Perspective natural sources of chondroprotectors

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Abstract. The research objects in the work were natural sources of chondroprotectors. The research purpose was to study perspective natural sources of substances with chondroprotective properties. Such natural chondroprotectors as nutraceutical products made from green tea are studied in the work. Turmeric and ginger have been used since ancient times to treat osteoarthrosis. It has been established that collagen is a part of combined chondroprotectors. The mass fraction of structural protein in various tissues and organs of a living organism varies to a large extent. In pig skin the mass fraction of structural protein reaches 64%, in human skin the content of collagen is 8% higher, in cattle skin 80%, in marine mammals more than 80%; a significant amount of collagen is found in the skin of fish. In the connective tissue of whale fat, up to 88% of collagen is contained, in whale fins up to 83%. The percentage of collagen-containing raw fish is as follows: skin up to 12.6% (of the total weight of the fish); fins up to 8%, air bladder up to 11.4%, scales to 6%, bones up to 19%, sturgeon chord up to 10.2%. Glucosamine, extracted from mollusk shells, chondroitin from shark and bovine cartilage, and collagen hydrolysates are widely used since they are the main components of cartilage matrix. The novelty of this work lies in the systematization of scientific data on perspective natural sources of substances with chondroprotective and combined properties.

1. Introduction

As is known, the complex therapy of certain pain syndromes uses chondroprotective drugs (slow-acting substances with symptom-modifying and structure-modifying effect). The prescription of this group of drugs is necessary, first of all, in cases of large joints diseases. By the symptom-modifying effect is meant the reduction of pain and improvement of joint’s function, by structure-modifying - a decrease in the progression of osteoarthrosis[1–5].

The articular cartilage consists of cells (chondrocytes) embedded in the matrix of fiber collagen within a concentrated aqueous proteoglycan gel. The integrity of this matrix determines the biomechanical properties of articular cartilage. Proteoglycans are large macro molecules consisting of a protein core, to which multiple chains and glycosaminoglycans and ligosaccharides are attached. Chondroitin sulfat (hereinafter – ChS) is an important class of glycosaminolikans necessary for the formation of proteoglycans of the articular cartilage. The primary biological role of glucosamine is directly determined by its ability to stimulate the biosynthesis of glycoses of aminoglycans and
hyaluronic acid, which are necessary for the formation of proteoglycans found in the structural matrix of joint. ChS provides an additional substrate for the formation of a healthy articular matrix [6, 7].

The mechanism of action of chondroprotectors is associated with the stimulation of chondrocytes, with a decrease in the activity of lisosomal enzymes (metalloproteinases), with a rise in resistance and chondrocytosis in the presence of inflammatory cytokines, activation of anabolic processes in the matrix and creating the prerequisites for the formation of sustainable cartilage [8, 9].

2. Materials and methods

The main materials are the following types of chondroprotectors:

1. Preparations based on chondroitin sulfate.
2. Preparations from bone and cartilage tissue of calves and marine organisms.
3. Means containing mucopolysaccharides.
4. Preparations based on glucosamine.
5. Means with combined composition. Glucosamine and chondroitin are included in the complex.
6. Chondroprotectors containing non-steroidal anti-inflammatory components.

Glucosamine (G) - glucosamine sulfate or glucosamine hydrochloride, is a natural aminomonosaccharide. Its source is chitin, extracted from crustacean shells. Glucosamine is synthesized in the body as glucosamine-6-phosphate.

In the joints and intervertebral disks, it is included in the structure of the molecules of glycosaminoglycans, heparan sulfate, keratan sulfate, and hyaluronan. Glucosamine is necessary for the synthesis of glycolipids, glycoproteins, glycosides of aminoglycans (mucopolysaccharides), hyaluronate and proteoglycans [10–12].

3. Results and discussion

Many researchers have described the sources of chondroprotectors [13]. For example, nutraceutical products made from green tea include green tea powder and concentrated extract obtained from green tea. In India and China, turmeric and ginger have been used since ancient times for the treatment of osteoarthritis (hereinafter – OA), in particular, for the treatment of pain in OA [14, 15]. Similarly, mussels have been used for centuries with the same purpose in New Zealand [16]. In recent years, other dietary supplements, such as fish oil, vitamins, and minerals, have also been used to treat OA with the expectation of relieving pain.

