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REVIEW ARTICLE

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Collagen: A review on its sources and potential cosmetic applications

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Summary

Collagen is a fibrillar protein that conforms the conjunctive and connective tissues in the human body, essentially skin, joints, and bones. This molecule is one of the most abundant in many of the living organisms due to its connective role in biological structures. Due to its abundance, strength and its directly proportional relation with skin aging, collagen has gained great interest in the cosmetic industry. It has been established that the collagen fibers are damaged with the pass of time, losing thickness and strength which has been strongly related with skin aging phenomena [Colágeno para todo. 60 y más. 2016. http://www.revista60ymas.es/InterPresent1/groups/revistas/documents/binario/ses330informe.pdf.]. As a solution, the cosmetic industry incorporated collagen as an ingredient of different treatments to enhance the user youth and well-being, and some common presentations are creams, nutritional supplement for bone and cartilage regeneration, vascular and cardiac reconstruction, skin replacement, and augmentation of soft skin among others [J App Pharm Sci. 2015;5:123-127]. Nowadays, the biomolecule can be obtained by extraction from natural sources such as plants and animals or by recombinant protein production systems including yeast, bacteria, mammalian cells, insects or plants, or artificial fibrils that mimic collagen characteristics like the artificial polymer commercially named as KOD. Because of its increased use, its market size is valued over USD 6.63 billion by 2025 [Collagen Market By Source (Bovine, Porcine, Poultry, Marine), Product (Gelatin, Hydrolyzed Collagen), Application (Food & Beverages, Healthcare, Cosmetics), By Region, And Segment Forecasts, 2014 – 2025. Grand View Research. http://www.grandviewresearch.com/industry-analysis/collagen-market. Published 2017.]. Nevertheless, there has been little effort on identifying which collagen types are the most suitable for cosmetic purposes, for which the present review will try to enlighten in a general scope this unattended matter.

KEYWORDS

animal sources, collagen, cosmetic industry, cosmetics, synthetic source

1 | BACKGROUND

Beauty has always been an aspect that marks society and its predicaments on physical aspects since a girl or a boy is born. As an example of this it can be encountered standards known as beauty marks, that can go from tattooed symbols in the skin as amozonic indigenous from Colombia consider, or radiant skin and curvy-skinny figures usually seen in occidental cultures.[1,2] Nowadays, young and healthy skin is beauty standard that generates the necessity of acceptance in consumers of this era, causing as a

consequence of the increase in research and acquisition of alternatives that will improve the skin texture to a desired smooth and young appearance.

Among the most common solutions available in the market, the consumer may encounter products such as skin peelings, facial creams, galvanic electricity, and the oral supplements with hydrolysate biomolecules[3] that can improve the skin condition. All these techniques converge in a common target, which translates to collagen production enhancement or replacement in the user skin.

Collagen is one of the most abundant proteins produced in the human body. It is responsible for the stability and strength of the body tissues by making support nets all along the cellular structures.[4] With the pass of time the fiber gets damaged and as one of the many effects, it gives the skin the undesirable wrinkle effect. After accurate research, it has been proven that damaged[5] fibers could be replaced by new ones when a subject ingested the hydrolyzed protein. This led to collagen production stimulation that helped the recovery and improved tissue appearance.[6,7] Thus, the cosmetic industry has made great efforts on incorporating this biomolecule on several available products.

It has been proven also that the collagen hydrolysate has shown bioactivities such as antioxidant properties, antihypertensive activity, lipid-lowering activity, as well as reparative properties in damaged skin.[8] Also, it has been observed that this particular presentation of collagen has a double action in the skin that in first instance provides the building block for elastin and collagen formation, and in second to act as ligands or binding receptors in fibroblasts to stimulate the prior-mentioned components and hyaluronic acid.[9]

It is important to mention that collagen has different types, and few efforts have been carried out to comprehend which types are the most suitable for cosmetic application. Through this review the reader can observe what types have been acknowledged until now, which ones are the most used in cosmetic industry, sources available, and future tendencies on the molecule usage in cosmetic industry in a general scope.

