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COLLAGEN: STRUCTURE, METABOLISM, PRODUCTION AND INDUSTRIAL APPLICATION

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This review presents the current scientific literature data about structure, properties, and functions of collagen, which is known as one of the most abundant human and animal proteins. The building of collagen molecule from the primary structure to submolecular formations, the main stages of its synthesis and biodegradation are briefly described. The information about collagen diversity, its features and metabolic ways in various tissues, including skin, tendons, bones, etc. is presented. The problems of pathologies caused by collagen synthesis and breakdown disorders as well as age-related changes in collagen properties and their causes are discussed.

A comparative analysis of the advantages and disadvantages of collagen and its derivatives obtaining from various sources (animals, marine, and recombinant) is given. The most productive methods for collagen extraction from various tissues are shown. The concept of collagen hydrolysis conditions influence on the physicochemical properties and biological activity of the obtained products is described.

The applications of collagen and its products in various fields of industrial activity, such as pharmaceutical, cosmetic industry and medicine, are discussed. Further prospective directions of fundamental and applied investigations in this area of research are outlined.

Key words: collagen types, collagen metabolism, sources of collagen production, collagen hydrolysis, application of collagen.

Collagen is an important structural protein component of intercellular substance of the connective tissue. It is the most abundant protein in mammals. Its relative content in all tissues is 25–35% of the total protein content in the body. Most collagen is found in fibrous connective tissues such as tendons, ligaments, bones and skin, where it is the main structural protein of the extracellular matrix. Exactly these tissues contain more than 80% of all collagen in the human body. 10% of collagen is found in the stroma of internal organs. In a significant amount, it is present in the endomysium of muscle tissue, especially in muscles with a great load during work (up to 6% of the muscle weight). Collagen is also found in blood vessels, intestines, intervertebral discs, dentin of teeth, cornea, placenta.

Collagen structure and types

Currently, about 30 types of collagen have been described [1], differing from each other in structure, although it should be noted that some of them are actually collagens, and the rest are proteins containing collagen-like domains. The number of types reflects the varied functionality of collagen. All types of collagens, depending on the structure, are divided into fibril-forming (the I, II, III, V, XI collagen types), associated with collagen fibrils (the IX, XII, XIV collagen types), reticular or non-fibrillar (the IV, VIII and X collagen types), microfibrils forming (the VI collagen type), anchored fibrils, etc. More than 90% of collagen in the human body is fibril-forming type I collagen [1]. Its molecule, as well as collagen molecules of the II, III, V, XI types, forms fibrils, the structural elements

of which are α-chains, which are left-handed spirals consisting of amino acids (three amino acid residues per turn). Helixes of α-chains are stabilized due to the force of pyrrolidine rings in proline and hydroxyproline residues spherical repulsion, and there are no hydrogen bonds in them (transcoiling). As a result of three α-chains combination with each other, which occurs due to the appearance of cross-hydrogen bonds between the oxygen of the carbonyl group and the hydrogen of the imino group of peptide bonds of neighboring chains, a tropocollagen molecule is formed, which has the form of a triple helix with a diameter of 1–1.5 nm and a length of up to 270 nm [2]. The main role in the tropocollagen molecule stabilization is played by the bonds that arise between the OH-groups of hydroxyproline of adjacent chains. Glycine, which does not have a side radical, ensures tight adhesion of the α-chains to each other at their intersections.

The tropocollagen triple helix is most often formed from three identical α1-chains or from two α1-chains and one α2-chain that differs from them in chemical composition, and sometimes — an α3-chain (in type V collagen) (Table). Collagens of all types necessarily contain at least one triple helix [3]. Some collagen fibrils are composed of 2 or more different types of collagen. For example, some tissues contain hybrid molecules formed by the V and XI types of collagen chains. Each α-chain consists of about 1000 amino acid residues. Of the amino acids, most of all in the collagen chains there are amino acid residues of glycine — 30%. If the α-chain of collagen is conditionally divided into amino acid sequences consisting of three amino acid residues, then all such conditional tripeptides will necessarily contain one glycine residue and any other two amino acids. Most often these are the residues of proline, 3- or 4-hydroxyproline (21%) [3].

Differences in the amino acid sequence of the collagen α-chains determine its belonging to one or another type [4]. So, the main type of the extracellular matrix collagen of most tissues (skin, bones, tendons, cornea) is type I collagen. It contains two type I α1-chains and one α2-chain, 33% consisting of glycine, 13% of proline, and 1% of hydroxylysine. It also contains a small amount of carbohydrates. Type II collagen, which is characteristic of cartilage, as well as non-cartilaginous tissues in the early stages of development, is formed from three type II α1 chains. A feature of this collagen type is the content of 5-hydroxylysine small amount (up to 1%) and a high content of carbohydrates (over 10%). Collagen of the type III, contained in the walls of blood vessels, and, therefore, in all organs and tissues, also consists of three α1-chains, but, accordingly, type III. This type of collagen is high in hydroxyproline. It also contains cysteine in its α-chains. Unlike previous types, type III collagen is weakly glycosylated. The type V collagen molecule, which is typical for soft tissues, placenta, vessels, chorion, consists of three different chains: α1-, α2- and α3-chains of type V (Fig. 1) [4].

In the extracellular environment, triple helices of tropocollagen are united by covalent

The most well-studied collagen types and the sets of α-chains in their molecule composition

Type	Molecule composition
I	$[\alpha1(I)]_3$ $[\alpha1(I)]_2\alpha2(I)$
II	$[\alpha1(II)]_3$
III	$[\alpha1(III)]_3$
IV	$[\alpha1(IV)]_2\alpha2(IV)$ α3(IV), α4(IV), α5(IV) α5(IV), α5(IV), α6(IV)
V	[α1(V)]2α2(V) α1(V), α2(V), $\alpha3(V)_3$ $[\alpha3(V)]_3$
VI and any of and	α1(VI), α2(VI) α3(VI), α4(VI), α5(VI) α6(VI)
VII	$[\alpha1(VII)]_3$
VIII	$[\alpha1(VIII)]_3$ $[\alpha2(VIII)]_3$
IX	α1(IX), α2(IX), α3(IX)
X	$[\alpha1(X)]_3$
XI	[α1(XI)]2α2(XI); α1(XI), α2(XI), α3(XI) $[\alpha2(XI)]_3$
XII	$[\alpha1(XII)]_3$
XIII	$[\alpha1(XIII)]_3$
XIV	$[\alpha1(XIV)]_3$
XV	$[\alpha1(V)]_3$
XXVII	$[\alpha1(XXVII)]_3$
XXVIII	$[\alpha1(XXVIII)]_3$

