Journal of Cosmetics, Dermatological Sciences and Applications, 2021, 11, 263-278
https://www.scirp.org/journal/jcdsa
ISSN Online: 2161-4512
ISSN Print: 2161-4105

Beauty from within: A Review of the Science behind Yuliv™ Collagen Drink: An Anti-Aging Nutraceutical

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How to cite this paper: Polonini, H., Dijkers, E. and Ferreira, A.O. (2021) Beauty from within: A Review of the Science behind Yuliv™ Collagen Drink: An Anti-Aging Nutraceutical. *Journal of Cosmetics, Dermatological Sciences and Applications*, **11**, 263-278.
https://doi.org/10.4236/jcdsa.2021.113022

Received: August 20, 2021
Accepted: September 26, 2021
Published: September 29, 2021

Abstract

The use of nutraceuticals to improve skin properties and decelerate skin aging has been gaining attention among dermatologists, over the last years. In this article, we are presenting the theoretical scientific support for Yuliv™ Collagen Drink, a liquid supplement containing bovine type I collagen peptides, ascorbic acid and *Camellia sinensis* (green tea) extract and its benefits on the skin. The available literature shows that the ingredients contained in the supplement have the potential to improve of skin hydration, dermis collagen density, and decrease the fragmentation of the dermal collagen network—and therefore reduce wrinkles and sagging and improving elasticity. Additionally, other health benefits could also be observed, such as protection against oxidative stress, contribution to the normal function of the immune system and reducing tiredness and fatigue, and reduction of skin inflammation, improvement of elasticity and prevention of oxidation. For those benefits to be visible, it is likely that continuous use of at least 4 weeks is needed.

Keywords

Collagen Peptides, Vitamin C, Green Tea, Beauty Supplement, Anti-Aging

1. Introduction

Throughout the aging process, the skin's dermal structure is progressively diminished, decreasing the amount and functionality (organization and normality) of collagen, hyaluronic acid, and other molecules related to the collagen. After 30 years of age, the collagen percentage in the skin starts to decrease; by the age of 40, collagen production decreases by approximately 25%, and by the age of 60 years this is further decreased to about 50% [1]. This opens the opportunities for cosmetic and cosmeceutical strategies to replace such loss of collagen, and

maintain skin integrity and function normality, preventing or delaying visible signs of aging. One of those possible strategies that have been gaining momentum amongst dermatologists in the late years is the concept of "beauty from within" (or "beauty inside-out"). The term refers to the use of oral nutraceuticals and dietary supplements to counteract the progressive decline in the amount and function of collagen and related dermal structures [2] [3]. The current arsenal of common nutraceuticals available to patients normally includes collagen peptides, vitamins, minerals, and antioxidants.

In this article, we have performed a literature review focused on one of these products: Yuliv™ Collagen Drink, a "beauty drink". The added value of this product is that it does not solely rely on hydrolysed collagen peptides, but also contains vitamin C, and green tea extract to further improve efficacy. The objective of the article is to give a full overview of the current evidence available in the literature to support the use of collagen peptides, vitamin C and green tea extract as oral anti-aging strategies.

2. Aging and Its Effects on the Skin

2.1. The Skin Structure in Short

The skin covers body surfaces and is one of the largest human organs, representing 16% of the total body weight. It has a complex structure, being formed by the epidermis (of ectodermal origin) and dermis (of mesodermal origin). In contact with the dermis is the hypodermis or subcutaneous cellular tissue, which is not part of the skin itself, it only forms a bridge between the skin and underlying organs. The skin's functions are multiple: the main protection against loss of water and withstand friction. It also protects against other environmental factors, such as heat and cold, and microbiological invasion. It functions as a selective barrier for chemical substances; it participates in the body's thermoregulation through its blood capillaries, adipose tissue, and glands; it collaborates in the excretion of substances by sweat; protects against ultraviolet rays, due to locally produced melanin and trans-urocanic acid; combined with solar radiation, it transforms precursors synthesized in the body into vitamin D3; and sends sensory information about the environment to the central nervous system. In addition, it also largely contributes to our individual visual appearance [4] [5] [6].

