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REVIEW ARTICLE

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Clinical studies and meta-analysis on the effects of collagen, vitamin, and nutrient supplementation for the rejuvenation of collagenic fibers: a systematic review

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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) increases the levels of collagenderived peptides in the bloodstream and improves skin properties. **Objective:** It was to carry 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 collagen, vitamins, and nutrients for the rejuvenation of collagen fibers. **Methods:** The search was carried out from October to December 2023 in the Scopus, 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 07 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. 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. Rejuvenation.

Introduction

Collagen prevails in connective tissues, constituting 80% of the dry weight of human skin **[1]**. Collagen characterized by a triple helix structure formed by the repetition of glycine in every third residue, and mainly by proline and hydroxyproline in the remaining residues, being the most prevalent component of the extracellular matrix **[2]**.

In this scenario, aging induces a decline in the enzymes involved in the post-translational processing of collagen, 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 a reduction in collagen synthesis and a decrease in skin vascularity, 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 collagen, the rather monotonous composition of collagen peptides is not only limited to the regular recurrence of the glycine residue, but this is also accompanied, in the following 2 positions, called positions X and Y, 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 greater abundance of one particular 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: the smaller the molecular weight of the peptides, the greater the capacity 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. Oral intake of HC increases levels of collagen-derived peptides in the bloodstream and improves skin properties such as elasticity, skin moisture, and transepidermal water loss. Furthermore, 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 on the stratum corneum of the skin. 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 collagen, vitamins, and nutrients for the rejuvenation of collagenic fibers.

Methods

Study Design

The present study followed the international systematic review model, following the rules of PRISMA (preferred reporting items for systematic reviews and meta-analysis). Available at: http://www.prisma-statement.org/?AspxAutoDetectCookieSupport=1. Accessed on: 12/12/2023. The methodological quality standards of AMSTAR-2 (Assessing the methodological quality of systematic reviews) were also followed. Available at: https://amstar.ca/. Accessed on: 12/12/2023.

Data Sources and Research Strategy

The literary search process carried out from October to December 2023 and was developed based on Scopus, PubMed, Lilacs, Ebsco, Scielo, and Google Scholar, covering scientific articles from various eras to the present. The descriptors (MeSH Terms) used: *"Collagen. Collagenic fibers. Vitamins. Nutrients. Rejuvenation"*, and using the Boolean "and" between MeSH terms and "or" between historical discoveries.

Study Quality and Risk of Bias

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 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 the Cohen test (d).

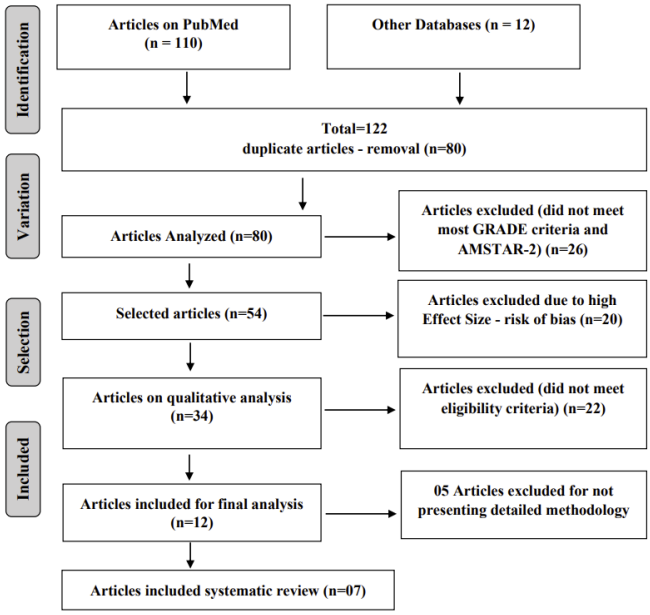
Results and Discussion

Summary of Findings

A total of 122 articles were found that were

subjected to eligibility analysis, with 07 final studies being selected to compose the results of this systematic review. The studies listed 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 showed 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.

