



Collagen Supplements for Aging and Wrinkles: A Paradigm Shift in the Fields of Dermatology and Cosmetics

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ABSTRACT **Introduction:** Slowing the aging process by use of collagen supplements has become a driving force in the field of dermatology and cosmetics. Generally, oral and topical collagen are used in anti-aging products, as reported in the literature.

Objectives: The overarching goal of this research is to collate the consequences of oral collagen with those of topical collagen in reducing or delaying the aging process.

Methods: We executed an electronic search in Google Scholar and PubMed. We considered a study eligible if it was original research, published in English between 2010 and 2020, and if it provided information on the topic of collagen and aging. We retrieved 12 full-text articles, and these were assessed by reviewers independently.

Results: All human studies included in the review were randomized controlled trials mainly conducted in high- to middle-income countries which highlighted that both oral and topical collagen supplements help to delay the aging process, with no differences arising between the two types of collagen. The evidence from the reviewed studies suggested that both collagen supplements improve skin moisture, elasticity, and hydration when orally administered. Additionally, collagen reduces the wrinkling and roughness of the skin, and existing studies have not found any side effects of its oral supplements.

Conclusions: Both oral and topical collagen can contribute to reducing or delaying skin aging. Future epidemiological studies with large sample sizes and thorough follow-up measures would be required to comprehensively understand the potential effects of these two types of collagen on the aging process.

Introduction

Aging of the skin is a continuous process related to a depletion in the physiological function of the skin [1]. Both natural and unnatural factors cause human beings and animals to experience physiological alterations in different organs as time passes [2]. Cutaneous aging is a multifactorial activity dependent on both inherent (genetic, hormonal, and metabolic), and extrinsic factors (perennial exposure to UV rays, smoking, air pollution, chemicals and poor nutrition) [3,4]. Aging has a detrimental effect on connective tissue in the skin, leading to declines in elastin and collagen fibers and thus resulting in fine lines and wrinkles [3]. Furthermore, aging reduces the production of proteoglycans and glycosaminoglycan (such as hyaluronic acid) in the skin, as well as cartilage [4]. As a result, skin tissue weakens, losing its integrity, and the skin becomes dry, unable to retain enough moisture. Although multiple intrinsic processes can affect the aging process, factors such as exposure to sun, liquid intake, lifestyle, and pollution can exacerbate the aging process [1]. Moreover, skin wrinkling also progresses as dermal thickness is reduced over time due to decreased collagen [5,6].

Most of the collagen supplements recommended by experts are enriched with peptides containing amino acids - including proline, glycine, and hydroxyproline - considered to be essential components of collagen [7-9]. Beyond this, researchers have claimed that increasing peptide production of hyaluronic acid in skin fibroblasts induces fibroblast migration and strengthens collagen, thus raising the amount of moisture in the stratum corneum [10]. Hence, the existing data suggest that the presence of these proteins in the body helps to maintain the amount of collagen in the skin [10]. Furthermore, collagen is considered crucial for skin health because both photo-aging and intrinsic aging decrease its presence in the body [11]. This in turn causes a decrease in the skin thickness, as well as a loss of elasticity and flexibility [12].

In recent years, collagen supplements have been increasingly used, as they are advertised as a potential remedy against the aging process [13]. It has been found that marine fish collagen has homology with human collagen and therefore it has been widely utilized as nutritional addendum along with collagen peptides [14]: they have a very good safety profile, biocompatibility, high bioavailability in the human gastrointestinal barrier, safety, and high bioactivity [15].

Objectives

Current research reveals that collagen use could result in a reduction of wrinkles, rejuvenation of skin, and reversal of skin aging [16], which may improve skin hydration and elasticity [17]. However, the available evidence regarding types of collagen or its mechanism of action, duration to

produce desired results and side effects have not been rigorously reviewed or synthesized. This could create controversy in using collagen to reverse the aging process. Moreover, it is yet unclear which type of collagen (topical or oral) needs to be used to produce these coveted effects. Therefore, we undertook this research to collate the consequences of oral collagen with those of topical collagen in reducing or delaying the aging process.

Methods

The researcher conducted this research to appraise, synthesize, and aggregate the available evidence to measure how both oral and topical collagen are used to reduce or delay the aging process.

Inclusion and Exclusion Criteria

The researcher carried out an electronic search on different attributes of collagen, such as the benefits of collagen supplements, types, mechanisms of action, and side effects, as well as how long it takes to produce results. Study inclusion eligibility was contingent on whether the research had focused the effects of collagen supplements on aging reversal and whether it was an original study published in English from 2010 to 2020 across both developed and developing countries. The researcher excluded secondary data, letters to the editor, case reports, and gray literature from this review.

