Biologically active substances of sea cucumbers and experience of their use in medicine. Overview

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SUMMARY

The article provides data on the chemical composition of marine echinoderms - sea cucumbers. Revealed a high content in these animals of biologically active substances capable of exerting a physiological effect on the human body (iodine compounds, B vitamins, ascorbic acid, etc.). The most significant compounds that make up sea cucumbers - triterpene glycosides, as well as their biological effects are considered. A description of well-known biologically active additives and medicinal preparations based on triterpene glycosides of sea cucumbers is given.

Key words: sea cucumbers, trepang, biologically active substances,triterpene glycosides, biologically active additives.

RESUME

This article studies the chemical composition of the sea cucumbers. In these animals a high content of substances, which have physiological effects on the human body (iodine compounds, B vitamins, ascorbic acid, etc.) was found. The most significant compounds of holothurias are triterpene glycosides. Their biological effects are examined. A description of known biologically active additives and drugs made with holoturian triterpene glycosides is given.

Keywords: holothuria, trepang, biologically active substances, triterpene glycosides, biologically active additives.

Holothurians are marine animals belonging to the Echinoderm type (lat.Echinodermata). They have a wide distribution area: they live in almost all seas, with the exception of the Baltic and Caspian. Holothurians are most often found in the Pacific region, in particular in the Sea of Japan and the Sea of Okhotsk. Holothurians can live both in shallow waters and in deep-sea depressions. The main refuge for them are coral reefs, as well as rocky soils overgrown with vegetation. The class of sea cucumbers is represented by 1150 species, divided into 6 orders. The commercial species used for food are united under the general name “trepang” [1, 2].

The first mentions of the use of trepang come from China and date back to 220-280 years. AD In ancient China, trepang (sea cucumber) was compared to a pearl, a great Gift of Nature, due to its beneficial properties [1]. The sea cucumber harvest was a traditional fishery in China [2].

Far Eastern sea cucumber is considered one of the most expensive gourmet products. Since ancient times, it has been mined in the seas of the Far East: trepang was actively mined in Russian waters in the 19th century. Until the 90s of the XIX century, the export of trepang to China, Korea and Japan reached 2000 poods (about 33 thousand kg) per year [3].

Holothoriaatra is one of the representatives of the sea cucumber class. In 2012, Akram Tehranifard and MR Rahimibashar (Department of Marine Biology, Islamic Azad University Lahijan, Iran) developed guidelines for the identification of holothurians of this species [4]. The sea cucumbers Holothoriaatra are black or dark brown in color, their body length is 90–500 mm, weight is 50–500 g. The body of the sea cucumbers of this species is oblong, widened in the middle, and pointed at the ends; the mouth opening is located on the ventral side of the body, surrounded by a fringe of 20 tentacles; the anus is located at the other end of the body. The integument of the body is formed by tiled scales; the body is slimy and rough to the touch. There are skin outgrowths, mainly located on the abdominal side of the body, skin outgrowths have papillae [4].

This species is omnivorous. Sea cucumbers feed mainly on plankton and organic remains, which are extracted from bottom silt and sand, passing it through the alimentary canal [4].

Spicules (mineral elements of the skeleton) are of great functional importance in the body of sea cucumbers. These formations support the body walls of animals, take part in the processes of digestion and nutrition, and also participate in protection from enemies. For a long time, no studies have been carried out to obtain quantitative data on the content of spicules in the tissues of sea cucumbers. However, in 1980 V.S. Levin investigated the relative development of the tentacles of sea cucumbers and the general content of spicules in them. The study showed that the number of spicules contained in the tissues of sea cucumbers varies significantly depending on the species. Thus, in the Holothoriaatra species, the relative mass of spicules of the skin of the body relative to the mass of the musculocutaneous sac is 10.0 ± 0.5% [5].

Since ancient times, holothurians have attracted people's interest due to the possibility of their use in food and in folk medicine. At the present time, these organisms also continue to be a valuable object of the fishery, as they are of great interest for pharmacology. In the last decade, sea cucumbers have become increasingly popular among researchers due to the emergence of new data on their chemical composition and physiological activity of biologically active ingredients isolated from these invertebrates [6].

The purpose of this work is to study the scientific literature on the chemical composition of sea cucumbers, the biological activity of the substances they contain and their use in medicine and pharmacology, to collect and analyze theoretical data, and to determine the level of development of the problem in the scientific literature.

