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COLLAGEN SUPPLEMENTATION: THERAPY FOR SKIN DISORDERS: A REVIEW

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ABSTRACT

The term cosmeceutical was first coined by Albert Kligman in 1984 to describe topical products that afford both cosmetic and therapeutic benefits. However, beauty comes from the inside. Therefore, for some time scientists have considered how nutrition reflects healthy skin and the aging process. The more recent link between nutrition and skin aging began in earnest around the year 2000 with the demonstrated increase in peer-reviewed scientific journal reports on this topic that included biochemical and molecular mechanisms of action. Thus, the application of: (a) topical administration from outside into the skin and (b) inside by oral consumption of nutritionals to the outer skin layers is now common place and many journal reports exhibit significant improvement for both on a variety of dermal parameters. Therefore, this review covers, where applicable, the history, chemical structure, and sources such as biological and biomedical properties in the skin along with animal and clinical data on the oral applications of: (a) collagen.

1. INTRODUCTION

Human skin is the largest organ of the body covering approximately 1.5–2.0 square meters and functions as a physical barrier to protect the body from pathogens, chemicals, physical agents, and solar ultraviolet (UV) radiation throughout life.[1–3] Additionally, a recent review by Slominski et al., 2018, described how UV light touches the brain and endocrine system through the skin.[4] The stratum corneum composed of 15 to 20 layers of corneocytes (dead cells) containing filamentous keratin in the outermost layer of the epidermis is a formidable barrier.[1,5] The skin layers also provide essential physiological functions including immune defense, free radical detoxifying enzymes, antioxidant molecules, thermoregulation, prevention of excessive water loss, sensory input via mechanoreceptors, and endocrine

(production of vitamin D) and metabolic mechanisms to sustain optimal health.[1,5–8] Lastly, the keratinocytes express a wide array of molecules including cytokines, growth factors and receptors.[5,9] There are several reviews on human skin aging (intrinsic or chronological and extrinsic or photo) that adequately cover this topic in more detail including the biochemical and molecular mechanisms that have been reported elsewhere.[1–3,9,10]

Topical Application of Cosmetics, Cosmeceuticals, and Oral Supplementation via Nutritionals

While the history of cosmetics goes back to early Egyptian times for hygiene and health benefits, the history of topical applications that provide a medicinal treatment to combat dermal aging is relatively new.[11,12] For example, the concept of cosmeceuticals represents the blending of cosmetics and pharmaceuticals. The term cosmeceutical was first coined by Albert Kligman in 1984 to describe topical products that afford both cosmetic and therapeutic benefits.[12] However, beauty comes from the inside, which means, for some time, scientists have considered how nutrition reflects healthy skin and the aging process.[12] The more recent link between nutrition and skin aging began in earnest around the year 2000 with the demonstrated increase in peer-reviewed scientific journal reports on this topic.[12] Thus, the application of: (a) topical administration from outside to inside the skin and (b) the inside by oral consumption of nutritionals to the outer skin layers is now common place and many journal reports exhibit significant improvement for both on a variety of dermal parameters.[11,13–17] This review covers, where applicable, the history, chemical structure and sources, biological and biomedical properties in the skin, and, lastly, animal and clinical data on the oral applications of: (a) collagen, (b) ceramide, (c) β-carotene, (d) astaxanthin, (e) coenzyme Q10, (f) colostrum, (g) zinc, and (h) selenium in their mode of action or function in improving skin health and various dermal endpoints. Since the oral application of collagen is relatively new compared to the other topics, this section is presented in more detail. Lastly, the importance of the human skin microbiome is briefly discussed in reference to the genomics, measurement, and factors influencing its expression and how it may alter the immune system, various dermal disorders, and potentially be involved in chemoprevention.

