International Journal of Nutrology
(Official Journal of the ABRAN - Brazilian Association of Nutrology)

REVIEW ARTICLE

DOI: 10.54448/ijn25205

Effects of supplementation of collagen types, vitamins, nutrients and exosome modulations for the rejuvenation of collagen fibers and improvement of skin aesthetics: a systematic review

Mauricio Fernando Cuadrado Berrones[1,2*], Andreia Borges Scriboni[2]

[1] Revitapiel Medical Specialties Center. Santo Domingo - Ecuador Tsafiqui Avenue and Augusto Gachet corner, Ecuador.
[2] UNORTE - University Center of Northern São Paulo, Dermatology department, São José do Rio Preto, São Paulo, Brazil.

*Corresponding author: Dr. Mauricio Fernando Cuadrado Berrones.
Revitapiel Medical Specialties Center. Santo Domingo - Ecuador
Tsafiqui Avenue and Augusto Gachet corner, Ecuador.
E-mail: maufer555@yahoo.es

DOI: https://doi.org/10.54448/ijn25205

Received: 01-18-2025; Revised: 03-21-2025; Accepted: 03-29-2025; Published: 04-08-2025; IJN-id: e25205

Editor: Idiberto José Zotarelli Filho, MSc., Ph.D., Post-Doctoral.

Abstract

Introduction: Collagen prevails in connective tissues, constituting 80% of the dry weight of human skin. Aging induces a decline in enzymes involved in the post-translational processing of collagen, reducing the number of fibroblasts that synthesize collagen and the vessels that irrigate the skin. Oral ingestion of hydrolyzed collagen together with vitamins and nutrients (especially apple exosomes/microRNAs) increases the levels of collagen-derived peptides in the bloodstream and improves skin properties. **Objective:** A systematic review was carried out to elucidate the main results of clinical studies and meta-analyses of clinical studies on the effects of supplementation of types of collagens, vitamins, nutrients and modulations of exosomes/microRNAs for the rejuvenation of collagen fibers and improvement of skin aesthetics. **Methods:** The search was carried out from November 2024 to January 2025 in the Scopus, Embase, PubMed, Science Direct, Scielo, and Google Scholar databases. The quality of the studies was based on the GRADE instrument and the risk of bias was analyzed according to the Cochrane instrument. **Results and Conclusion:** A total of 122 articles were found, and 12 articles were evaluated in full, and 08 were included and developed in the present systematic review study. Considering the Cochrane tool for risk of bias, the overall assessment resulted in 20 studies with a high risk of bias and 26 studies that did not meet GRADE and AMSTAR-2. Most studies showed homogeneity in their results, with X^2=62.4%>50%. Oral nutritional supplements containing collagen peptides can reduce skin vulnerability in the elderly and thus prevent conditions such as skin lesions. Thus, microRNA (miR-181b) may negatively regulate the proliferation of HEKs in psoriasis by targeting TLR4. The direct effects of collagen peptides on fibroblasts, M2-like macrophages, and mechanisms related to oral tolerance are the possible mechanisms for the beneficial effects of collagen supplementation. Special collagen peptides together with acerola extract, vitamin C, vitamin E, biotin, and zinc showed a significant improvement in the skin's collagen structure. The proven positive nutritional effect on collagen structure was fully consistent with the quality of healthy skin. Finally, apple-derived nanovesicles (exosomes) also reduce the degradation of the extracellular matrix, increasing collagen synthesis (COL3A1, COL1A2, COL8A1, and COL6A1) and negatively regulating the production of metalloproteinases.

Keywords: Collagen. Collagenic fibers. Vitamins. Nutrients. Exossomes. microRNAs. Rejuvenation.

Introduction

In the context of skin health and aesthetics, collagen is prevalent in connective tissues, constituting 80% of the dry weight of human skin **[1]**. Collagen is

characterized by a triple helix structure formed by the repetition of glycine every three residues, and mainly by proline and hydroxyproline in the remaining residues. It is the most prevalent component of the extracellular matrix **[2]**.

