

Collagen – A Review

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ABSTRACT

Collagen is a fibrillar protein that forms the connective and conjunctive tissues in humans, essentially bones, joints and skin. Collagen is the mostly available in majority of the living things suitable for its connective function in biological structures. Due to its large quantity, potency and its direct proportionality with skin aging, collagen has obtained obvious attention in cosmetic industry. It is recognized that collagen fibers are prone for damage with time, loses its thickness and potency which is abundantly related to skin aging criteria. The utilization of nutraceuticals such as collagen specifically for skincare is in rise, but complete regulations are deficient on its quality, efficacy and absorption. There are numerous possible health uses that nutraceuticals supplements can offer. However, researchers have not completely studied the assumed health benefits. As with any supplements, the Food and Drug Administration (FDA) did not confirm the allegations that a cosmetic or Pharmaceutical company makes on how sound their collagen products actually work. This review covers the basic concepts and chemistry of collagen. This provides a thorough knowledge on collagen and its chemical composition for further research.

KEYWORDS: *Collagen, macromolecule, amino acid, supplement, protein, structure.*

1. INTRODUCTION

Collagen

Collagen makes up concerning twenty fifth to thirty fifth of the whole-body macromolecule content in cellular animals. Being major macromolecule of connective tissues in animals, collagen (albuminoid) is cosmopolitan in skin, bones, teeth, tendons, ligament, cartilage, eyes, blood vessels, gut, inter-vertebral discs and most alternative tissues and the most abundant family is the collagens with more than 20 different collagen types identified so far.

Recently, aboard clarification of the biological functions of collagen as Associate in Nursing animate thing matrix macromolecule, it's been attracting attention as a biomaterial with several distinctive characteristic like high durability, low antigenicity, bioresorbability, smart biocompatibility, induces natural process of blood platelets, affects cell differentiation, wound healing, management of varied characteristics through physical and chemical modifications, mouldability, thick and simple for purification. The skin of vertebrates and invertebrates square measure the most supply of collagen used for pharmaceutical, cosmetic and medicine analysis [1].

“Collagen” is generated from the Greek words– “kola”, which means “glue”, and suffix–gen, means “producing”. It’s got a spread of medicine and pharmaceutical applications. Their applications embody treatment of pain related to degenerative joint disease, cardiovascular disease, use in tissue engineering, implants in human, inhibition of angiogenic diseases, etc. it's additionally used as dermal filler, as haemostat, for drug delivery, skin substitutes, expandable intra-arterial stents and cell attachment substrate [2].

Its contents vary, looking on fish species. The physical and chemical properties of collagen disagree looking on the tissues like skin, air bladder & the myocommata in muscle. Fish collagen is heat sensitive because of labile cross links as compared to mammals; the amino acid content is lower, varied from 4-10%.The amount of amino acids, particularly amino acid, depends on the environmental temperature within which the fish lives and it affects the thermal stability of the collagens and gelatines. Collagens which are derived from fishes living at cold temperatures contain lower amounts of amino acid and that they exhibit lower thermal stability than those from fish living in heat environments. This can be attributable to the involvement of amino acid in inter-chain atomic number 1 bonding, which stabilizes the triple spiral structure of collagen. Collagen film proved as a promising carrier for antitumor drug delivery system and ophthalmic drug delivery system attributable to its immobility, structural stability and smart biocompatibility [3].