2 | OBJECTIVES

To comprehend which type of collagen and source is more suitable for the needs of cosmetic industry.

2.1 | Definition of collagen

According to Protein Data Bank, Collagen is the most abundant structural protein in the human body that gives support to various tissues such as tendons, skin, and teeth (collagen joined to mineral crystals). All proteins that have a structure based on three helix polypeptidic chains[10] (Figure 1) belong to the collagen family, being identified 26 types until now.[11]

The three polypeptidic fibrils can have a diameter of 10-500 nm,[12] an approximate molecular weight of 285 kDa,[13] with a length of 1400 amino acids that will characteristically have a glycine

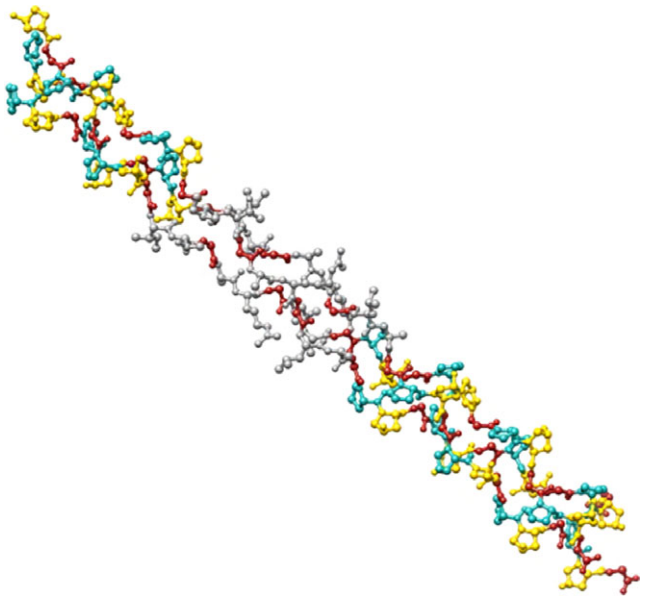

FIGURE 1 Collagen triple-helix structure[47]

every three residues,[14,15] aspects that give its characteristic fibrillar helicoidal structure.

Collagen fibers are commonly white, opaque, and readily recognized in tissues. It is considered as a viscoelastic material that possesses high tensile strength and low extensibility. Its isoelectric point is around pH 5.8[16]; and in terms of temperature, the shrinkage temperature (Ts) of most mammalian fibrils is between 62°C and 65°C, whereas fish fibrils Ts ranges from 38°C to 54°C. On the other hand, the denaturation temperature Tm is less by 25°C - 30°C than Ts.[17]

It is known that collagen is a molecule with low immunogenicity, diminishing the possibilities of not being accepted when ingested or injected to a foreign body. The only fractions capable of occasioning immune response are located in the helical region of the chains and in the telopeptide region.[18]

Even though this molecule has low antigenicity, it can be modified to eliminate any immune response. An alternative can be carried out by the elimination of banded structure through heat or chemical treatment[19] degradation of nonhelical section by proteinases or cross-linking.[20]

2.2 | Types of collagen and uses

Until now, the molecule has been classified in 26 different types that are grouped into eight families depending on its structure, chain bonding, and position in the human body. Among the classifications, it can be found the fibril-forming, basement membrane, microfibrillar, anchoring fibrils, hexagonal network-forming, fibril-associated collagens with interrupted triple helix [FACIT], transmembrane, and multiplexins.[11] The characteristical structure of the most commonly found groups is depicted in Figure 2.