Glucosamine, extracted from mollusk shells, hondroitin from shark and bovine cartilage, and collagen hydrolysates, also known as gelatin, from animal by-products such as bone and connective tissue, have been widely used, since they are the main components of the cartilage matrix. In recent years, many nutraceuticals have been evaluated by clinical trials, and their effectiveness in alleviating pain has been demonstrated. Although the clinical evidence for their efficacy against pain is not very significant, the new efforts are aimed at identifying new nutraceuticals or a thorough assessment of the therapeutic effects of known nutraceuticals.

Although the specific mechanism underlying the influence of these nutraceuticals on pain during OA is not known to a significant degree, more and more data indicate that it can be at least partly due to their anti-inflammatory action [17].

Unsaponifiable substances from avocado and soybean (hereinafter - ASU) showed chondroprotective, anabolic, and anticatabolic properties in clinical trials in addition to an effective pain reduction in clinical trials in humans. ASU is the remaining (approximately 1%) fraction of the extracts of avocado and soybean oils that cannot be turned into soap during saponification [18]. There are several ASU statements. The most widely used composition is one third of avocado and two thirds of unsaponifiable soybeans. Although the active component is not known, it is believed that the content of steroids in ASU is behind most of its biological activity in articular chondrocytes [19]. In a 3-month clinical study, daily intake of high and low doses of ASU significantly reduced pain [20]. Piaskledin at a dose of 300 mg, consisting of 100 mg avocado and 200 mg soybean oil taken daily for 6 months, was as effective as chondroitin sulfate, with a 50% reduction in pain. Two months of observation after
treatment showed that the effect of transfer is negligible [21]. A six-month large-scale observational study in Poland showed a significant improvement in the performance of patients taking ASU daily [22]. It is interesting that, in addition to pain, it was suggested that ASU exert a modifying effect on OA of hip; there was a decrease of 20% in patients who had joint loss in the ASU group versus placebo after 3 years [21].

Gum resin, obtained from trees of the genus Boswellia, better known as olibanum, was used to treat arthritis and inflammatory diseases in traditional medicines of many cultures. Boswellic acids have shown efficacy against inflammatory factors and subsequent chondroprotective and oxidative factors. As a result of cross-sectional clinical research, it was found that patients who took capsules of Boswellia serrata tree extract three times a day for 8 weeks showed a significant decrease in the knee pain, an increase in bending of the knee and an increase in walking, as well as the frequency of swelling, despite the absence of X-ray changes. High-performance liquid chromatography determined that the extract contained 40% Boswellia acid and 2% 3-O-acetyl-11-keto-beta-Bosella acid based on the main potentially active ingredient [12]. In another study, 5-loxin, enriched with the Boswellia serrata tree extract with 30% active capsaicins, was administered to patients in two doses, 100 mg/day and 250 mg/day. Both doses improved pain and physical functions and improved indicators of painful OA. The group with high doses experienced an improvement after 7 days already [13]. A burning sensation was registered in 67% of patients, but not a single one withdrew for this reason [18]. Cucapsaicin, a synthetic capsaicin cis-enantiomer, acts similarly to capsaicin, but with a higher tolerance [19]. At week 12 of the trial, 0.075% of cream of cucapsaicin significantly improved symptoms compared to those that received creams of 0.001%. Patients achieved an improvement in pain indicators and improved their overall assessment. The effect of capsaicin persisted when the study was extended for 52 weeks [20].

Ginger has a long history of use dating back 2,500 years to treat diseases such as nausea, arthritis, and vascular diseases. The spicy hot characteristic of the plant is caused by the content of non volatile oils, especially its acute phenol gingerol [23]. Tablets with ginger extract administered to patients for 6 weeks could reduce pain when standing, pain after walking, and stiffness indices [24]. The addition of ginger powder (for example, 1 g/day) can reduce the markers of inflammation in patients. After 3 months of the supplements intake and the concentration of nitric oxide (NO) and C-reactive protein in serum decreased.