Information Sources and Search Strategy

The research was conducted by the researcher who completed a search of published articles in 2020, scanning databases such as PubMed and Google Scholar. An independent search was carried out by the author, who examined the results for potentially appropriate studies, retrieving any needed full-text articles. The researcher grouped search terms into 4 major categories by PICOS (Population, Intervention, Comparison, Outcomes and Study) design as a framework to formulate eligibility criteria. The researcher identified a combination of Medical Subject Heading (MeSH) keywords and text words. The most prevalent search terms found in abstracts and titles included the following: “collagen supplement and aging,” “collagen supplement and wrinkles,” “role of collagen supplement in skin rejuvenation,” “collagen supplement and aging reversal,” “benefits of collagen supplements in reducing aging,” “types of collagen in reducing aging,” “mechanism of collagen supplements in reducing aging” and “side effects of collagen supplements used for anti-aging”.

Data Extraction

All appropriate research studies were imported into the reference manager software (Endnote, Clarivate Analytics) file, where each study was reviewed, and titles were also screened for duplicates. The abstracts were not considered for further

review, which did not explicitly explore the study objective. Finally, the full-text articles of the remaining germane articles were obtained and examined. This action was followed by abstracting and summarizing the articles that met the eligibility criteria using a proforma standard. Aside from this, the bibliography of the remaining studies was scrutinized to avoid missing any useful studies. This process of searching the articles was carried out independently by the author, and their judgments and extracted summaries were matched to identify the differences and to resolve them accordingly.

Independent reviewers filled out a standardized data extraction sheet for the eligible research articles. The reviewers compared the data extraction tables to ensure including the imperative findings of the eligible studies and pilot tested these sheets before beginning the extraction process. Besides, prevailing research articles on the chosen topic were reviewed to describe the data extraction proforma objectives. Any discrepancies between the independent reviewers were resolved by consensus between two other reviewers.

Results

Decisions Reached Regarding the Search Strategy

The researcher screened the identified articles initially by titles, then by abstracts, and finally, a full-text article assess-

ment was carried out, discarding any articles not meeting the pre-defined eligibility criteria. As a result, the initial search identified 820 citations in PubMed and Google Scholar; however, 150 articles were duplicates. Of the remaining 670 unique studies, the researcher reviewed titles and abstracts, finding 150 relevant abstracts. Upon reviewing the latter, 135 articles did not meet the eligibility criteria. Hence, the researcher was able to retrieve the complete texts of 15 articles, though more than 12 articles met the necessary criteria and were included in the review, as shown in Figure 1.

Usage of Oral Collagen Supplements: Evidence from Human Studies

A study was conducted in Japan in which authors gave collagen peptides to patients with aging, wrinkled skin (Table 1). These patients included 66 women from Japan who were more than 40 years old, about whom researchers recorded any improvements in skin parameters. These patients were given either 10 g of collagen for 56 continuous days or no treatment at all (placebo) [18]. The authors observed a statistically noteworthy dissimilarity in the moisture of the skin throughout the experiment, accompanied by a substantial increase in the moisture for the group under treatment when compared with the placebo group. Skin moisture analyzers were utilized to test skin moisture; they are portable devices that test different skin factors utilizing

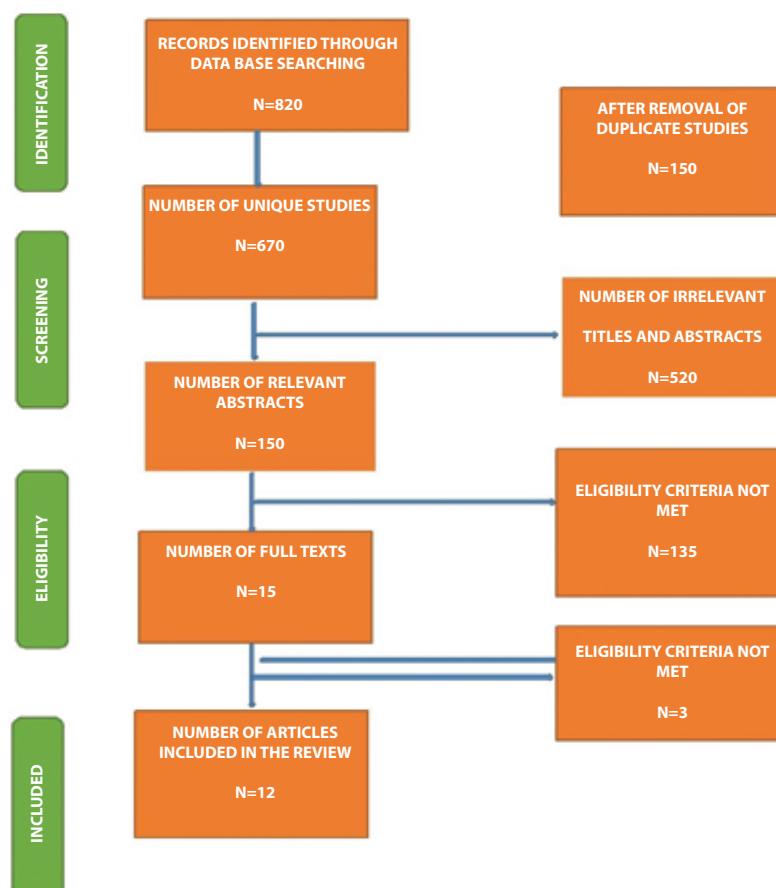


Figure 1. Flow chart summarizing the identification and selection of papers.

bioelectric impedance analysis. The level of skin moisture is ascertained by the time it takes for the current to travel across the skin. Additionally, the same study enrolled French women of more than 40 years old and followed a similar protocol for collagen treatment for about 3 continuous months. At the completion of treatment, the author found a noteworthy moisture elevation in the collagen treatment group compared with the placebo group [18].