When zooming in into the different layers of the skin, the epidermis is the outermost layer and is histologically constituted by keratinized stratified squamous epithelium. The cells that compose it can be divided into corneocytes, also called keratinocytes, and non-corneocytes. Non-corneocytes are: melanocytes, which produce the pigment melanin, the substance that gives color to the skin; Langerhans cells, which are part of the immune system in the function of antigen-presenting cells, having a relevant role in local immunological reactions, in addition to containing the proliferation of corneocytes; and Merkel cells, which function as nociceptors, being responsible for the touch and the transmission of

nerve pain impulses through their connection with nerve fibers. The corneocytes, in turn, are flattened, dead cells, with no nucleus and which have a cytoplasm rich in keratin, which is an intermediate and amorphous filament protein that gives the epidermis its great resistance and impermeability. They are so-called because they are cells that have differentiated themselves with the unique function of synthesizing keratin. They are the main cells of the corneal layer (stratum corneum), which protects our body from external agents. This layer constitutes the main obstacle for the effective penetration of drugs through the topical/transdermal route since the tortuosity of its cells and their adhesion are obstacles that are difficult to transpose. In addition, this is a stratum that is continually renewed, since there are large amounts of epithelial stem cells in the so-called basal layer of the epidermis, which provides substitute keratinocytes in a period of two to four weeks. It also plays a role in beauty: either cosmetics need to surpass this structure to reach the dermis; or they are rather intended to work in the stratum corneum and have a direct impact on the visual aspect of the skin [7] [8] [9].

The dermis is composed of connective tissue and serves as a support for the epidermis, serving as a link between it and the subcutaneous tissue, or hypodermis. It is richly vascularized and innervated and has many lymphatic vessels. In addition to these structures, it is in the dermis that hair follicles, sebaceous glands, and sweat glands are found, although these are considered epidermal appendages, as they have the same embryological origin [10]. Important cells found in the dermis and related to aesthetics are the fibroblasts, the most common cells of connective tissue in humans and synthesizes extracellular matrix proteins and structural framework (stroma) for tissues, takes part in the wound healing process, and produces collagen and elastin [11] [12]. Collagen is one of the most prominent molecules related to skin health and aesthetics. Types I and III collagens comprise more than 90% of all collagens in our body and are found in skin, muscles, bones, hair, and nails. Type II collagen is found in cartilage and joints. Collagen's functionalities are linked to other molecules: glycosaminoglycans, notably dermatan sulphate, and hyaluronic acid, this latter a polymeric molecule that can vary from 10 to 10^4 kDa in size, as it is composed of alternating units of N-acetylglucosamine and glucuronic acid. Those structures altogether play a major role in skin hydration and elasticity [13] [14] [15].

The hypodermis is formed by loose connective tissue and is responsible for the union between the dermis and the underlying tissues and organs, albeit in an unsteady manner. For this very reason, it allows a certain sliding between the skin and the structures on which it rests. Because it is rich in adipose tissue, depending on the region of the body in which it is found, it protects against cold and mechanical shocks, in addition to shaping the body according to the amount of fat it may contain [16].

2.2. Effects of Aging on Skin Structure and Function

Aging, in the broad sense, can be currently understood as the gradual process of

decreasing physical and mental capacity, together with an increased risk of disease, and ultimately, death [17]. Several theories try to explain the triggers of aging—for instance, the endocrinological, according to which the decline in the circulating amount of hormones responsible for regulating body metabolism and stimulating cell growth and renewal would be its main trigger, leading to deterioration at cellular, tissue and organ levels [18]. However, there is no consensus, and a very intricated multifactorial process is more likely to be in place.

Independent on the origin, the fact is that aging affects all structures in the human body, the skin included—and the main current focus on that process is on the dermis, where many cells and structures are found and account for a major role on the aesthetics of the individuals [6].

In young, healthy skin, the dermal layer is kept optimal in terms of width and composition. During aging, however, the dermal structure is progressively lost, decreasing the content and functionality (organization and normality) of collagen, hyaluronic acid, and other molecules related to the collagen. As previously stated, by 60 years old the decrease in collagen production reaches 50% [1].

The process of collagen degradation/fragmentation is linked to the role of the matrix metalloproteinases (MMPs), which play a part in shaping the skin's structure through their action [19]. MMP-1 seems to be especially involved in this process, which leads to the loosening of the skin cells and structures [20] [21]. This also impacts the water content of the skin (hydration), as the skin retention within the skin is dependent on all skin structures working normally and contributing to maintaining skin health [22] [23].