These molecules have multiple applications. Among them, it has been described as an anchor in glass and beads for cell culture cell,

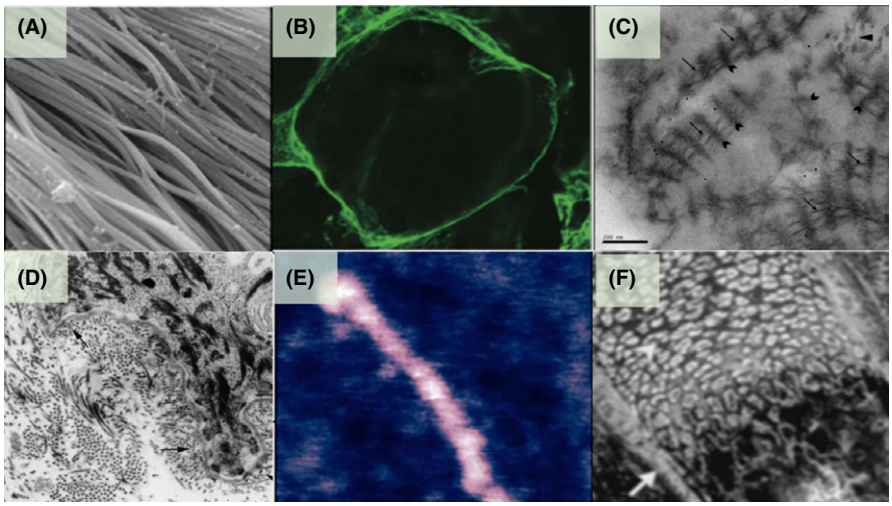

FIGURE 2 Microscopy of the most common collagen groups showing in A, fibril-forming (collagen type I),[48] B, basement membrane (collagen type IV),[49] C, microfibrillar (collagen type VI),[50] D, anchoring fibrils (collagen type VI),[51] E, FACIT(collagen type XIII),[52] F, transmembrane (collagen type XIII)[53]

as biomaterial for vascular prosthesis,[21] as microparticles for subcutaneous injection,[22] as regeneration of tissue scaffold,[22] and as feedstock for gelatin, glues, and cosmetics,[15] also for the production of oral administration hydrolysates,[3] and other many uses that are listed in Table 1.

Is important to mention that even though a great number of types have been discovered, only de fibril-forming types have been the most used nowadays for corrective purposes. In the cosmetic industry, collagen is an electable feedstock for cosmetic formulations because of its availability, biocompatibility, and biodegradability.[23] Reasons that make it an excellent option target in the aging process, which mainly happens in the dermis where collagens type I and III compose the 90% of this skin layer in a distribution of 60%-80% type I and 15%-20% type II.[24]

In the following sections, the most relevant collagen sources for cosmetic industry are going to be described, and collagens used for medical purposes will not be included because the present reviews scope focuses on cosmetic applications of collagen.

2.3 | Natural sources

Collagen sources can be obtained from animal and vegetable sources. From animal sources, the most common are bovine, porcine,[25] human collagen, and marine organism such as scale fish[8,9] and fish skin.[11] Among these animal sources, bovine collagen is commonly used as a temporary cover for extra-oral wounds[26] and also for the burns on the body. It has large applications because of its helpfulness and biocompatibility.[27] Porcine collagen matrices, on the contrary, have the potential to be useful for grafting of soft tissues.[28] It provides a biocompatible surgical material as an alternative to an autogenous transplant.[29]

Animal terrestrial sources comprise from chicken, kangaroo tail, rat tail tendons, duck feet, equine tendon, alligators bon/skin, bird's feet, sheepskin, and frog skin. Types I and II come from equine skin, cartilage, and flexor. Types I, II, III, and V come from chicken neck. Type IX is found in chicken embryo sternal cartilage, I and III from skin, and IV from muscular tissue.[30]

The mentioned sources are cheap and easy to acquire, but after prolonged use and concrete characterization, collagen of this sources tended to be allergenic and misfolded provoking several diseases such as osteogenesis imperfecta.[31,32] As a solution to this problem, some modifications were made to the molecule as mentioned in section 1, and also new sources were researched. Another feasible natural source is marine collagen. It has been reported that has no risk of transmitting diseases, it has been considered as GRAS (Generally recognized as safe) by the FDA,[33] and also is a cheap feedstock of production because many of the body parts that contain it, and end up as waste of human consumption. Some of the most common of marine collagen sources are listed in Table 2.

