ISSN: 0975-833X

Available online at http://www.journalcra.com

International Journal of Current Research
Vol. 16, Issue, 01, pp.27081-27086, January, 2024
DOI: https://doi.org/10.24941/ijcr.46629.01.2024

INTERNATIONAL JOURNAL OF CURRENT RESEARCH

RESEARCH ARTICLE

COLLAGEN AS A PRECIOS DERMOCOSMETIC INGREDIENT

Andrei Felicia

University of Medicine and Pharmacy "Victor Babes", Faculty of Pharmacy, Department I, Dermatopharmacy and Cosmetology, 300041, 2 Eftimie Murgu Square, Timisoara, Romania

Toma Ana, Avram Ştefania, Popa Valentin, Gencia Ioana, Cristodor Patricia

University of Medicine and Pharmacy "Victor Babes", Faculty of Medicine, Department XIV of Dermatology, 300558, 17 Daliei str., Timişoara, Timisoara, Romania

ARTICLE INFO

Article History:
Received 19th October, 2023
Received in revised form
18th November, 2023
Accepted 15th December, 2023
Published online 30th January, 2024

Key words:
Aging, stress, structural units, fibrils, photodamage

***Corresponding author: Andrei Felicia**

ABSTRACT

Collagen is the most abundant protein in many living organisms and plays an important structural role in determining the mechanical properties and shape of biological tissues. Since its discovery, collagen has been actively researched for cosmetic applications, successfully used in microplastic surgery, as a component of cosmetic products, and as a dietary supplement for anti-aging effects. The increased demand for cosmetics with collagen has generated the need for further studies in this domain. The purpose of this study was to investigate the efficacy and safety of collagen in dermocosmetology and to compare the effectiveness of collagen peptides for oral use and topical use of preparations containing collagen. An analysis of the published studies on the subject was carried out, comparing the effectiveness of using collagen in different ways to improve skin conditions. Part of the investigation was a review of the scientific literature on collagen as a material for improving skin characteristics, the history of the discovery of this protein, its structural characteristics, its chemical composition, its general systemic and topical applications, the sources of collagen, and how it penetrates the skin. The concept of hydrolyzed collagen and its antioxidant properties are considered. The methods of investigating and monitoring the safety of cosmetic preparations are described. It has been concluded that topical collagen, similarly to nutraceutical supplements with collagen peptides, can slow down and reduce the signs of skin aging and can increase skin elasticity, density and moisture in equal measure. No side effects have been reported with the use of the medications. In addition, collagen was a safe component of drugs for local and internal use. Although the harmlessness of collagen is beyond doubt and has been confirmed by studies, the effectiveness of using one type of collagen or another requires further investigation.

Citation: Andrei Felicia, Toma Ana, Avram Ştefania, Popa Valentin, Gencia Ioana, Cristodor Patricia, 2024. *"Collagen as a precios dermocosmetic ingredient.". International Journal of Current Research, 16, (01), 27081-27086.*

INTRODUCTION

Human skin is a protective barrier between the body and external environmental factors, various types of pathogens, chemicals, solar ultraviolet radiation, and physical irritations (1). The process of natural ageing is aggravated by the continuous action of adverse causes. Internal factors are also important for skin health: the nature of nutrition, features of the endocrine system (2), and individual properties of the patient's skin. As a person grows older, the skin undergoes changes consisting of an accumulation of toxic metabolic products and an increase in the biological ageing of cells. The influence of ageing on the psychological state of a person is also important. The presence of atopic dermatitis signs on the skin, itching, dryness, redness, and wrinkles causes psychological stress in the patient. Although there is no direct evidence of the effects of stress on degenerative processes in the skin, it has been found that stress stimulates the autonomic nervous system, produces glucocorticoids, corticotropin-releasing hormone, adrenaline, which trigger immune-suppressive mechanisms, activates the release of pro-inflammatory mediators, disrupts the sebaceous glands and other mechanisms that lead to pathologies (3; 4). The problem of preserving youth and health has preoccupied mankind for centuries. Preventing degenerative skin changes, and improving the current condition of tissues by maintaining the constituent elements of the connective tissue is the basis of research in the cosmetic industry. Many researchers have long been attracted by the unusual structural properties of collagen and its biological role. In Romania, collagen is available to most of the population and is used in the form of nutraceuticals and food supplements in various forms, in creams, masks, lotions, and serums for topical application. It is possible to use collagen stimulation