2. Collagen

Collagen is the most abundant protein in the human body where it is responsible for structure, stability, and strength especially within the dermal layers.[1–3,9,18] The discovery by Wyckoff et al. and Clark et al. in the mid-1930s demonstrated that collagen was composed of a regular

structure at the molecular level.[19,20] With regard to aging, the deposition of collagen (and elastin) decreases with chronological-aging (with the passage of time) and particularly with photo-aging (exposure to the sun).[1–3,9] In addition, it can be broken down by hydrolyzing proteins such as matrix metalloproteinases (MMPs), which results in dermal damage and undesirable skin wrinkles.[1–3] The cosmetic industry's focus on enhancing collagen is known to improve the appearance of the skin especially in the facial and neck areas. Collagen is not only used in the cosmetic industry, but it is also used in pharmaceuticals and the beverage, food, and health care sectors driving the growth of collagen's use worldwide with the current global market estimated in USD at 3.7 billion and an estimated growth to over 6.6 billion by 2025.[21]

2.1. Structure of collagen

Collagen provides support to various tissues such as tendons, ligaments, skin, teeth, and many other connective tissue structures. So far, 28 types of collagen have been identified and described that can be grouped into eight families depending on its structure.[1–3,18,21] All collagen proteins have a structure based on three helical polypeptide chains with glycine (Gly) occurring every three amino acid residues while proline (Pro) and hydroxyproline (Hyp) make up about 1/6 of the total sequence of collagen.[21,22] The sequence often follows the pattern Gly-Pro-X or Gly-X-Hyp where X may be any of various other amino acid residues.[22] A typical collagen triple-helix structure can have a diameter of 10 to 500 nm, an approximate molecular weight of 285 kDa, and is composed of 1400 amino acids.[21] Collagen is a viscoelastic material with high tensile strength with low immunogenicity where it can be ingested or injected into a foreign body and can be further modified to eliminate any immune response by heat or chemical treatment.[1,21]

2.2. Sources of collagen

Collagen can be obtained from animal and vegetable sources with the most common coming from bovine, porcine, human, and marine organisms such as fish scale and fish skin.[21] There are also synthetic sources of collagen that is commercially known as "KOD" to avoid immune problems.[21,22] These recombinant collagens have been produced from mammalian, insect, yeast, and plant cell cultures.[21] Marine sources of collagen, which have advantages over animal sources due to their greater absorption from their low molecular weight, and negligible biological contaminants such as toxins and low inflammatory effects are more feasible for commercial extraction.[21,22]

2.3. Biological/Biomedical properties of collagen

It is known that collagen hydrolysate has several positive biological properties such as antioxidant, antihypertensive, and lipid-lowering activities as well as the established reparative actions in damaged skin.[1–3,21] Furthermore, collagen has a dual action in the skin where it first provides the building block components for collagen (and elastin) and, secondly, it binds receptors in fibroblasts located in the dermal layers to stimulate the synthesis of collagen and elastin as well as hyaluronic acid.[1–3,21]

2.4. In vitro studies

Collagen Enhances Fibroblasts and Extracellular Matrix Proteins and Decreases Metalloproteinases (MMPs) Since fibroblasts located in the dermal layers of mammals synthesize and release a variety to extracellular matrix proteins that improve skin health, there has been a focus on this theme where investigators have examined how collagen supplementation in vitro may result in positive changes in skin and skin-related parameters. There are several in vitro studies that have been reported where collagen enhanced fibroblast activities, increased collagen levels to improve collagen's structural properties, and inhibited MMPs. These have been reviewed.[1,2,21,22] In 2018, Zague et al. reported that collagen peptides modulate the metabolism of extracellular matrix proteins by human dermal fibroblasts (in culture) that were derived from sun-protected and sun-exposed body sites.[23]

The in vitro collagen hydrolysate treatment increased the dermal matrix precursors along with procollagen type I and collagen type I proteins. The increased levels of collagen were attributed to enhanced biosynthesis of collagens by fibroblasts but also decreased collagen type I metabolism through the inhibition of metalloproteinases (MMP 1 and MMP 2) activities.[23] The authors concluded that food-derived collagen hydrolysates improved skin cells and dermal health by enhancing collagen production and inhibiting the enzymes that break it down.