Moving forward, researchers undertook a randomized controlled trial (RCT) in order to evaluate the potency of collagen peptides [19]. Recruited participants were randomly assigned to ingest either oral liquid supplements containing collagen peptides (50 ml) or placebo daily for 12 weeks [19]. No noteworthy dissimilarity in skin elasticity was noticed between the 2 arms (Table 1). However, in the subgroup analysis, the authors noticed that study participants who underwent cosmetic surgeries in the treatment group showed improvement in skin elasticity, as opposed to their counterparts, who showed no improvement. At the completion of the study, participants in the therapeutic arm achieved higher marks in some skin parameters like hydration and elasticity [19].

In another RCT, women were allocated to 4 different arms [20]. The first arm received 2.5 grams of collagen hydrolysate, the second arm was given 5.0 grams of collagen hydrolysate, the third arm received 2.5 grams of a placebo, and the fourth arm was given 5.0 grams of placebo [20]. Participants were followed for around 60 days, and it was found that each treatment arm with a different dose of collagen hydrolysate showed a statistically noteworthy rise in the elasticity of the skin when juxtaposed with their counterparts in 2 placebo groups. Improvement in elasticity was noticed among elderly women relatively earlier (ie, at 1-month follow-up) [20]. Furthermore, a positive correlation was observed between treatment with collagen hydrolysate and skin moisture and evaporation, with statistically insignificant results [20].

Another double-blinded RCT was undertaken to assess the collagen (with low molecular weight) effects on the elasticity of the skin elasticity, hydration, and finally wrinkling [21]. This study was conducted with Korean women at least 40 years old (n = 64) who were randomized to 1000 mg of collagen or to placebo every day for 3 months [21]. The authors found noteworthy elevations in skin hydration in the treatment arm even at 6 weeks of follow-up when compared to the placebo group. Furthermore, different parameters of skin wrinkling (all 3 parameters) and skin elasticity (1/3 parameters) were notably elevated in the treatment arm when compared with the placebo group, as shown in Table 1 [21].

In the same vein, 1 more RCT was conducted to find out the effects of collagen hydrolysate constituted of the bioactive dipeptides, prolylhydroxyproline, and hydroxypropylglycine on Chinese women (n = 85) of at least 35 years of

age [22]. The study was comprised of 3 main groups: 1 was randomized to receive collagen peptides (higher content), 1 was randomized to collagen peptides (lower content), and the last group received placebo [22]. The total duration of the study was roughly 2 months, and participants took their respective treatments daily. Both intervention arms demonstrated substantial improvement in skin moisture, especially around the cheek and canthus, as opposed to the placebo group, which displayed no such improvements. Moreover, the findings also showed a substantial increase in the moisture and elasticity of the skin, as well as a reduction in wrinkling and roughness in the first treatment group, unlike either the second or the placebo groups, as shown in Table 1 [22].

Usage of Oral Collagen Supplements: Evidence from Animal Studies

Apart from studies conducted on human beings, animals have been examined as well to assess the effect of collagen [23]. In animal models, the authors have used clinical and histological appearance, along with gene expression, to study the necessary outcomes. One research was carried out to assess the consequences of collagen hydrolysates on 9-month-old mice for 24 weeks. The results of the study revealed a significant increase in both distribution and density of said collagen and ratio between type I and type III collagen, with a particular dose-response relationship [23].

In another study, collagen peptides were given to mice for one and a half months [24]. The authors found a higher expression of genes, along with their upregulation in the skin [24]. One more study was conducted on mice, in which they were fed a diet containing collagen hydrolysate for roughly 3 months. The study revealed improvements in the water content of their skin and an increase in elasticity, as opposed to the mice in the control group, who experienced no such benefits [25]. Lastly, mice were observed on a diet rich in prolylhydroxyproline and hydroxypropylglycine for around 5 weeks in one more study. The mice that received collagen hydrolysates showed increased skin hydration [26].