therapy, and injections of collagen filler are used from existing minimally invasive procedures, as hardware procedures: ion-, electro, ultraphonophoresis. Although it is believed that the structural units of collagen were discovered in 1954, the first mentions of the regular structure of fibrils were published back in 1930 (5). It was found that the structure of collagen is more complex than the structure of DNA.

D.M.Reilly and *J.Lozano* contributed to the control of the skin condition by outlining the mechanism of combating skin ageing with the help of collagen. They have described the synthesis and structure of collagen, the oxidative damage and reconstruction of this protein, and the ability of nutricosmeceutical supplements to improve skin appearance and maintain beauty and health (6). There has also been research into the mechanism of influence of UV radiation on skin structure, and the physiological role of collagen against photoageing. It was found that collagen peptides participate in the protection against photodamage, preserving the moisturising factor of the dermis (7). In the study by *M.Shenoy et al.,* the structural features, synthesis and applications of resorbed collagen were examined (8). Currently, there are 29 types of this protein having a different set of amino acids, among which the most widespread are fibrillar collagens of types I-III, type I makes up 90% of the collagen of the human body, is found in tissues such as skin, joints, tendons, ligaments, organ capsules, fascia and cornea of the eye.

H.Wang studied the effectiveness of collagen in skin regeneration, its structure, and extraction methods, assessed the disadvantages of using collagen in the form of allergic reactions, including marine collagen, and the risk of infection with infections when using bovine and porcine collagen (9). The use of non-surgical rejuvenation methods has achieved great results in recent decades. The effect of injectable collagen filler of human origin on reducing the severity of wrinkles in a model of photoaging in mice was studied by *J.H.Kim* et al., the presented results indicated excellent biodegradability of the drug and a decrease in the formation of wrinkles (10).

The strength of tissues containing fibrillar collagen is formed by the triple helix and fibrils, which are produced during the creation of polypeptide α-chains of protein, which differ in length and repetition of the amino acid set. Non-fibrillar collagens form two- and three-dimensional networks whose spiral units are shorter and discontinuous; their function is to fix a group of fibres to each other and to surrounding tissues, to form the basis of basal membranes, and to maintain the interstitial tissues of the body. Studies of the functional capabilities of collagen in the composition of anti-ageing cosmetics have reached a certain level, many studies confirm a positive effect on the condition of the skin, improving elasticity, moisturising, and reducing wrinkles. However, there is not enough data on the effectiveness and safety of the use of collagen in cosmetology in the long term. This study addressed the use of collagen, its chemical structure, functional properties and the efficacy and safety of its use to improve the physiological condition of the skin and protect against ageing processes.