Also, aging induces a decline in the enzymes involved in the post-translational processing of collagen by gene modulation of exosomes and microRNAs, reducing the number of fibroblasts that synthesize collagen and the vessels that irrigate the skin **[3]**. The decline in skin quality with age is characterized by reduced collagen synthesis and decreased vascularization of the skin, leading to decreased elasticity and the formation of wrinkles. These changes are due to the decline in fibroblast activity and the decrease in the number of blood vessels in the skin **[4]**.

Although there are almost 20 different types of collagens the rather monotonous composition of collagen peptides is not limited only to the regular recurrence of the glycine residue. Still, it is also accompanied, in the following 2 positions, called X and Y positions, by a frequent Y position occupied by hydroxyproline, in up to 50% of cases, and hydroxylysine, in most of the remaining sequences **[5]**.

The most abundant type of collagen, called type I, which is present in the skin, bones, tendons, blood vessels, and cornea, has a triple chain composition formed by 2 α1 and 1 α2 chains. Elastin also has an extremely regular amino acid composition, but a much higher abundance of a specific amino acid, leucine **[6-8]**. In this sense, hydrolyzed collagen (HC) is a popular ingredient considered an antioxidant. This low molecular weight protein has been widely used due to its excellent biocompatibility, easy biodegradability, and weak antigenicity. It is a safe cosmetic biomaterial with good moisturizing properties on the skin. The antioxidant properties of HC depend on the size of the molecule, that is, the lower the molecular weight of the peptides, the greater the ability to donate an electron or hydrogen to stabilize the radicals. The antioxidant capacity of HC is mainly due to the presence of hydrophobic amino acids in the peptide **[9]**.

Some aromatic amino acids and histidine play an important role in antioxidant activity, mainly by activating exosomes and microRNAs that play an important immunological role. Oral intake of HC increases the levels of collagen-derived peptides in the bloodstream and improves skin properties such as elasticity, skin moisture, and transepidermal water loss. In addition, daily intake of HC protects the skin against UV melasma and increases the production of fibroblasts and the skin's extracellular matrix. HC has been identified as a safe cosmetic ingredient for topical formulations with good moisturizing properties in the stratum corneum of the skin. It reduces the effects of skin aging, such as dryness, sagging, and wrinkles **[9]**.

Therefore, the present study carried out a systematic review to elucidate the main results of clinical studies and meta-analyses of clinical studies on the effects of supplementation of types of collagens, vitamins, nutrients, and modulations of exosomes/microRNAs for the rejuvenation of collagen fibers and improvement of skin aesthetics.

Methods

Study design

The present study followed the international systematic review model, following the PRISMA rules (preferred reporting items for systematic reviews and meta-analyses). Available at: http://www.prisma-statement.org/?AspxAutoDetectCookieSupport=1. Accessed on: 12/12/2024. The methodological quality standards of AMSTAR-2 (Methodological Quality Assessment of Systematic Reviews) were also followed. Available at: https://amstar.ca/. Accessed on: 12/12/2024.

Data sources and search strategy

The literature search process took place from November 2024 to January 2025 and was developed based on Scopus, Embase, PubMed, Lilacs, Ebsco, Scielo, and Google Scholar, covering scientific articles from different periods to the present day. The descriptors (DeCS and MeSH Terms) used were: "Collagen. Collagenic fibers. Vitamins. Nutrients. Exosomes. microRNAs. Rejuvenation", and using the Boolean "and" between MeSH terms and "or" between historical discoveries.

