

Furocoumarins as potential sources of new drugs

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Furocoumarins as potential sources of new medicines

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SUMMARY

The article provides an overview of the biological activity of a group of substances of plant origin - furocoumarins. These are phenolic compounds derived from coumarin, typical mainly for representatives of the families of celery (Apiaceae) and rue (Rutaceae). Furocoumarins are synthesized by plants in response to stress and to protect against pests (fungi, bacteria and insects).

Since the mid-70s of the XX century, furocoumarins have been used in medicine as photosensitizing drugs for the treatment of skin diseases. Currently, their anti-inflammatory, antimicrobial, antitumor and other types of activity are being widely studied. Parsnip (*Pastinaca sativa* L.) is a promising source of furocoumarins. This plant is widespread in the flora of Russia, and is also cultivated. The rich chemical composition of parsnip fruits allows us to consider them as a potential source of new medicines.

Key words: furocoumarins, bergapten, imperorin, pharmacological activity, *Pastinaca sativa* L.

RESUME

The article is an overview of the biological activity of a group of substances of plant origin - furocoumarins. These are phenolic compounds derived from coumarin, which are characteristic mainly for Apiaceae and Rutaceae families. Furocoumarins are synthesized by plants in response to stress and for protection against pests (fungi, bacteria and insects). Since the 70s of the XX-th century, furocoumarins have been used in medicine as photosensitizing drugs for the treatment of skin diseases. At present, their anti-inflammatory, antimicrobial, anti-cancer and other activities are widely studied. A promising source of furocoumarins is a *Pastinaca sativa* L. This plant is growing widely in

the flora of Russia, and also is cultivated. The rich chemical composition of the fruit of *Pastinaca sativa* L. allows to consider them as a potential source of new medicines.

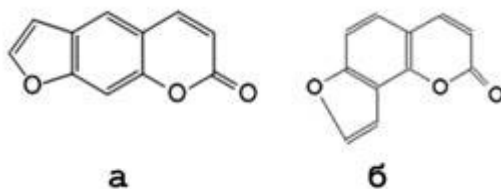
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INTRODUCTION

Furanocoumarins (furocoumarins) are phenolic compounds derived from coumarins. They are formed as a result of the condensation of a coumarin molecule with a furan ring. Furocoumarins are divided into two types: linear, known as psoralens, which include psoralen (Figure 1a), xanthotoxin, and bergapten, and angular, known as angelicins, which include angelicin (Figure 1b), spondin, and pimpinellin.

Linear furanocoumarins have been found in large quantities in members of the families Apiaceae, Rutaceae, Fabaceae, and Moraceae. Angular furanocoumarins are less widespread and are mainly found in representatives of the Apiaceae and Fabaceae families [1].

Furocoumarins are synthesized by plants in response to stress and to protect against pests (fungi, bacteria and insects). Furocoumarins react with the DNA of these organisms and, when exposed to ultraviolet light, disrupt its replication. Thus, they inhibit microbial growth and cause the death of insects; therefore, furocoumarins are considered natural pesticides [2].



Rice. 1. Structural formula of furocoumarins: a - psoralen, b - angelicin (isopsoralen).

The effect of furocoumarins on the human body is complex, but many questions remain regarding the safety of their use in medicine and as food [3, 8]. Thus, furocoumarins are well known as inhibitors of cytochrome P450 (CYP), which is involved in the metabolism of a number of drugs in the human body. Furocoumarins to a greater extent inhibit the activity of the isoform of the P450 enzyme - CYP3A4. Therefore, the joint consumption of foods rich in furocoumarins and drugs, the metabolism of which is associated with CYP3A4, can lead to a sharp increase in the concentration of these drugs in the blood plasma and cause an overdose ("grapefruit effect") [1, 3]. These drugs, for example, include statins (atorvastatin, lovastatin), nifedipine, amiodarone, cyclosporine,

The search and identification of promising plant sources for obtaining furocoumarins is an urgent task of medicine and pharmacy. Inalienable

A condition for the creation and production of phytopreparations is the availability of a sufficient raw material base of wild-growing plants and / or the availability of proven agro-technological methods for cultivated species. In this regard, plants of the genus Pasternak (*Pastinaca*) related to family of umbrella (celery) - Apiaceae [4].

The purpose of this information-analytical study is to analyze and generalize information about the main types of biological activity of furocoumarins and the possibilities of using parsnip as a promising source of their production.

RESULTS AND ITS DISCUSSION

Results of a study of the pharmacological activity of furocoumarins

Photosensitizing Activity

Since the 70s of the XX century, the photosensitizing properties of furocoumarins have been widely studied. Psoralen has been used in combination with long-wave UV radiation (PUVA therapy) to treat skin conditions such as psoriasis and vitiligo. The therapeutic effect is based on the ability of furocoumarins to be excited under the influence of long-wave irradiation and to form adducts (products of direct attachment of molecules to each other without cleavage of any fragments) of photocycloaddition with thymine DNA bases [5]. However, this therapy allows to get an improvement in symptoms only in the short term, and is also associated with a high risk of developing skin cancer, even several years after the cessation of therapy [1].

Currently, among the series of furocoumarins, active research is being carried out on the synthesis of new derivatives and the creation of photosensitizers for PUVA therapy, devoid of this drawback [6, 7]. In addition, the photosensitizing properties of furocoumarins make it possible to use them for extracorporeal photophoresis in the treatment of not only skin diseases, but also autoimmune diseases (systemic lupus erythematosus, Crohn's disease, type 1 diabetes or multiple sclerosis), as well as cutaneous T-cell lymphoma and rejection of organ transplants. It is important to note that furocoumarins, both as individual compounds and in combination with other drugs, are promising candidates for the development of new treatments or the improvement of existing ones [7].