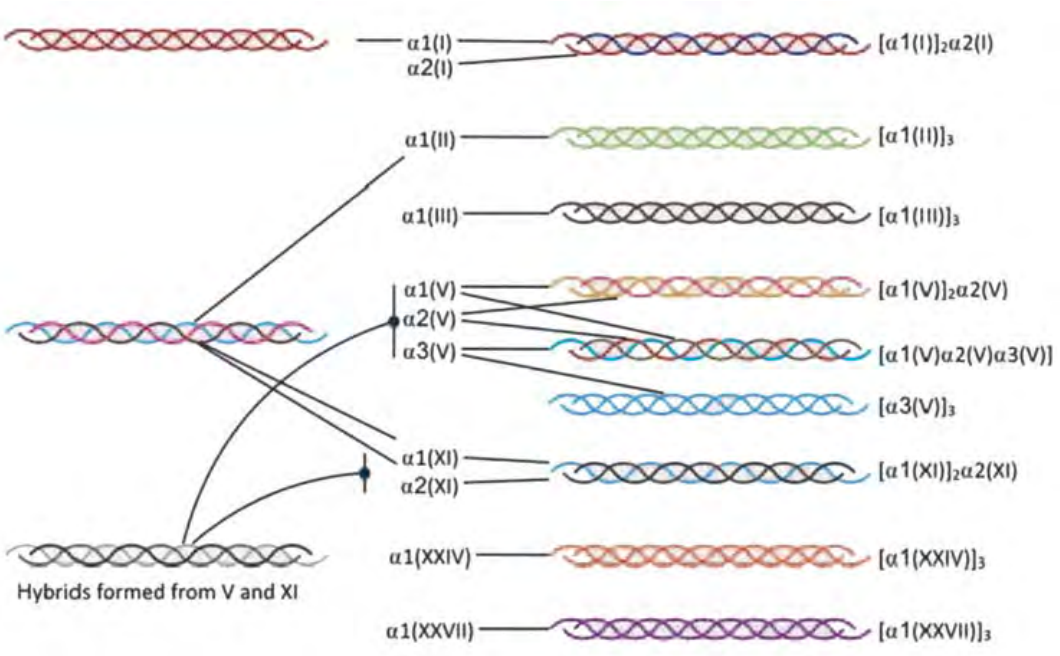

Fig. 1. **Schematic diagram of the chain composition of the fibril forming collagens [4]**

bonds into helical microfibrils (chelises) with a diameter of 1–12 μm and a length of 10 μm, which, in turn, also through cross-links form quaternary collagen structures — fibers of different thicknesses (20–200 μm) [4].

The formation of a fibrillar structure is ensured by the high content of glycine in the tropocollagen molecule, since only the residue of this amino acid (glycyl) is placed between the three peptide chains in the center of the triple helix. Proline and hydroxyproline, which, unlike other amino acids, do not contain an amine ($-NH_2$), but an imine *p*–NH–) group, in fact, they are not amino acids, but imino acids, prevent the rotation of the polypeptide chain. Thus, due to the structure of proline radical, bends take place in the polypeptide chain, which helps to stabilize the left-handed helical conformation, making the collagen helix more unfolded compared to globular proteins. Amino acid radicals located between lysine residues form the surface of a triple helix [5].

Forming fibrils, tropocollagen molecules are displaced relative to each other by one quarter of their length and are arranged as if in steps. This explains the striation with a period of 67 nm visible under a microscope, which is characteristic of native fibrils, which form the basis of connective tissues, fascia, and tendons [6]. Calcium phosphate crystals can be deposited in the 35–40 nm gaps formed between tropocollagen molecules. Depending on the degree of tissue mineralization, collagens can be rigid (bone), mixed (tendons), or have a gradient from rigid to mixed (cartilage).

The assembly of tropocollagen molecules into microfibrils is preceded by some of the lysine and hydroxylysine residues modification under the action of lysyl hydroxylase, which catalyzes their transformation into aldehyde derivatives [4]. As a result of the formation of covalent cross-links arising due to the interaction of lysine, hydroxylysine and aldehyde derivatives, intermolecular covalent bonds are formed and collagen fibrils are stabilized. Later, from the microfibrils combined in this way, thicker fibrils are formed, and from them collagen fibers and fiber bundles.

Collagen fibers are located differently in different tissues. The collagen fibers of the skin can be represented in the form of spirals that straighten along the load axis and can lengthen by no more than 10–20%, thus providing tissue strength and limiting their stretching [5]. In this case, collagen fibrils form a three-dimensional network of fibers. Due to the nature of the collagen fibers interlacement, human skin can significantly increase its length without breaking. Collagen fibers of tendons, ligaments, and also the walls of blood vessels are not intertwined and it seems as if they laid loosely at rest. A feature of the tendons is that the parallel bundles of fibers are surrounded by thin

loose layers of unformed fibrous connective tissue. In the connective tissue of lamellar bones, transversely oriented collagen fibers are entwined into the intermediate layers between the bone plates, thereby providing high bone strength. Loose connective tissue contains relatively little collagen. At the same time, strongly crimped collagen fibers form a disordered network, as a result of which this tissue has low strength and high stretchability [7].

The group of non-fibrillar collagens includes collagen proteins of the types IV, VIII and X, which are able to form reticular structures. The type IV collagen is the most abundant protein in this group. The type IV tropocollagen molecule consists of one type IV α1 and two α2 chains. Unlike fibrillar collagens, the α-chains of the type IV collagen molecule contain non-collagen amino acid regions and, in the process of self-aggregation, interact with each other, forming dimers and trimmers, which, due to lateral interactions and end-to-end bonds, are capable of supercoiling, leading to the formation of three-dimensional network-like structures with hexagonal units. This type of collagen is the main structural protein of the basal membrane, a specialized form of the extracellular matrix of normal tissue that forms a discrete structure that separates the cell layers from each other [8]. The basal membrane, ensuring the maintenance of tissue architectonics, delineates various tissue structures and influences the migration, differentiation and phenotyping of cells in them.

Proteins belonging to the class of collagen fibrils-associated are not capable of forming fibrils, but, by binding to fibrillar collagens of the types I and II, they limit the length, thickness, and orientation of their fibrils. This type of collagens is characterized by the presence of both globular and fibrillar domains in their structure. For example, type IX collagen α-chains (one α1-, α2- and α3- chain type IX each) consist of 3 fibrillar and 4 globular domains united by cross-covalent bonds with type II collagen fibrils [9]. In addition, the type IX collagen molecule contains a side glycosaminoglycan chain and a large number of positively charged groups, due to which, and it is very important, negatively charged molecules of hyaluronic acid and chondroitin sulfate can attach to it.

Proteins that form microfibrils are collagen of the type VI. This short-chain protein forms microfibrils consisting of peptide tetramers and located between collagen fibrils of the interstitium. In addition to the ability to bind to interstitial collagen fibrils, type VI collagen can also bind to proteoglycans and glycosaminoglycans. The molecules of this collagen contain numerous Arg-Gly-Asp sequences, which, when attached to membrane adhesion proteins, integrins, provide cell adhesion [9].