In addition, the natural aging process can be exacerbated by external factors such as excessive sunlight (notably UVA rays; photoaging), an unbalanced diet (e.g., high sugar levels, as glucose reacts with free amino groups and proteins and remain in the tissue; glycation), stress, pollution, and smoking [21] [24] [25] [26] [27] [28]. Altogether, the aging process in the skin will lead to visible signs of aging and aesthetics visual of aged, non-healthy skin—and this is more emphasized in the face, as it is the most exposed skin area to sun radiation and pollution.

3. Nutrition and Dietary Supplementation for a Healthy Skin

Oral nutraceuticals and dietary supplements to counteract the progressive decline in the amount and function of collagen and related dermal structures have gained interest over the last years [2] [3]. Those nutraceuticals include collagen peptides, vitamins, minerals, and antioxidants and have the intend to slow down the natural aging process [29] [30].

Possibly the most important focus on such supplements is currently to replenish collagen in the skin. Collagen itself, however, is a large molecule that cannot permeate via the skin, neither be absorbed via the gastrointestinal tract, where it suffers digestion. Therefore, products to supplement collagen contain (hydrolysis generated) collagen peptides; they form the "bricks" necessary to stimulate endogenous collagen production. It is estimated that only peptides in the mole-

cular weight range of 1 - 10 kDa can be absorbed by the intestines [31]. In comparison, natural collagen (non-bioavailable by oral route) has 285 - 300 kDa molecular weight, while hydrolysed collagen (bioavailable by oral route) is composed of small peptides with 3 to 6 kDa [32].

3.1. Yuliv™ Collagen Drink: Ready-To-Drink Solution for Skin and Health

As above mentioned, the ingredients of Yuliv™ Collagen Drink, containing hydrolysed collagen peptides, but also contains vitamin C, and green tea extract will be reviewed.

3.1.1. Collagen Peptides

The main ingredient in Yuliv™ Collagen Drink are the collagen peptides. Collagen peptides can be understood as the natural bioactive ingredients composed of peptides of different lengths obtained from enzymatic digestion/hydrolysis of natural collagen from connective tissues in animals, and are usually abundant in amino acids hydroxyproline, glycine, and proline [33]. From those amino acids, hydroxyproline can be considered as the marker of the amount of collagen in food supplements, as it is unique to collagen [34]. They are safe to use, as the European Food Safety Authority (EFSA) considers that the hydrolyzation of collagen does not pose any threat to human health [35].

Previous studies show that collagen peptide supplementation can potentially decrease the fragmentation of the skin collagen, possibly because they can reduce expression of MMP-1 through the induction of tissue inhibitor of metalloproteinase 1 (TIMP-1) [34] [36]. In addition, collagen peptides also seem to increase fibroblast elastin synthesis, while inhibiting the release of MMP-1 and MMP-3 and elastin degradation, suggesting that the oral consumption of collagen peptides can enhance the formation of stable dermal fibroblast-derived extracellular matrices [37].

The absorption process of the collagen peptides starts with their digestion into di- and tripeptides [38]. Then, they pass the intestinal mucosa via transporter Peptide Transporter 1 (PEPT-1) [39], can be found after one hour of ingestion in blood [40] and can stay circulation up to 6 hours [41]. They can reach the skin [42] and be retained within it for 2 weeks [41]. The absorption process occurs mainly by transcellular transport: first, there is the uptake of peptides by epithelial cells across the brush-border membrane, which is dependent on hydrogen ion-coupled peptide transporters (PEPT-1, in the specific case of the collagen peptides, such as Pro-Hyp and glycine-Pro-Hyp) [39]; then, absorption into the bloodstream across the basolateral membrane [43]. There is evidence that this absorption is also mediated by the capacity of the collagen peptides to bind calcium ions, which increases their biocompatibility [44] [45]. After absorption, distribution occurs and is dependent on chemical features such as molecular size and polarity.

Collagen peptides can be extracted from different natural sources: bovine

(skin, tendons, ligaments or lungs), porcine (skin), marine (fish, jellyfishes or sponges) or alternative sources (chicken legs/feet or Chinese brown frog) [32]. The source configures an important factor for collagen supplementation (as collagen peptides), together with the production process, as they can impact the bioavailability (and therefore the clinical outcome) of the supplement [46]. Yuliv™ uses Peptan® B collagen peptides, obtained from bovine sources, in a high dose (10,000 mg/dose). Bovine can be considered currently the main source of collagen type I, due to its high bioavailability and biocompatibility [32].

A vast body of evidence can be found for the biological actions of collagen peptides and the skin. The most relevant (to the best of the authors' knowledge) were selected and can be seen in **Table 1**.