MATERIALS AND METHODS

This article combines various scientific research methods, analysing the content of scientific literature in the online platforms *PubMed*, *UpToDate*, *Elsevier*, *ScienceDirect, Medscape*, and *CochranLibrary*, reviewing scientific journals, articles and publications in which collagen is mentioned as a substance used in the dermo-cosmetic industry. Findings of the last 5 years (from 2018 to 2022, excluding the historical facts section) related directly to the study of collagen for cosmetic applications were taken as a theoretical basis. To reach the stated objective of this study, articles on the definition of collagen, the history of its discovery, its structure, chemical composition, the biosynthesis of collagen, the mechanism of using this protein as a drug that affects the skin and halts the ageing process have been analysed separately. Understanding the chemical and structural bases of this substance allows correct interpretation of the mechanisms of action on the organisation of the cellular composition of the skin. The concept of hydrolysed collagen has been studied using a method of analysis, and its ability to penetrate deep into the skin tissue has been analysed (11). The data obtained on the sources of native collagen extraction, their characteristics and problems of use are analysed. An analysis of the currently available information on the ways of penetration of hydrolysed collagen through the skin barrier and methods of improvement has been carried out. Developments have been analysed, with the authors studying the structure and properties of collagen, coming to conclusions and discoveries, and presenting their results publicly. The biological functions of collagen, as a natural component of the skin, and the mechanisms of blocking the ageing processes of cells were studied. Using the generalisation method, data on the functional properties of collagen as a component of cosmetic preparations were structured during the study. An analysis of published studies on the use of collagen as a component of dermo-cosmetic preparations for topical application in combination with other substances for the treatment of skin blemishes of various etiologies has been carried out. Several studies on the use of collagen were analysed. Investigations on the combined use of oral collagen peptides with topical collagen-containing agents have been reviewed. Some features of the safety assessment of cosmetic ingredients, in particular, collagen before admission to the market of the European Union (EU) are considered. The method of comparative analysis made it possible to evaluate the effectiveness of oral and local collagen on skin changes associated with ageing, the comparison of these two methods with each other was made to establish the activity of collagen depending on the conditions of use of this protein. Data on the presence of adverse effects and adverse reactions of collagen-containing products used to improve skin condition have been analysed. Using the method of synthesising data on the properties of collagen, conclusions were drawn about the ability of this protein to participate in maintaining healthy skin, its ability to regenerate and to resist the development of damaging ageing processes. Conclusions were drawn about the effectiveness and harmlessness of the use of collagen in cosmetics.

RESULTS

This study reviewed collagen as a natural substance used to improve the physiological properties of the skin and halt the ageing process, analysing the efficacy and safety of this protein. The effectiveness and harmlessness of the local and systemic ways of using collagen are compared. Data on the molecular and functional structure of collagen, peculiarities of collagen substrates, and the synthesis process of this protein, all this information provides insight into the effects on the properties of the final cosmetic product and possible modifications in the parameters of the dermis with the occurrence of pathology. Disruptions in collagen synthesis can lead to impaired wound healing, lack of ascorbic acid leads to impaired electron transfer in hydroxyproline and hydroxylysine formation reactions, and damage to the structural integrity of the extracellular matrix leads to wrinkle formation.

Collagen is an extracellular fibrillar protein consisting of three helical polypeptide chains (Figure 1) connected by hydrogen bonds,

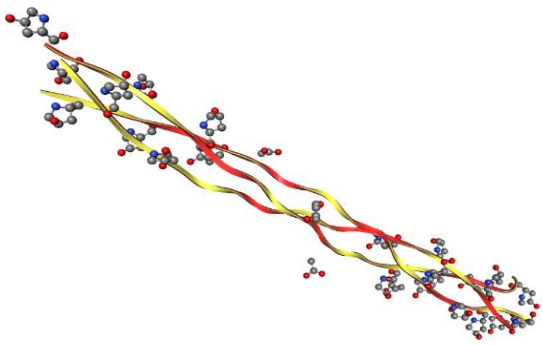

Figure 1. Molecular model of collagen (MolView)

including a different set of amino acids. Collagen is a component of most human body tissues and is the supporting framework of bones, skin, tendons and the protective glycoprotein sheath of internal organs.

Discovery history: The discovery of the molecular structure of collagen fibres has eluded scientists for decades. After the success of *R.Wyskoff et al.* (5), many researchers worked on the structure of the collagen molecule. In 1395, *G.L.Klark, E.A.Parker, J.A.Schaad, W.J.Warren* published their study on the molecular structure of collagen (12). The fundamental advance on the prototype structure of collagen was published in 1954 by *G.N.Ramachandran* and *G.Kartha* (13), after which the structural units in collagen fibrils were discovered by *A.C.T.North, P.M.Cowan* and J*.T.Randall* (14). *E.J.Miller and V.J.Matukas* identified type II collagen from chicken cartilage tissues (15). A review of the collagen family was performed by *R.Garrone et al.* in 1991(16). *D.J.S.Hulmes* demonstrated a model of suprafibrillary structures of connective tissues (17). *M.H.Schweitzer* et al. contributed to the discovery of the collagen structure by discovering type I collagen in the fibrous tissue of the cortex and medulla of the bones of the fossil *Tyrannosaurus rex* (18). Also, *P.K.Bhagwat et al.* advanced the data about the structure of collagen in 2018 (19). Our insights into the molecular structure and types of collagen continue to evolve.