MATERIALS AND METHODS

The main method in writing this article was to conduct a documentary analysis of scientific articles, research papers and patent documentation on the chemical composition of sea cucumbers, their use in medicine, pharmacology and other activities.

The study area covered articles and works of Russian and foreign authors published in journals specializing in marine biology and scientific discoveries: "Biology of the Sea", "Scientific Works of Dalrybvtuz", "Izvestia TINRO", Journal of Basic and Applied Sciences, etc.

To describe the results of research in the field of studying the chemical composition of sea cucumbers and methods of their application, the latest scientific works were taken up to 2018.At the same time, the works published since 1952 served as a basis for the historical review and general characteristics.

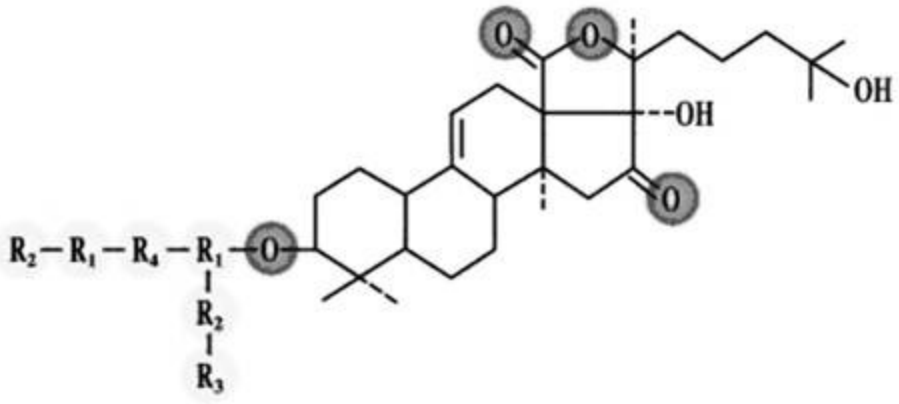
RESULTS AND DISCUSSION

Marine hydrobionts, in particular sea cucumbers, are a promising source of raw materials for the manufacture of dietary supplements. In the work of A.D. Pepper has a high content of copper and iron compounds in trepang meat. Trepang also contains 100 times more iodine compounds than other invertebrates [7]. B vitamins (B12, thiamine, riboflavin) and ascorbic acid were found in the meat of these echinoderms. The proteins contained in trepang meat are high in the following amino acids: glycine, proline and aspartic acid. In total, there are about 17 amino acids, of which about a third are indispensable [7].

According to research by N.B. Ayushina et al. (Pacific Research Fisheries Center), the amount of glycine, proline, aspartic and glutamic acids in the trepang tissues is 54–56% of the total amino acid content, which determines the positive physiological effect of production from sea cucumbers [8].

The active component of biologically active carbohydrate complexes that make up the trepang meat are hexose amino sugars: galactosamine and glucosamine [9].

Of greatest interest are the triterpene glycosides contained in sea cucumbers, which have a wide spectrum of pharmacotherapeutic action. It is believed that it is due to the presence of triterpene glycosides that sea cucumbers have high biological activity. The content of these substances, which are not typical for other groups of animals, makes holothurians unique: they are the only representatives of the animal kingdom that produce triterpene glycosides. These compounds are contained in almost all organs and tissues of sea cucumbers, and in the pre-spawning period, their content significantly increases in the gonads of females [10].



Rice. 1. Triterpene glycosides of sea cucumbers. General structure of triterpene glycosides
using holothurin B as an example: R1 = D-xylose, R2 = D-glucose, R3 = 3.0. methyl-D-glucose, R4 = D-quinovoz [14]

Before triterpene glycosides were found in sea cucumbers, compounds of this class were considered exclusively metabolites of higher terrestrial plants (for example, ginseng) [11]. For the first time, information on the content of plant-like triterpene glycosides in the tissues of sea cucumbers appeared in the 1950s – 1960s. [12].

By their chemical nature, triterpene glycosides are compounds containing a polycyclic alcohol as an aglycone and an oligosaccharide fragment (carbohydrate chain) attached to it. This is common in the structure of the glycosides of sea cucumbers and ginseng. However, in holothurian glycosides, aglycone is based on the so-called holostan carbon skeleton, which is characteristic only of these echinoderms. This is the main difference between the triterpene glycosides of ginseng and sea cucumbers [13].