Usage of Topical Collagen Application on Delaying the Aging Process

Generally, there have been fewer studies assessing the effect of topical collagen on the aging process when compared with the studies conducted for oral collagen supplements. For instance, one conducted by Sanz et al in 2015 revealed that those women who were asked to apply a product containing collagen performed better than those in the control group [27]. More specifically, around three quarters of the treated women showed anti-wrinkling effects and substantial increases in the dermal density and elasticity of their skin after 7 days of treatment [27]. Similarly, Matthias et al conducted a retrospective study in Germany and South Africa on 480

Table 1. Previous usage of Oral Collagen Supplements: Evidence from Human Studies

Study Author	Study Year	Country	Study Design	Sample Size	Participants	Age (Years)	Intervention	Control Arm	Study Results	Adverse Effects
Sangsuwan et al [40]	2020	Thailand	RCT	36	Post-menopausal women	50-60	5 grams of oral collagen hydrolysate	Placebo	<ul style="list-style-type: none"> - Skin elasticity was found to be significantly different between intervention and control groups. 	None
Žmitek et al [39]	2020	Germany	RCT	34	Caucasian Healthy females	40-65	10 mL of a syrup having fish collagen and other active ingredients	10 mL of colored placebo having flavors without active ingredients	<ul style="list-style-type: none"> - Dermis density was improved. - Periorbital wrinkle area was reduced - Improvement in skin smoothness. - Skin hydration improved. - Dermis thickness, trans-epidermal water loss and viscoelasticity did not improve. 	None
Campos et al [29]	2019		RCT	60	Healthy study participants	40-50	Topical and hydrolyzed collagen	Placebo in oral form	<ul style="list-style-type: none"> - Topical collagen improved skin elasticity and viscoelasticity parameters. - Skin elasticity, hydration and echogenicity of dermis were improved after 1 month of topical collagen application, as well as oral collagen. 	None
Bolke et al [41]	2019	Germany	RCT	72	Healthy females	≥ 35	2.5 grams of collagen and other active ingredients	Placebo	<ul style="list-style-type: none"> - Hydration of skin, elasticity and density were improved. - There was reduction in skin roughness. - All test parameters were different between intervention and placebo groups, which also remained at the time of follow-up. 	None
Kim et al [21]	2018	Korea	RCT	64	Korean women	40-60	Collagen with low molecular weight	Placebo	<ul style="list-style-type: none"> - The intervention group showed improvement in the hydration values of skin at 6 and 12 weeks. - Three parameters of skin wrinkling improved drastically in the intervention, as opposed to the placebo. - 1/3 parameters improved substantially in the intervention group after 12 weeks as opposed to placebo group. - 2/3 parameters in the intervention arm improved after 12 weeks. 	None

Table1 continues

Table 1. Previous usage of Oral Collagen Supplements: Evidence from Human Studies (continued)

Study Author	Study Year	Country	Study Design	Sample Size	Participants	Age (Years)	Intervention	Control Arm	Study Results	Adverse Effects
Inoue et al [22]	2017	China	RCT	85	Chinese women	35-55	Collagen hydrolysate having a higher content of bioactive collagen-hydrolysate having a lower content of bioactive collagen	Placebo	- The intervention arm demonstrated a significant improvement over the placebo arm in moisture, elasticity, wrinkles, and roughness.	None
Genovese et al [19]	2017	Rome (Italy)	RCT	120 F:111 M: 9	Volunteer subjects	47.72 (6.5) 49.65 (6.5)	50 mL of collagen	Placebo	- No difference was seen between the intervention and placebo arms for skin elasticity. -Subjects who had cosmetic surgeries demonstrated increased skin elasticity.	No adverse events
Sanz et al [27]	2015	Spain	Open and intra-individual study clinical Study	32 women	Women with sensitive skin bearing wrinkles	45-55 (median: 49)	Serum containing an amalgamation of pro-collagen lipopeptide, extract of apple, creatine, and urea	Self-control	- 71% of the women in the intervention group experienced anti-wrinkle effects. - Dermal density improved by 11% after 1 week. - Significant improvement was seen in cutaneous hydration and cutaneous elasticity (cheekbone) after 1 week when compared with baseline.	Not reported
Asserin et al [42]	2015	Japan and France	RCT	66 Japanese and 106 French women	Japanese and French women	40-59 40-65	10 g of collagen	Placebo	- Significant improvement in skin hydration and dermis density after 8 weeks of intake - A significant reduction was seen in the fragmentation of the dermal collagen network.	None
Proksch et al [20]	2013	Not reported	RCT	69	women	35-55 years old	2.5 g of CH ₂ and 5.0 g of CH	2.5 g of placebo, and 5.0 g of placebo	- A significant improvement was seen in elasticity of skin in both intervention arms, as compared to the placebo arm. - Elderly women showed a statistically significantly higher skin elasticity level. - No effect of CH was seen on skin hydration and evaporation.	None

Table1 continues

Table 1. Previous usage of Oral Collagen Supplements: Evidence from Human Studies (continued)