Collagen metabolism in tissues

Collagen synthesis and its excretion into the extracellular matrix are carried out by almost all blast cells: chondroblasts, osteoblasts, epithelial cells and endothelial cells, but the most numerous type of cells synthesizing collagen are fibroblasts. The formation of collagen fibrils is a complex multistage process that includes several stages that take place both inside and outside the cell. At the intracellular stage, translation and post-translational modification of polypeptide chains take place, and at the extracellular stage, protein modification occurs, resulting in the formation of collagen fibers. The collagen synthesis process begins on the polyribosomes of the rough endoplasmic reticulum, where translation of amino acid residues occurs and the assembly of peptide chains takes place [10, 11]. The peptide chains synthesized on ribosomes, due to the presence of a hydrophobic signaling site at the N-terminus, penetrate through the membrane into the cavity of the endoplasmic reticulum, where the signal peptide is cleaved with the participation of a specific proteinase. A number of post-translational modifications of the immature collagen chain occurs in the cavity of the endoplasmic reticulum. In particular, under the action of iron-containing collagen prolyl- and lysyl- hydroxylases (procollagenprolyl-4-dioxygenase, procollagenprolyl-3-dioxygenase, and procollagen lysyl-5-dioxygenase), some proline and lysine residues are hydroxylated with the formation of hydroxyproline and hydroxylysine [12, 13]. This process begins in the cisterns of the endoplasmic reticulum during the translation of the polypeptide chain and continues until its separation from the ribosomes. For the hydroxylation reaction to proceed, O_2 and 2-oxoglutarate are required, as well as ascorbic acid as a cofactor. Also in the endoplasmic reticulum, glycosylation of part of the hydroxylysine residues occurs under the action of glycosyltransferases, as a result of which covalent O-glycosidic bonds are formed between the 5-OH group of hydroxylysine and the galactose residue or

the disaccharide galactosylglucose, and the amide group of N-asparagine is attached to N-acetylglucosamine or mannose molecules. After hydroxylation and glycosylation, each pro-α-chain is hydrogen-bonded to two other pro-α-chains, forming a triple helix of procollagen. Hydroxyproline is required to stabilize this triple helix of collagen, since its hydroxyl groups are involved in the formation of hydrogen bonds between the α-chains. At the end of hydroxylation and glycosylation, all pro-α-chains are interconnected by hydrogen bonds, and disulfide bridges are formed in the region of the C-terminal propeptides. At the next stage, procollagen molecules from the endoplasmic reticulum cavity enter the Golgi apparatus, where they are included in secretory granules, which are excreted into the extracellular space. All intermediate products of collagen synthesis formed at this stage are water-soluble. In the extracellular space, as a result of detachment by specific procollagen peptidases of N- and C-terminal peptides, tropocollagen molecules (mature, insoluble collagen) are formed, which combine into microfibrils, which, in turn, due to the formation of cross-links, form collagen fibers [13]. These bonds are formed as a result of oxidative deamination of lysine and 5-hydroxylysine residues, which occurs with the participation of the copper-containing enzyme lysyl oxidase and leads to the formation of aldehyde derivatives of lysine and 5-hydroxylysine — allysine and oxyallysine, which can react with lysine or allysine residues of another collagen chain, forming aldimines or aldols, which can then be structured to form multivalent cross-linking in a three-dimensional transverse network of collagen fibrils [13]. The spatial organization of fibrils is completed with the participation of fibronectin, proteoglycans, and collagens associated with fibrils. Glycosaminoglycans and the proteoglycan complexes formed with their participation enter into characteristic interactions with collagen and form a continuous network of collagen fibrils between individual cells. At the same time, free glycosaminoglycans not associated with the core protein act as inhibitors of fibrillogenesis. It should be noted that not all tropocollagen turns into fibrils: about 25% of tropocollagen molecules disintegrate without forming fibrils, and the resulting fragments perform signaling functions and stimulate collagenogenesis, for which they are partly a substrate.

Collagen metabolism in tissues is a relatively slow process. The half-life of collagen is weeks or even months. Native collagen is resistant to most tissue proteases and digestive enzymes. To trigger its catabolism, the presence of a specific enzyme, collagenase, is necessary, which cuts all three peptide chains of the collagen molecule between the residues of glycine and leucine (or isoleucine) at about one quarter of the distance from the C-terminus. Cleavage of the collagen molecule can also be catalyzed by some nonspecific proteases and matrix metalloproteinases: MMP-1, -8, -13, -14, -18 [14], as well as MMP-2 and -9 (gelatinase A and gelatinase B). The resulting fragments are soluble in water and easily denatured by lysosomal proteases to oligopeptides, the peptide bonds of which become available for hydrolysis by various peptide hydrolases. Along with this, N-propeptides, after their cleavage, inhibit the translation of collagen according to the principle of negative feedback.

Congenital abnormalities and age-related changes in the structure, properties and metabolism of collagen

The imbalance between collagen synthesis and degradation leads to various pathological changes in connective tissue. So, with its excessive synthesis and, accordingly, the formation of “extra” collagen fibers, fibrosis of the organ develops, characterized by the proliferation of loose fibrous connective tissue, which under some circumstances (for example, with chronic inflammation) can turn into dense [15]. Similar phenomena are observed in the case of wound healing, accompanied by chronic inflammation, causing increased proliferation of collagen-producing fibroblasts. In addition to factors of chronic inflammation, damaging factors leading to the fibrosis development can be chronic exposure to toxins, microbial invasion, hypoxia, etc. If the action of damaging factors is eliminated in time, then further fibrous tissue remodeling can be avoided and involution of fibrous tissue will begin. If the action of damaging factors becomes chronic, then fibrosis becomes irreversible and progresses to sclerosis or cirrhosis. Acute inflammation, which occurs in the early stages of wound healing, on the contrary, accelerates the degradation of collagen [16].

It has been also found that during ontogenesis there is a decrease in the rate of collagen metabolism, which is explained by the lower availability of collagen in an aging organism for the action of collagenase due to

its molecular rearrangement, an increase in the number of cross-links, leading to an increase in stiffness and a decrease in fiber tortuosity [17].

Currently, intensive research is being carried out aimed at studying the biological properties of collagen. In particular, due to the fact that in the so-called "collagen diseases" the connective tissue and its constituent collagen fibers undergo certain changes [18], many experiments are aimed at studying the role of collagen metabolism disorders in the etiology of these pathologies and the possibility of medical application of this protein for the treatment of diseases of bones and skin, as well as in connection with the study of the mechanisms of such important biological processes as inflammation, regeneration, aging, etc.