Antineoplastic activity

The ability of furocoumarins to interact with DNA and disrupt its replication is of great interest in the development of antitumor agents. Extracorporeal photophoresis is currently a promising treatment for cutaneous T-cell lymphoma. During this treatment, T-lymphocytes *ex vivo* irradiated with UV light in the presence of psoralen and transfused to the patient [8].

Research *in vitro* showed that furocoumarins can inhibit growth

various types of cancer cells, including breast cancer and large cell lung cancer [9].

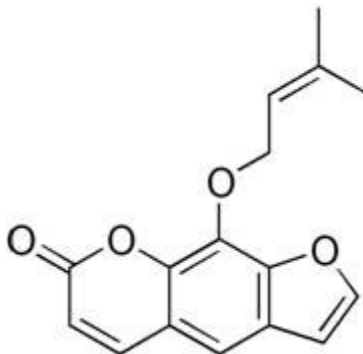
The experiment has shown that furocoumarin bergapten and its combination with UV irradiation significantly affect proliferation in breast cancer cell lines MCF-7, ZR-75 and SKBR-3. Bergapten inhibited the PI3K / AKT signaling pathway in MCF-7 cells even when stimulated with insulin-like growth factor (IGF-I). In addition, bergapten, and to a greater extent its combination with UV irradiation, increased the activity of p53 mRNA and the protein content. The results obtained confirm that both bergapten and its photoactivated compound have an antiproliferative effect and induce apoptotic reactions in breast cancer cells [9].

The study of the antitumor activity of bergapten in hepatocellular carcinoma (HCC) showed its interaction with nuclear receptors LXRs (α and β). The activation of LXRs correlates with the modification of the PI3K / Akt signaling pathway. It was also established that these receptors play an important role in maintaining lipid homeostasis by regulating ABCA1, IDOL, SREBP1, LDLR, as well as some lipogenic genes such as FASN and SCD1. Molecular analysis of the interaction of bergapten with LXRs (α and β) was performed using the Maestro system and compared with reference ligands. Next, an assessment of the antitumor activity of bergapten was carried out *in vitro* using cellular lines HepG2 and *in vivo* in a model of induced HCC in albino rats Wistar. The results obtained showed the presence of polar and hydrophobic interactions of bergapten with LXR (α and β). Research *in vitro* identified the potential ability of bergapten to reduce lipid accumulation in HepG2 cells, which correlated with an increase in LXR protein expression (α and β). In research *in vivo*, while taking bergapten, weight indicators improved body mass, liver mass, and there was a significant restoration of changes in mRNA and protein expression due to the regulation of LXR (α and β), ABCA1, IDOL, SREBP1 and LDLR. Bergapten also modulated the expression of the PI3K / Akt signaling pathway and some lipogenic genes such as FASN and SCD1, and reduced the level of lipid droplets in liver cancer cells. The described results prove the role of bergapten in maintaining lipid homeostasis and substantiate its antitumor potential in HCC [10].

Effects on the nervous system

A comparison was made of the anticonvulsant activity of four natural furanocoumarins (bergapten, emperorin, oxypeucedanin and xanthotoxin). The anticonvulsant effect of furanocoumarins was assessed after 15, 30, 60, and 120 minutes after their intraperitoneal administration. Tonic expansion of the hind limb (seizure activity) was induced in adult albino mice by a current (sinusoid, 25 mA, 500 V, 50 Hz, stimulus duration 0.2 s) supplied through auricular electrodes. The results obtained showed that imperorin and xanthotoxin at a dose of 300 mg / kg have a strong anticonvulsant effect, while bergapten and oxypeucedanin at the same dosage did not show any anticonvulsant activity in this model [2].

Imperatorin (9- (3-methylbut-2-enoxy) -7-furo [3,2-] chromenone), a furocoumarin found in some plants of the celery family (Fig. 2), is able to improve the cognitive abilities of mice and protect hippocampal cells and cortex from damaging factors in an experiment using a model of nicotine-induced oxidative stress [11].



Rice. 2. Structural formula of the Emperor

The interaction of furocoumarins with benzodiazepine receptors, their dopaminergic and serotonergic affinities, as well as their ability to inhibit the enzymes cholinesterase and monoamine oxidase (MAO) are currently being discussed. Natural or synthetic coumarins are considered potential drugs for the treatment of psychiatric and neurodegenerative disorders, including Alzheimer's and Parkinson's diseases, schizophrenia, epilepsy, depression and anxiety [12, 13].

Research in vitro have shown that most of these compounds exhibit significant activity as selective inhibitors of MAO and self-induced aggregation of A β 1-42 [14]. In particular, synthetically obtained derivatives of 3-coumarone (benzofuran-3(2H)-one), as well as psoralen and isopsoralen, isolated from *Psoralea corylifolia* L. [33], umbelliferone and xanthotoxin isolated from the terrestrial part *Dictamnus albus* L. [34].

Antibacterial activity

The level of resistance of microorganisms to drugs that has increased in recent years is a serious problem in clinical medicine and necessitates the search and development of new methods of antimicrobial and antifungal therapy.