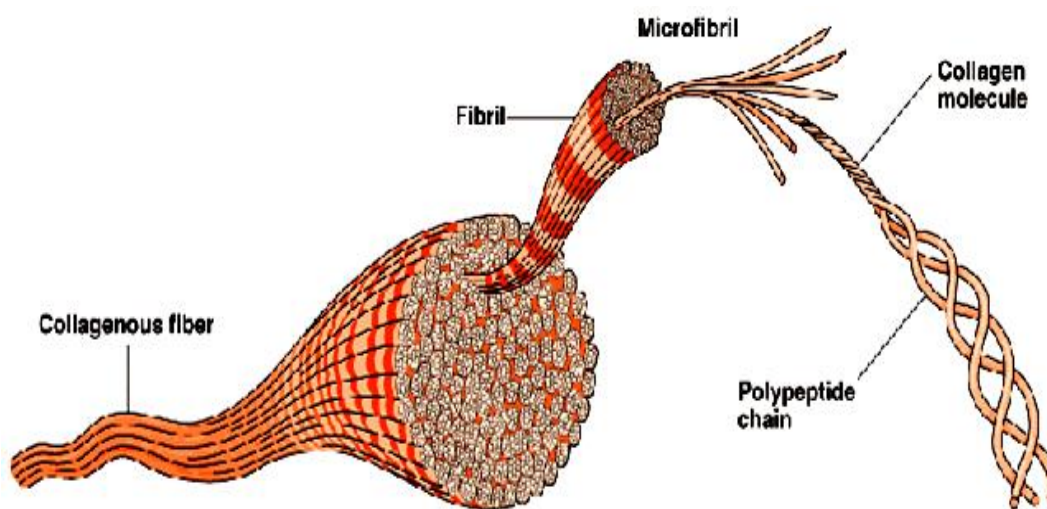


Figure 1. Collagen

Characteristics of Collagen

The collagen family has been well delineated and section provides a short discussion of collagens, specializing in their body and characteristics. In humans, twenty nine distinct collagen sorts are known so far on the idea of macromolecule and/or desoxyribonucleic acid sequence data. Data of collagen types and other few tissues within which they are established is illustrated in Table 1.

Medical applications of collagen utilize preparations containing pure types of collagen in an exceedingly high magnitude relation that reflects the composition of the tissue from that the collagen was isolated. For example, a poster scale technique was used for the withdrawal of collagen from bovine origin [4].

Collagen

Collagen accounts for concerning 1/3 of the macromolecule of humans and of the dry weight of skin. To date, twenty nine kinds of differing types of Collagen are known (type XXIX belongs to the category of collagens containing von Willebrand issue type X domains¹¹), and every one of them show a triple-helical tertiary structure. They can be separated into many teams consistent with the structure they form:-

- I. **Fibrillar (Type I, II, III, V, XI)**
- II. **Non-fibrillar:**
 - Fibril connected Collagens with broken up Triple Helices. (FACIT) (Type IX, XII, XIV, XIX, XXI)
 - Short chain (Type VIII, X)
 - Basement membrane (Type IV)
 - Multiplex in (Multiple Triple Helix domains with Interruptions) (Type XV, XVIII)
 - Membrane-Associated Collagens with Interrupted Triple Helices. (MACIT) (Type XIII, XVII)
 - Other (Type VI, VII) [4].

Table 1. Collagen types and Tissues

S. No.	Collagen type	Tissues
1	Type I	Most connective tissues, i.e., bones, tendon, skin, blood vessels, etc.
2	Type II	Cartilage and vitreous of the attention
3	Type III	Blood vessels
4	Type IV	Basement membranes all told organs
5	Type V	Tendons, cornea, and opening tissues
6	Type VI	Liver, kidney, and perichondrium
7	Type V II	Epidermal/dermal junction
8	Type VIII	Endothelial cells
9	Type IX	Cartilage
10	Type X	Hypertrophic and mineralizing gristle
11	Type XI	Cartilage
12	Type XII	Tendons and fibre associated albuminoid
13	Type XIII	Epidermis, hair follicles, and nail root cells
14	Type XIV	Most connective tissues, i.e., bones, skin, tendon, blood

		vessels, etc. (Same as kind I)
15	Type XV	Many tissues, similarity to kind XVIII
16	Type XVI	Under study
17	Type XVII	Hemidesmosomes and skin
18	Type XVIII	Liver and urinary organ
19	Type XIX	Eyes, brain, testes, and embryonic tissues
20	Type XX-XXIX	Unknown

Structure of Collagen

Collagen protein consists of a triple helix that typically consists of two chains, identical chains (α_1) and an extra chain (α_2) that differs slightly in its chemical composition. At molecular level one finds tropocollagen, that would be a fractional unit of measurement of the add of collagen that forms fibrils that unit 300 nm long and 1.5 nm in diameter, consisting 3 peptide strands remarked as alpha chains. It's roughly 300 nm long and 1.5 nm in diameter and it's created of three peptide strands. Every of these strands possess the conformation of a left-handed helix, before obtaining twisted along into a right-handed coiled-coil, that's thought as triple-helix or super helix [5].