The rate of collagen metabolism can be inferred by examining the content of hydroxyproline in blood and urine, since this amino acid is typical exclusively for this protein. An increase in the concentration of hydroxyproline in blood plasma and urine is an indicator of collagen breakdown [19]. Determination of the amount of type I collagen degradation products (N- and C-telopeptides) is also informative in this regard [20]. Increased proline content in blood plasma may indicate impaired collagen maturation [21]. Factors that negatively affect the synthesis and maturation of collagen can exert their effect both at the intra- and extracellular stage. The hydroxylation of lysine and proline is necessary for the subsequent formation of covalent bonds between collagen molecules and the assembly of collagen fibrils. The lack of ascorbic acid can lead to a decrease in the rate of hydroxylation of lysine and proline that is observed in such a disease of avitaminous etiology as scurvy [22]. Due to the disruption of intracellular glycosylation process of procollagen α-chains, which is a consequence of cells inability to capture glucose from blood plasma, that occurs in diabetes mellitus, carbohydrates attach to the procollagen molecule after its release into the extracellular space in a non-enzymatic way and disrupt the structure of collagen fibrils (this also applies to non- extracellular matrix proteins).

Many hereditary diseases manifested in damage to the ligamentous apparatus, cartilage, skeletal system, in the presence of heart valves defects, etc., for example, such as latirism, Ehlers-Danlos syndrome, osteogenesis imperfecta, Marfan's disease, mucoviscidosis, dermatosporaxis (in animals), are the result of genetically determined disorders of collagen synthesis [23]. In rheumatism, rheumatoid arthritis, systemic lupus erythematosus, as well as in ostheoarthrosis, chronic periodontal disease, malignant tumors, increased bone resorption, aneurysm of the arteries and heart and other diseases that are a kind of collagenoses, there is an increase in collagen breakdown.

Mutations in genes encoding the amino acid sequence of preprocollagen can be the cause of collagenoses development. The loss or, conversely, the addition of an amino acid in the collagen polypeptide chain, the replacement of one amino acid for another (especially, the replacement of a glycine residue for another amino acid residue), occurring due to mutations in the collagen domain, lead to a change in the shape of the collagen triple helix [24, 25]. Mutations in non-collagen domains can also lead to incorrect spatial assembly of α-chains into fibrils or networks [26]. All this is reflected in the properties of tissues and organs, and, consequently, on their functioning. Any mutation of one or another of the enzymes involved in collagen synthesis, a deficiency of these enzymes or a deficiency of copper, vitamins C, B_6, B_{13} can have the same consequences. The presence of any of these factors can also lead to a change in the shape of the collagen molecule. Thus, the deficiency of proline and lysine hydroxylases, glycosyltransferases, N-procollagen and C-procollagen peptidases, and lysyl oxidases leads to disruption of cross-linking formation process [27–29].

Various exogenous and endogenous factors can directly influence the rate of collagen metabolism. So, ascorbic acid stimulates not only the production of collagen and proteoglycans by fibroblasts, but also the proliferation of the fibroblasts themselves. Glucocorticoids have a suppressive effect on collagen synthesis, and estrogens have a stimulating effect.

Much attention is paid to the study of collagen role in morphogenesis, development and aging of humans' and animals' organs and tissues [30], since, as is known, the morpho-functional properties of collagen-containing tissues of human and animal body change with age. With age, there is a gradual physiological degradation of both collagen itself and the connective tissue in general, and it becomes more difficult for them to perform their specific functions. In the process of body development, a certain dynamic is observed in the ratio of different types of collagen in the connective tissue. At different ages, tissues

can contain either one type or several collagen types in different ratios [30, 31]. In particular, qualitative changes in the populations of collagen molecules synthesized by tissue cells are associated with their differentiation at the initial stages of ontogenesis. It is found that in the process of ontogenesis in the skin there is an increase in the content of type I collagen and a decrease in the content of type III collagen, and in the ossifying areas of the bone tissue type I collagen replaces type II collagen [32].

There are also age-related changes in the physico-chemical properties of collagen. It becomes less soluble, more rigid and less elastic, more resistant to the action of specific and nonspecific proteases [31, 33]. With age, the fractions of neutral-soluble (immature) collagen and acid-soluble (more mature) collagen decrease, and the fraction of collagen, which is insoluble even under severe chemical influences, increases [34]. With age, there is a decrease in the proline/hydroxyproline ratio and a decrease in the content of oxylysine residues in the polypeptide chains of collagen [35, 36].

These age-related changes in collagen properties are associated with various enzymatic and non-enzymatic processes leading to an increase in cross-linking between collagen molecules, which manifests itself in an increase in the total number of bonds, their stabilization and the replacement of some types of bonds with others.

In various types of connective tissue, there is a decrease in the activity of prolyl-, lysyl hydroxylases and glucosyl-, galactosyl transferases participating in the post-translational modification of collagen by hydroxylation and glycosylation which are key moments in the formation and stabilization of the procollagen triple helix [36, 37, 38, 39].

With aging, the number of bonds formed with the participation of lysine and oxylysine increases that is confirmed by the proven decrease with age in the number of free aldehyde and ε-NH_2-groups of lysine and oxylysine in the collagen of various tissues [40, 41]. This leads to an increase in the structural stability of the submolecular collagen formations. However, it is found that in the early stages of ontogenesis, the opposite tendency is observed. As it is known, cross-covalent bonding occurs as a result of the interaction of two COH-groups (aldol bond), or ε-NH_2-group with COH-group (aldimine bond). Moreover, crosslinks of submolecular collagen structures are formed due to covalent bonds of free ε-NH_2- and COH-groups. A comparative invstigation of skin collagen in rats of different ages, the task of which was to determine the relationship between the thermal stability of submolecular collagen structures with the degree of proline hydroxylation and ε-NH_2-groups of lysine and hydroxylysine oxidative deamination showed [36] that at an early age (1 month) the newly synthesized collagen is characterized by significantly higher content of COH-groups of allysine and hydroxyalysine than the content of ε-NH_2 groups. Thus, in young animals (1-3 months), in the assembly process of submolecular collagen structures, the formation of aldols by binding COH-groups to each other prevails, which ensures the formation of intramolecular crosslinks. After 3 months of age, when there is a decrease in the activity of lysyloxylase and, as a consequence, an increase in the relative content of ε-NH_2-groups of lysine and hydroxylysine in submolecular collagen, the formation of intermolecular bonds of the aldimine type, arising due to the interaction between -NH_2- and COH-groups begins to prevail [36].

Although in the process of aging in collagen, as mentioned above, an increase in the number of cross-links is observed, the content of intermolecular bifunctional aldimine cross-links decreases with age, and in many tissues of the adult organism they are not detected at all. Obviously, this becomes possible due to the qualitative and quantitative heterogeneity of the collagen molecules cross-linking, which is especially noticeable when comparing different types of connective tissue, as a result of which the types of bonds change during ontogenesis [43].

Also, during aging, the number of intramolecular bifunctional bonds of the aldol type increases in collagen, as evidenced by the increase in solutions of denatured collagen obtained from different types of connective tissue, the number of intramolecularly bound δ- and γ-particles [43].