A wide range of physiological activity of triterpene glycosides in sea cucumbers opens up great prospects for their practical use as drugs and biologically active food additives [15]. According to various studies, triterpene glycosides of sea cucumbers have the following types of action [16, 17]:

- hemolytic, cytotoxic, cytostatic, antitumor, antifungal, immunomodulatory;

- antihyperlipidemic and hypocholesterolemic;
- antimicrobial, antiparasitic, antiviral against a wide range of bacteria and viruses;
- selective effect on the cardiovascular system [16, 17]. The published research results confirm the following mechanisms and types of action of triterpene glycosides in sea cucumbers:

1. The hemolytic activity of triterpene glycosides is due to their the ability to interact with erythrocytes, as a result of which the cell membrane becomes permeable to hemoglobin [12].

2. The hypocholesterolemic action consists in the influence of triterpene

glycosides on the exchange of cholesterol in the body: in the gastrointestinal tract of animals, glycosides bind cholesterol, as a result of which its concentration in the blood decreases [12].

3. Due to the presence of triterpene glycosides, sea cucumber hydrolysates have antiradical activity (the ability to bind free radicals). The antiradical properties of products of technological and biotechnological modification of sea cucumbers can be used as components in fat and oil emulsion products to reduce the rate of lipid oxidation [18].

4. The total amount of glycosides in sea cucumbers includes such substances as cardonalids. Under the influence of these substances, the muscle membrane of the blood vessels relaxes, which causes their expansion and a decrease in blood pressure. There is also an increase in the strength of heart contractions, and the duration of diastole increases, which has a positive effect on the elasticity and permeability of blood vessels [16].

5. Pronounced antifungal (antifungal) activity
triterpene glycosides. It manifests itself in a wide range of concentrations from 1 to 100 μg / ml. The most potent glycosides have a 100% inhibitory effect at concentrations of 1–20 μg / ml. Plant triterpene glycosides of plant origin have antifungal effect at much higher concentrations [15]. From this, it can be concluded that it is advisable to use sea cucumbers as a raw material for the production of triterpene glycosides.

The mechanism of antifungal actions triterpene glycosides consists in their interaction with sterols of cell membranes of fungi, which causes leakage of ions, amino acids from the cell, disruption of cellular metabolism and leads to the death of the fungal cell [7].

6. A number of studies confirm the antitumor effect of triterpene glycosides. For the first time this property of compounds contained in sea cucumbers was discovered by Nigelli in 1952. In the course of his research, it was proved that the introduction of a fraction containing triterpene glycosides isolated from sea cucumbers into sarcoma 180 (Crocker) suppressed tumor growth in mice [19]. Later it was found that triterpene glycosides inhibit the growth of epidermal carcinoma cells [20]. Studies by Mieke Hemiawati Satari (Universitas Padjadjaran Indonesia) have shown that the extract from sea cucumbers precisely due to the presence of triterpene glycosides in it has a cytotoxic effect on SP-C1 cancer cells (tongue cancer cells) [21]. Thus, sea cucumbers can be considered a potential source of raw materials for the manufacture of medicines in oncology.

7. In the work of scientists of the Pacific Institute of Bioorganic Chemistry the perspective of using triterpene glycosides of marine invertebrates, in particular sea cucumbers, in the development of therapeutic and prophylactic anti-infectious drugs is considered. The study notes that the glycoside cucumarioside A2-2 is able to increase nonspecific resistance to bacterial and viral infections, and the A1 holotoxin has

stimulating effect on the development of the immune response to corpuscular antigens [22].

Taking into account the described numerous biological effects of the compounds that make up sea cucumbers, it can be concluded that the use of these marine echinoderms is promising as a potential raw material for the manufacture of drugs and biological products for the treatment and prevention of a wide range of diseases.

At present, sea cucumbers are widely used in cooking: they are eaten raw in Japan (after removing the entrails, they are cut into slices and seasoned with sauce), and in addition to the skin-muscle sac, the intestines and gonads of sea cucumbers, which are more expensive, are also used for food. Preserves and canned foods from these invertebrates are presented on the market. According to Chinese recipes, sea cucumbers can be cooked with pork or lamb. Due to the presence in the composition of sea cucumbers of macro- and micronutrients necessary for the normal functioning of the human body, sea cucumbers are considered a valuable food product [6].