Structure and synthesis of collagen: The collagen family consists of 29 types, identified by Roman numerals (I-XXIX). The skin mainly contains type I, III, and IV collagens, but type I is predominant. Differentiation of collagen is established by differences in α-chains, supramolecular structures, and protein isoforms. Molecules can be homomeric, with genetically identical α-chains, or heteromeric, containing different α-chains. A common property of collagen α-chains is the content of three amino acids, where the third amino acid from the composition is always glycine (*G*) (20), which faces the centre of the triple helix, due to its small size. The first and second amino acids are often represented by proline (*P* or *Pro*) and hydroxyproline (X or O), while X can be replaced by any of the 17 amino acids. The ternary helix is usually more than 300 nm long and has 1000 amino acids in its composition. The arrangement of these molecules has a striped structure, a special periodic axisymmetric modulation of density, the so-called D-band, with slit and overlapping sections (21). Collagen fibrils contain five collagen molecules set in a staggered arrangement. Fibrils are grouped into fibres and form the basis of organs and tissues. The synthesis of fibrillating collagen occurs in fibroblast cells in the form of progenitor cells (procollagen). The process is carried out at the intracellular level with posttranslational modification, the formation of a pro-α chain, in the extracellular space, peptidase enzymes cleave the propeptide to form a tropocollagen. After that, collagen fibres are formed with the help of lysyl oxidase (22).

Sources of collagen: Nowadays, there are many natural and synthetic sources of collagen in use. On a commercial scale, this protein is extracted from cattle, bovine collagen is used more frequently due to its biocompatibility and availability, and pork products are also used, due to their similarity to human collagen. To a lesser extent, birds, seafood and human tissue are used (23; 24; 25). The raw material used is animal parts that are particularly rich in collagen, such as hides, cartilage, bones, tendons of mammals, fish scales, starfish, squid, jellyfish, and sea cucumbers. Recombinant collagen is synthesised from mammalian, insect, and plant cells (26). Synthetic collagen has a similar structure to natural fibrils (27). The bovine and porcine collagen extraction is an especially popular and affordable method, but not economically viable. Besides the adverse factors of collagens derived from animal by-products, namely reported cases of prion diseases such as bovine spongiform encephalopathy, mad cow disease, swine flu, and swine vesicular disease have created some limitations in the use of collagen from these animals. The advantage of using collagen of marine origin is the low probability of disease transmission, high bioavailability, and the possibility of using by-products from the fish industry to obtain a more cost-effective method. In addition, by-products of the fishing industry can pollute the marine environment, making extracting collagen from such products even more rational. Another important factor is the possibility of contamination of marine life with a high level of heavy metals (29), which in turn will lead to the toxicity of the derived product. Thus, the origin of collagen affects the safety of the cosmetic product used and the final results concerning the qualitative characteristics of the skin. The selection of a collagen supplement should be carefully considered for the possible dangers described.

Functional properties: Collagen is successfully used in dermo cosmetology due to its ability to form a protective layer on the skin surface, retain water and regenerate damaged areas (30). The properties of collagen can be divided into two types: gel-forming capabilities and surface properties (24). The gel-forming properties include thickening, texturing, gelling and water-binding functions. Surface functions include emulsification, film formation, colloidal property, foaming, adhesion and cohesion. When collagen is denatured, partial destruction of the tertiary or secondary structure occurs with the formation of gelatin (31). The emulsifying and foaming properties of collagen determine the presence of hydrophobic and hydrophilic amino acids in the composition and reduce the surface tension of the emulsion (32). The film-forming property is used for the production of biodegradable collagen films. Their mechanical properties are advanced by the addition of various ingredients (33; 34).