With aging, an increase in the degree of collagen binding with polysaccharides is observed [44, 45].

Thus, age-related changes in collagen play an important role in the aging process. Werzar, who has been studying this problem since the 50s of the last century, even put forward a "collagen" theory of aging [46], according to which, age-related increase in the number of covalent cross-links in collagen makes it less soluble and, as a consequence, excessive accumulation of this protein occurs in tissues, leading to disorders in the functioning of organs and the whole organism.

The application of collagen and its derivatives

The application of collagen in medicine, biotechnology, bioengineering, agriculture, food and cosmetic industries is of considerable interest. Due to its structural affinity for human tissues and organs, its ability to be easily metabolized and utilized by the body, collagen is considered as one of the most promising biopolymers for use in restorative and reconstructive surgery in order to eliminate skin defects, deforming scars, pigmentation, as well as for the healing of wounds of various origins, including extensive burn wounds, tendon surgery, muscle injuries, etc. [47–49]. The healing properties of collagen preparations are associated with its hemostatic and wound healing effects, combined with the antigenicity absence. The pharmaceutical industry has developed and widely used in medicine various means: soft and liquid dosage forms, special plasters, films, threads, tubes and sponges, implants for orthopedics and ophthalmology (vitreous body implants), traumatology, maxillofacial surgery, etc. A large number of dietary supplements have been created on the basis of lyophilized collagen, the intake of which is recommended in the postoperative period, after injuries, as well as as a supplement to nutrition during sports.

The works are underway to study the possibility of using collagen hydrolysis products as a matrix for immobilizing biologically active substances (for example, antibiotics) in order to create new effective drugs [50]. This direction is very promising, considering the large number of active functional groups in the polypeptide chains of collagen molecule.

When collagen is included in the composition of medicines prescribed in the treatment of wounds as a wound covering, due to its high osmotic activity, it has a dehydrating effect on tissues in the inflammation focus, which contributes to the prolongation of the active substances of these drugs action. The use of collagen to close the wound surface in the treatment of patients with extensive burns, as the basis of a kind of artificial skin, can significantly reduce the risk of infection [51].

Back in 2007, the first successful clinical trials of skin transplantation artificially grown from human dermal fibroblasts on a matrix of human collagen were carried out. The results of this first study showed that artificial grafts were well vascularized, accepted and expanded, providing continuous wound closure without scarring or contractures, and did not cause any serious side effects [52].

Currently, there are many clinical trials of artificial porous scaffolds (frameworks) based on collagen and elastin, designed to restore various soft tissues. The results of these studies show that already 7 days after scaffold implantation, the invasion of this engineering structure by the recipient's own blast cells, producing extracellular matrix (in particular, fibroblasts producing type I collagen), and vascularization of the newly formed tissue begins. At the same time, the components of the implanted scaffold degrade: collagen in 15 and elastin in 90 days [53].

The works of Weinberg, Bell, who in the 80s in experiments *in vitro* proved the possibility of creating artificial vessels based on collagen [54], laid the foundation for a new direction in vascular surgery [55, 56].

Many cosmetic collagen-containing products have been developed to improve skin elasticity, as well as to strengthen nails and hair [57, 58]. One of the collagen properties, which determines its widespread use as a raw material in cosmetics, is postulated by its ability, or rather, the ability of its degradation products, to stimulate the production of its own collagen by the skin. However, as it is known, for unhindered penetration through the basal skin barrier, a substance must be fat- or water-soluble and have microscopic molecules. Due to the lack of these qualities, the native collagen molecule, when the agent containing it is applied to the skin, is not able to penetrate the stratum corneum of the epidermis, and as a substrate for the own collagen synthesis by fibroblasts, only the products of its partial

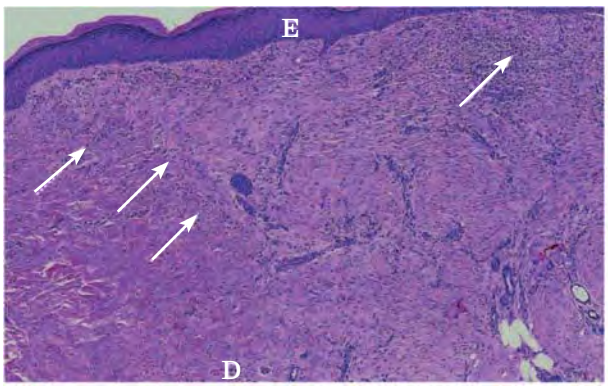

Fig. 2. **The section (magnification 50×) shows fibers of host tissue at the union of host–graft are evident (dashed arrows) and some inflammatory cells are apparent in the graft (solid arrows). D — Dermis; E — Epidermis [52]**

decay as peptides and amino acids, which under certain conditions can penetrate deep into the skin, can be used. Collagen, usually hydrolyzed or (recently) hydrated, is included in the formulations of many creams, gels, masks, shampoos, etc. as a nourishing and moisture-retaining ingredient. The effectiveness of above-mentioned cosmetics is mainly due to the fact that collagen forms a film that reduces transepidermal water loss, thereby increasing the moisture content of the skin stratum corneum [59].

The introduction of collagen by injection (subcutaneous, intradermal, intramuscular, intra-articular) has only a temporary effect, since it cannot be incorporated into the collagen fibers of the patient's tissue [60, 61]. In addition, when injecting preparations containing protein molecules, there are risks of infection with viruses, the occurrence of an immunological reaction, etc. The temporary positive effect of such injections, expressed in the preservation of tissue (skin) volume and resiliency, is explained by the ability of collagen to bind and retain water by hydration and swelling. The fact is that collagen is highly hydrating. Although collagen contains mainly amino acid residues with non-polar radicals, it is able to bind a fairly large amount of water due to the formation of hydrogen bonds between its peptide groups and water molecules. However, unlike most proteins, which, like other hydrophilic high-molecular compounds, when dissolved in water, first swell and then go into a dissolved state, collagen, absorbing a large amount of water, remains in a swollen form without dissolving at the same time. If, as a result of swelling, water binds to non-polar collagen groups rather weakly and is easily removed, then in the process of hydration, water, due to the formation of ion-dipole bonds with ionized protein groups or through hydrogen bonds with peptide and hydroxyl groups, organically enters the structure of collagen and promotes it stabilization. It is very difficult to separate hydration water from protein by, for instance, mechanical pressure.

