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PURPOSE SEARCH FOR BIOLOGICALLY ACTIVE COMPOUNDS AND MANUFACTURE ON THEIR BASIS OF MEDICINAL SUBSTANCES

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ЦЕЛЕВОЙ ПОИСК БИОЛОГИЧЕСКИ АКТИВНЫХ СОЕДИНЕНИЙ И ПРОИЗВОДСТВО НА ИХ ОСНОВЕ ЛЕКАРСТВЕННЫХ ВЕЩЕСТВ

Summary. Nowadays there are quite high production rates in synthetic organic chemistry. However, biologically active compounds are extremely important in the creation of new pharmacologically effective drugs. New biologically active compounds are needed to create medications aimed at combating infectious, fungal and oncological diseases. These drugs should not only have anti-infective efficacy, but also act differently, without involving healthy cells of the body. The search for new sources for the creation of new medicinal substances is an urgent problem not only in medicine but also in agronomy in the fight against plant diseases. The personal interest of researchers is attracted by plant extracts. The analysis of literature sources shows that most plant extracts have antimicrobial, wound healing and anti-inflammatory effects. However, the technology of obtaining herbal medicines is quite complex and long.

Promising sources of drugs are extracts of fungi. Technologies for obtaining fungal extracts are simple and can also be used to create pharmacological substances. World and domestic experiments in marine pharmacy indicate the enormous potential of marine aquatic organisms as biologically active compounds. They can help to create new pharmaceutical substances and medicinal substances.

Аннотация. В настоящее время синтетическая органическая химия имеет достаточно высокие темпы производства. Однако биологически активные соединения чрезвычайно важны для создания новых фармакологически эффективных лекарств. Новые биологически активные соединения необходимы для создания лекарств, направленных на борьбу с инфекционными, грибковыми и онкологическими заболеваниями. Эти препараты должны не только обладать противоинфекционным действием, но и действовать иначе, не затрагивая здоровые клетки организма. Поиск новых источников для создания новых лекарственных веществ - актуальная проблема не только медицины, но и агрономии в борьбе с болезнями растений. Личный интерес исследователей вызывают экстракты растений. Анализ литературных источников показывает, что большинство экстрактов растений обладают антимикробным, ранозаживляющим и противовоспалительным действием. Однако технология получения лечебных трав достаточно сложна и долгая.

Перспективными источниками лекарств являются экстракты грибов. Технологии получения экстрактов грибов просты и также могут использоваться для создания фармакологических веществ. Мировые и отечественные эксперименты в морской фармации указывают на огромный потенциал морских водных организмов как биологически активных соединений. Они могут помочь в создании новых фармацевтических субстанций и лекарственных субстанций.

Key words: biologically active compounds, medicinal substances, pharmaceutical industry, plant derivatives, aquatic organisms.

Ключевые слова: биологически активные соединения, лекарственные вещества, фармацевтическая промышленность, производные растений, водные организмы.

Relevance. The modern domestic pharmaceutical market is estimated at 12-15 billion dollars per year. It is 1.7-2.1% of the world economy. So, the problem of importing medicines has become very acute. The variaty of medicines produced by domestic pharmaceutical companies is extremely low-quality if we compere them to modern highly effective drugs.

The state policy in the field of medicine and pharmacy is insufficiently effective. This situation has led to the fact that the basis of the pharmaceutical industry - the production of pharmaceutical substances of drugs - in the domestic market has declined. So, the country produced 272 types of pharmaceutical substances with a volume of 17.5 thousand conventional tons in 1992. And this provided the needs for the production of finished synthetic drugs by 70 %, antibiotics - by 85 %, vitamins - by 90 % and immunobiological drugs – 100 %. Most domestic substances were also exported.

Their total production has decreased threefold fot the last 15 years. In physical terms – in 18 times, including: substances for synthetic drugs - 12 times, for antibiotics - 100 times and for vitamins - 500 times. From year to year there was a reduction in capacity in this industry: the average daily production capacity for the production of pharmaceutical substances.