A study of the lethal effect of UV light on a strain of *Staphylococcus aureus* and its combination with various concentrations of furocoumarins: 8-methoxypsoralen (MOP), 4,5-, 8-trimethylpsoralen (TMP) and 3-carbethoxypsoralen (CEP) was carried out. Irradiation with UV light in the presence of MOP and TMP had a stronger bactericidal effect than UV light alone. With an increase in the concentration of MOP, an increase in the bactericidal effect was observed, with an increase in the concentration of TMP, on the contrary, a decrease in activity was observed. The addition of CEP protects bacteria from damage caused by UV rays, which can be explained by the inhibition of the formation of cyclobutyl-pyrimidine

dimers. The different effects of the tested furocoumarins in combination with UV irradiation on the lethality of microorganisms may be associated with different chemical characteristics of each molecule, which affect the number and types of adducts formed, contributing to the observed photosensitizing or photoprotective effects [15].

The antibacterial activity of some furocoumarins against multi-resistant strains of *Staphylococcus aureus*, such as bergapten, xanthotoxin, isopimpinellin and imperorin, isolated from members of the rutaceae family (*Metrodorea mollis* and *Pilocarpus spicatus*). Antimicrobial activity was assessed in terms of the minimum inhibitory concentration (MIC) using the microdilution method. For all coumarins tested, MIC was > 256 g / ml. Analysis of the effect on drug resistance of strains showed that treatment with isopimpinellin reduced the MIC of erythromycin by 4 times, the best result was shown by imperorin, which reduced the MIC of tetracycline by 2 times, erythromycin and norfloxacin by 4 times [16].

The antifungal activity of furocoumarins (8-methoxypsoralen (8-MOP), isopimpinellin, and a mixture of two coumarins - 7-metoxicoumarin and citropten) in combination with UV irradiation has been studied in vitro on phytopathogenic strains mushrooms *Colletotri-chum acutatum* and *Aspergillus nidulans*. UV radiation combined with 8-MOP (50 μ M) led to a 4-fold decrease in the survival rate of conidia of both species, and in combination with a mixture of two coumarins (12.5 mg / L) - 4-fold for *A. nidulans* and 3 times for *C. acutatum*. Isopimpinelline (50 μ M) reduced survival *A. nidulans* in 4 times, but less than 2 times *C. acutatum*. Washing conidia to remove unbound photosensitizers before exposure to light significantly reduced photodynamic inactivation *C. acutatum* as with 8-MOP, and with a mixture of two coumarins, in the case of *A. nidulans* did not significantly decrease observed [17].

Anti-inflammatory activity

Experimental research in vitro and in vivo showed that bergapten (5-methoxypsoralen) has anti-inflammatory properties. The mechanism of action of bergapten has been studied in a lipopolysaccharide (LPS) -stimulated inflammatory response model. According to the results of the experiment, it was found that bergapten inhibits LPS-stimulated production of TNF- α , IL-1 β , IL-6, PGE2 and NO, as well as the expression of iNOS and COX-2 enzymes, and at the same time increases LPS-induced release of IL-10 in a dose-dependent manner in the RAW264.7 cell line [18, 19]. Bergapten also suppresses the activation of the JAK / STAT signaling pathway, but does not affect the activity of MAPKs and NF- κ B. In addition, bergapten, as an antioxidant, prevents the accumulation of reactive oxygen species, which also provides an anti-inflammatory effect. Research in vivo have shown that bergapten reduces the mortality of mice caused by the introduction of LPS [18, 19].

Currently, furocoumarins are being investigated for other types of activity, including as potential therapeutic agents for osteoporosis [20],

cystic fibrosis [7] and herpes infection [21].

2. Parsnip (*Pastinaca sativa* L.) as a promising source furocoumarins

Characteristics of the producing plant

Plants of the genus *Pasternak* (*Pastinaca*) belong to the umbrella family - Umbelliferae or celery - Apiaceae, to the order Umbelliferous - Apiales, to the Rosida subclass - Rosidae in the Dicotyledonous class - Magnoliopsida (Dicotyledones) of the Angiosperms division - Magnoliophyta (Angiospermae) [22].

This genus of plants includes 15 species: *Pastinaca argyrophylla* (Delip., 1990), *P. armena* (Fisch. & CAMEy., 1838), *P. aurantiaca* ((Albov) Kolak., 1948), *P. austriaca* (Calest., 1905), *P. clausii* (Calest., 1905), *P. glandulosa* (Boiss. & Hausskn., 1872), *P. hirsuta* (Pančić, 1874), *P. latifolia* (DC., 1830), *P. lucida* L., 1767, *P. pimpinellifolia* (M.Bieb., 1798), *P. sativa* (L., 1753), *P. trysia* (Stapf & Wettst., 1886), *P. yildizii* (Dirmenci, 2008), *P. zozimoides* (Fenzl, 1860) and two subspecies *P. sativa* L.: *P. sylvestris* (Mill., 1768), *P. umbrosa* (Steven ex DC., 1830) [23].

On the territory of the Russian Federation, the plant is widespread in its European part, in Western Siberia and in the North Caucasus. In the wild, it is found in Europe, in the Altai Territory and in the south of the Urals, in the Caucasus, in Turkey, North America. Of the wild species, the most common wild parsnip (*Pastinaca sylvestris* Mill.), Biennial fusiform, grows as a weed, it can be seen in grassy areas, meadows, glades, along roads [24]. Cultivated plant of the Sowing parsnip species (*Pastinaca sativa* L.) obtained by selection from the widespread wild parsnip. The cultivated form of the plant is cultivated in small areas as a food and medicinal plant practically all over the world [25].