The positive effects of collagen and its hydrolysis products in various dosage forms, dietary supplements and cosmetics are not limited to its ability to retain moisture and stimulate the production of own collagen by tissues, as mentioned above, but also to the biological activity of some low molecular weight peptides resulting from degradation of collagen α-chains. *In vivo*, collagen peptides are formed in connective tissue as a result of the action of endogenous proteolytic enzymes. Some peptide fragments of collagen, like fragments of other proteins of the extracellular matrix (for example, fibronectin or elastin), are capable of exerting a regulatory effect on tissue cells, stimulating or suppressing the production of extracellular matrix proteins [62, 63]. *In vitro* experiments on the culture of human fibroblasts showed that the C-terminal fragment of type I procollagen is able to activate the synthesis of type I and III collagen, as well as the production of fibronectin [64]. Later, a minimal peptide sequence (Lys-Tre-Tre-Lys-Ser) was isolated from this fragment, which has the ability to stimulate the production of extracellular matrix *in vitro* [65]. Tripeptide (Gly-L-His-L-Lys), which is also a fragment of collagen α-chain, has a high affinity for copper, a cofactor of such important enzymes as superoxide dismutase and lysyl oxidase (involved in collagen production) [62]. Biologically active peptides-derivatives of collagen, which have an antitumor effect are of particular note. For example, type IV fragment of collagen (Col IVα3), which is characteristic of the basal membrane, formed as a result of proteolysis due to the action of MMP-9, tumstatin, is able to suppress pathological angiogenesis and tumor growth [66]. Arresten, a peptide originated from the non-collagen domain of the α1-chain of type IV collagen, is also an endogenous inhibitor of angiogenesis. It has been shown in *in vitro* experiments and in an organotypic model [67] that arresten can directly or through integrin affect the HSC-3 carcinoma cells of the tongue, effectively inhibiting the migration and invasion of carcinoma cells. An antiangiogenic factor is also the peptide endostatin, which is a C-terminal fragment of the α-chain of type XVIII collagen of the basal membrane cut off by MMP-2. Due to their antiangiogenic action, endostatin and arresten are also involved in the formation of non-vascular zones in the cartilaginous tissue [68, 69]. It has been shown that endostatin has an inhibitory effect on cell adhesion, proliferation, and trophoblast invasion, contributing to a successful pregnancy [70, 71]. Obviously, under the action of matrix metalloproteases, many biologically active peptides are formed from collagen, which, like peptides formed as a result of the same enzymes action from fibrinectin, are involved in remodeling of the extracellular matrix and basal membrane in a number of diseases [72, 73]. Currently, a new area of molecular biology is developing, the task of

which is to create synthetic peptides based on biologically active collagen peptides and other proteins of the extracellular matrix. Thus, by lipid-conjugation of the aforementioned pentapeptide, the synthetic peptide palmitoyl-Lys-Tre-Tre-Lys-Ser was created and tested, which has a rejuvenating effect on photoaged facial skin [74]. The synthetic peptide Gli-Glu-Lys-Gly is able to increase the expression of mRNA of type I procollagen, fibronectin and hyaluronic acid, as well as the secretion of type I procollagen from human fibroblasts, which has been demonstrated both *in vitro* and *in vivo* (in humans) [75].

The most effective cosmetic products are gels containing collagen fragments, the three-helix structure of which is preserved. Hydrated tropocollagen, which preserves the structure of the triple collagen helice, has a transdermal effect, due to the fact that after application of the gel-like agent containing it to the skin, it undergoes controlled decomposition (at skin surface temperature) with the formation of peptide chains that can easily penetrate into the epidermis. Lipid conjugation [76], sonopheresis, microdermabrasion, and electroporation [62] also increase the transdermal delivery of collagen peptides, but these methods have a number of important limitations, since they are cytotoxic and damage tissues.

Sources and methods of collagen obtaining

The solubility of collagen derivatives, their physico-chemical properties and biological activity depend on the source and method of production. Collagen used in the cosmetic and pharmaceutical industries is divided into three technological types. Usually, the formulations of the proposed products indicate the source from which collagen is obtained (in fact, most often these are products of collagen hydrolysis). There are three types of collagen on the modern market: animal, marine and plant [59]. As for the latter, then, of course, in relation to this protein product, which is a hydrolyzed protein of wheat or other cereals containing neither hydroxyproline nor oxylysin, the name “collagen” is highly incorrect, and is nothing more than an advertising ploy by some manufacturers of cosmetics and dietary supplements. Most of the products contain animal collagen obtained during the processing of by-products (bones, cartilage, but mainly skin) of cattle and, less often, pigs and some other mammals and birds [59, 77]. Recently, more and more cosmetics containing so-called marine collagen have appeared on the market. It is isolated from various aquatic organisms, but mainly from the skin and scales of fish (and, moreover, recently, mainly not from marine, but from freshwater species). The transition to this source is due to the fact that, first, as it is believed, in its composition it is more than an animal collagen similar to that of a human [78]. Secondly, due to a significantly lower denaturation temperature (20–28) °C than that of animal collagen, when cosmetics containing large fragments of marine collagen molecules are applied to the skin, they break down into peptides small enough for unhindered penetration into the skin. Third, and it is not unimportantly, due to the recent increased risk of human infection with various viral and prion infections of cattle and pigs [79], many manufacturers refuse to use animal collagen in their formulations and switch to marine collagen.

Sometimes in the formulations of various agents, most often for medical purposes, artificially synthesized peptides are used, corresponding in amino acid sequence to fragments of collagen α-chains, which were already mentioned above. Manufacturers call these substances microcollagens. An example is a synthetic oligopeptide with hemostatic properties corresponding to a fragment of collagen α-chain of 36 amino acid residues [80]. This peptide can form a triple helix and become saturated with water until the formation of a hydrogel, which also has the ability to bind platelets, causing their aggregation, without causing an inflammatory reaction, as is sometimes the case with the use of animal collagen, as demonstrated in experiments *in vitro*. This allows the substance to be used as a hemostatic agent.

The introduction of technologies for the production of human recombinant collagen with the use of bioreactors based on mammalian [81], insects [82–84], yeast [85–90] cell cultures, as well as using transgenic production systems, such as mammary glands of mice and cows [91, 92], silkworm pupae [93], cell cultures, and tobacco plants [94–96] is very promising. With the help of recombinant technology, it is possible to obtain collagens with a triple helix, which have the same amino acid sequence as collagen obtained from human tissues. It should be noted that only mammalian cells transfected with collagen genes produced full length hydroxylated collagens. When using other systems, the proline in the collagen

produced by them was not hydroxylated or insufficiently hydroxylated. As a result, self-assembly of collagen fibrils was ineffective and such collagen was unstable and susceptible to proteolytic degradation, which made it unsuitable for many tissue engineering applications [97]. Combining the expression of collagen and cDNA genes encoding prolyl 4-hydroxylase subunits can help to solve this problem and achieve the synthesis of fully hydroxylated, thermostable collagens [98]. By using this approach, which allows an equivalent degree of proline hydroxylation to be achieved, recombinant collagens can be produced with the same degree of stability as natural material. Recombinantly produced single triple-helical collagen molecules are used to create more complex three-dimensional structures: scaffolds for bone repair, the basis for the engineering of skin, cartilage and other tissues. Nevertheless, it should be noted that although recombinant collagen is fully consistent with the solution of the problem of minimizing the risk of diseases transmitted by animals, its production process requires complex processing steps involving a large number of enzymes [99].