As a result, production capacity decreased by almost 6 times. The average level of usage of nominal capacity is approximately 17.5 %, including 18.3 % for synthetic drugs, 9.6 % for antibiotics and 4.6 % for vitamins [1].

Problem statement and its connection with important scientific issues. Today there are quite high production rates in synthetic organic chemistry. However, biologically active compounds are extremely important in the creation of new pharmacologically effective drugs. This problem is explained by a number of factors: high growth rates of antibiotic-resistant strains of microorganisms, which requires a rapid and effective solution in medicine. First of all, new biologically active compounds are needed to create drugs aimed at combating infectious, fungal and oncological diseases. These drugs should not only have anti-infective efficacy, but also act differently, without involving healthy cells of the body.

The aim of the study: to analyze and direct the search for the most common, geographically and economically available biologically active compounds of plant origin and aquatic organisms. Biologically active compounds can be used in the pharmaceutical industry during the creation of medicinal substances. New mididcines can be based on them.

The analysis of previous research and publications. Such prominent domestic scientists as Karomatov I.D., Konopleva M.M., Golovko A.M., Pinsky O.V., Chala I. V., Harutyunyan A.P., Shatalov S.V. and many other dealt with the issues of focused search of new biologically active compounds for the purpose of creating pharmacologically effective and safe therapeutic dosage forms.

Nowadays, the country's pharmaceutical industry produces about 3,000 types of drugs, most of which are obsolete generics.

That is why the country has a task of creating a high-tech pharmaceutical industrial complex that will meet the world level. Efforts need to be focused on resuming the production of pharmaceutical substances, developing new technologies, ensuring the production of competitive medicines in accordance with international standards and the ability to replace imported products. The identified problems are posed to the medical and biological scientific spheres. It is about the development of new medical technologies, pharmaceutical substances and drugs.

This applies to affordable domestic drugs. They are needed to treat primarily socially significant diseases - cardiovascular, pulmonary, oncological, endocrine, allergic, psychoneurologica and viral ones. The developers of new pharmaceutical substances and drug manufacturers should focus their attention in this direction.

The main part. It is known that the usage of biologically active compounds of plant origin in medicine has a number of advantages over synthetic drugs. However, the search for new sources of plant origin is an urgent problem not only in medicine but also in agronomy in the fight against plant diseases. The personal interest of researchers is attracted by plant extracts.

In general, an analysis of the literature was made. The usage of plant extracts for creation medicines as well as other prospects of their usage was under study. One of the reasons for this interest is the availability of the necessary literature and the ease of obtaining the extract.

A large number of scientists have developed and tested a dosage form based on the extract of *burdock leaf* (Arctium lappa L.), which has antimicrobial, anti-inflammatory and deodorizing effects [2].

Shomkina O.A. has created the composition and technology of gel and cream with antimicrobial and anti-inflammatory action. It was created on the basis of the results of physicochemical, structural, mechanical and microbiological studies about eucalyptus and eucalyptus leaf extract [3, 4]. A gel dosage form for the usage in dentistry was developed on the basis of compositions of plant origin, which contain the juices of *nettle* (Urtica dioica L.) and saps of plants of the genus Kalanchoe (Kalanchoe Adans.) [5].

An emulsion ointment has been developed on the basis of the extract of Astragalus falcatus Lam. It can be used to treat simple purulent wounds in the second and third recovery phases, stimulating reparative processes, as well as to treat various lesions in dermatological diseases [6]. However, some researchers create not only ointment forms on the basis of plant research, but also tablets and granules. Thus, there was a composition and technology for the manufacture of tablets with a sedative effect on the basis of dry extract from the leaves of Elaeagnus angustifolia L. [7].

A composition and technology for obtaining granules with anti-inflammatory and antipyretic action have been developed on the basis of the extract of

licorice root and paracetamol [8].

There was developed a technology for making a gel for the treatment of some viral infections on the basis of hyporamine, purified extract of sea buckthorn leaves (Hippophae rhamnoides L.) [9].