Polyphenols are widely distributed in the plant world and contribute to a number of advantages for health. Polyphenols in tea and pomegranate have shown anti-inflammatory and antioxidant efficacy in vitro, and more recently, they have been shown to relieve pain in OA in human studies [25, 26]. The use of green tea counts thousands of years in China and Japan [27]. It is reported that its antioxidant activity is 25-100 times higher than that of vitamins C and E [28]. The main activity of green tea is attributed to its catechins, especially epigallocatechin-3-gallate. Clinically, daily consumption of 200 ml of juice without sugar and additives for 6 weeks improved the overall score of the index and osteoarthritis, as well as scores on the evaluation of physical function and stiffness in a patient with OA [29]. Polyphenols, tanning agents, and anthocyanidins in pomegranate juice are believed to have an antioxidant and anti-inflammatory effect and are therapeutically active ingredients [30]. Phenolic compounds called oligomeric proanthocyanidins or oligomeric procyanide (OPC) are recognized for the therapeutic ability of pine bark, patented and standardized as pycnogenol, grape seed extract, cinnamon, and also peel , seeds, and bark of other plant components. In particular, pycnogenol has been studied in several clinical trials for efficacy in pain in OA. 100 mg of pycnogenol in 3 months improved the condition of the patient.

The function of proteoglycans (hereinafter - GAGs) lies in their immense water-binding ability and organizing properties. The resistance of articular cartilage to deformation mainly correlated with the number of GAGs [31]. There are four major classes of GAG in the cartilage, including hyaluronan, cerican sulfate, dematan sulfate, and chondroitinsulfate (ChS). ChS composes more than 80% ChS in the articular cartilage and exhibits gel-like properties, such as lubrication, water retention, and resistance [32]. Chondroitin-4-sulfate and chondroitin-6-sulfate are two of the most common disaccharide isomers among ChS.
To date, there have been a few studies of ChS in patients with osteoarthritis. Proteoglycans were removed from the cartilage of a patient with OA, and it was reported that about 90% of the GAGs consist of an equal mixture of ChS and CS [33]. Sulfotransferases involved in the ChS sulfation are subdivided into 3 types.

Some of these enzymes cause pathological genetic diseases, for example, Ehlers-Danlos syndrome [32], Kashin-Beck disease [60]. These clinical and laboratory observations showed that deregulation of the sulfate group in ChS can cause abnormal ChS structures and impaired cartilage. As mentioned above, most of the existing studies of ChS and OA are limited to small groups of patients and did not take into account possible variations in the microanatomy of cartilage [33].

Chondroprotectors (symptomatic delayed-release drugs) are a group of drugs used for prevention and treatment of osteoarthritis and tendinopathies, as well as other diseases of the joint as part of complex therapy. The main active substances on the basis of which chondroprotectors are produced are collagen hydrolysate, chondroitin sulfate (ChS), and glucosamine (GA).

Chondroprotectors (hereinafter - ChP) - structural elements (glycosaminoglycans) of natural cartilage, necessary for the construction and renewal of articular cartilage, capable of modifying the course of the disease, inhibiting inflammation in the tissues of the joint, improving phosphorus – calcium metabolism [34]. The most acceptable drugs for BNS therapy, which have an effect on metabolic processes in the cartilaginous, synovial, and bone tissues, inhibiting the synthesis of inflammatory mediators, are chondroitin sulfate and glucosamine sulfate.

ChP can be prescribed in any stage of a degenerative disease of the joints. Corrections of metabolism of bone and cartilage tissue on the basis of chondroitin sulfate have a chondroprotective and chondrostomulating effect. ChS is a sulfated GAG consisting of repeating disaccharide units of D-glucuronic acid and N-acetyl-D-galactosamine [23].

It is established that collagen is a part of combined chondroprotectors [22].

It is known that in terrestrial and marine animals about one third of the total amount of nitrogenous substances accounts for a fraction of collagen compounds. The term “calla gene” comes from the Greek words “calla” - glue and “gene au” - born. This concept is associated with a widespread group of proteins found only in the animal world. Collagen fibers are formed from collagen.

It is known that in terrestrial and marine animals, collagen compounds make up about one third of the total amount of nitrogenous substances. The term “collagen” comes from the Greek words “colla” - glue and “gene” - born. This concept is associated with a widespread group of proteins found only in the animal world. Fibers of connective tissue are formed from collagen. The main features of collagen are its resistance to change under physiological conditions, chemical inertness, a special aminoacid composition, and the ability to dissolve and pass into gelatin or glue when heated in water. Collagen is always concentrated in the connective tissues of marine and terrestrial animals - in the skin, bones, grasslands, tendons, and in other parts and organs of animal organisms. The most important types of connective tissue are known: elastic tissue (tendons), tightly interwoven tissue (skin integument), cartilage tissue (trachea), bone tissue (dentine, bones), chord supporting tissues (intestines), reticular connective tissue (nerves, capillary) [35].