The first mention of parsnips dates back to the 1st century BC. During archaeological excavations of the villages of the Neolithic era, the seeds of this plant were found. The ancient Roman scientists Dioscorides and Pliny mentioned the healing properties of the plant in their treatises. Dioscorides used parsnips as a diuretic [25].

This plant was cultivated by the Quechua Indians. The plant's root vegetable, valuable with biologically active substances, was used as an aphrodisiac, analgesic, stimulating metabolic processes, and expectorant [25].

As a cultivated vegetable and fodder plant, parsnip became known from the end of the 12th century, and before the appearance of potatoes it had an important nutritional value in Europe. And only from the 17th century parsnips, known as "field borscht", began to be actively cultivated in Russia on private plots and vegetable gardens as a valuable agricultural crop, rich in vitamins and minerals [25].

Other Russian names or synonyms for parsnips are meadow parsnip, spindle root, white carrot, field wrestler, lamb carrot, goat, deer grass, parsnip, posternak, reindeer feed [26].

Sowing parsnip (*Pastinaca sativa* L.) is a biennial herb with a fleshy, succulent root. The stem is erect, angularly grooved,

pubescent, up to 1.5–2 m in height. Parsnip leaves are pinnately dissected, long-petiolized, shiny from above, but from below they are covered with soft, thick hairs, the lobes of the leaf blade have sharp teeth and deep cuts. Leaves secrete essential oils in hot weather. Parsnip bloom begins in July and lasts until September. The flowers are bisexual, regular, small, yellow in color, collected in complex umbrellas, which have 8-12 rays. The calyx is five-toothed, with a lower two-celled ovary, five petals, and five stamens. The fruits (seeds) of parsnips ripen in early autumn. Flat-squeezed - crocodiles, round-elliptical in shape, usually splitting into two semi-fruits - mericarp. The mericarps from the dorsum are weakly convex, with three filiform and two marginal pterygoid ribs. In the hollows between the ribs, there are four dark brown secretory canals; there are two such canals on the ventral side. Fruit length - 4–8 mm, width - 3–6 mm. Color from greenish straw to dark brown. The smell is pleasant, peculiar. The taste is spicy, slightly pungent [27].

In the first year of life, forms a rosette of leaves, as well as a fusiform or conical, fleshy root vegetable, white with a yellowish-cream shade of color. The mass of a cone-shaped root crop reaches 300 grams, and its length is 300 mm (Student variety). Flowering occurs in the second year [28].

Parsnips are propagated by sowing seeds. Seedlings can withstand frosts down to - 5 ° C. The plant is practically not damaged by diseases and pests, and is also unpretentious in cultivation. The most common varieties of parsnip are the following [23]:

The white stork is a mid-season fruitful variety. Root crops are conical, white, smooth, with white and juicy pulp weighing up to 100 g. They are leveled and well stored in winter.

Guernsey is a late-ripening variety. Root crops of a conical shape, up to 25 cm, weighing up to 200 g. White pulp, sweet, aromatic, good taste.

Gladiator is a mid-season fruitful variety. Root crops are conical, smooth, with white skin. The pulp is white, fragrant, sugary.

Delicacy is a mid-early variety. Root crops are round, up to 8 cm, weighing 200–350 g. White pulp with yellowish spots. The taste is good, with a strong aroma.

Round - the earliest and most productive variety with a growing season 105-110 days. The root crop is rounded-flattened, sharply tapering towards the base, 10–15 cm long, up to 10 cm in diameter, weighing up to 150 g. The outer color of the root crops is grayish-white, the flesh is white, dense, has a very sharp aroma, mediocre taste.

The culinary specialist is a medium-early variety. The period from full germination to the beginning technical ripeness 80-85 days. The rosette of leaves is erect. The root crop is conical-conical in shape, rounded-flattened at the base, white, the surface is uneven, the head is medium. The root crop is completely submerged in the soil. Root weight 130-160 g.

Best of all - mid-season parsnip with growing season 115-120 days. Root vegetable weighing up to 200 g, conical, with an extended top and

running down, 15–20 cm long. The outer color and the color of the pulp is white, has a good aroma. The variety has a high yield and easily adapts to various growing conditions.

Petrik is a mid-season variety with a growing season up to 125-130 days. The variety is very productive. Root crops are conical, up to 30 cm long.

The heart is a mid-season fruitful variety. Root crops are conical, whitecreamy, smooth, weighing up to 100 g, with white flesh, well stored in winter.

Student is a late-ripening variety with a growing season 150-160 days. Root vegetable weighing up to 300 g and up to 30 cm long with a gradual downward slope. The surface of the root crop is white, the pulp is clean, dense, white, fragrant. The variety has a high yield.

The agricultural technology for growing parsnips is in many ways similar to the agricultural technology for growing carrots or parsley. Sowing is often single-line with row spacing of 30-50 cm, seeds are laid to a depth of 1.5-2 cm, and on light soils - up to 3.5 cm. You can also use tape sowing with a distance between the belts of 50 cm, and between the lines - 25 cm After sowing, the soil must be rolled or slammed so that the seedlings are friendly. Seedlings are thinned out in the phase of 2-3 true leaves, leaving 5 cm between plants. The next thinning is carried out already at 5–7 leaves, leaving a distance of 10–15 cm between plants. Moreover, young root crops can be used for food [23].