2.4 | Synthetic sources

Collagen is widely used to help blood clotting, healing, and tissue remodeling. Animal-derived (natural) collagen is used in many clinical applications, but there are some concerns with respect to its role in inflammation, batch-to-batch variability, and possible disease transfection.[18] To avoid immune problems, some synthetic sources have been found, for example, the material commercially named KOD.

This is a synthetic protein made of 36 amino acids that self-assemble into triple-helix nanofibers and hydrogels; it mimics natural collagen and it could improve upon commercial sponges or therapies based on naturally derived collagen. The sequence of the peptide is (Pro-**Lys**-Gly) (Pro-**Hyp**-Gly) (**Asp**-Hyp- Gly), and in single-letter amino acid, abbreviation is (P-**K**-G) (P-**O**- G) (**D**-O-G), giving it the name KOD (Figure 3).[18]

This material presents theoretical analogues to native collagen in protein structure and folding, as well as procoagulatory fractions that could promote platelet activation and adhesion.[18] It can be used as a hemostat or a clotting agent thanks to its capacity to trap red blood cells to stop bleeding. It also binds and activates platelets to form clots and promote healing without promoting inflammation.[34]

TABLE 1 Types of collagen and uses among the industry or functions in the human body

Family	Type	Distribution in tissue	Application/function
Fibril-forming	I	Tendon, ligaments, bone, and cornea	Membranes for guided tissue regeneration[54]
	II	Lung, cornea, reticular fibers, cartilage, vessel wall, nucleus pulposus, bone, vitreous body, and skin	Cartilage repair and arthritis treatment.[55]
	III		Hemostats and tissue sealants[30,55]
	V		Feedstock for biomaterial in corneal treatments[56]
	XI	Vitreous body and cartilage	mAbs development for osteoarthritis[57]
Basement membrane	IV	Basement membranes	Attachment enhancer of cell culture (mouse neuroblastoma)[58] and diabetic nephropathy indicator[59]
Microfibrillar	VI	Dermis, placenta, lungs, cartilage, intervertebral disk, and placenta.	Hemostat
Anchoring	VII	Oral mucous, cervix, dermal & epidermal junctions, and skin	Subdermal injection as treatment for dystrophic epidermolysis bullosa (DEB)[12]
FACIT	IX	Cornea, cartilage, and vitreous humor	It co-distributes with type II collagen in cartilage and the vitreous body.[11,60]
	XII	Tendon, perichondrium, and ligaments	Associated to collagen I-containing fibrils.[61] XIV collagen is also a fibril diameter regulator in early stages of fibrillogenesis[11]
	XIV	Vessel wall, placenta, liver, dermis, and lungs	
	XIX	Human rhabdomyosarcoma	Located in the basement membrane zone and show antiangiogenic and antitumoral properties.[61]
	XX	Embryonic skin, tendon, corneal epithelium, and sternal cartilage.	Similar to XII and XIV collagen types. The function of this collagen is relatively unknown.[27]
	XXI	Blood vessel wall	Closely related to XII, XIV, and XX collagens. Its expression is stimulated by platelet-derived growth factor, which indicates that this collagen might contribute to matrix assembly of vascular network during blood vessel formation.[29]
Transmembrane	XIII	Hair follicle, intestine, liver, dermal & epidermal junctions, epidermis, and lungs	Affects bone formation and may have a function in coupling the regulation of bone mass to mechanical use.[61] Involved in inflammation and vasculogenesis.[27]
	XVII	dermal & epidermal junctions	Its putative function is to stabilize adhesion of epithelial cells to the surrounding extracellular matrix. It has important roles in teeth formation[27]
Multiplexins	XV	Kidney, smooth muscle cells, fibroblasts, and pancreas.	It forms a bridge linking large, banded fibrils, likely fibrils containing collagens I and III.[61]
	XVI	Keratinocytes and fibroblasts	As it has been implicated in several diseases, it can be possibly used as a drug target or biomarker.[62]
	XVIII	Liver and lungs	It has major role in determining retinal structure and in closure of the neural tube.[62]

