 ± 0.035. The values are comparable, but taking to account that the first method is more common and does not require a long extraction as in percolation, maceration was chosen.

The resulting alcohol-water extraction is an intermediate product for the design of a soft dosage form - a gel with roughly antiarthritic and antiarthrosique activity.

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Дата поступления в редакцию: 23.04.2020
После рецензирования: 28.05.2020
Дата принятия к публикации: 31.05.2020