Dermal penetration methods: Recent research on enhancing the delivery of cosmetics deep into tissues has focused on understanding the system regulating diffusion through the stratum corneum, studying the lipid barrier and damaging skin protection mechanisms. The molecule size, molecular weight, solubility, pKa, and hydrophilic-lipophilic gradient are important (35). Also, the penetration of molecules into the epidermis varies depending on the place and duration of application, the thickness of the skin, the state of its cellular composition, and metabolism. Collagen molecules can penetrate directly into the skin through hair follicles, sweat ducts, sebaceous glands or through the stratum corneum of the skin. Recently, a lot of research has been directed at studying the transdermal pathway of penetration. These include subcutaneous injections, transdermal plasters, creams and lotions for topical use. Micro-needles (36), electrical methods such as ultrasound, ionophoresis, electroporation, mechanical stimulation by thermal, radiofrequency and laser ablation can also improve delivery (37). Transdermal penetration can be increased by using nanocollagen, a protein reduced to the size of nanoparticles. In cosmetology, it is used to form nanoemulsions that have the ability of rapid absorption and high stability of the product (38).

Protein denaturation: Hydrolyzed collagen is successfully used as a cosmetic and nutraceutical component to improve the condition of the skin. Collagen in its native form has a large molecular weight, about 300 kDa (39), which makes it poorly soluble in water and makes it difficult to use in the cosmetology industry. Denaturation of native collagen is done by separating the α-chains under the influence of temperature above 40°C and proteolytic enzymes, with the formation of small peptides. The resulting substance is a hydrolysed collagen (HA). Other extraction methods include exposure to pressure, temperature, and acidic or alkaline media. The extraction process reduces the molecular weight of native collagen to 1-10 kDa, which ensures high biocompatibility, biodegradability and low antigenicity of the product.

DISCUSSION

Research on collagen: The effect of oral natural compounds and minerals, in particular collagen, on the skin microbiome was evaluated. Many animal and human studies have shown an improvement in skin and nail parameters after taking collagen peptides (40). A triple-blind, randomised, parallel placebo-controlled,

placebo-controlled study of the effects of freshwater marine collagen on wrinkles and skin elasticity has also been reviewed. The skin condition was assessed using cytometry, a visual analogue skin condition scale and the *VISIA skin analyser system.* The results showed that the use of additives including freshwater marine collagen is safe, reduces the number of wrinkles by 35%, and improves skin elasticity (41). Another mono-centre randomised controlled trial evaluating the effectiveness of hydrolysed collagen on skin elasticity, hydration and wrinkle depth was evaluated instrumentally. The tolerance of the gastrointestinal tract during administration was also considered. 35% of the 52 volunteers who were treated with collagen for 28 days showed an improvement in skin softness, and 54% after 56 days of treatment. Skin elasticity increased in 27% and 58% of the collagen group after 28 and 56 days, respectively. The visibility of wrinkles decreased in 38% of the group participants, after 56 days of collagen application. Effectiveness of an oral collagen-based nutraceutical in a randomised placebo-controlled trial, assessing skin quality by corneometry (skin moisture), cytometry (elasticity), skin ultrasound (density) and digital *in-vivo* optical 3D phase measurement (42). Several studies on the use of PMMA with collagen are reviewed. A single-group study using topical collagen tripeptide hydrolysate on skin properties was reviewed, and the results were evaluated using a 3D camera image analysis (43). No side effects were observed during the entire study period (44). In addition, the combined use of collagen peptides in combination with water-soluble coenzyme *Q*10 has been described, the effectiveness was determined by changes in skin smoothness, wrinkle characteristics, and the degree of skin hydration. The results showed an improvement in smoothness, skin density and a reduction in the measured area of periorbital wrinkles (45).