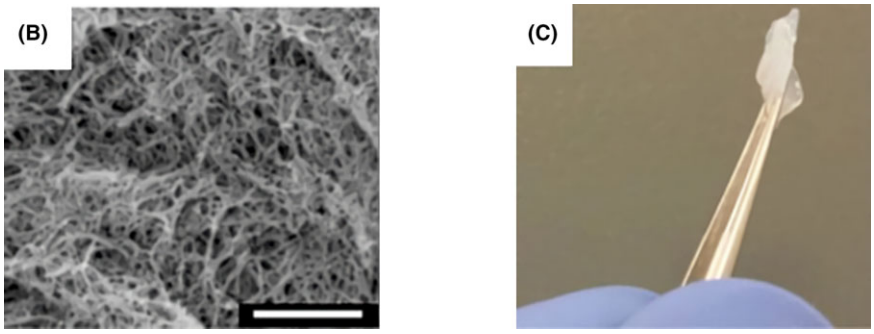

FIGURE 3 (A) (Fiber networks resembling native collagen (SEM, scale bar 1 μm). (B) Synthetic collagen matrices form a rigid gel that is resistant to mechanical handling by tweezers and other methods[13]

Another synthetic source for collagen has been developed using recombinant technology to produce high quality and animal-derived contaminant-free collagens.

These recombinant collagens have been produced in mammalian cells, insect cell cultures, yeast, and mostly in plant cell culture. The production of plant-derived recombinant collagen has been reported

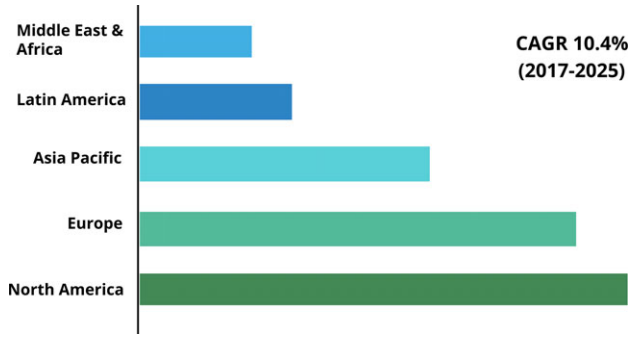

FIGURE 4 Global tissue-engineered collagen biomaterial market revenue[36]

TABLE 2 Marine sources of collagen and species feasible for extraction[42]

Source	Tissue
Fish	Skin, bones, fins, and scales up to 50%-70%. spp—Baltic cod skin. Seared fish, black drum, and sheepshead seabream collagen type I
Marine Sponge	Fibrillar collagen source in organic components of the sponge. Rich source of collagens I and IV spp—*Geodia cydonium*, *Speriditae*, and *Icinia fusca*
Jelly fish	Has a 60% of collagen mostly types IV, V and II. spp—*Rhopilema asamushi*, *Stomolophus meleagris*, *Catostylus tagi*, and *Rhizostoma pulmo*

using tobacco, transgenic maize seed, and barley.[35] They have been used in bone, ocular, and skin applications mostly as sponges, but also more recently as fibers and gels, and have been compared favorably with animal collagens in terms of process ability and therapeutic efficacy. Even though these are promising signs, recombinant technologies have some disadvantages such as high cost, low yield, and the lack of cofactors or enzymes in the systems, which are critical to the stable formation of biofunctional and bioactive collagens. These deficiencies have made animal collagen to remain as the standard for use in both research and clinical fields.[36]

Although some synthetic sources for collagen have been found, there is another alternative natural safe source: marine animals. The bones, skin, fins, scales of fresh or saltwater fishes, starfish, jellyfish, sponges, sea urchin, octopus, squid, cuttlefish, sea anemone, and prawn are mainly used for this purpose, and these have got ample advantages over the land animal sources such as greater absorption due to low molecular weight, almost negligible presence of biological contaminants and toxins, low inflammatory response, among others.[22] Some natural safe sources of collagens and the species where they can be found at are listed in Table 2.