Study Author	Study Year	Country	Study Design	Sample Size	Participants	Age (Years)	Intervention	Control Arm	Study Results	Adverse Effects
Byrne et al [30]	2010	Ireland	RCT	22	Caucasian female subjects	39 to 60	Triple peptide complex (3%)	Placebo	<ul style="list-style-type: none"> - There was substantial reduction in the frequency of wrinkles, total wrinkle surface average, wrinkle length and average wrinkle depth in the intervention group, as opposed to placebo group. - There was improvement in the wrinkle parameters by 10–19% compared with the untreated baseline, and this improvement was 13–28% when compared to the placebo group. 	None
Aust et al [28]	2008	Germany	Retrospective analysis	480 F: 400 M: 80	Patients	The mean (SD) was 49 ± 15.5 years	Percutaneous collagen	Self-control	<ul style="list-style-type: none"> - There was improvement in the skin by 60 to 80%. - A substantial upsurge in collagen and elastin deposition on histological examination was observed in the subset of patients. - There was a roughly 40% thickening of the epidermis mainly stratum spinosum after 1 year of treatment. 	Not reported

CH = collagen hydrolysate; SD = standard deviation; RCT = randomized control trial.

patients with wrinkles, lax skin, scarring, and stretch marks [28]. These patients were administered percutaneous collagen after preparing their skin with necessary vitamins and creams for at least 1 month [28]. The findings demonstrated that patients were found to have skin 60% to 80% improved from before the treatment. Furthermore, researchers carried out a histologic examination on a subset of patients that demonstrated a substantial upsurge in collagen and elastin deposition. There was around 40% thickening of the epidermis, mainly stratum spinosum, 1 year after treatment [28].

Similarly, Campos et al evaluated the consequences of topical and oral collagen additions in the skin enhancement of 60 healthy female subjects. The findings showed that females who were given a topical product demonstrated a substantial rise in skin hydration and elasticity at the end of 1 month. On the other hand, the group with oral supplementation showed more noticeable results in dermal echogenicity and decreasing pore size at the end of 3 months without any adverse effects [29]. Another study demonstrated that those patients who received topical treatment showed a noteworthy depletion in the total wrinkle surface, number of wrinkles, and average wrinkle length and depth were observed in comparison with those who underwent placebo.

In addition, the anti-wrinkle activity of the topical triple peptide complex (3%) has been reported by a clinical research conducted by Byrne et al in 2010. Their findings suggested that topical application significantly improves the photo-damaged skin by the end of 1 month when compared with the placebo group [30]. These studies revealed noteworthy relative depletions in the number of wrinkles and total wrinkle surface - in conjunction with increase in their mean depth and length - at the end of 1 month, ranging from 10% to 28% [30].

Mechanism of Action of Collagen Supplements

One of the proteins found in abundance in human beings is collagen, and it helps to maintain the structure, stability, and strength of the dermal layers [31]. The studies have shown antioxidant and established reparative actions of collagen in wrinkled or damaged skin. Skin experiences the double action of collagen: first, it provides the skin essential components for both elastin and collagen, and second, it is attached to the fibroblast receptors in the dermis to initiate the production of elastin and hyaluronic acid [32]. So far, oral collagen has been studied to a greater extent than topical collagen. The available literature suggests that the topical application of collagen improves both skin elasticity and texture. However, topical collagen does not infiltrate the skin completely owing to its high molecular weight [33]. In contrast, oral collagen ingestion has been found to improve mechanical properties by increasing both the density and the diameter of collagen fibrils [34]. Orally consumed collagen bioactive peptides are

absorbed relatively quickly because such collagen products have lower molecular weights, distributing these peptides easily across several tissues [35]. Additionally, evidence from the animal models suggested that oral administration of collagen reduces the intensity of skin hydration caused by UV radiation and also reduces hyperplasia of the epidermis caused by UV rays [36]. Furthermore, oral intake of collagen enhances the moisture content of the skin, especially the stratum corneum, as well as the elasticity of the skin, reducing wrinkling and roughness [37]. Overall, collagen causes an increase in fibroblasts and extracellular matrix proteins and a decrease in metalloproteinase. These rising fibroblasts found in the various layers of the human dermis produce a plethora of extracellular matrix proteins that enhance skin health and thus slow skin aging [38].

Side Effects of Collagen Supplements Reported in Human Studies

Generally, no adverse effects of oral and topical collagen have been observed in any of these studies [39]. There have been no side effects such as vomiting, diarrhea, nausea, or constipation reported in the treatment or control groups of any of the studies [40]. For example, trials conducted in 2019 and 2020 found no adverse effects of collagen until they observed their participants [39,41]. These findings were also confirmed by a research by Inoue et al in 2017, where they conducted a RCT to assess the effect of high versus low doses of collagen and placebo [22]. Likewise, Genovese et al had shown analogous findings concerning the side effects during the period of study while comparing the effect of supplements on skin elasticity, wrinkling, and roughness with the placebo [19]. Besides, these findings were further endorsed by a study conducted in 2013 by Proksch et al: the authors found no side effects in any of the 4 groups that were assigned to high-dose collagen, low-dose collagen, a high-dose placebo, or a low-dose placebo [20]. One more double-blinded RCT conducted on Korean women showed no adverse events related to the treatment or intervention throughout the study period [21]. Similarly, there were no adverse effects of topical collagen in various studies [28-30].