Nikitina N.V. proposed a dermatological ointment on the basis of a two-phase extract of black poplar buds, which has antimicrobial, wound-healing and anti-inflammatory action. It is experimentally confirmed in animal experiments [10].

The creation of new dosage forms of plant origin expands the possibilities of their usage. So, thick extract obtained and standardized on the basis of the leaves of Corylus avellana L. The developed suppositories can be used in proctology and urology [11]. The technology of obtaining a spray based on the extract of sage (Salvia officinalis L.) is used in dentistry [12].

Available work concerning the integrated usage of biologically active compounds. So, a dry extract of linden (Tilia cordata L.), enriched with a complex of biologically active substances (BAS) (flavonoids and coumarins) and suppositories were created on its basis. Linden extract has anti-inflammatory, analgesic and antihypoxic effects. It is a promising substance for use in pharmacy [13]. The composition and technology of granules and tablets of the drug "Glesol" have been developed. “Glesol” is recommended for the treatment of respiratory diseases of inflammatory nature. The active ingredients of "Glasol" are some phytomedications [14].

The osmotic activity of the ointment based on the extract of thick oak bark was studied. The ointment is recommended for the treatment of the second phase of the wound process, which has moderate osmotic properties, which creates favorable conditions for faster wound healing. [15].

The analysis of literature sources shows that most plant extracts have antimicrobial, wound healing and anti-inflammatory effects. However, the technology of obtaining herbal medicines is quite complex and long. Promising sources of medicines producing are extracts of fungi. Technologies for obtaining fungal extracts are simple and can also be used to create pharmacological substances.

Drugs based on keratinase secreted by Pénicillium citrinum are being developed. The enzyme has a high activity against various keratin substrates and extremely low against collagen, which makes it possible to use it to obtain dosage forms of selective action [16].

The possibility of using the antitumor and antiviral enzyme L-lysine-a-oxidase as a strain of the fungus Trichoderma harzianum Rifai has been proved. Mushroom extract, as it is shown below, can be used as an agronomic inhibitor of a number of dangerous viral and bacterial diseases of plants: Tobacco Ringpot virus, necrotic balsamic spot, as well as pathogens of bacterial burns of fruit crops Erwinia amylovora (Burril) Winslow et al [17-21]. The multifunctional possibilities of fungal extracts are still insufficiently studied and it is necessary to conduct wider general studies of strained fungi in order to use them not only in the medicinal environment.

World and domestic experience of marine pharmacy shows the huge potential of marine aquatic organisms as raw materials for the creation of original pharmaceutical substances and drugs [22]. In contrast to species, the phylogenetic (macrotaxonomic) diversity of the sea is much higher: of the 33 types of multicellular animals, 31 types are found in the sea, 17 types - in fresh water and only 11 types - on land [23].

Due to the adaptation to various environmental factors of a number of marine animals and plants, there is a serious ability to produce unique secondary metabolites, many of which have extremely high pharmacological activity [24, 25, 26]. Sources of new new pharmacological compounds of marine origin can be representatives of royal bacteria (Eubacteria), cyanobacteria (Cyanobacteria) and protists (Protista), as well as several typical substanses: Porifera, Bryozoa, Mollusca, echinodermata and Tunicata subtype.

According to some researchers, sea sponges are more fertile sources of new antitumor, antiviral and anti-inflammatory drugs compared to a group of terrestrial organisms [27].

According to various authors, marine aquatic organisms produce from 10,000 to 18,000 chemical compounds, many of which have pharmacological activity. Among them are both simple linear peptides and complex macrocyclic polyesters, such as galichondrin B [28]. Biologically active substances (BAS) of marine origin can be used as pharmaceutical substances and intended as starting compounds for the preparation of drugs with new or improved pharmacological characteristics. Below is a short list of BAS isolated from marine organisms that have pharmacological activity [24].

Bacteria

Penicillin was discovered in 1929. Since then about 50,000 compounds have been isolated from microorganisms, of which more than 10,000 have biological activity and more than 100 are used as antibiotics, antitumor agents and agrochemicals. Marine organisms of the bacterial kingdom here look much more modest due to the difficulty of cultivation. However, they are able to synthesize BAR without occurring on terrestrial objects. This is especially true for deep-sea and hyperthermophilic microorganisms. Gram-positive bacteria from donor pellets have been shown to produce abnormal macrolactics by inhibiting melanoma cell proliferation in rodents [29].