Study quality and risk of bias

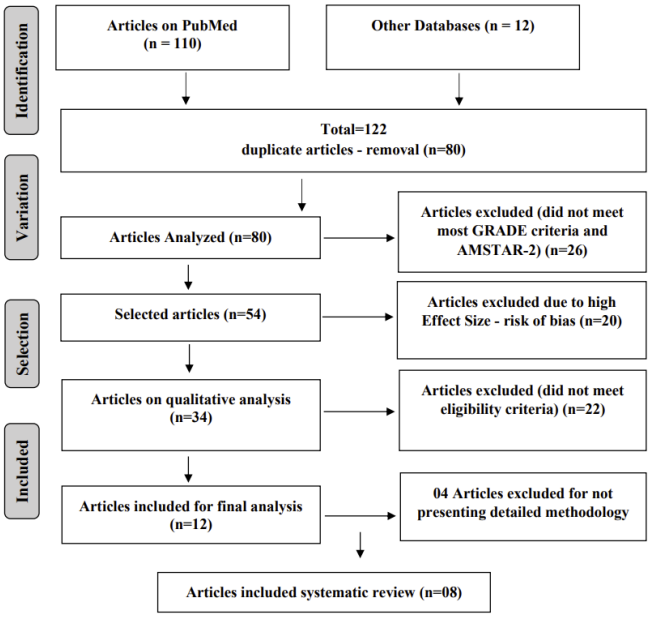
The quality is classified as high, moderate, low, or very low in terms of risk of bias, clarity of comparisons, precision, and consistency of analyses. The most evident emphasis was on systematic review articles or meta-analyses of randomized clinical trials, followed by randomized clinical trials. The low quality of evidence was attributed to case reports, editorials, and brief communications, according to the GRADE instrument. The risk of bias was analyzed according to the Cochrane instrument by analyzing the Funnel Plot graph (Sample size versus Effect size), using Cohen's test (d).

Results and Discussion

Summary of Findings

A total of 122 articles were found and submitted to eligibility analysis, with 08 final studies being selected to compose the results of this systematic review. The listed studies were of medium to high quality (Figure 1), considering the level of scientific evidence of studies such as meta-analysis, consensus, randomized clinical, prospective, and observational. The biases did not compromise the scientific basis of the studies. According to the GRADE instrument, most studies presented homogeneity in their results, with X^2=62.4%>50%. Considering the Cochrane tool for risk of bias, the overall assessment resulted in 20 studies with a high risk of bias and 26 studies that did not meet GRADE and AMSTAR-2.

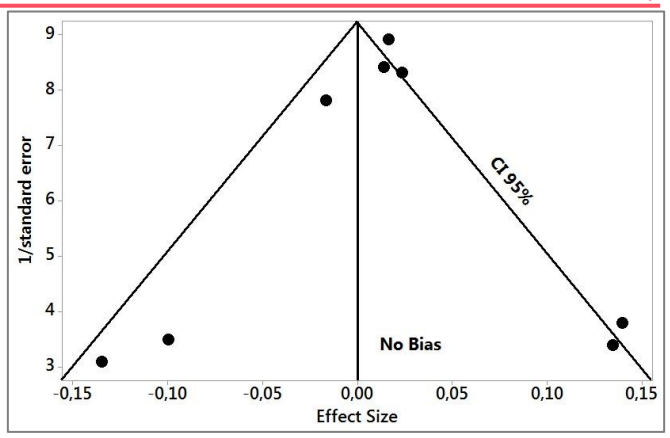
Figure 1. Flowchart of the article selection process.



Source: Own authorship.

Figure 2 presents the results of the risk of bias of the studies using the Funnel Plot, showing the calculation of the Effect Size (Magnitude of the difference) using Cohen's Test (d). Precision (sample size) was determined indirectly by the inverse of the standard error (1/Standard Error). This graph had symmetrical behavior, suggesting no significant risk of bias, both among studies with small sample sizes (lower precision) that are shown at the bottom of the graph, and in studies with large sample sizes that are shown at the top.

Figure 2. The symmetrical funnel plot suggests no risk of bias among the studies with a small sample size shown at the bottom of the graph. Studies with high confidence and high recommendations are shown above the graph (n=08 studies).



Source: Own authorship.