Crop care consists in weeding, loosening, watering as needed; as a rule, frequent watering of parsnips is not required. As for fertilizing the soil, it is better to apply them in liquid form. Usually, equal amounts of ammonium nitrate, superphosphate and potassium salt are used and 1 g of the mixture is dissolved in 1 liter of water. Complex fertilizers can also be used in the same doses. On small areas, 5-10 g of ammonium nitrate and 10-15 g of superphosphate and potassium salt per 1 m²... Fertilization is usually done after thinning, combined with loosening [23].

Parsnips are harvested in late autumn before the onset of frost. Root vegetables are stored like other spicy root crops of the celery family in a cellar, vegetable store, cellars, refrigerators at a temperature of 1-3 ° C. To avoid wilting, it is better to store them in perforated film bags or dug in the sand. Root crops are perfectly stored until spring. You can simply leave them to winter in the soil, digging them up for consumption in early spring. At the same time, the leaves are cut off and the roots are slightly spud for the winter. For control, you can lightly cover the parsnip with straw or pine needles where the winters are cold. In the Northwest, it winters well [23].

Seed production of parsnips in areas with mild winters is carried out, leaving root crops to winter in the soil. For this method, parsnips are sown with row spacing of 70 cm. In the same place where winters are harsh, seed roots are harvested in autumn. Select the root vegetables typical of the variety and cut the leaves so as not to damage the growing point. In the spring, they are planted with row spacing of 70 cm.

Since parsnips are a cross-plant, the spatial isolation between different cultivars should be at least 2 km. Caring for the testes includes weeding, disease and pest control. The seeds are harvested when

the umbrellas will turn brown. Usually, the most mature umbrellas are selectively cut first. The seeds ripen in August [23].

The chemical composition of parsnip

Scientists Barral and Korevinderr determined from 17 to 20% of dry matter in fresh parsnip roots. According to the study, dry matter contains nitrogen compounds up to 8%, fats up to 1.8%, starch and extractives up to 65%, sugar up to 11.6%, fiber about 9% and total ash up to 5% [29].

The root of parsnip is rich in protein compounds, fresh parsnip roots contain about 0.378% of protein substances, while in other root crops it is only from 0.161 to 0.24 9%. And also fresh root vegetables contain pectins (about 7%), pantothenic and niacin acids, riboflavin, carotene, thiamine, ascorbic acid, vitamins PP, B2, minerals (calcium, potassium, phosphorus, magnesium, zinc, etc.) [29].

Parsnips (*Fructus Pastinacae sativae*) contain essential oil. The content of essential oil in different areas of growth ranges from 1.1 to 3.6%. The essential oil contains heptyl, hexyl and octyl butyl esters of butyric acid. In addition, flavonoid glycosides (hyperin, rutin, pasternazide) were found in fruits [27, 28].

Thirteen furanocoumarins (up to 2.6%) were identified in parsnip fruits. The content of different furocoumarin components varies in different parsnip varieties. The main ones are bergapten, pimpinellin, methoxalen, isopimpinellin, xanthotoxin, spondin, imperorin and fellopterin. Biangelikol, heraclenin, isobergapten, biacangelicin, heraclenol, psoralen and isobiachangelicin were also isolated using semi-preparative high performance liquid chromatography. The latter compound is a new compound found in a member of the Apiaceae family. Sfondin in all varieties is contained in insignificant amounts, mainly xanthotoxin and bergapten predominate [29, 30].

Parsnips contain up to 10% fatty oil. Unstable acetylene compounds (polyins) were isolated from unripe fruits. Macronutrients (mg / g) are also found in fruits: K - 18.70; Ca - 10.20; Mg - 3.00; Fe - 0.10 and trace elements (PPM): Mn - 0.12; Cu 0.66; Zn 0.58; Cr 0.10; Al - 0.01; V - 0.01; Se 27.50; Ni - 0.56; Sr - 0.13, etc. [8, 12].

Parsnip herb contains essential oil, vitamin C, carotene, riboflavin, thiamine, folic acid, furocoumarins [27, 28].

Due to the high nutritional value and rich variety of biologically active components in its composition, the parsnip plant is used in many areas of the national economy [25; 26; 28; 29]:

In cooking. Parsnips are popular in cooking and confectionery, where all parts of the plant (fruit, root, grass) are applied. The roots of the plant have a spicy, sweetish taste and faint aroma. Parsnips are eaten fresh, fried, stewed and dried. Fresh and dried, powdered parsnip root is added to first courses, salads, sauces.

Parsnip

used as a seasoning for meat and fish dishes. Fruits (seeds) are added to marinades and pickles. Fresh parsnip leaves give the salads a pungent spicy flavor. Parsnips are often found in canned vegetables and mixtures for soups in dry and frozen form [27, 28].

In agriculture. Sowing parsnips are grown as feed for animals, in particular for cows, since such a product improves the quality of milk, as well as for fattening oxen and pigs and even horses, which, as you know, are rarely given root crops with the exception of carrots. Sowing parsnips can survive in the field in winter, despite the freezing of the soil, and quickly drive out strong foliage in the spring, used as a green forage. The same plant during flowering is an excellent honey plant. Parsnip honey is light and of high quality [27, 28].

In cosmetology. Due to the rich mineral complex and the presence in the composition of the plant ascorbic acid, parsnips are widely used in cosmetology. The essential oil of the plant is used for cellulite, eliminates acne and other skin inflammations, helps smooth fine wrinkles, and has antioxidant properties. Masks based on parsnip root have a whitening effect and well nourish the skin [27, 28].