Conclusions

Based on the existing literature from both animal and human studies, it seems that oral collagen supplements improve skin elasticity, turgor, and hydration and reduce skin wrinkling and roughness. The existing premise reveals that neither oral nor topical collagen is superior to the other; rather, both types reduce or delay skin aging. Thus, products of collagen peptides can be considered to be anti-aging remedies by dermatologists, especially in cosmetics. However, the existing evidence has not provided enough robust evidence for collagen

supplements due to differences in the weights of collagen being topically and systemically absorbed. Hence, more epidemiological and interventional studies with large sample sizes and required follow-up appointments are requested to assess the effectiveness of the topical compounds containing collagen on wrinkled and aging skin while comparing the same to the oral collagen supplement instead of the placebo. As the trend of both forms of collagen supplement use might continue to rise, more thorough research is required to validate their potential positive effects before they are widely used.

One of the strengths of the included studies was research design, as all the studies on human beings were RCTs that provided solid evidence due to the balance of known and unknown confounders between the treatment and control groups. However, the types and doses of collagen were not similar across the studies; therefore, further studies with consistent doses in different settings may be required before making any judgments about the use of oral collagen. This is crucial because some of the proponents of collagen might try to apply the results of animal models to human beings, but animal studies cannot be generalized to humans due to differences in physiological and biological mechanisms. In the same way, these collagen products have usually been tested in the developed or high-income sectors of different age groups. Thus, there is no evidence about whether these products could produce analogous results in the various populations residing in low- to middle-income countries with limited resources. Hence, this warrants the replication of similar studies in developing countries by using a similar study design. Lastly, the review found no side effects of either topical or oral collagen treatment during the study period, and most of the studies had followed their participants for 12-24 weeks. Thus, there is no clear evidence about how these collagen products function after the study ends and whether these products tend to produce adverse effects in the long run that need to be further explored.

References

1. Tobin DJ. Introduction to skin aging. *J Tissue Viability*. 2017;26(1):37–46. DOI: 10.1016/j.jtv.2016.03.002. PMID: 27020864.
2. Barbosa MC, Grosso RA, Fader CM. Hallmarks of aging: an autophagic perspective. *Front Endocrinol (Lausanne)*. 2019;9:790. DOI: 10.3389/fendo.2018.00790. PMID: 30687233. PMCID: PMC6333684.
3. Cannarozzo G, Fazia G, Bennardo L, et al. A New 675 nm Laser Device in the Treatment of Facial Aging: A Prospective Observational Study. *Photobiomodul Photomed Laser Surg*. 2021;39(2):118-122. DOI: 10.1089/photob.2020.4908. PMID: 33449869.
4. Nistico SP, Silvestri M, Zingoni T, Tamburi F, Bennardo L, Cannarozzo G. Combination of Fractional CO2 Laser and Rhodamine-Intense Pulsed Light in Facial Rejuvenation: A Randomized Controlled Trial. *Photobiomodul Photomed Laser Surg*. 2021;39(2):113-117. DOI: 10.1089/photob.2020.4876. PMID: 33449867.
5. Varani J, Dame MK, Rittie L, et al. Decreased collagen production in chronologically aged skin: Roles of age-dependent alteration in fibroblast function and defective mechanical stimulation. *Am J Pathol*. 2006;168(6):1861–1868. DOI: 10.2353/ajpath.2006.051302. PMID: 16723701. PMCID: PMC1606623.
6. Lee DH, Oh J-H, Chung JH. Glycosaminoglycan and proteoglycan in skin aging. *Journal of Dermatological Science*. 2016;83(3):174–181. DOI: 10.1016/j.jdermsci.2016.05.016. PMID: 27378089.
7. Reilly DM, Lozano J. Skin collagen through the lifestages: importance for skin health and beauty. *Plast Aesthet Res*. 2021;8:2. DOI: 10.20517/2347-9264.2020.153
8. De Melo F, Nicolau P, Piovano L, et al. Recommendations for volume augmentation and rejuvenation of the face and hands with the new generation polycaprolactone-based collagen stimulator (Ellansé®). *Clin Cosmet Investig Dermatol*. 2017;10:431-440. DOI: 10.2147/CCID.S145195. PMID: 29184426. PMCID: PMC5685142.
9. Li P, Wu G. Roles of dietary glycine, proline, and hydroxyproline in collagen synthesis and animal growth. *Amino Acids*. 2018;50(1):29–38. DOI: 10.1007/s00726-017-2490-6. PMID: 28929384.
10. Felician FF, Xia C, Qi W, Xu H. Collagen from marine biological sources and medical applications. *Chem Biodivers*. 2018;15(5):e1700557. DOI: 10.1002/cbdv.201700557. PMID: 29521032.
11. Cho BA, Yoo S-K, Seo J-S. Signatures of photo-aging and intrinsic aging in skin were revealed by transcriptome network analysis. *Aging (Albany NY)*. 2018;10(7):1609-1626. DOI: 10.18632/aging.101496. PMID: 30021930. PMCID: PMC6075446.
12. McCabe MC, Hill RC, Calderone K, et al. Alterations in extracellular matrix composition during aging and photoaging of the skin. *Matrix Biol Plus*. 2020;8:100041. DOI: 10.1016/j.mbplus.2020.100041. PMID: 33543036. PMCID: PMC7852213.
13. Zhang L, Zhang S, Song H, Li B. Ingestion of collagen hydrolysates alleviates skin chronological aging in an aged mouse model by increasing collagen synthesis. *Food Funct*. 2020;11(6):5573-5580. DOI: 10.1039/d0fo00153h. PMID: 32520042.
14. Exposito JY, Valcourt U, Cluzel C, Lethias C. The fibrillar collagen family. *Int J Mol Sci*. 2010;11(2):407-426. DOI: 10.3390/ijms11020407. PMID: 20386646; PMCID: PMC2852846.
15. Zhang Z, Wang J, Ding Y, Dai X, Li Y. Oral administration of marine collagen peptides from Chum Salmon skin enhances cutaneous wound healing and angiogenesis in rats. *J Sci Food Agric*. 2011;91(12):2173-2179. DOI: 10.1002/jsfa.4435. PMID: 21560132.
16. Sionkowska A, Skrzyński S, Śmiechowski K, Kołodziejczak A. The review of versatile application of collagen. *Polymers for Advanced Technologies*. 2017;28(1):4–9. DOI: 10.1002/pat.3842.
17. Choi SY, Ko EJ, Lee YH, et al. Effects of collagen tripeptide supplement on skin properties: A prospective, randomized, controlled study. *J Cosmet Laser Ther*. 2014;16(3):132-137. DOI: 10.3109/14764172.2013.854119. PMID: 24131075.
18. Addor FASA, Vieira JC, Melo CSA. Improvement of dermal parameters in aged skin after oral use of a nutrient supplement. *Clin Cosmet Investig Dermatol*. 2018;11:195-201. DOI: 10.2147/CCID.S150269. PMID: 29750046. PMCID: PMC5933363.
19. Genovese L, Corbo A, Sibilla S. An insight into the changes in skin texture and properties following dietary intervention with a nutraceutical containing a blend of collagen bioactive peptides