2.5. Oral Administration and Bioavailability of collagen

GI Absorption, Distribution into the Bloodstream, and Deposition into the Skin In recent years, many nutritional supplements and functional foods containing collagen (peptides, etc.) have been marketed for use in skin care.[22] This section describes how orally ingested collagen (and/or collagen-derived products) via metabolic and absorptive mechanisms have positive effects on skin physiology.[22] The initial studies examined animal models for

absorption, transport via the bloodstream, and subsequent distribution or deposition into skin and nails (Figure 1).

2.6. Oral administration of collagen improves skin (and Nail) parameters in animal studies

It is generally thought that collagen (derived products) are hydrolyzed into amino acids in the gastrointestinal tract (GI) prior to being absorbed into the blood circulation (Figure 1). However, increasing evidence suggests that peptides might also be absorbed directly.[22,23]

In 1999, Oesser et al., demonstrated that when mice were fed a 14C-labeled gelatin hydrolysate, more than 90% of the radioactive tracer was absorbed by the GI tract after 6 h and, at 12 h, the radioactivity reached maximal values in the skin while more than 85% of the radioactivity disappeared from the blood plasma after 24 h.[24] This report showed that peptides with molecular weights ranging from 1 to 10 kDa were absorbed in the GI tract, transferred to the blood, and deposited into cartilage.

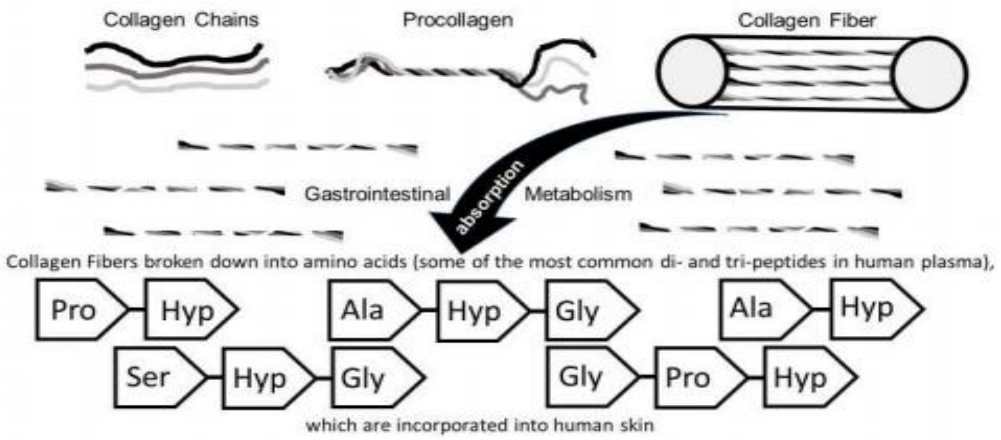

Figure 1. Collagen fiber structure, absorption/metabolism and deposition into skin cells and dermal layers. It is generally thought that collagen (derived products) are hydrolyzed into amino acids in the gastrointestinal tract (GI) prior to being absorbed into the blood circulation, which are then deposited into the skin cells and/or utilized as building block components for extracellular matrix proteins produced by fibroblasts [25–28]. ALA = Alanine, HYP = Hydroxyproline, GLY = Glycine, PRO = Proline, and Ser = Serine.

In a porcine animal study in 2006, nine healthy 66-day-old piglets were orally administered porcine skin-derived collagen hydrolysate (0.2g/kg body weight) with a molecular weight range of 3 to 5 kDa for 62 days.[29] Compared to the control group, oral ingestion of collagen hydrolysate resulted in significant increases in both the diameter and density of the collagen fibrils, which suggests that the mechanical properties improved.[29]

In 2009, Tanka et al. examined the daily administration of collagen peptides (0.2 g/kg body weight) prepared from fish scales on skin damaged by repeated exposure to UV radiation (VU-B, 03. mW/cm2) for six weeks in six-week-old hairless mice.[30] The oral collagen treatment suppressed the UV-B-induced decreases in skin hydration, hyperplasia of the epidermis, and the decreased levels of collagen type I in the skin of the mice.[30]