In folk medicine. In folk medicine, roots, seeds (fruits) are used and parsnip leaves. An aqueous infusion and decoction of parsnip roots, the properties of which are of medicinal value for the body, are drunk as an expectorant to separate phlegm in bronchitis, pleurisy, pneumonia and tuberculosis, used as an antispasmodic for pain of various origins, gastric, renal and hepatic colic, gout ... Grated fresh root vegetable also relieves pain attacks, is used for cholelithiasis. In medieval Europe, it was believed that "he arouses love if he is generously received" (Odo iz Mena). Parsnips are used for diseases of the liver, spleen, and back pain. The root of the plant is used as a diuretic for urolithiasis and dropsy. Infusion of parsnip root has a calming effect, strengthens the walls of capillaries, relieves spasms of blood vessels. Parsnip is used for muscle cramps, neuroses, angina pectoris, hypertension, insomnia. The plant is taken as a tonic, immunomodulatory agent. Alcohol tincture of the herb and roots of the plant helps to get rid of hallucinations and bad moods. In folk cosmetology, a decoction of parsnip root or juice of a raw root vegetable helps with baldness, activates the growth of hair follicles. Decoction of seeds (fruits) smears lichen stains, treat vitiligo.

In official medicine. Parsnip is a pharmacopoeial plant of Belarus. In India, parsnip root is used in homeopathy. In Russia, the fruits of the sowing parsnip (*Fructus Pastinacae sativae*) are used as photosensitizing, antispasmodic agent [27, 28].

In accordance with domestic regulatory documents, the following quality indicators are monitored in fruits: moisture content - no more than 10%, content of the sum of furocoumarins - no less than 1%, total ash content - no more than 6%, organic impurity content - no more than 2%, content

mineral impurity - no more than 1% [35]. Parsnip fruits are used to obtain medicines Beroxan and Pastinacin [29, 31, 32].

Beroxan is a sum of furocoumarins (xanthotoxin and bergapten) obtained from the fruits of parsnip (*Pastinaca sativa* L.). It is a photosensitizing drug. Beroxan is indicated for the treatment of vitiligo, psoriasis, and nested hair loss (alopecia areata) [29].

Pastinacin is the sum of furocoumarins obtained from the fruit of the parsnip (*Pastinaca sativa* L.) grade "Student". It is an antispasmodic drug. Pastinacin is used for coronary-cardiosclerosis, coronary neuroses, for spasms of coronary vessels, bronchi, biliary and urinary tract [29].

Procurement of raw materials

For food and prophylactic purposes, parsnip root and stems with leaves are used, and for medicinal purposes - its fruits. For food purposes, only parsnips are harvested, wild-growing parsnips are toxic, they are not used for culinary purposes. A high-quality root crop should be white (the whiter, the sweeter it is), firm (softness is a sign of the beginning of the decay process), without cracks, damage and dark spots [23].

Parsnips are harvested in late autumn, with precautions: in hot weather, the essential oil released from the leaves can provoke burns on the skin. Root crops are not washed, but cleaned from the ground. The cut off top will extend the shelf life of the parsnips. Parsnips are stored by sprinkling with wet sand in a dark, cool room. For drying, the roots are cut into strips (about 3 mm thick), then dried in a hot air dryer at a temperature of no more than 50 ° C, stirring occasionally. The resulting raw materials are stored in closed glass jars or in plastic bags under vacuum [23].

Parsnips reach harvest maturity when the umbrellas turn from bright green to brown. Ripening of fruits and browning of umbrellas in the inflorescence does not occur simultaneously. Overripe fruits crumble easily, so harvesting is carried out in 2 steps. First, the first brown umbrellas are cut off (about 50%), and after 1.5–2 weeks, when all the remaining umbrellas are brown, the plants are mowed entirely and tied into sheaves. The collected inflorescences are dried and threshed. Threshed fruits are ground to free them from other parts of the inflorescences, winnowed and sorted. The average yield of parsnips is 10 c / ha. The fruits are stored in dry rooms in bags. Fruits remain viable for 2-3 years [23].

Features of collection, drying and storage of raw materials containing coumarins
The procurement of raw materials containing coumarins is carried out in compliance with certain safety rules. Coumarins have the ability to increase the sensitivity of the skin to UV rays. In sunny weather, even

light contact with plants containing coumarins can cause burns. Therefore, in order to comply with safety regulations, the collection of raw materials is carried out in dry, but not sunny weather, using mittens [23].

CONCLUSION

Thus, having a chemical composition rich in furocoumarins, and having a secure raw material base, parsnip can be considered a promising source of furocoumarins - biologically active compounds exhibiting a wide range of pharmacological activity. Carrying out in-depth studies of the chemical composition of parsnips and methods for obtaining both individual compounds and extractive preparations from it is relevant and will expand the range of herbal medicines.

CONCLUSIONS:

1. Furanocoumarins - coumarin derivatives, characteristic mainly for representatives of the families celery (Apiaceae) and rue (Rutaceae). Currently, they are widely used for PUVA therapy for skin diseases.

2. In recent years, numerous studies of furanocoumarins have been carried out. as potential drugs with anti-inflammatory, antimicrobial, photosensitizing, antitumor and other types of activity.

3. A promising source of furocoumarins is parsnip. (*Pastinaca sativa* L.). This plant is widespread in the flora of Russia, and is also cultivated. The rich chemical composition of parsnip fruits allows us to consider them as a potential source of new medicines.