Another area of application of sea cucumbers is the production of soft drinks based on them. These drinks have a tonic effect and can act as an alternative replacement for energy drinks. The technology consists in clarifying the cooking water of the trepang using chitosan from the shell of the Kamchatka crab. The final product is a transparent pinkish liquid containing a large amount of triterpene glycosides and with a taste of red caviar [23].

Various biologically active food additives (hereinafter referred to as "dietary supplements") based on sea cucumbers have become very popular recently. There are different technologies for obtaining such dietary supplements:

1. Obtaining dietary supplements from sea cucumbers using ultrasonic treatment. This method provides grinding of components, activation of chemical processes, an increase in the reactivity of substances and acceleration of dissolution processes [24].

2. Biomodification of trepang wastes by enzymatic preparations of proteolytic and glycolytic action, which leads to an increase in the content of selenium and glycosides in them, followed by the use of cooking water of biomodified waste to obtain a biologically active food supplement [25].

3. Technology of obtaining a biologically active additive based on a mixture trepang and honey using xanthan gum to give the product an optimal structure. This method contributes to the long-term stabilization of products and the lengthening of their shelf life [26].

The most famous dietary supplements based on sea cucumbers at the moment are the following:

1. "Akmar" - freeze-dried powder from cooking water for culinary processing cucumaria or trepang. Patent No. 2236155 - Method for complex processing of sea cucumbers, biologically active additive "Akmar", feed biologically active additive. Biologically active components that make up this dietary supplement are triterpene glycosides

holothurian (not less than 2.0 mg / cap.) and selenium (not less than 2.7 mg / cap.) The effect is to increase physical activity, normalize sleep [12]. In the course of research it was also found that "Akmar" has antioxidant activity, has an adaptogenic effect. The product is recommended to be used as a means of increasing the efficiency of the body and providing a stimulating effect under stress [27].

2. "Thingol-1" is a hydrolyzate of cucumaria muscle tissue Japanese, the active components of which are triterpene glycosides - 250 μg / ml, B vitamins, hexosamines, sugars, proteins, macro- and microelements (Fe, Mn, Co, Zn, etc.) [28]. The effect of this dietary supplement is to increase the overall tone and performance in healthy people. In patients, "Thingol-1" normalizes the ratio of T- and B-lymphocytes, stops dysproteinization [12].

3. "Tingol-2" - alcoholic extract of the guts of Japanese cucumaria, containing triterpene glycosides - 650 μg / ml [28]. Has a stimulating effect under stress and when exposed to radiation, increases physical activity [12]. The use of "Thingol-2" prevents involution of the thymus, and also protects against degenerative changes in the myocardium [29].

4. "Trepang on honey." RF patent No. 2636158 - a method for preparing trepang on honey.

This dietary supplement is obtained by crushing the muscle tissue of the sea cucumber and mixing it with honey. The product also contains ascorbic acid and xanthan gum. In terms of the amount of triterpene glycosides, this drug is superior to other known dietary supplements from sea cucumbers, while the recommended dosages remain within the permissible level [26].

On the basis of sea cucumbers, not only dietary supplements for food are being developed, but also medicines. In particular, as a result of the research work of scientists from the Pacific Institute of Bioorganic Chemistry (TIBOC), Far Eastern Branch of the Russian Academy of Sciences, a new immunomodulatory drug was created in the laboratory of the chemistry of marine natural compounds, which was named Kumazid. The technology for producing Kumazid was patented in 2004 (Patent RU 2 271 820 C). This drug is created on the basis of the triterpene glycoside of cucumarioside A2-2 and is a complex of a glycoside with cholesterol. The study of the specific activity of Kumazid showed that the drug in small doses stimulates phagocytosis of bacteria and enhances the bactericidal ability of human leukocytes, has a significant effect on humoral immunity,

CONCLUSIONS

1. Holothurians - marine echinoderms, which are a valuable object fishing due to their great pharmacotherapeutic value.

2. Due to the presence in the composition of sea cucumbers of numerous biologically active substances, they are a promising potential raw material for the manufacture of new drugs.

3. The greatest medico-pharmaceutical interest is triterpene glycosides with various biological activities.

4. The carried out information and analytical research allowed to establish that triterpene glycosides have antifungal, hemolytic, antitumor and many other types of activity.

5. To date, several dietary supplements have been registered. made on the basis of sea cucumbers. Their action is mainly aimed at increasing physical activity and performance.

6. Further research and use of holothurians in medical pharmaceutical practice is appropriate.

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