- and antioxidants. *Skin Pharmacol Physiol*. 2017;30(3):146-158. DOI: 10.1159/000464470. PMID: 28528342.
20. Proksch E, Segger D, Degwert J, Schunck M, Zague V, Oesser S. Oral supplementation of specific collagen peptides has beneficial effects on human skin physiology: A double-blind, placebo-controlled study. *Skin Pharmacol Physiol*. 2014;27(1):47-55. DOI: 10.1159/000351376. PMID: 23949208.
 21. Kim D-U, Chung H-C, Choi J, Sakai Y, Lee B-Y. Oral intake of low-molecular-weight collagen peptide improves hydration, elasticity, and wrinkling in human skin: A randomized, double-blind, placebo-controlled study. *Nutrients*. 2018;10(7):826. DOI: 10.3390/nu10070826. PMID: 29949889. PMCID: PMC6073484.
 22. Inoue N, Sugihara F, Wang X. Ingestion of bioactive collagen hydrolysates enhance facial skin moisture and elasticity and reduce facial ageing signs in a randomised double-blind placebo-controlled clinical study. *J Sci Food Agric*. 2016;96(12):4077-4081. DOI: 10.1002/jsfa.7606. PMID: 26840887.
 23. Wang Z, Wang Q, Wang L, et al. Improvement of skin condition by oral administration of collagen hydrolysates in chronologically aged mice. *J Sci Food Agric*. 2017;97(9):2721-2726. DOI: 10.1002/jsfa.8098. PMID: 27747904.
 24. Le Vu P, Takatori R, Iwamoto T, et al. Effects of food-derived collagen peptides on the expression of keratin and keratin-associated protein genes in the Mouse Skin. *Skin Pharmacol Physiol*. 2015;28(5):227-235. DOI: 10.1159/000369830. PMID: 25721900.
 25. Oba C, Ito K, Ichikawa S, et al. Effect of orally administered collagen hydrolysate on gene expression profiles in mouse skin: A DNA microarray analysis. *Physiol Genomics*. 2015;47(8):355-363. DOI: 10.1152/physiolgenomics.00009.2015. PMID: 26058835.
 26. Shimizu J, Asami N, Kataoka A, et al. Oral collagen-derived dipeptides, prolyl-hydroxyproline and hydroxyprolyl-glycine, ameliorate skin barrier dysfunction and alter gene expression profiles in the skin. *Biochem Biophys Res Commun*. 2015;456(2):626-630. DOI: 10.1016/j.bbrc.2014.12.006. PMID: 25498544.
 27. Sanz MT, Campos C, Milani M, et al. Biorevitalizing effect of a novel facial serum containing apple stem cell extract, pro-collagen lipopeptide, creatine, and urea on skin aging signs. *J Cosmet Dermatol*. 2016;15(1):24-30. DOI: 10.1111/jocd.12173. PMID: 26424007.
 28. Aust MC, Fernandes D, Kolokythas P, Kaplan HM, Vogt PM. Percutaneous collagen induction therapy: an alternative treatment for scars, wrinkles, and skin laxity. *Plast Reconstr Surg*. 2008;121(4):1421-1429. DOI: 10.1097/01.prs.0000304612.72899.02. PMID: 18349665.
 29. Maia Campos PMBG, Melo MO, Siqueira César FC. Topical application and oral supplementation of peptides in the improvement of skin viscoelasticity and density. *J Cosmet Dermatol*. 2019;18(6):1693-1699. DOI: 10.1111/jocd.12893. PMID: 30834689.