LITERATURE

1. Furanocoumarins: biomolecules of therapeutic interest, studies in natural products / Antonio Del Río, Licinio Díaz, David García-Bernal, Miguel Blanquer, Ana Ortuño, Enrique Correal, José María Moraleda // Chemistry. - 2014. - Vol. 43. - P. 145-195.
2. Anticonvulsant effects of four linear furanocoumarins, bergapten, imperatorin, oxypeucedanin, and xanthotoxin, in the mouse maximal electroshock-induced seizure model: a comparative study / Jarogniew J. Łuszczki, Marta Andres-Mach, Michał Glensk, Krystyna Skalicka-Woźniak // Pharmacological Reports. - 2010. - Vol. 62. - P.1231-1236.
3. Melougha M. Melissa. Dietary furocoumarins and skin cancer: A review of current biological evidence / Melissa M. Melougha, Ock K. Chun // Food and Chemical Toxicology. - 2018. - Vol. 122. - P.163-171.
4. Evaluation of furanocoumarins from seeds of the wild parsnip (*Pastinaca sativa* L. sl) / Jorens Kviesis Igors Kļimenkovs Lauris Arbidans Anton Podjava Māris Kļaviņš Edvards Liepiņš // Journal of Chromatography B. - 2019. - Vol. 1105. - P.54-66.
5. Synthesis of 1H-1,2,3-triazole linked aryl (arylamidomethyl) - dihydrofurocoumarin hybrids and analysis of their cytotoxicity / AV Lipeeva, MA Pokrovsky, DS Baev, MM Shakirov, IY Bagryanskaya, TG Tolstikova, AG

Pokrovsky, EE Shults // *Eur. J. Med. Chem.* - 2015. - Vol.100. - P.119-128).

6. Lipeeva AV Synthetic transformations of peucedanin: dissertation. ... Ph.D. - Novosibirsk, 2011. -- 167 p.

7. Development of a novel furocoumarin derivative inhibiting NF- κ B dependent biological functions: Design, synthesis and biological effects / Monica Borgatti, Adriana Chilin, Laura Piccagli, Ilaria Lampronti, Nicoletta Bianchi, Irene Mancini, Giovanni Marzaro, Francesco dall'Acqua, Adriano Guiotto, Roberto Gambari // *European Journal of Medicinal Chemistry.* - 2011. - Vol. 46. - P.4870-4877.

8. Melougha M. Melissa. Furocoumarins: A review of biochemical activities, dietary sources and intake, and potential health risks / Melissa M. Melougha, Eunyoung Chob, Ock K. Chuna // *Food and Chemical Toxicology* - 2018. - Vol. 113. - P.99-107.

9. Breast cancer cell survival signal is affected by bergapten combined with an ultraviolet irradiation / Maria Luisa Panno, Francesca Giordano, Fabrizia Mastroianni, M. Grazia Palma, Viviana Bartella, Amalia Carpino, Saveria Aquila, Sebastiano Andò // *FEBS Letters.* - 2010. - Vol. 584. - P.2321-2326.

10. Bergapten inhibits liver carcinogenesis by modulating LXR / PI3K / Akt and IDOL / LDLR pathways / Shakti Prasad Pattanayaka, Pritha Bosea, Priyashree Sunitab, Mohd Usman Mohd Siddiquec, Antonio Lapenna // *Biomedicine & Pharmacotherapy.* - 2018. - Vol. 108. - P. 297-308.

11. Effects of imperatorin on nicotine-induced anxiety- and memory-related responses and oxidative stress in mice / Barbara Budzynska, Anna Boguszezewska-Czubarac, Marta Kruk-Slomka, Krystyna Skalicka-Wozniak, Agnieszka Michalak, Irena Musik, Grazyna Biala, Kazimierz Glowinski // *Physiology & Behavior.* - 2013. - Volume 122. - P.46-55.

12. A comprehensive review on synthesis and designing aspects of coumarin Derivatives as monoamine oxidase inhibitors for depression and Alzheimer's disease / Pravin O. Patil, Sanjay B. Bari, Sandip D. Firke, Prashant K. Deshmukh, Shailesh T.Donda, Dilip A. Patil // *Bioorganic & Medicinal Chemistry.* - 2013. - Volume 21. - P.2434-2450.

13. Implication of coumarins towards central nervous system disorders / Krystyna Skalicka-Woźniaka Ilkay, Erdogan Orhanb Geoffrey A., Cordellcd Seyed, Mohammad Nabavie, Barbara Budzyńska // *Pharmacological Research.* - 2016. - Vol. 103. - P. 188-203.

14. Multifunctional coumarin derivatives: Monoamine oxidase B (MAO-B) inhibition, anti- β -amyloid ($A\beta$) aggregation and metal chelation properties against Alzheimer's disease / Ming Huang Sai-Sai Xie Neng Jiang Jin-Shuai Lan Ling-Yi Kong Xiao-Bing Wang // *Bioorganic & Medicinal Chemistry Letters.* - 2015. - Vol. 25. - P. 508-513.

15. Modulation of the UVB-induced lethality by furocoumarins in *Staphylococcus aureus* / Emanuelle BF Silva, Ideltônio F. Barbosa, Humberto M. Barreto, José P. Siqueira-Júnior // *Journal of Photochemistry and Photobiology B: Biology.* - 2014. - Vol. 130. - P.260-263.