Actinomycetes is filamentous gram-positive bacteria that belong to the type of Actinobacteria, produce a huge number of BAS. Antitumor activity on various cell lines has been proven in more than 70 compounds belonging to different structural classes: polypeptides, indolocarbozoles, isoprenoids, macrolides, non-ribosomal proteins and others.

Their main products are taxa Streptomyces, Actinomycètes, Actinomadura, Actinobacterium, Salinispora, Micromonospora, Saccharopolyspora and others. In vitro, almost all of these substances are used in micromolar and nanomolar concentrations. These

compounds have antitumor activity due to the induction of apoptosis, mastered by inhibition of topoisomerase and DNA fragmentation, as well as impaired permeability of mitochondrial membranes [30]. In addition, compounds obtained from marine bacteria have great potential in the treatment of infectious diseases [31].

Cyanobacteria and Protists

Blue and green algae (Cyanophyta) and dinoflagellates (Pyrrophyta) are of interest as sources of B vitamins and vitamin E, as well as carotenoids and phycobiliproteins. Representatives of strains belonging to the genera Synechocystis and Synechococus produce compounds that have antifungal and antibacterial activity [32]. Substances extracted from Lyngbya lagerhaimanii and Phormidium tenue show anti-HIV activity.

Cytonimin with anti-inflammatory and antiproliferative properties was found in cyanobacteria Stigonems spp. Goniodomin-A, a polyester macrolide with antifungal activity, isolated from dinoflagellates of Goniodoma pseudogoniaulax. Curacin-A, a thiazoline-containing compound derived from Lyngbya majusculata, has a strong antiproliferative effect by blocking tubulin polymerization and is selective for breast, intestinal and prostate cancer cells.

Peptide compounds such as venturamide A from cyanobacteria Oscillatoria sp., Dragomabin from Lyngbya majuscula, dragonamide B and halminamide A from Schizjthrix have antimalarial activity [33]. Marine diatomaceous extracts belonging to the genera Melosira, Amphora, Phaeodactylum and Nitzschia induce apoptosis and necrosis of rat IPS-81 myelogenous cells and also show some signs of antithrombotic effect [34].

Marine macroalgae with their huge biomass are of a great importance as sources of BAS. Polysaccharides of red and brown algae (carrageenans, fucoidans, alginates) and their derivatives have a wide pharmacological activity and can form the basis for new drugs with antitumor, antiulcer, immunostimulatory and sorption action [35].

Halogenated monoterpene halomon isolated from the green alga (Portieria hornemannii) was opened for preliminary testing due to its high toxicity to brain, intestinal and prostate tumor cells. A number of steroid compounds from the green alga (Codium iyengarii) showed antibacterial activity and sterols from brown algae of the genus Sargassum showed antifungal activity [29]. Traditionally, seaweed is considered a source of iodine and omega-3 polyunsaturated fatty acids [36].

Sea sponges are the richest source of pharmacologically biologically active compounds among marine organizations. More than 5,300 different substances come from the sponges or their associations with microorganisms and each year this list is more than 200 names. 75% of patents on the antitumor activity of natural compounds are patents for spongy compounds.

Sponges form an independent type corresponding to the Parazoa subdivision and consist of low-organized multicellular cells with high differentiation. They have a tendency to develop tissues, without changing organs and definitive tissues. The type has about 5,000 species, many of which form symbioses with bacteria, fungi, cyanobacteria and microalgae. Sea sponge composition can provide a potential cure for most known diseases.

More than 100 antitumor substances were isolated from sponges, their synthetic analogues during in vitro production studies on various tumor cell lines. Spongothymidine and spongouridine from the sponge Tethya cripta became a prototype for the synthesis of antiviral drugs. Discodermolid is a polyhydroxylated lactone isolated from the deep-water sponge Discodermia sp. It has undergone clinical trials as an antitumor agent.