The collagen biostimulant polymethylmethacrylate (PMMA) in combination with extracted collagen, as an injectable treatment for post-inflammatory skin formations, atrophic scars, and consequences of moderate to severe acne, has also been reviewed (46). Review of a 12-month study of the effectiveness and harmlessness of polymethylmethacrylate-collagen gel for correcting the volume deficit of the middle zone of the face, which was performed using the global scale of aesthetic improvement and evaluation of *GAIS* doctors (47). The efficacy and safety of the PMMA complex with collagen in the correction of acne scars all over the face in an open, non-randomized, multicentre pilot study were also considered. From 42 participants treated, 92% and 95% had improved by ≥1 point on a 5-point acne scar scoring scale after 4 and 7 months, respectively. According to the results of the aesthetic improvement scale (GAIS), 95% noted improvement after 4 months and 90% after 7 months. No serious adverse effects were observed during the study (48). The effectiveness and safety of PMMA gel with collagen for correction of the submandibular furrow were evaluated. Effectiveness was assessed using the total static improvement scale (*GAIS*). Samples were collected at weeks 4, 12, 26, 52 and 104. After 12 weeks, 79% of the participants in the study group reported an "improvement" or "significant improvement" in their jawline assessment. The results for 52 weeks were 76%, on the 104th week they increased to 90%. At weeks 52 and 104, 285 and 100% of the group respectively were "somewhat satisfied". All undesirable events were insignificant (49). In a study of the use of a patch with microneedles filled with a fragment of fatty collagen(*ACF*) to prevent photoaging in mice, prolonged administration of *ACF* for more than two weeks with effective delivery was demonstrated, which contributed to effective skin rejuvenation (50). Also, the use of a combination of local and oral collagen in a test on healthy women shows positive results. Skin viscoelasticity, echogenicity, water saturation of the stratum corneum and the nature of the skin pores were assessed.

Component safety: In the EU, food additives are regulated as food products by the European Food Safety Agency. A directive has been established to protect the consumer against possible risks associated with food additive components, controlling the safety of their composition. The deregulation establishes a list of possible vitamins and minerals that can be used in the product, the maximum and minimum allowable amounts of the constituents. The harmlessness of cosmetic products lies in the safety of the components, which are determined by toxicological studies. In *silico* methods are actively investigated when it is impossible to test the toxicological danger of cosmetic materials in *vivo*. In *vivo* methods for determining acute toxicity have been significantly modified to reduce animal suffering and pain, dosing schemes for test materials have been modified, and the fixed-dose method and the up-down technique have been introduced. Skin corrosion and irritation tests are also used to prove the innocuousness of the cosmetic material, determining the potential of the substance to cause reversible and irreversible damage to the skin layers from epidermis to dermis, after the substance under investigation has been applied to the skin and aged for 3 minutes to 4 hours. Corrosion does not have to be excluded from the formulation to prevent this process, it can occur in interaction with another component of the cosmetic, the route of application, the concentration and the *pH* of the material. *TER* (percutaneous electrical resistance test), *EpiSkin, EpiDerm, EpiEthic, and epiCS* tests are used to evaluate the results. Reproductive toxicity is investigated to identify female and male reproductive disorders and to assess the risk of non-hereditary side effects in the offspring. The Whole Embryo Culture (*WEC*) is tested on animals. Tests for carcinogenicity include *in-silko* methods and *in vitro* methods aimed at detecting genotoxic materials, non-genotoxic carcinogens and substances with mutagenic properties.

The ratio of oral to topical collagen: The difficulty in comparing the efficacy of topical and internal collagen lies in the different 'pathways' of this protein from extraction from the substrate to direct use by the consumer. The conditions applied during collagen extraction (temperature, pressure, time of the procedure, concentration of the solvent) directly affect the properties and structure of this protein in a cosmetic product. The collagen extraction base also has a different set of characteristics that need to be accounted for when marketing the product. The aggregate properties of the applied cosmetic substance after its interaction with the various components of the cosmetic product with the substance in question also influence the functional and structural characteristics of the cosmetic preparation as a whole. Therefore, it is only possible to fully evaluate the result of using various methods.