These marine collagens were considered good alternative sources because there is no risk of disease transmission, and they have a high yield. Nevertheless, the use of collagen in diverse applications often depends on thermal stability, which is related with body temperature and living environment of the organism. Marine collagen and its low thermal stability limit its applications.[37]

2.5 | Collagen in cosmetic industry

As mentioned before, collagen has been recognized for its biological action, with a great potential to be used in the cosmetic, pharmaceutical, and clinical fields.[38] The major, most abundant collagens are types I, II, and III; they form the structural fibrils of tissues, while the others only take part in the association of these fibrils with others.[21] For this reason, the other types of collagen have not been used for cosmetic solutions.

As for fibril-forming collagen, type I is the most used on product manufacturing in several cosmetic applications as it is considered to be the gold standard due to its high biocompatibility with the human body.[22] It has been reported that in tissue engineering, biomaterials are based on fibril-forming collagen mainly (type I, II, III, V, XI). Also, collagen type I is used as an ingredient in cosmetics, dental composites, skin regeneration templates, biodegradable matrices, and collagen shields in the field of ophthalmology. Other noncosmetic reported applications have been its use as solid-support microcarrier in the production of enzymes.[39]

As to collagen sources, researchers and developers are focusing on different sources to avoid the use of bovine collagen this due, as mentioned priorly, to the protein misfolding and allergenicity. For instance, marine collagen (type I) is being presented as excellent functional ingredients, also because its source is cheap and avoids bovine spongiform encephalopathy (BSE)[40] making it an appealing option for product developers.

Because of this, it has started to be used in fields that require high efficiency and biocompatibility. For example, in the medical field, it is often used for implants such as artificial skin grafts, wound dressings, and nerve conduits due to its low immunogenicity.[41] Now in cosmetics, its properties take to the development of creams and gels with high moisturizing action, but other activities are also foreseen, such as anti-aging, antiwrinkling, UV radiation protectors, and healing of wounds among other applications.[41] Its inclusion in cosmetic formulations has to do with its film-forming properties, when applied covers the skin and decreases the transepidermal water loss, protecting skin from corrosive elements.[42]

In spite of the risk of BSE, bovine collagen is still a commonly used source for extraction and synthesis of collagen-based products. Porcine source category is the second most commonly used source for the extraction of collagen and related products; nevertheless, the marine collagen segment is anticipated to grow and take the first place at the fastest rate during the forecast years.[43]

2.6 | Conclusions—future perspectives

Collagen is the most abundant protein found in the animal kingdom, and there are different types identified that have specific functions in our body; each type of collagen exhibits different distinctiveness based on their structural features.[22] Collagen-based biomaterials are very important for tissue engineering and regenerative medicine because of its superior biocompatibility and low immunogenicity[44] due to the sources where collagen is taken from.

Many more types of this protein are yet to be found out as well as alternative sources to avoid outbreaks of transmissible diseases and immune problems.[40] Because of this, research is still on its way to identify the various unexplored sources of collagen[22] that can be used in the future.

In 2016, the global collagen market (Figure 4) size was estimated at USD 3.71 billion and is expected to witness an important growth over the next years, and it is anticipated to reach USD 6.63 billion by 2025. This is mainly as a result of the growing demand of beverages and food, cosmetics, and health care, among others previously mentioned; this growth can be attributed to the growing global population.[41] The global tissue-engineered collagen biomaterial market will likely progress at a robust CAGR (compound annual growth rate) of 10.4% during the period between 2017 and 2025.[42]

It is important to say that because of all the types of collagens now exist, all cosmetic and pharmaceutical products should indicate which type they are using in their formula and why. Not only to know what role it is going to have in the body but also because of the sources where the used collagen was taken from that could interfere with the patient homeostasis.

All the natural sources of collagen that have been found as well as the development of synthetic sources had a great impact on the collagen industry. It is expected that it will expand more and more in the next years, opening in these way, new strong and interesting opportunities in the research field applicable to the cosmetic industry.

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