In addition to the data shown in **Table 1** for skin, collagen peptides (type I) did also show additional benefits for health in general as, for example, a joint-protective effect for osteoarthritis (OA) [56] [57] [58] [59]. It also acts specifically on osteoblast, which acts on bone remodeling [60].

Given the studies that have been performed, the bovine type I collagen in Yuliv™ (10 g/dose) could have a beneficial effect on the skin as well as a joint-protective effect.

3.1.2. Vitamin C

The second ingredient in Yuliv™ is vitamin C (ascorbic acid). Ascorbic acid is an important molecule for human nutrition and has been the focus of research worldwide. Up to date it is the only nutrient with a health claim approved by EFSA regarding collagen production ("Vitamin C contributes to normal collagen formation for the normal function of skin") [61]. The EFSA Panel concluded that a cause-and-effect relationship could be established between the dietary intake of vitamin C and normal collagen formation. This conclusion was based on the available evidence of ascorbic acid and collagen. Collagen is required for the normal structure of several tissues in the body including bones, cartilage, gums, skin, tendons, and blood vessels. Ascorbic acid, in its turn, acts as a coenzyme for the three dioxygenase enzymes that stabilize the triple helix structure of collagen, by catalyzing the addition of hydroxyl groups to proline and lysine—which makes that the ascorbic acid deficiency (namely scurvy) presents clinically with signs attributable to impaired collagen synthesis [61] [62] [63] [64].

Apart from the effects on collagen itself, vitamin C has been shown to improve the signs of aging in human skin also by other mechanisms, and markedly aid wound healing by minimizing the appearance of elevated scars [65]. It also influences gene expression of antioxidant enzymes, the organization, and accumulation of phospholipids, and promotes the formation of the stratum corneum and the differentiation of the epithelium in general [66]. Finally, through the improvement of antioxidant capacity and inhibition of NO production, ascorbic acid demonstrated protection against UVA radiation in melanogenesis, being compared to kojic acid in terms of lightening power in hyperpigmentation [67].

Table 1. Main studies (pre-clinical and clinical) on the effects of oral collagen peptides on skin health).

Effects of collagen peptides on skin health	Type of study	Results/conclusion
Increase of hyaluronic acid production in dermal fibroblasts	*In vitro*. Cell culture using human dermal fibroblasts [47].	The collagen peptides (type I) enhanced cell proliferation (1.5-fold) and hyaluronic acid synthesis (3.8-fold), which was concomitant with a 2.3-fold elevation of hyaluronan synthase 2 (HAS2) mRNA levels. This indicates that the collagen peptides stimulate hyaluronic acid synthesis mediated by activation of HAS2 transcription.
	In vivo. Oral intake of collagen peptides in hairless mice [48].	The collagen peptides suppressed the negative effects of the UVB radiation exposure, improving skin elasticity and dermal hyaluronic acid content (after 4 weeks of supplementation).
Improvement of skin barrier function by increasing the water content of the stratum corneum	*In vivo*. Oral intake of collagen peptides in hairless mice [48].	The collagen peptides prevented the increase in transepidermal water loss (TEWL) and the decrease in stratum corneum water content (after 4 weeks of supplementation).
	In vivo. Oral intake of collagen peptides in hairless mice [49].	Daily administration of collagen peptides improved skin barrier dysfunction (decreased TEWL, and significantly increased water content of stratum corneum).
	In vivo. Oral intake of collagen peptides in hairless mice [50].	The collagen peptides suppressed the UV-B-induced decrease in skin hydration and hyperplasia of the epidermis.
Induction of the synthesis of collagen on the mRNA and protein level	*In vivo*. Oral intake of collagen peptides in Sprague-Dawley rats [36].	The collagen peptides increased the expressions of pro-collagen type I and III mRNA via the activation of the Smad signaling pathway with up-regulated TGF-βRII (TβRII) expression level. The collagen peptides also inhibited collagen degradation through attenuating MMP-1 expression and increasing tissue inhibitors of metalloproteinases-1 expression.
	In vivo. Oral intake of collagen peptides in Wistar rats [51].	The relative amount of type I and IV collagens significantly increased after four weeks of collagen peptides administration, in relation to the control group. The supplement also decreased proenzyme and active forms of MMP2, suggesting that the collagen peptides may act on aging through stimulation of anabolic processes in skin tissue.
Induction of the production of stronger collagen fibrils	*In vivo*. Oral intake of collagen peptides in pigs [52].	Fibroblast density and diameter and density of collagen fibrils were significantly larger in the collagen peptide group, after 62 days. The ratio of dermatan sulfate (derived from fibril-bound decorin) was also the largest in the collagen peptide group. This suggests that ingestion of collagen peptide induces increased fibroblast density and enhances the formation of collagen fibrils in the dermis.
Promotion of skin fibroblasts growth	*In vitro*. Cell culture, using mouse skin fibroblasts [53].	Prolyl-hydroxyproline (found in human peripheral blood after ingestion of collagen peptide) enhanced the growth of fibroblasts in a dose-dependent manner.
Induction of fibroblast migration (wound healing)	*In vitro*. Cell culture, using human dermal fibroblasts [54].	Cleavage collagen exhibited chemotactic activity.
	In vitro. Cell culture, using human dermal fibroblasts [55].	Peptides from digested collagen (types I, II, and III) exhibited chemotactic activity, suggesting that they can attract fibroblasts to affect the repair of damaged tissue.
Skin hydration, collagen density, and fragmentation of dermal collagen network	*In vivo*. Two placebo-controlled clinical trials in human subjects (oral supplementation with 10 g of collagen peptides) [34].	The collagen peptides increased skin hydration (after 8 weeks) and collagen density in the dermis (after 4 weeks). The fragmentation of the dermal collagen network significantly decreased (after 4 weeks). Effects seem to be mediated by induction of collagen and glycosaminoglycan production.