In another animal study of rats, Watanabe-Kamiyama et al. in 2010 examined the administrationof 288 mg of chicken feet collagen hydrolysate (800 Da) containing Gly-[14C]Pro-Hyp and [14C]Proas radioactive tracers.[31] The radioactivity in the plasma reached a maximal value at 3 h after oral administration along with peak values in the skin at the same time interval. After 14 days of administering this treatment, 70% of the radioactivity was found in the skin while, for the most part, other tissues such as the liver, kidney, spleen, brain, and muscle show decreased radioactivity.[31] In 2011, Zague et al. studied how oral collagen hydrolysate administration increased skin collagen expression while, at the same time, it suppressed the activity of the matrix metalloproteinase enzyme (MMP 2) in Wistar rats.[32] The authors suggested that oral collagen hydrolysate administration may reduce skin aging in other mammals.

In 2012, Okawa et al. showed that the oral administration of collagen tripeptide improves dryness and pruritus in the acetone-induced dry skin model in mice.[33] The oral administration of collagen peptides (80 or 500 mg/kg body weight/day) for three days in mice significantly decreased trans-epidermal water loss, suppressed scratching behavior, and normalized axon-guidance factors in the epidermis in addition to reducing pruritus.[33] In 2017, Song et al. examined the effects of collagen hydrolysates from sliver carp skin on UV-induced photo-aging in mice and found that lower molecular weight peptides exerted beneficial effects when compared to high molecular weight collagen hydrolysates on hyaluronic acid levels and moisture content of the skin.[34] In 2017, Chen et al. studied the effect of early enteral nutrition supplemented with Alaska pollock skin-derived collagen peptides on post-burn inflammatory responses in mice.[35] The supplemental treatment decreased NF-κB and TNF-α and IL-6 levels, which suggests that the immune-nutrient supplement may improve post-burn outcomes in burn patients.[35]

Lastly, in 2018, Song et al. examined the effects of collagen peptide intake (400 mg/kg body weight/day) for two months in one-year-old female Kunming mice.[36] The results via cytokine array analysis revealed that, in skin, platelet release and a variety of growth factors

was inhibited. In plasma, nine cytokines were down-regulated and the authors suggested that collagen peptide may combat cancer and cardiovascular disease via the changes in the quantified parameters.[36]

2.7. Oral Administration of Collagen Improves Skin (and Nail) Parameters in Human Studies

In 2005, Iwai et al. found that healthy human volunteers who ingested 9–23 g of hydrolysates from porcine skin, chicken feet, and cartilage after 12 h of fasting displayed a maximal concentration of 20–60 nmol/mL in plasma 1 to 2 h after ingestion, which was reduced to half the maximal values at 4 h after ingestion.[37] The porcine skin and chicken feet consisted of collagen type I while the chicken cartilage was collagen type II.[37]

In 2006, Matsumoto et al. investigated the effects of daily intake of 7 g of commercially available collagen hydrolysate containing 5 g of fish type I collagen hydrolysates on skin parameters of 25 Japanese female subjects (35 ± 5 years of age) who had dry and rough skin in the winter.[38] After six weeks of treatment, the moisture content of the stratum corneum (face-cheek, forearm, and the back of the neck) increased along with improvement in the pliability and elasticity of the skin, which resulted in greater smoothness, fewer wrinkles, and less skin roughness.[38]

In 2007, Ohara et al., in a single-blind crossover study examined five healthy volunteers (33 + 6 years old) who ingested type I collagen hydrolysates (0.385 g/kg body weight) with an average molecular weight of 5 kDa from fish scales, fish skins, and porcine skins after fasting for 12 h.[25] Within 24 h after ingestion, the different hydroxyproline containing peptides in human blood were quantified where fish scales > porcine skins ≥ fish skins, which suggests that the source of collagen provide clues about how these molecules are absorbed and transported into blood.[29] In 2012, Schwartz and Park in a pilot open-label study investigated the effect of a dietary supplement known as BioCell Collagen, which contained hydrolyzed collagen type II, hyaluronic acid, and chondroitin sulfate in 26 healthy females with visible signs of natural and photo-aging in the face.[39] The oral daily supplement of 1 g for 12 weeks led to a significant reduction in skin dryness/scaling and global lines/wrinkles with increased content of hemoglobin and collagen observed, which suggests that the collagen supplement enhanced facial blood (microcirculation) and reduced the signs of aging in the face.[39]