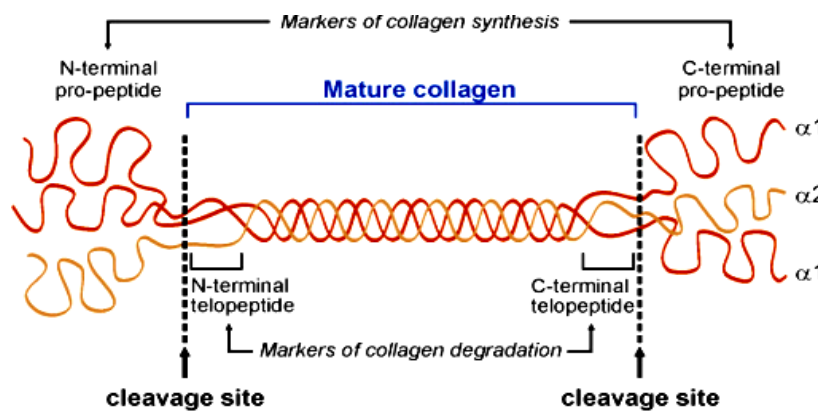


Figure 2. Structure of collagen

However, the foremost distinguishable feature of the collagen in its regular arrangement of amino acids, wherever a sequence following a pattern like Gly-Pro-X or Gly-X-Hyp area unit determined, wherever X is additionally the variant of different organic compound residues. One sixth of such sequences unit founded by Proline or hydroxyproline, whereas glycine accounts for 1/3rd of the same. The aminoalkanoic acid composition of a collagen is atypical for proteins, significantly with relevance its high aminoalkanoic acid content [6].

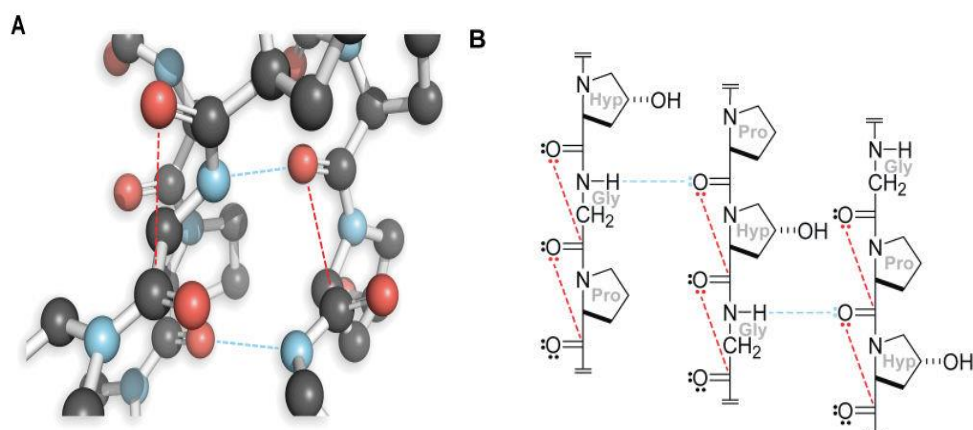


Figure 3. Structure of triple-helical collagen. Hydrogen bonds, blue dashed lines; $n \rightarrow \pi^*$ interactions

These amino acids unit organized in an exceedingly reiterative tripeptide sequence, Gly-X-Y, within which X is any aminoalkanoic acid, however is commonly a proline and Y is usually a hydroxyproline or Hydroxylysine. the three α -chains that type the right-handed super helix have one staggered residue between adjacent chains, and arranged as in an exceedingly super coil spherical a regular central axis in an exceedingly right-handed thanks to provide the triple helix structure. The triple helical collagen domain is characterised by a glycine in each third position of the peptide chain that makes a (Gly-X-Y) $_n$ repeat structure. Fibril-forming collagens unit concerning cardinal organic compound residues long and have a perfect Gly-X-Y triplet structure. For non-fibrillar collagens, all of them have a minimum of 1 interruption within the triple helices. N-peptide or N-propeptide is that the amino finish of a fibrillar collagen. It normally consists of a minimum of 1 little triple spiral domain, remarked because the minor helix [7].