Major Clinical Findings

A study by Feng et al. (2017) **[10]** explored the role of microRNA-181b (miR-181b) and TLR in regulating human epidermal keratinocyte (HEK) cell proliferation in psoriasis. Twenty-eight patients diagnosed with psoriasis vulgaris were selected as the case group with their lesional and non-lesional skin tissues collected. A control group consisted of 20 patients who underwent plastic surgery with healthy skin tissues collected. Real-time quantitative fluorescence polymerase chain reaction (RT-qPCR), in situ hybridization, and immunohistochemistry were used to detect the expressions of miR-181b and TLR4 in HEKs from healthy skin, psoriatic lesional skin, and non-lesional skin, respectively. The 3′ untranslated region (3′UTR) of TLR4 combined with miR-181b was verified by a dual-luciferase reporter assay. Western blotting and bromodeoxyuridine were applied for the corresponding detection of TLR4 expression and cell mitosis. The expression of miR-181b in HEKs from psoriatic lesional skin was lower than that in healthy skin and nonlesional skin with psoriasis. In psoriatic lesional and nonlesional skin, the rates of TLR4-positive cells and the number of positive cells per square millimeter were higher than those in healthy skin. Luciferase assay verified that miR-181b targets TLR4. HEKs transfected with miR-181b mimics showed decreased TLR4 expression along with decreased mitotic indices and BrdU labeling indices. However, HEKs transfected with miR-181b inhibitors showed increased TLR4 expression, mitotic indices, and BrdU labeling indices. HEKs transfected with miR-181b and siTLR4 inhibitors decreased mitotic indices and BrdU labeling indices. These results indicate that miR-181b may negatively regulate HEK proliferation in psoriasis by targeting TLR4.

A randomized clinical trial analyzed the effect of an oral nutritional supplement containing collagen peptides on stratum corneum hydration and skin elasticity. Once-daily oral administration of a nutritional supplement containing collagen peptides (10.0 g) was instituted in

39 inpatients aged 65 years or older who were assigned to the intervention or control group using a block randomization design. Stratum corneum hydration and skin elasticity were measured at baseline and 2, 4, 6, and 8 weeks after the start of the intervention. Mean stratum corneum hydration increased significantly from 43.7 at baseline to 51.7 at week 8 post-intervention in the intervention group. Differences in skin elasticity from baseline were significant at week 6 post-intervention and week 8 **[11]**.

In this sense, skin aging has become a recurring concern even among younger people, mainly due to increased life expectancy. In this context, the use of nutricosmetics as supplements has increased in recent years. A meta-analysis study analyzed the effects of hydrolyzed collagen supplementation on human skin. A pooled analysis of studies showed favorable results of hydrolyzed collagen supplementation compared to placebo in terms of skin hydration, elasticity, and wrinkles. Therefore, taking hydrolyzed collagen for 90 days is effective in reducing skin aging, as it reduces wrinkles and improves skin elasticity and hydration **[12]**.

Another systematic review study evaluated the effects of collagen supplements on skin health parameters in healthy individuals and patients, focusing on the mechanisms of action. The results showed that oral administration of intact or hydrolyzed collagen improved the clinical manifestation of skin health. Almost all included studies reported the beneficial effects of collagen supplementation, and no inconsistencies were observed in this regard between studies **[13]**.

Furthermore, a randomized, placebo-controlled, triple-blind clinical study in 60 healthy volunteers evaluated the cosmetic effects on skin quality of a dietary supplement containing special collagen peptides together with acerola extract, vitamin C, vitamin E, biotin, and zinc after a 12-week intake. To minimize evaluation bias and increase the accuracy and objectivity of the results, the study design was triple-blind. The expert evaluator who evaluated the confocal laser scanning microscopy images was additionally blinded to when the image was obtained (on days 1 or 85). Objective, blinded, and validated image analyses using confocal laser scanning microscopy showed a significant improvement in the collagen structure of the facial skin (primary outcome) after intake of the test product, while no improvement was found after intake of the placebo. The demonstrated positive nutritional effect on collagen structure was fully consistent with positive subjective assessments of relevant skin parameters such as elasticity, wrinkling/wrinkling, and uniformity in different areas of the body, such as the face, hands, décolleté, neck, back, legs, and abdomen **[14]**.

The use of nutraceuticals such as collagen for skin care has increased, but regulations regarding quality, absorption, and efficacy are lacking. One study evaluated available randomized controlled trials using collagen supplementation for treatment efficacy to skin quality, anti-aging benefits, and potential application in medical dermatology. Eleven studies with a total of 805 patients were included for review. Eight studies used hydrolyzed collagen, 2.5 g/day to 10 g/day, for 8 to 24 weeks, for the treatment of pressure ulcers, xerosis, skin aging, and cellulite. Two studies used collagen tripeptide, 3 g/day for 4 to 12 weeks, with notable improvements in skin elasticity and hydration. Finally, a study using collagen dipeptide suggested that anti-aging efficacy is proportional to collagen dipeptide content. Preliminary results are promising for the short- and long-term use of oral collagen supplements for wound healing and skin aging. Oral collagen supplements also increase skin elasticity, hydration, and dermal collagen density **[15]**.