As part of the multifunctional ingredients in Yuliv^{TM}, the additional benefits to general health on top of the benefits to the skin are [61]:

- contributes to the normal function of the immune system;
- contributes to normal energy-yielding metabolism;
- contributes to the normal functioning of the nervous system;
- contributes to normal psychological function;
- contributes to the protection of cells from oxidative stress;
- contributes to the reduction of tiredness and fatigue.

Concluding, the presence of vitamin C in the Yuliv™ Collagen Drink helps to improve skin health and support the hydrolysed collagen.

3.1.3. Green Tea Extract

The third active ingredient in the Yuliv™ drink is *Camellia Sinensis* (green tea extract). The Kuntze (green tea plant) contains a high concentration of bioactive components, predominantly the polyphenols and the flavanols (catechins). Together, they are responsible for approximately 20% - 30% of the tea's dry matter [68] [69]. The major catechins are: (+)-catechin, (−)-epicatechin, (−)-catechin 3-gallate, (−)-epicatechin 3-gallate, (−)-gallocatechin, (−)-epigallocatechin, (−)-gallocatechin 3-gallate, and epigallocatechin 3-gallate (EGCG) [70].

Green tea has been used for centuries in traditional medicine, to maintain and improve the general health condition and even to prevent diseases—either by oral or other routes, including topical and even buccal (mouthwash to reduce oral and gingival inflammation) [71] [72]. Here, we focus on the beauty benefits, summarized in **Table 2**. The presence of green tea extract from the Yuliv™ Collagen Drink seems to support beneficial effects on the skin and general health (such as inflammation and body composition).

Table 2. Main studies on the effects of oral green tea extract on normal function of skin.

Parameter	Effect
Skin vitality	Significant improvement in elastic tissue content (after 8 weeks) [73].
	Inhibition of lipoxygenase, metalloproteinase-2, hyaluronidase, and collagenase [74] [75].
	Strong antioxidant capacity, demonstrated by in vivo studies [76] [77] [78].
	Improvement in erythema and telangiectasias after 12 months [79].
	Suppression of melanin production via inhibition of tyrosinase and tyrosinase-related protein-2 activities [75].
UV protection	Protection of skin against harmful UV radiation and helped to improve overall skin quality (in terms of elasticity, roughness, scaling, density, and water homeostasis; results evaluated after 12 weeks) [80].
	Dose-dependently reduce UVR induced cells DNA damage in fibroblasts and keratinocytes cell cultures [81].
Others (inflammation and body composition)	Inhibition of adipogenesis (shown in cell lines, animal models, and humans) [82].
	Reduction in body fat, systolic blood pressure, and low-density lipoprotein cholesterol (after 12 weeks) [83].
	Increasing energy expenditure via thermogenesis, fat oxidation, and fecal lipid excretion [84].
	Attenuation of the development of obesity, symptoms associated with the metabolic syndrome, and fatty liver (after 16 weeks), via decreased lipid absorption and decreased inflammation [85].
	Downregulation of over 100 genes related to tissue inflammatory responses [86].