Commercial interest in complex dietary supplements has grown significantly recently and continues to increase, and with it the development of the use of oral collagen. The findings prove their anti-ageing properties in the short and long term. Collagen peptides in nutraceutical supplements can reach the deeper layers of the skin through the bloodstream and persistently lead to improvements in elasticity, hydration and transepidermal water loss. Also, long-term use of collagen peptides contributes to the formation of fibroblasts and extracellular matrix of the skin. Side effects (nausea, vomiting, headache, abdominal pain, stool disorders) were not observed during the administration of collagen peptides in all studies. Supplementation with collagen allows the correction of nutritional errors, improving the result of pathological changes that are beyond the patient's control in a longer, non-surgical and gentler method.

Studies about the topical application of collagen, both non-invasive and minimally invasive methods have proven its ability to smooth wrinkles, retain and attract water, moisturise, and remove imperfections, unevenness, and scarring. The main advantage of using collagen with non-surgical methods is the rapidity of results, visible changes requested by the patient, immediately after application or injection, and rapid healing.

Collagen in high concentrations is better suited for deep and moderate wrinkles (deep acne scars, lip edges, nasolabial folds). In this regard, before using substances containing bovine and pig collagen, it is always necessary to conduct skin tests. The adverse effects of using collagen include drug overdose, sclerosis, abnormalities and hypersensitivity to the drug. With a properly performed procedure, severe side effects are extremely rare. Studies on the use of hydrolysed collagen as an antioxidant have also shown good results in topical and oral applications, due to its high affinity to natural collagen, quality biodegradability, and weak antigenicity. The small

size of the hydrolysed collagen molecule makes it easier to absorb in all applications.

CONCLUSION

Researchers have been trying to challenge the ageing process for many years. Since the discovery of collagen, a great deal of work has been done to study its potential to be realised in dermo-cosmetic products. Collagen is an integral part of the body, determines the basis of the connective tissue skeleton, and has a high degree of biodegradability, biocompatibility, and low level of antigenicity. The special role of this protein lies in its ability to maintain human health, inhibit the ageing process and regenerate tissue. Collagen can be extracted from a variety of animal and marine products. Due to its water-binding, gel-forming, emulsifying and stabilising properties, collagen is successfully used as a component of topical cosmetic preparations. The antioxidant function of collagen is to reduce oxidative damage and inhibit inflammatory reactions in cells. Low molecular weight hydrolysed collagen is used to improve the delivery of collagen preparations. Studies of collagen-containing preparations before market approval include *in vivo, in silico and in vitro* methods, with a focus on reducing the number of animal experiments and switching to analytical technology. Both oral and topical use of collagen can improve skin health and delay the ageing process.

Quantitative or qualitative degradation with fibre stiffening of the collagen occurs as part of the chronological ageing process, but also in photoaging. Destruction of the fibre network as well as stiffening by glycation (deposition of carbohydrate catabolites on the collagen macromolecule) represent only two fundamental stages in these processes. At the same time, with ageing, the collagen synthesis capacity decreases relative to its destruction (negative balance of the synthesis), which contributes, additionally, to the ageing of the skin organ. However, practice has shown that the use of collagen for cosmetic purposes causes some problems, at least for two reasons: collagen is an ingredient of animal origin, so it may be immunogenic and the collagen macromolecule has a reduced penetration into the skin, because of the large size of the molecule.

Oral administration of collagen peptides, resistant to gastrointestinal digestion, improves skin elasticity, texture, moisture, smoothness and softness. Also, hydrolysed collagen promotes the growth of its skin cells, extracellular matrix, and the formation of fibroblasts. It can slow down and reduce the effects of the ageing process: dryness, wrinkles, dullness and fading. The results of clinical studies indicate a high level of safety, absence of side effects and good tolerance of collagen in the composition of cosmetic preparations. They also show the complementary effect of local and oral use of collagen in improving the skin. Given that, collagen supplements are widely available but the need for nutraceutical supplements must be assessed on a case-by-case basis and it must be ensured that patients cannot use them uncontrollably. Additional longer-term studies with a larger sample of patients are required to sufficiently comprehend the efficacy of the various collagen applications.

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