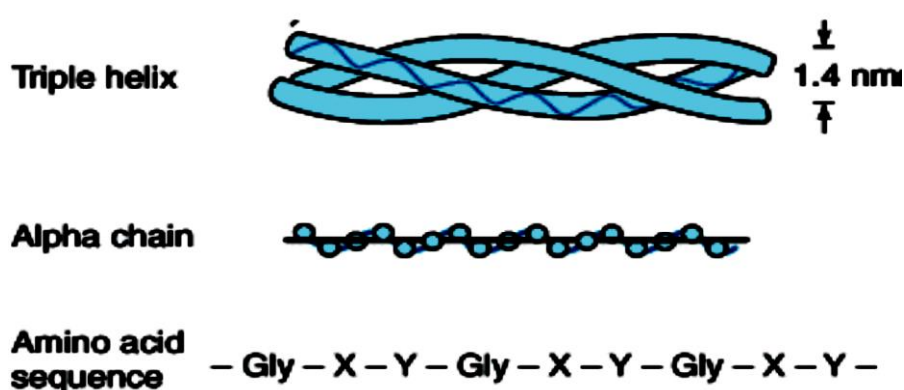


Figure 4. Molecular structure of triple-helical collagen

The name “collagen” is utilized as a generic term for proteins typing a characteristic triple helix of three peptide chains and each one members of the collagen family form these supramolecular structures within the physical object matrix though their size, operate and

tissue distribution vary significantly. So far, twenty nine genetically distinct collagen sorts are delineate.

Based on their structure and supramolecular organization, they'll be sorted into fibril-forming collagens, fibril-associated collagens (FACIT), network- forming collagens, anchoring fibrils, transmembrane collagens, basement membrane collagens et al with distinctive functions [7].

Table 2. Vertebrate Collagens

Type	Class	Composition	Distribution	Pathology
I	Fibrillar	$\alpha 1[\text{I}]2\alpha 2[\text{I}]$	Abundant and widespread: dermis, bone, tendon, ligament	OI, Ehlers–Danlos syndrome, osteoporosis
II	Fibrillar	$\alpha 1[\text{II}]3$	Cartilage, vitreous	Osteoarthritis, chondrodysplasias
III	Fibrillar	$\alpha 1[\text{III}]3$	Skin, blood vessels, intestine	Ehlers-Danlos syndrome, arterial aneurysms
IV	Network	$\alpha 1[\text{IV}]2$ $\alpha 2[\text{IV}]$ $\alpha 3[\text{IV}]\alpha 4[\text{IV}]$ $\alpha 5[\text{IV}]$ $\alpha 5[\text{IV}]2$ $\alpha 6[\text{IV}]$	Basement membranes	Alport syndrome
V	Fibrillar	$\alpha 1[\text{V}]3$ $\alpha 1[\text{V}]2\alpha 2[\text{V}]$ $\alpha 1[\text{V}]\alpha 2[\text{V}]\alpha 3[\text{V}]$	Widespread: bone, cartilage, cornea, dermis	Bethlem myopathy
VI	Network	$\alpha 1[\text{VI}]\alpha 2[\text{VI}]$ $\alpha 3[\text{VI}]d$ $\alpha 1[\text{VI}]\alpha 2[\text{VI}]$ $\alpha 4[\text{VI}]$	Widespread: bone, cartilage, cornea, dermis	Bethlem myopathy
VII	Anchoring fibrils	$\alpha 1[\text{VII}]2$ $\alpha 2[\text{VII}]$	Dermis, bladder	Epidermolysis bullosa acquisita
VIII	Network	$\alpha 1[\text{VIII}]3$ $\alpha 2[\text{VIII}]3$ $\alpha 1[\text{VIII}]2$ $\alpha 2[\text{VIII}]$	Widespread: dermis, brain, heart, kidney	Fuchs endothelia corneal dystrophy
IX	FACIT	$\alpha 1[\text{IX}] \alpha 2[\text{IX}]$ $\alpha 3[\text{IX}]$	Cartilage, cornea, vitreous	Osteoarthritis, multiple epiphyseal dysplasia
X	Network	$\alpha 1[\text{X}]3$	Cartilage	Chondrodysplasia
XI	Fibrillar	$\alpha 1[\text{XI}] \alpha 2[\text{XI}]$ $\alpha 3[\text{XI}]$	Cartilage, intervertebral disc	Chondrodysplasia, osteoarthritis