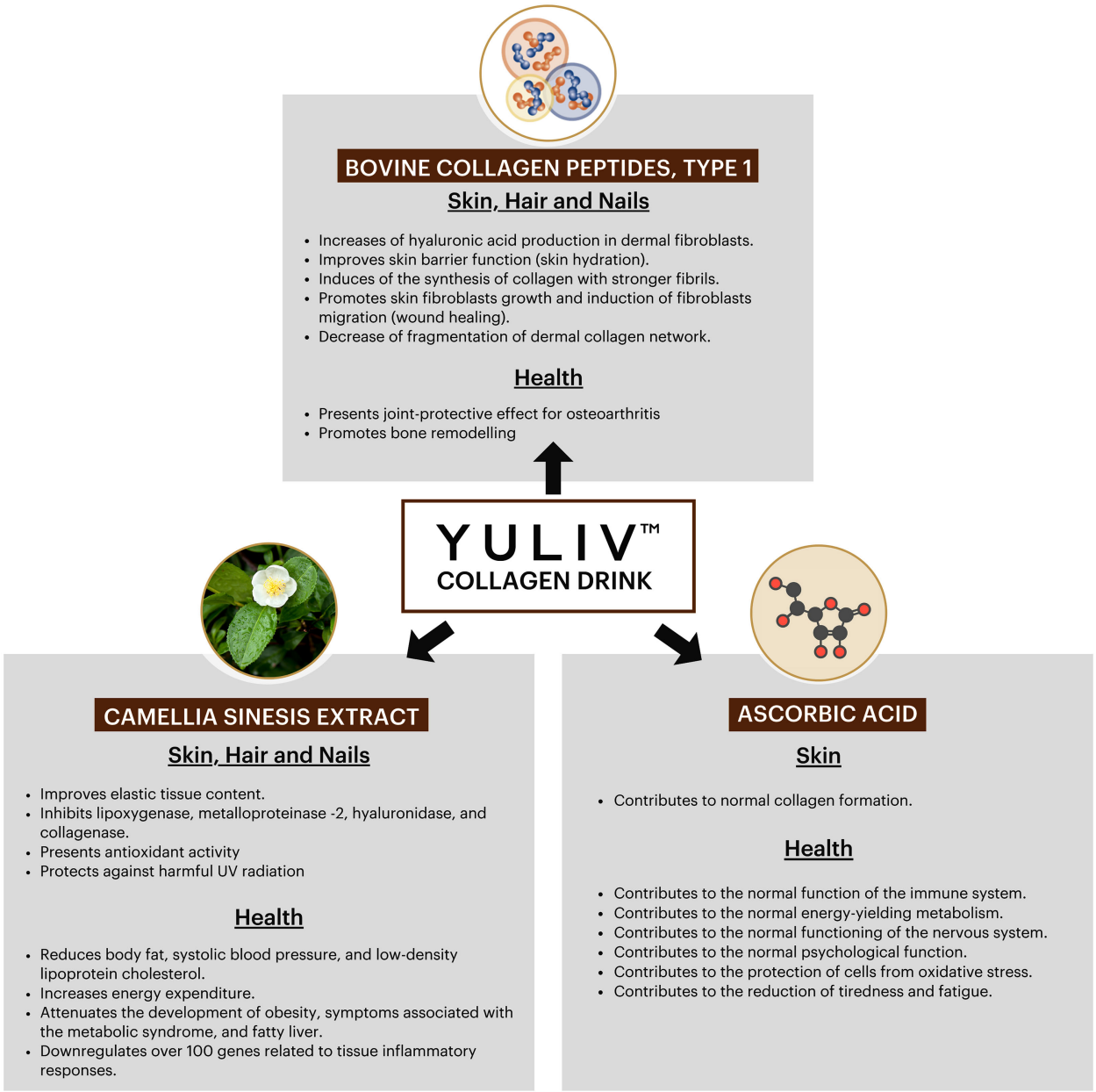

Figure 1. Main scientific-proven effects on skin and health provided by the daily consumption of Yuliv™ Collagen Drink.

4. Conclusion

In summary, based on the literature available, the ingredients of the Yuliv™ Collagen Drink, seem to have a beneficial effect on the skin's and general's health, when used on a daily basis for at least a month. The potential and substantiated benefits of oral collagen peptides, vitamin C, and green tea extract are then summarized in Figure 1.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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