Collagen-containing raw material is mainly the connective tissue, which consists of cells, intercellular matter and collagen fibers, and in addition it contains a small amount of elastin and reticulin fibers, as well as passing nasal vessels. The connective tissue ensures the strength of the external and internal structures of the animal organism, is rich in valuable mineral substances, and contains mineral acids, physiologically active substances in a sufficient amount.

Collagen-containing raw material of the sperm whale’s head cavity is in contact with permacetate fat, which is used to treat burns, ulcers, skin diseases, and in the perfume industry. Such a unique combination of natural biologically active substances is quite rare.

The most common is the division of collagen-containing raw materials into two large groups: soft raw materials - skin, tendon; bone with raw materials – all types of bones.

According to the technological principles, the collagen-containing raw materials are separated into the raw, containing wool and bristles along with collagen; bare – almost pure collagen; sagged collagen.
For their intended purpose, collagen-containing raw materials are divided into those intended for the production of gelatin and glue, for the production of Belkozin sausage casings, for the production of special adhesives, for medicine, for the production of various protein products - flour, feed, fertilizers, hydrolyzates.

Depending on the source, the collagen is divided into fibrous collagen of skin dermis and tendons, hyaline collagen of bone tissue - ossein, chondrin collagen of cartilage, ichthyulin collagen of fish bubble – ichthyolica and collagen fish collagen - ichthylepilin.

The aminoacid composition of the collagen is characterized by the obligatory presence of oxyproline, which is a distinct connective tissue and, and the absence of tryptophan, which is a label of any muscle tissue. The amount of collagen in any body can be calculated from the amount of oxyproline. This is used in biochemistry for the recognition of collagen in various tissues and organs, in the food industry - for the detection of unacceptable waste in meat, in the gelatin industry - for controlling the purity of gelatin, in leather and fur production - for establishing waste.

The collagen content in the organs and tissues of any living organism is different: the greatest amount of collagen is concentrated in the bones, skins, cartilage, tendons and intestines. The collagen content in the skin of pigs and dogs is 64%, in the skin of humans – 72%, in the skin of cattle – 80%, in the skin of marine mammals – over 80%; a significant amount of collagen is found in the skin of fish; connective tissue of whales’ fat contains from 74 to 88% collagen, up to 83% in fins of whales and 89% in sperm whale organ tissues. The percentage of collagen-containing raw fish looks as follows: skin - 2 - 12.6% (of the total weight of fish); fins – 0.8 - 8%, air bladder – 0.4 – 11.4%, scales – 0.8 – 6%, bones – 9 – 19%, sturgeon chord – 7.6 – 10.2 %.

The mass composition of whale fins (saivals and finwals) is 1.7%, the bones are 30.2%, the sperm whale felts have a mass of about 2%, and the mass of collagen-containing raw materials of the sperm organ of the sperm whale is about 8% of carcass meat, which averages about 2.5 tons [36].

The most rational method of preserving collagen-containing raw materials is freezing.

4. Conclusion
From collagen-containing raw materials, a wide variety of food, medical, feed and technical products are obtained: glue, gelatin, shells, films, sponges, suture material, dentures, skin, furs, various feed products. Fish glue from air bubbles was widely used at the dawn of aerial construction, and special adhesives from fish skin were used in the production of picture tubes for color television sets. Collagen pore films and sponges from collagen-containing raw whales were successfully tested in the Burn Center of the Institute of Surgery named after A.V. Vishnevsky, whale leather was used to make shoes; shark and other fish skins were used to make various leather goods; skins of sea lions and other marine mammals were used to make valuable fur.

Resources of industrial collagen raw materials as terrestrial animals and hydrobionts are very large. However, the collagen-containing resources of terrestrial animals have been studied more thoroughly than the raw materials of aqueous hydrobionites [37].

Thus, in this work, perspective natural substances with chondroprotective and combined properties are studied.

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