16. Modulation of the antibiotic activity against multidrug resistant strains of coumarins isolated from Rutaceae species / Sara AL Madeiro, Nathalie HPB Borges, Augusto L. Souto, Pedro TR de Figueiredo, Jose P. Siqueira-Junior, Josean F. Tavares // *Microbial Pathogenesis* - 2017. - Vol. 104. - P. 151-154.

17. Furocoumarins and coumarins photoinactivate *Colletotrichum acutatum* and

Aspergillus nidulans fungi under solar radiation / Henrique D.de Menezes, Ana Pereira, Guilherme TP Brancini, Helton Carlosde Leão, Nelson S. Massola Júnior, Luciano Bachmanne, Mark Wainwright, Jairo Kenupp Bastos, Gilberto UL Braga // Journal of Photochemistry and Photobiology B: Biology. - 2014. - Vol. 131. - P.74-83.

18. Anti-inflammatory and proresolution activities of bergapten isolated from the roots of *Ficus hirta* in an in vivo zebrafish model / Yi Yanga, Kangdi Zheng, Wenjie Mei, Yandong Wang, Chuqin Yua, Bangwei Yud, Shanbin Denga, Jinhua Hu // Biochemical and Biophysical Research Communications. - 2018. - Vol. 496. - P.763-769.

19. Bergapten prevents lipopolysaccharide-induced inflammation in RAW264.7 cells through suppressing JAK / STAT activation and ROS production and increases the survival rate of mice after LPS challenge / Yi Zhoua Jing Wanga Weidong Yanga Xiaowen Qia Lei Lana Lan Luob Zhimin Yin // International Immunopharmacology. - 2017. - Vol. 48. - P. 159-168.

20. Bergapten suppresses RANKL-induced osteoclastogenesis and ovariectomy-induced osteoporosis via suppression of NF- κ B and JNK signaling pathways / Guiping Chena, Qiang Xua, Min Daia, Xuqiang Liu // Biochemical and Biophysical Research Communications. - 2019. - Vol. 509. - P.329-334.

21. Antiviral effect of compounds derived from *Angelica archangelica* L. on Herpes simplex virus-1 and Coxsackie virus B3 infections / Barbara Rajtar, Krystyna Skalicka-Woźniak, Łukasz Świątek, Agnieszka Steca, Anastazja Boguszewska, Małgorzata Polz-Dacewicz // Food and Chemical Toxicology. - 2017. - Vol. 109. - P.1026-103.

22. All about medicinal plants in your beds / ed. Radelova S. Yu. - SPb: "SZKEO", 2010. - P.183. - 224 p.

23. Atlas of medicinal plants of Russia / ed. Professor Bykov V.A. - M.: VILAR, 2006. -- S. 345.

24. Atlas of the main species of weeds in Russia / V. N. Sheptukhov, R. M. Gafurov, T. V. Papaskiri [et al.] - M.: Kolos S, 2009. - 192 p.

25. Biologically active substances of plant origin // The Russian Academy of Sciences. - M.: Nauka, 2001. -- S.337.

26. Gizatulin A. N. Medicinal Plants in Scientific and Traditional Medicine / Gizatulin A.N., Gizatulina F.T. - Troitsk, 1999. - pp. 117-119.

27. *Pastinaca sativa* L. (*P. sylvestris* Mill.) - Sowing parsnip / I. A. Gubanov [and others] // Illustrated guide to plants of Central Russia. In 3 volumes - M.: I-nauch. ed. KMK, Institute of technologist. issl., 2003. - T. 2. Angiosperms (dicotyledonous: dicotyledonous). - S. 639.

28. Meadow parsnip (common parsnip) - *Pastinaca sativa* L. / V.N. Sheptukhov, R. M. Gafurov, T. V. Papaskiri [and others] // Atlas of the main species of weeds in Russia. - M.: Kolos, 2009. -- S. 125. - 192 p.

29. Medicinal products from plants (VILAR experience): scientific publication / S.A. Vichkanova, V.K. Kolkhir, T.A. Sokolskaya [and others]. - M.: Adris, 2009. -- 432 p.

30. Cosman V.M. Information support for the identification of phenolic compounds of plant origin. Coumarins and furocoumarins / Kosman V.M., Zenkevich I.G., Komisarenko N.F. // Plant resources. - 1997. - T. 39. - Issue. 3. - pp. 32-37.

31. State Register of Medicines [Electronic resource]. -

Access mode: <http://grls.rosminzdraV.ru/>.

32. Copyright certificate. 226099 USSR. Method of obtaining beroxan / Maksyutina N.P., Kolesnikov D.G., Zaichenko V.M. - publ. 1968. - No. 28. - P. 64.

33. Inhibition of rat brain monoamine oxidase activities by psoralen and isopsoralen: implications for the treatment of affective disorders / LD Kong, RX Tan, AY Woo, CH Cheng // Pharmacol Toxicol. - 2001. - Vol. 88 (2). - P.75-80.

34. Monoamine oxidase inhibitory coumarins from the aerial parts of *Dictamnus albus* / Seon Hwa Jeong Xiang Hua Han Seong Su Hongji Sang Hwangji Hye Hwang Dongho Lee Myung Koo Leejai Seup Ro Bang Yeon Hwang // Archives of Pharmacal Research. - 2006. - Vol. 29. -- P.1119.

35. FS 42-2548-88 Fruit of sowing parsnip.

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Furocoumarins as potential sources of new drugs / P.V. Krutov, E.V. Ferubko, T. D. Dargaeva, K.A. Pupykina, R.R. Shakirova // Traditional Medicine. - 2019. - No. 2 (57). - S.45-54.

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