As for the use in medicine and cosmetology of human collagen obtained from the tissues of corpses, abortive material and placenta, the use of the first two sources is limited due to moral, ethical and legal reasons. More or less widely used in medicine is decellularized intercellular matrix obtained from cadaveric bones and skin, the main substance of which is collagen [100]. Recently, more and more attention has been paid to the development of extraction methods and the use of placental collagen. Not only the human placenta [101] is used as a source of collagen, but also the placenta of cattle [102].

The potential for collagen use in one direction or another is determined by manifestation degree of such qualities as resistance to hydrolysis, tendency to hydration, solubility and the ability to self-assembly of its structural units. All these properties depend both on the source chosen as a raw material and on various physico-chemical factors that have an effect on collagen in the process of its obtaining. The main such physico-chemical factors are temperature, pH, and salt composition of the isolation medium.

As it is known, during freezing and heating of solutions and mixtures containing proteins, hydrophobic interactions and hydrogen bonds, which determine and stabilize the tertiary and quaternary structures, can be disrupted. It has been established that changes in the hydration shell of native collagen fibrils can lead to changes in their morphology. Thus, upon watering, a change in the mutual orientation of tropocollagen within the fibrils takes place [103]. When cooled by 1 °C, the contraction of the collagen fibril is 0.1 μm per 1 mm of length and the twisting of the fibril occurs. The reason for such conformational changes in collagen is water molecules, which, when cooled, are incorporated into the three-helix collagen helis, tighten and fold it. When heated, collagen fibrils unwind and lengthen.

The temperature factor plays an especially important role in the collagen denaturation process. Collagen denaturation occurs at different temperatures in the range of 58–67 °C. When the denaturation temperature is reached, the hydrogen bonds of collagen, due to which its tertiary structure is maintained, weaken and break. As a result of changes in collagen structure, an increase in the number of -COOH and -OH groups, which play the role of hydrophilic centers, occurs. These changes are irreversible and it is with them that the actual denaturation process of the fibrillar protein begins [104]. At the denaturation temperature, collagen transforms with the formation of compounds with a lower molecular weight, it is peptization. Typically, this high-temperature denaturation of collagen is used in the food industry for the production of gelatine, gelatose, glutin, which, after cooling, form strong jellies. The higher is the content of proline and hydroxyproline amino acid residues, the higher is the ability of collagen heat treatment products to gel formation. The temperature of collagen denaturation also depends on their total content. The more they are contained in a protein, the higher its denaturation temperature [105]. In addition, hydroxyproline, due to its ability to form hydrogen bonds through OH-groups, helps stabilize the collagen triple helix.

Thus, the temperature factor plays a huge role in collagen transformation and, apparently, in the possibility of its release from tissue, which is used as a raw material. However, currently, the issues of tissues low-temperature pretreatment in the technology of obtaining collagen and its derivatives are praically not studied. In view of the prospect of a significant increase in the yield of collagen and its derivatives as a result of freezing to low temperatures at different rates at which the raw material is exposed to the action of various physico-chemical factors, this subject research is highly relevant. The

process of collagen hydrolysis is accelerated not only by temperature, but also by the acidic environment. The properties of collagen-containing products depend on the pH value of their aqueous solutions. It is known that the isoelectric point of collagens is in the pH range from 6.0 to 6.75. The isometric tension of collagen fibers decreases with decreasing pH [104]. A shift in pH to the alkaline or acidic side causes changes in the distribution of positive and negative charges on the surface of collagen molecule, which leads to a change in their functional properties. A decrease in pH level below the isoelectric point leads to a significant decrease in denaturation temperature: at pH 3, the collagen denaturation temperature corresponds to 35–40 °C, at pH 1 it corresponds to 30 °C [106]. In addition, the pH value also affects the collagen solubility in water. It has been shown that with an increase in pH from 5.6 to 7.4, a decrease in collagen solubility is observed [107]. This is explained by the fact that at low pH values the destruction of covalent and some peptide bonds occurs [96].

As mentioned above, the dissolution of proteins is preceded by the hydration and swelling of its molecules. The degree of protein molecules swelling increases when they interact with acids and alkalis. Collagen has the ability to react with both acids and alkalis. The effect on the rate and degree of collagen hydration depends on the concentration and strength of the electrolyte. It has been established that an increase in acid or alkali concentration enhances the collagen swelling and accelerates its dissolution [108, 109]. Under the influence of a strong acid, molecular chains are deformed due to electrostatic repulsion, which leads to thickening and shortening of the collagen fiber [108, 110]. This is followed by the gradual rupture of intramolecular hydrogen bonds and the destruction of the structure based on hydrogen bridges. Ultimately, this effect results in a decrease in the temperature of collagen denaturation.

In acid treatment, the swelling and subsequent dissolution of collagen occurs as a result of the combined action of osmotic and electrostatic forces. It has been shown that molecular adsorption with collagen (mainly by peptide bonds) prevails in concentrated acid solutions, and ionic sorption processes in dilute acid solutions [109]. Weakly dissociated organic acids (for example, acetic acid) are sorbed either in the form of ions or in non-ionized form. They do not completely suppress the ionization of the main protein groups; therefore, high concentrations of such acids and a longer exposure are required to destroy the collagen structure. But even under these conditions, the collagen fiber does not completely dissolve [111].

As a result of acid treatment, proteins acquire positive charges and form salts with anions of the added acid. When a strong base is added, the charge of protein molecules becomes negative, and their carboxyl groups in the ionized state form salts with an added alkali cation [108].

Collagen can also be modified by treatment with salt solutions. The direction and degree of these changes depend on the concentration, type and strength of anions and cations, as well as their affinity for collagen protein. The differences in the salt composition of the isolation medium are most reflected in collagen hydration and swelling [108]. For example, iodine and chlorate anions, calcium and magnesium cations increase collagen swelling. Sodium chloride is able to uncouple hydrophobic and hydrogen bonds and change the structure of water in the immediate proximity of the binding sites, which disturbs the collagen gels stabilization [112]. It has been shown that collagens obtained from various sources (different types of animals, tissues) differ in the degree of susceptibility to the influence of acidity, salt composition and concentration of the isolation medium. Thus, collagen extracted from bone tissue is more resistant to NaCl at a concentration of 4–6 % than skin collagen [113]. Fish collagen is less stable than mammalian collagen due to the low level of imino acids (proline and hydroxyproline) [114].