In 2014, Proksch et al. conducted a double-blind, placebo-controlled trial examining 69 women aged 35 to 55 years of age that were randomized and received 2.5 or 5.0 g of collagen peptides or placebo once daily for eight weeks (n = 23 subjects per group).[40]

At the end of the study, skin elasticity in both collagen groups significantly improved over the placebo group while skin moisture also improved in the collagen groups but did not reach significance over placebo levels. This suggests that oral supplementation of collagen peptides has beneficial effects on skin physiology.[40] Additionally, in 2014, Proksch et al. examined the influence of a specific bioactive collagen peptide VERISOL in 114 women aged 45 to 65 years of age that were randomized to receive 2.5 g VERISOL or placebo (n = 57 subjects per group) once daily for eight weeks.[41] By suction blister biopsies, a variety of skin parameters were analyzed. With the ingestion of VERISOL, at four and eight weeks, a significant reduction in eye wrinkle volume occurred and, at eight weeks, significantly higher procollagen type I and elastin levels were quantified, which suggests that oral administration of collagen peptides (via VERISOL) reduced skin wrinkles and skin aging.[41] Notably, this journal article and reported results were reviewed in 2016.[42]

Furthermore, in 2014, Borumand and Sibilla examined, in a clinical study, a nutritional supplement composed of hydrolyzed collagen, hyaluronic acid, vitamins, and minerals (50 mL per day for 60 days), which led to a reduction in skin dryness, wrinkles, and nasolabial fold depth.[26] Additionally, Choi et al., in another clinical study, investigated the effect of collagen tripeptide (3 g/day for four weeks) on wound healing and skin recovery after fractional photo-thermolysis treatment in eight healthy adult volunteers.[26] There were improvements in wound healing parameters in the experimental vs. the controls and the recovery of skin hydration after fractional laser treatment was faster with oral supplementation of the collagen peptides.[26]

In 2015, Asserin et al. used two placebo-controlled clinical trials to assess the effect of daily oral supplementation with collagen peptides on skin hydration and collagen density in volunteers.[43] After four weeks of supplementation, dermal collagen deposition significantly increased and, by eight weeks, skin hydration significantly increased. Both enhanced skin parameters persisted after 12 weeks and the ex vivo results showed that collagen peptides induced collagen as well as glycosaminoglycan production.[43]

In 2017, Yazaki et al. examined the oral ingestion of collagen hydrolysates in humans (and mice) where the tripeptide collagen was transported into blood with particularly enriched Gly-Pro-Hyp levels that were then deposited into the skin with enriched Pro-Hyp concentrations presumably after hydrolysis.[27]

In 2017, Hakuta et al. conducted a clinical study of seventeen patients with atopic dermatitis who were randomly assigned to receive a daily (for 12 weeks) 3.9 g of either collagen tripeptide or normal collagen peptides and each subject served as their own control.[28] When their keratinocytes were analyzed, several inflammatory biomarkers were reduced and, in the 13 subjects that completed the study, trans-epidermal water loss was significantly reduced, but the blood parameters were not improved in either treatment group.[28]

In 2017, Hexsel et al. performed a clinical study in which they examined an open label, single-center trial of 25 participants who took 2.5 g of VERISOL once daily for 24 weeks followed by a four-week off-therapy period to determine if nail growth and nail health was influenced by the oral VERISOL treatment.[44]

The VERISOL treatment increased nail growth by 12% and decreased the frequency of broken nails by 42%. A majority of the participants (80%) agreed that the VERISOL supplement improved their nails' appearance.[44]

CONCLUSION

Thus, there was an abundance of pre-clinical and clinical reports that provide evidence for collagen hydrolysates supplementation, which supports the enhancement and/or improvement of dermal health via oral administration and via nutritional products.

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