Authors Pu et al. (2023) **[16]** performed a meta-analysis of 26 randomized controlled trials (RCTs) involving 1,721 patients to evaluate the effects of hydrolyzed collagen (HC) supplementation on skin hydration and elasticity. The results showed that HC supplementation significantly improved skin hydration and elasticity compared with the placebo group. However, there were no significant differences in the effects of different collagen sources or corresponding measurements on skin elasticity.

Finally, authors Trentini et al. (2022) **[17]** analyzed apple-derived nanovesicles (exosomes) (ANVCs) as novel anti-inflammatory compounds capable of altering extracellular matrix production in dermal fibroblasts. Total RNA sequencing analysis revealed that ANVCs negatively influence Toll-like receptor 4 (TLR4) activity and thus downregulate the pro-inflammatory NF-κB pathway. ANVCs also reduce extracellular matrix degradation by increasing collagen synthesis (COL3A1, COL1A2, COL8A1, and COL6A1) and downregulating the production of metalloproteinases (MMP1, MMP8, and MMP9). Topical applications for skin regeneration were evaluated by associating ANVCs with hydrogel and hyaluronic acid-based adhesives.

Conclusion

It was concluded that oral nutritional supplements containing collagen peptides can reduce skin vulnerability in the elderly and thus prevent conditions such as skin lesions. miR-181b can negatively regulate the proliferation of HEKs in psoriasis by targeting TLR4. Direct effects of collagen peptides on fibroblasts, and M2-like macrophages, and mechanisms related to oral

tolerance are the possible mechanisms for the beneficial effects of collagen supplementation. Special collagen peptides together with acerola extract, vitamin C, vitamin E, biotin, and zinc showed a significant improvement in the collagen structure of the skin. The proven positive nutritional effect on collagen structure was fully consistent with the quality of healthy skin. Finally, apple-derived nanovesicles (exosomes) also reduce the degradation of the extracellular matrix, increasing the synthesis of collagen (COL3A1, COL1A2, COL8A1, and COL6A1) and negatively regulating the production of metalloproteinases.

CRediT

Author contributions: **Conceptualization-** Mauricio Fernando Cuadrado Berrones, Andreia Borges Scriboni; **Formal Analysis-** Mauricio Fernando Cuadrado Berrones; **Investigation-** Mauricio Fernando Cuadrado Berrones; **Methodology-** Mauricio Fernando Cuadrado Berrones; **Project administration-** Mauricio Fernando Cuadrado Berrones, Andreia Borges Scriboni; **Supervision-**Andreia Borges Scriboni; **Writing - original draft-** Mauricio Fernando Cuadrado Berrones, Andreia Borges Scriboni; **Writing-review & editing-** Mauricio Fernando Cuadrado Berrones, Andreia Borges Scriboni.

Acknowledgment

Not applicable.

Ethical Approval

Not applicable.

Informed Consent

Not applicable.

Funding

Not applicable.

Data Sharing Statement

No additional data are available.

Conflict of Interest

The authors declare no conflict of interest.

Similarity Check

It was applied by Ithenticate®.

Peer Review Process

It was performed.