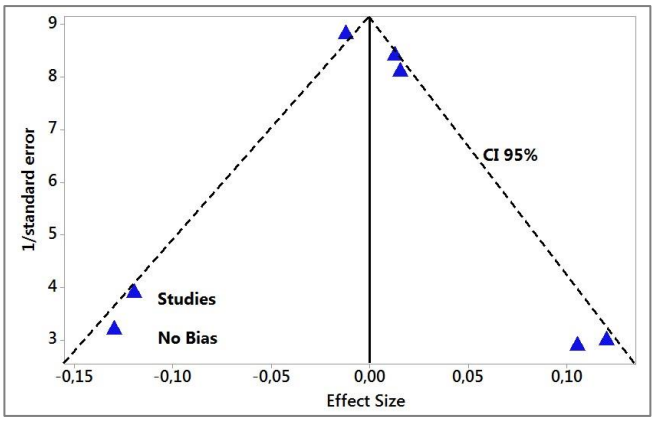
Figure 1. Flowchart showing the article selection process.



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 the Cohen Test (d). Precision (sample size) was determined indirectly by the inverse of the standard error (1/Standard Error). This graph had a symmetrical behavior, not suggesting a significant risk of bias, both between studies with a small sample size (lower precision) that are shown at the bottom of the graph and in studies with a large sample size that are presented at the top.

Figure 2. The symmetric funnel plot suggests no risk of bias among the small sample size studies at the bottom of the graph showed. High confidence and high recommendation studies are shown above the graph (n=07 studies).



Source: Own authorship.

Major Clinical Results (n=7 major studies)

A randomized clinical study 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 and 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 **[10]**.

In this regard, skin aging has become a recurring concern even among younger people, mainly due to the increase in life expectancy. In this context, the use of nutricosmetics as supplements has increased in recent years. A meta-analysis study looked at 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, ingesting hydrolyzed collagen for 90 days is effective in reducing skin aging, as it reduces wrinkles and improves skin elasticity and hydration **[11]**.

Another systematic review study evaluated the effects of collagen supplements on skin health parameters in healthy individuals and patients, focusing on 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 **[12]**.

Furthermore, a randomized, placebo-controlled, and triple-blind clinical study on 60 healthy volunteers

was to evaluate the cosmetic effects on skin quality of a food supplement containing special collagen peptides together with acerola extract, vitamin C, vitamin E, biotin, and zinc after a 12-week intake. To reduce evaluation bias as much as possible and increase the precision and objectivity of the results, the study design was triple-blind. The expert rater who evaluated the confocal laser scanning microscopy images was additionally blinded to when the image was obtained (on days 1 or 85). Objective, blinded, validated image analyses using confocal laser scanning microscopy showed a significant improvement in facial skin collagen structure (primary outcome) after ingestion of the test product, whereas no improvement was found after ingestion of the placebo. The proven positive nutritional effect on collagen structure was fully consistent with positive subjective assessments of relevant skin parameters such as elasticity, wrinkling/wrinkles, and evenness in different areas of the body such as face, hands, décolleté, neck, back, legs, and belly **[13]**.

Added to this, the use of nutraceuticals like collagen for skin care has increased, but regulations on quality, absorption, and effectiveness are lacking. One study evaluated available randomized clinical trials utilizing collagen supplementation for treatment efficacy regarding 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, 2.5g/day to 10g/day, for 8 to 24 weeks, for the treatment of pressure ulcers, xerosis, skin aging, and cellulite. Two studies used collagen tripeptide, 3g/d for 4 to 12 weeks, with notable improvements in skin elasticity and hydration. Lastly, a study using collagen dipeptide suggested that anti-aging efficacy is proportional to collagen dipeptide content. Preliminary results are promising for short- and long-term use of oral collagen supplements for wound healing and aging skin. Oral collagen supplements also increase skin elasticity, hydration, and dermal collagen density **[14]**.

Furthermore, authors Pu et al. (2023) **[15]** 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 to the placebo group. However, there were no significant differences in the effects of different collagen sources or corresponding measurements on skin elasticity **[15]**.

Finally, the authors Trentini et al. (2022) **[16]** analyzed apple-derived nanovesicles (exosomes) (ADNVs) as new anti-inflammatory compounds, capable of altering the production of extracellular matrix in dermal fibroblasts. Total RNA sequencing analysis revealed that ADNVs negatively influence Toll-like Receptor 4 (TLR4) activity and thus negatively regulate the pro-inflammatory NF-κB pathway. ADNVs also reduce the degradation of the extracellular matrix, increasing collagen synthesis (COL3A1, COL1A2, COL8A1, and COL6A1) and negatively regulating the production of metalloproteinases (MMP1, MMP8, and MMP9). Topical applications for skin regeneration were evaluated by the association of ADNVs with hydrogel and hyaluronic acid-based adhesives **[16]**.

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. 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.

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Ethical Approval

Not applicable.

Informed consent

Not applicable.

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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 applied.

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