 30. Byrne AJ, Al-Bader T, Kerrigan D, Hickey S, Laloef A, Rawlings AV. Synergistic action of a triple peptide complex on an essential extra-cellular matrix protein exhibits significant anti-aging benefits. *Cosmet Dermatol*. 2010;9(2):108-116. DOI: 10.1111/j.1473-2165.2010.00494.x. PMID: 20618556.
 31. Ricard-Blum S. The collagen family. *Cold Spring Harb Perspect Biol*. 2011;3(1):a004978. DOI: 10.1101/cshperspect.a004978. PMID: 21421911. PMCID: PMC3003457.
 32. Lephart ED. Equol's anti-aging effects protect against environmental assaults by increasing skin antioxidant defense and ECM proteins while decreasing oxidative stress and inflammation. *Cosmetics*. 2018;5(1):16. DOI: 10.3390/cosmetics5010016
 33. Bos JD, Meinardi MM. The 500 Dalton rule for the skin penetration of chemical compounds and drugs. *Exp Dermatol*. 2000;9(3):165-169. DOI: 10.1034/j.1600-0625.2000.009003165.x. PMID: 10839713.
 34. Matsuda N, Koyama Y, Hosaka Y, et al. Effects of ingestion of collagen peptide on collagen fibrils and glycosaminoglycans in the dermis. *J Nutr Sci Vitaminol (Tokyo)*. 2006;52(3):211-215. DOI: 10.3177/jnsv.52.211. PMID: 16967766.
 35. Watanabe-Kamiyama M, Shimizu M, Kamiyama S, et al. Absorption and effectiveness of orally administered low molecular weight collagen hydrolysate in rats. *J Agric Food Chem*. 2010;58(2):835-841. DOI: 10.1021/jf9031487. PMID: 19957932.
 36. Tanaka M, Koyama Y, Nomura Y. Effects of collagen peptide ingestion on UV-B-induced skin damage. *Biosci Biotechnol Biochem*. 2009;73(4):930-932. DOI: 10.1271/bbb.80649. PMID: 19352014.
 37. Matsumoto H. Clinical effects of fish type I collagen hydrolysate on skin properties. *ITE Lett Batter New Technol Med*. 2006;7:386-390.
 38. Avila Rodríguez MI, Rodríguez Barroso LG, Sánchez ML. Collagen: A review on its sources and potential cosmetic applications. *J Cosmet Dermatol*. 2018;17(1):20-26. DOI: 10.1111/jocd.12450. PMID: 29144022.
 39. Žmitek K, Žmitek J, Rogl Butina M, Pogačnik T. Effects of a combination of water-soluble coenzyme Q10 and collagen on skin parameters and condition: Results of a randomised, placebo-controlled, double-blind study. *Nutrients*. 2020;12(3):618. DOI: 10.3390/nu12030618. PMID: 32120787. PMCID: PMC7146335.
 40. Sangsuwan W, Asawanonda P. Four-weeks daily intake of oral collagen hydrolysate results in improved skin elasticity, especially in sun-exposed areas: A randomized, double-blind, placebo-controlled trial. *J Dermatolog Treat*. 2021;32(8):991-996. DOI: 10.1080/09546634.2020.1725412. PMID: 32009486.
 41. Bolke L, Schlippe G, Gerß J, Voss W. A collagen supplement improves skin hydration, elasticity, roughness, and density: Results of a randomized, placebo-controlled, blind study. *Nutrients*. 2019;11(10):2494. DOI: 10.3390/nu11102494. PMID: 31627309. PMCID: PMC6835901.
 42. Asserin J, Lati E, Shioya T, Prawitt J. The effect of oral collagen peptide supplementation on skin moisture and the dermal collagen network: evidence from an ex vivo model and randomized, placebo-controlled clinical trials. *J Cosmet Dermatol*. 2015;14(4):291-301. DOI: 10.1111/jocd.12174. PMID: 26362110.