Antifungal activity was found in two sexviterpenoids - curcuphenol and curcudiol - isolated from Didiscus oxeata. Antimicrobial and antimycobacterial activity was found in alkaloids from the sponges Pachichalina sp. Manzamine A (with antimalarial, anti-TB and anti-HIV activity) and psammaplin A (with antibacterial activity) are in preclinical studies.

Dozens of other compounds are being tested for antibacterial, antifungal, antiviral and antiseptic activity [37]. The sesquiterpenoid mananoid from Luffariella variabilis is one of the most powerful natural inhibitors of phospholipase A2, has strong analgesic and anti-inflammatory activity and is recognized as a treatment for psoriasis [38].

More than 60 secondary metabolites of marine origin provide antimalarial activity. Axisonitrile-1, isolated from sponges Axinella cannabina, became “the ancestor” of industrial isonitrile-containing drugs and their analogues. Isonitrile- and isothiocyanate-containing sesquiterpenoids were obtained from other sponges belonging to the family Axinellidae and Halicondridae.

Moss

The most well-known moss compound is briostatin-1 - a representative of macrocyclic lactones (polyketides). This lactone isolated from Bugula neretina inhibits proteinase C and is considered a promising compound for complex (in combination with taxol or cisplatin) chemotherapy for leukemia, breast, ovarian and lung cancer. Bryostatin-1 selectively kills cancer cells without compromising normal healthy tissues. Unlike most cytostatics, which have a hemotoxic effect, it stimulates erythropoiesis and undergoes the final phases of clinical trials [39]. Alkaloids from Cribricellina cribreria and Flustra foliacea show antimicrobial, antibacterial and antiviral activity [29].

Sea fish and snakes

Representatives of these groups of animals are sources of a small number of secondary metabolites.

Fish fats enriched with Omega-3 polyunsaturated fatty acids, which form the basis of dietary supplements for food and drugs intended for the treatment and prevention of cardiovascular diseases, skin diseases, arthritis and malignant neoplasms.

Other components of marine fats, in particular alkylglycerols and fatty acid ethanolamides (N-acylethanolamines), are also noteworthy. The first ones are glycerolipids with an alkyl bond. They are found in animal products, but sea fish and dairy products are the most enriched with them. Alkylglycerols can be used in cases of live metabolism disorders and as immunomodulators [40].

Conclusions and suggestions

Development of biomedical research for the purpose of focused search and creation of new effective medicines on the basis of biologically active compounds should become one of priority directions of activity of domestic academic science. First of all, this will ensure a significant reproduction of the domestic pharmacology, pharmacy and pharmaceutical industry.

According to various estimates, from 40 to 70 % of new drugs are created from natural compounds or their synthetic analogues. Drugs with fundamentally new pharmacological properties can be developed on the basis of natural compounds. This will provide greater therapeutic activity or qualitatively new pharmacological effects. In this regard, representatives of terrestrial and marine flora and fauna are of a great interest.

It should be emphasized that the development of new drugs should combine the efforts of researchers in various fields, such as bioorganic chemistry, biotechnology, experimental pharmacology, pharmaceutical technology, clinical pharmacology. These scientific spheres, as well as basic subjects - botany, zoology, structural chemistry and other sections of physicochemical biology - in one or another form are presented in the departments of higher education institutions and state research institutions.

However, the current situation does not meet the objectives. It is necessary to create new specialized pharmacological and biopharmaceutical well-equipped labs. It is very important to study modern publications and support the scientists who are united by the task of creating new drugs.

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АМБИВАЛЕНТНОСТЬ РЕЛИГИОЗНЫХ ВЗГЛЯДОВ ВИКТОРА ФРАНКЛА

Аннотация. Статья посвящена религиозным взглядам В. Франкла. Выделены эпизоды биографии В. Франкла, определившие его построение своих и, по его мнению, в будущем универсальных религиозных взглядов. На примере его браков рассмотрено соблюдение им религиозных традиций и сделан вывод об