In addition to chemical hydrolysis, collagen can be extracted from most sources by processing the raw materials with enzymes. Chemical hydrolysis, as a rule, is used in the food industry, and enzymatic hydrolysis or its combination with mild chemical hydrolysis is more suitable for obtaining substances from collagen that are suitable for biomedical purposes [115]. Enzymatic hydrolysis allows the resulting collagen fragments to be retained in their native molecular form. Although collagen obtained by such methods is safer and more compatible with human tissues and cells, the process of it obtaining is much more complicated and more expensive than chemical hydrolysis. Research efforts are aimed both at finding new sources of collagen and at developing new efficient and cost-effective methods for its isolation.

Animals and humans placenta as a promising source of collagen

The search for new collagen sources has led to studies of the functional properties of collagens from a number of previously unconsidered sources, including those from the placenta of cattle or from humans [101, 105]. The placenta is also of interest as a source of various bioactive substances. Due to this, placenta extracts are used in the formulations of various cosmetics. Often, these products also contain collagen obtained from other sources, or rather, the products of its hydrolysis. It would be very rational to combine collagen and bioactive substances obtained from one source, namely placenta, in one recipe. In our opinion, this can be especially useful when creating products (creams, gels, emulsions, etc.) designed to accelerate and improve wound healing. It was already mentioned above about the use of collagen and products derived from it in the wounds of various origins treatment [47]. The wound healing effect of placenta extract is also well known, due to its cleansing, anti-inflammatory and antimicrobial properties [116, 117]. The placenta, as a source of collagen, is unique, because it is one of the few organs, which contained type V collagen, in addition to type I and type III collagens in its connective tissue. Since this type of collagen is also typical for the eye cornea, this may partly explain the positive effects of using placenta drugs in the treatment of corneal injuries and some inflammatory diseases (keratitis) in order to accelerate repair and prevent scarring.

In the process of wound healing, as it is known, the balance between degradation and synthesis of the extracellular matrix is very important. Retarded degradation of necrotic tissue delays healing, and the proteolytic activity excess can lead to the destruction of growth factors and their receptors, as well as inhibit the disintegration of granulation tissue and angiogenesis, which ultimately leads to tissue damage [118–120]. The balance between degradation and regeneration of the extracellular matrix is regulated by proteases and their inhibitors. Collagenases play an important role in this process. In work [121], it was shown that the aqueous extract of the placenta has collagenase activity due to the presence of ubiquitin-like protein in its composition. This gives reason to hope that in the process of producing placenta extract, due to the partial enzymatic hydrolysis of tropocollagen, which occurs without the addition of exogenous proteases, it will be possible to obtain a product containing, in addition to the bioactive components of the placenta, also soluble collagen derivatives. It is also possible to achieve an increase in the yield of soluble (immature) collagen by inhibiting some enzymes involved in the synthesis of insoluble tropocolagen at the stages of formation and stabilization of the triple helix, occurring inside (hydroxylation of proline by prolyl hydroxylase) or outside (hydroxylation of lysine by lysilyl hydroxylase) of the cell. Proline hydroxylation is necessary for the formation of a triple helix, while lysine hydroxylation leads to the formation of covalent cross-links between α-chains [122]. It is known that, for example, prolyl hydroxylase can be inhibited by succinate [123]. The content of soluble immature collagen can also be increased by inhibiting specific procollagen peptidases that catalyze partial proteolysis of the procollagen triple helix released into the extracellular matrix, without which the formation of collagen monomer is impossible [124]. This can be achieved, for instance, by acidifying the isolation medium, since these enzymes are active at neutral pH values.

Thus, based on the analysis of the available literature, we can conclude that the use of collagen and its derivatives in cosmetology, pharmacy and bioengineering is a very promising direction. The search for natural sources of collagen that have good biocompatibility with human tissues, low antigenicity and biodegradability into physiologically non-toxic products, as well as the development of new methods for its isolation and obtaining of preparations with high efficiency are especially relevant today. Based on the analysis of scientific publications and the results of our own experimental studies [101, 102, 116, 117, 121, 125–130], it can be concluded that one of the most appropriate sources is the placenta, as human and animal origin. The use of low temperatures for collagen and its derivatives isolation in combination with treatment with media of different composition and pH will significantly improve the quality of the resulting product and reduce the cost of this technological process.

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КОЛАГЕН: СТРУКТУРА, ОБМІН, ОТРИМАННЯ ТА ВИКОРИСТАННЯ В ПРОМИСЛОВОМУ ВИРОБНИЦТВІ

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В огляді викладено сучасні дані наукової літератури щодо структури, властивостей та функцій колагену — одного з найпоширеніших протеїнів в організмі людини і тварин.

Стисло описано будову колагену від первинної структури до субмолекулярних формувань, основні етапи його синтезу і біодеградації. Наведено інформацію про різноманітність та особливості типів колагену і його обміну в різних тканинах: шкірі, сухожиллях, кістках тощо. Розглянуто питання патологій, спричинених порушеннями синтезу і деградації колагену, а також вікових змін властивостей колагену і причин, що їх зумовлюють.

Подано порівняльний аналіз переваг і недоліків отримання колагену та його похідних з різних джерел: тваринного, морського, а також рекомбінантного. Показано найбільш продуктивні способи отримання колагену з різних тканин. Викладено уявлення про вплив умов гідролізу колагену на фізико-хімічні властивості та біологічну активність одержуваних продуктів.

Описано можливості застосування колагену і його продуктів в різних галузях виробничої діяльності: фармацевтичній, косметичній промисловості та в медицині. Окреслено подальші перспективи робіт у цьому напрямі в науковому і прикладному плані.

Ключові слова: типи колагену, обмін колагену, джерела отримання колагену, гідроліз колагену, застосування колагену.

КОЛЛАГЕН: СТРУКТУРА, ОБМЕН, ПОЛУЧЕНИЕ И ПРИМЕНЕНИЕ В ПРОМЫШЛЕННОМ ПРОИЗВОДСТВЕ

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В обзоре изложены современные данные научной литературы о структуре и свойствах одного из наиболее распространённых протеинов в организме человека и животных.

Кратко описано строение коллагена от первичной структуры до субмолекулярных образований, основные этапы его синтеза и биодеградации. Представлена информация о разнообразии и особенностях типов коллагена и его обмена в различных тканях: коже, сухожилиях, костях и др. Затронуты вопросы патологий, обусловленных нарушениями синтеза и распада коллагена, а также возрастных изменений свойств коллагена и причин, их вызывающих.

Приведен сравнительный анализ преимуществ и недостатков получения коллагена и его производных из различных источников: животного и морского, а также рекомбинантного. Показаны наиболее продуктивные методы извлечения коллагена из различных тканей. Изложены представления о влиянии условий гидролиза коллагена на физико-химические свойства и биологическую активность получаемых продуктов.

Описаны возможности применения коллагена и его продуктов в различных областях производственной деятельности: фармацевтической, косметической промышленности и в медицине. Намечены дальнейшие перспективы работ в данном направлении в научном и прикладном плане.

Ключевые слова: типы коллагена, обмен коллагена, источники получения коллагена, гидролиз коллагена, применение коллагена.