XII	FACIT	$\alpha 1$ [XII]3	Dermis, tendon	—
XIII	MACIT	—	Endothelial cells, dermis, eye, heart	—
XIV	FACIT	$\alpha 1$ [XVII]3	Widespread: bone, dermis, cartilage	—
XV	MULTIPLEX IN	—	Capillaries, testis, kidney, heart	—
XVI	FACIT	—	Dermis, kidney	—
XVII	MACIT	$\alpha 1$ [XVII]3	Hemidesmosomes in epithelia	Generalized atrophic epidermolysis bullosa
XVIII	MULTIPLEX IN	—	Basement membrane, liver	Knobloch syndrome
XIX	FACIT	—	Basement membrane	—
XX	FACIT	—	Cornea (chick)	—
XXI	FACIT	—	Stomach, kidney	—
XXII	FACIT	—	Tissue junctions	—
XXIII	MACIT	—	Heart, retina	—
XXIV	Fibrillar	—	Bone, cornea	—
XXV	MACIT	—	Brain, heart, testis	Amyloid formation
XXVI	FACIT	—	Testis, ovary	—
XXVII	Fibrillar	—	Cartilage	—
XXVII I	—	—	Dermis, sciatic nerve	Neurodegenerative disease

Chemistry of Collagen

It consists of a triple helix, which generally consists of two similar chains ($\alpha 1$) and an extra chain that varies slightly in its chemical composition ($\alpha 2$). Organic compound makeup of collagen is uncharacteristic for proteins, mainly considerably to its hydroxyproline substance. The final motifs within the amino acid series of collagen square determine glycine-proline-X and glycine-X-hydroxyproline. [Table 3]

Table 3. The common aminoalkanoic acid composition for fish and mammal skin

S. No.	Amino acid	Abundance in mammal skin (residues/ 1000)	Abundance in fish skin (residues/ 1000)
1	Valine	22	21
2	Tyrosine	3	3
3	Tryptophan	0	0
4	Threonine	19	26
5	Serine	36	46
6	Proline	129	108
7	Phenylalanine	13	14
8	Methionine	6	13

9	Lysine	29	26
10	Leucine	24	23
11	Isoleucine	11	11
12	Hydroxyproline	95	67
13	Hydroxylysine	6	8
14	Histidine	5	7
15	Glycine	329	339
16	Glutamic acid	74	76
17	Cysteine	1	1
18	Aspartic acid	47	47
19	Arginine	49	52
20	Alanine	109	114

Source of Collagen

Bovine and porcine skins square measure the most industrial sources for collagen production. Ranging from the 1930s, the primary stuff to be used for the assembly of collagen was porcine skin, and to the present day, the foremost vital stuff for large-scale industrial productions continues to be porcine skin. Porcine skin collagens are rumoured to contain bovine spongiform neurological disease (BSE), whereas fish collagen encompasses a lower risk of getting unknown pathogens like animal disease. Besides, religious sentiments for the Jewish and Islamic believers whom proscribe the consumption secular of pork, whereas Hindus forbid the consumption of cow product, have caused pessimism and considerations among customers to use class collagen as a supply. Therefore, plenty of researches are done to seek out an alternate supply of collagen. So far, fish waste collagen was found to own the foremost similar characteristics to class collage [8].

Uses of Collagens

Medical Uses: Cardiac applications:-

The collagenous cardiac skeleton which has the four heart valve rings is histologically, elastically and unambiguously absolute to heart muscle. The cardiac skeleton additionally includes the separating septa of the centre chambers – the interventricular septum and the chamber septum.

Cosmetic Surgery:-

Collagen has been wide employed in cosmetic surgery (facelift), as a healing aid for burn patients for reconstruction of bone and a good form of dental, orthopedic, and surgical functions. Each human and bovine scleroprotein (collagen) is wide used as dermal fillers for treatment of wrinkles and skin aging. Some points of interest are:

1. Once used cosmetically, there's an opportunity of sensitivity inflicting prolonged redness; but, this could be just about eliminated by straightforward and inconspicuous patch testing before cosmetic use.
2. Most medical collagen comes from young oxen (bovine) from certified BSE-free animals. Most makers use donor animals from either "closed herds", or from countries that have not had an according case of mad cow disease like Australia, Brazil, and New Zealand.

Bone Grafts:-

As the skeleton forms the structure of the body, it's very important that it maintains its strength, even when breaks and injuries. Collagen is employed in bone graft because it includes a triple coiling structure, creating it an awfully robust molecule. It's ideal to be used in bones, because it doesn't compromise the structural integrity of the skeleton. The triple coiling structure of collagen prevents it from being diminished by enzymes, it permits adherence of cells and it's vital for the correct assembly of the living thing matrix [9].