References

1. Lordan R. Dietary supplements and nutraceuticals market growth during the coronavirus pandemic. Implications for consumers and regulatory oversight. PharmaNutrition. 2021;18:100282. doi: 10.1016/j.phanu.2021.100282.
2. Uitto J. Connective tissue biochemistry of the aging dermis. Age-related alterations in collagen and elastin. Dermatol. Clin. 1986;4:433–446. doi: 10.1016/S0733-8635(18)30806-4.
3. Shoulders MD, Raines RT. Collagen structure and stability. Annu. Rev. Biochem. 2009;78:929–958. doi: 10.1146/annurev.biochem.77.032207.120833.
4. Frantz C., Stewart K.M., Weaver V.M. The extracellular matrix at a glance. J. Cell Sci. 2010;123:4195–4200. doi: 10.1242/jcs.023820.
5. Calleja-Agius J., Muscat-Baron Y., Brincat M.P. Skin ageing. Menopause Int. 2007;13:60–64. doi: 10.1258/175404507780796325.
6. Bolognia JL, Braverman IM, Rousseau ME, Sarrel PM. Skin changes in menopause. Maturitas. 1989;11:295–304. doi: 10.1016/0378-5122(89)90026-1.
7. Castelo-Branco C., Duran M., González-Merlo J. Skin collagen changes related to age and hormone replacement therapy. Maturitas. 1992;15:113–119. doi: 10.1016/0378-5122(92)90245-Y.
8. Dioguardi FS. Nutrition and skin. Collagen integrity: a dominant role for amino acids. Clin Dermatol. 2008 Nov-Dec;26(6):636-40. doi: 10.1016/j.clindermatol.2007.09.004.
9. Aguirre-Cruz G, León-López A, Cruz-Gómez V, Jiménez-Alvarado R, AguirreÁlvarez G. Collagen Hydrolysates for Skin Protection: Oral Administration and Topical Formulation. Antioxidants (Basel). 2020 Feb 22;9(2):181. doi: 10.3390/antiox9020181.
10. Feng C, Bai M, Yu NZ, Wang XJ, Liu Z. MicroRNA-181b negatively regulates the proliferation of human epidermal keratinocytes in psoriasis through targeting TLR4. J Cell Mol Med. 2017 Feb;21(2):278-285. doi: 10.1111/jcmm.12963. Epub 2016 Sep 19. Retraction in: J Cell Mol Med. 2021 Mar;25(6):3173.
11. Nomoto T, Iizaka S. Effect of an Oral Nutrition Supplement Containing Collagen Peptides on

Stratum Corneum Hydration and Skin Elasticity in Hospitalized Older Adults: A Multicenter Open-label Randomized Controlled Study. Adv Skin Wound Care. 2020 Apr;33(4):186-191. doi: 10.1097/01.ASW.0000655492.40898.55.

12. de Miranda RB, Weimer P, Rossi RC. Effects of hydrolyzed collagen supplementation on skin aging: a systematic review and meta-analysis. Int J Dermatol. 2021 Dec;60(12):1449-1461. doi: 10.1111/ijd.15518.
13. Barati M, Jabbari M, Navekar R, Farahmand F, Zeinalian R, Salehi-Sahlabadi A, Abbaszadeh N, Mokari-Yamchi A, Davoodi SH. Collagen supplementation for skin health: A mechanistic systematic review. J Cosmet Dermatol. 2020 Nov;19(11):2820-2829. doi: 10.1111/jocd.13435.
14. Laing S, Bielfeldt S, Ehrenberg C, Wilhelm KP. A Dermonutrient Containing Special Collagen Peptides Improves Skin Structure and Function: A Randomized, Placebo-Controlled, Triple-Blind Trial Using Confocal Laser Scanning Microscopy on the Cosmetic Effects and Tolerance of a Drinkable Collagen Supplement. J Med Food. 2020 Feb;23(2):147-152. doi: 10.1089/jmf.2019.0197.
15. Choi FD, Sung CT, Juhasz ML, Mesinkovsk NA. Oral Collagen Supplementation: A Systematic Review of Dermatological Applications. J Drugs Dermatol. 2019 Jan 1;18(1):9-16.
16. Pu SY, Huang YL, Pu CM, Kang YN, Hoang KD, Chen KH, Chen C. Effects of Oral Collagen for Skin Anti-Aging: A Systematic Review and Meta-Analysis. Nutrients. 2023 Apr 26;15(9):2080. doi: 10.3390/nu15092080.
17. Trentini M, Zanolla I, Zanotti F, Tiengo E, Licastro D, Dal Monego S, Lovatti L, Zavan B. Apple Derived Exosomes Improve Collagen Type I Production and Decrease MMPs during Aging of the Skin through Downregulation of the NF-κB Pathway as Mode of Action. Cells. 2022 Dec 7;11(24):3950. doi: 10.3390/cells11243950