Tissue Regeneration:-

Collagen scaffolds are employed in tissue regeneration, whether or not in sponges, skinny sheets, or gels. Collagen has the proper properties for tissue regeneration like pore structure, porousness, hydrophilicity and its stable in vivo. Collagen scaffolds are ideal for the deposition of cells, like osteoblasts and fibroblasts and once inserted growth is in a position to continue as traditional within the tissue.

Reconstructive Surgical Uses:-

Collagens are wide utilized within the construction of the synthetic skin substitutes employed in the management of severe burns and wounds. These collagens is also derived from bovine, equine, porcine, or maybe human sources; and are typically employed in combination with silicones, glycosaminoglycans, fibroblasts, growth factors and alternative substances.

Wound Healing:-

Collagen is one amongst the body's key natural resources and an element of skin tissue that may profit all stages of the wound healing method. Once collagen is created on the market to the wound bed, closure will occur. Wound deterioration, followed typically by procedures like amputation, will so be avoided.

Collagen could be a natural product, so it's used as a natural wound dressing and has properties that artificial wound dressings don't have. It's resistant against microorganism, that is of significant importance in a very wound dressing. It helps to stay the wound sterile, as a result of its aptitude to fight infection. Once collagen is employed as a burn dressing, healthy granulation is in a position to make terribly quickly over the burn, serving to it to heal apace [10].

Throughout the four phases of wound healing, collagen performs the subsequent functions in wound healing:

- Guiding function: collagen fibres serve to guide fibroblasts. Fibroblasts migrate on an animal tissue matrix.
- Chemotactic properties: the big expanse on the market on collagen fibres will attract fibrogenic cells that facilitate in healing.
- Nucleation: collagen, within the presence of sure neutral salt molecules will act as a nucleating agent inflicting formation of fibrillar structures. A collagen wound dressing may function as a guide for homing new collagen deposition and capillary growth.
- Haemostatic properties: Blood platelets act with the collagen to create a haemostatic plug.

Collagen Supplementation

In spite of its high quantity in humans, collagen has turn out to be one of the top-sold supplements alleged to progress nails, hair and skin, which are the key machinery of the

maintenance of youth. Collagen initially noticed as a key excipient in skin care preparations. But, its efficiency as skin application formulation was a disbelief by dermatologists also. Collagen fibers have huge structure that should permeate through skin's outermost layers, and this will be a disadvantage for collagen.

Collagen supplements administered through oral route in the form of tablets and powders are supposed to be highly and effectively accumulated in the body. Collagen peptides and hydrolyzed collagen are the broken forms of collagen that is proven to be more absorbed when compared to topical forms. Major research with respect to collagen supplements is connected to joint care and skin wellbeing. A few randomized controlled clinical trials confirmed that collagen supplements progress skin elasticity but research on human beings is still lacking. Other few clinical studies have confirmed that the supplements are involved in improving joint movements and joint pain reduction such as with osteoarthritis or in athletes. But surprisingly drawback of collagen supplements is unknown. In the U.S., the supplement industry is not yet regulated by the Food and Drug Administration, and on the top there are few concerns of collagen supplements containing heavy metals.

2. CONCLUSION

Collagen is a protein with connective role and is highly abundant in many of the living organisms. Because of its abundance, strength and its relation with respect to skin aging, collagen has gained much interest in cosmetic industry. It's studied that collagen fibres degrade with time and lose its strength and thickness, these parameters are directly related to skin aging. This led to research and the cosmetic industry utilized collagen as one of the key ingredients in treating various skins and aging related issues. The collagen is incorporated in cream, solution, tablets (Nutritional supplements) and other formulations for the well being and beauty of the human. Therapeutically it is also involved in bone and cartilage renewal, vascular and cardiac rebuilding, skin substitution, and intensification of soft skin. Its market dimension is valued greater than USD 6.63 billion by 2025 because of its intensified use. Nevertheless, there has been tiny attempt on recognizing which types of collagen are the utmost suitable for cosmetic rationale for which the current review will try to make clear in a general possibility to understand this unattended matter.

3. ACKNOWLEDGMENT

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