

Effective Topical and Oral Treatments for Skin Aging: Review

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ARTIGO DE REVISÃO

ABSTRACT

The utilization of both systemic and topical treatments in dermatology with the expectation that their combination will enhance attributed benefits and provide preventive dermatology has gained interest. In order to identify effective combined treatments for skin aging, a systematic review was conducted, which comprehensively searched the Capes Journal Portal of E-Journals. Out of the 4543 articles evaluated, only 24 were deemed eligible for final analysis. The findings were characterized as clinical studies that evaluated various combinations of treatments. It was concluded that the efficacy of collagen peptides, antioxidants, moisturizers, and lifestyle changes in mitigating skin aging resulted in improvements in the firmness, elasticity, hydration, and antioxidant protection of human skin.

Keywords: Skin aging, oral intake, Controlled trial, Systematic review.

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INTRODUCTION

The utilization of systemic and topical treatments in dermatology has been in practice for decades, though there are still controversies regarding the efficacy of this strategy in preventing aging. The most common practice is to use these treatments separately, either via oral or topical dermatological route. An example of separate and proven effective use is the use of oral isotretinoin or topical retinoic acid for treating acne vulgaris. These treatments not only control the disease but also provide anti-aging benefits¹. Oral vitamin D has been indicated for patients with psoriasis who need this supplementation² and consumption of fatty acids has been shown to improve the barrier function of the skin of menopausal women³.

Nutritionists, dermatologists and pharmacists are the main prescribers of nutricosmetics, nutraceuticals, and cosmeceuticals⁴ for the prevention and treatment of skin aging. Nutricosmetics, nutraceuticals, and cosmeceuticals can be used in isolation or in combination, when the combination is performed, it is called "in-out" treatment (inside and out), with the expectation that the combination enhances the benefits attributed and thus have a preventive dermatology.

This knowledge extends to the prevention of skin aging, which can be increased when there is the combined use of specific nutrients, such as vitamins A, E and C, in addition to minerals such as zinc, copper and selenium, among others, which increase the antioxidant defenses of the skin and consequently its resistance to ultraviolet radiation^{5,6}. Certain functional foods, also called nutricosmetics, containing polyphenols, antioxidant vitamins, peptides and other substances can promote skin improvement⁷.

Antioxidants have been widely used in dermatology and are indicated for photoaging, melasma, psoriasis, alopecia and skin cancer prevention^{8,9}. They are important for the redox balance of the skin and preventing damage caused by free radicals arising from exposure to ultraviolet radiation and pollution¹⁰. Wen et al.¹¹ states in their review of resveratrol, a substance derived from grapes with antioxidant, photoprotective and anti-inflammatory functions demonstrated mainly in vitro, that resveratrol still requires clinical validation for its use to be indicated with more assertiveness.

Still regarding aging, the presence of patches (dyschromia) is a factor that impacts the quality of life, and according to Handel; Miot; Miot¹² "*melasma is a chronic acquired hypermelanosis of the skin, characterized by irregular brown macules symmetrically*

distributed on sun-exposed areas of the body, particularly on the face” and which can be prevented by the use of photoprotectors and antioxidants.

Prescribers have considered the efficacy studies on each nutraceutical or cosmeceutical carried out in isolation to prescribe combined treatments, observing in their clinical practice whether or not a benefit for the patient occurs, requiring a review of clinical studies that address the combination of these treatments. The aim of this research was to conduct a systematic literature review to identify which topical and oral treatments, combined or not, were effective in preventing skin aging and improving photoaged skin.

METHODOLOGY

A systematic literature review was conducted using the Capes Journal Portal (it was officially created by the Coordination for the Improvement of Higher Education Personnel, a foundation of the Ministry of Education, on November 11, 2000, Brazil), which aggregates several major health databases including Medline and Scielo. The review was conducted by two independent researchers and any disagreements were resolved by a third independent reviewer.

The research protocol utilized clear research questions to eliminate selection bias and was based on PRISMA statement guidelines.

The search was performed using the following MESH terms: topical, oral intake, controlled trial, both inside & out, skin aging, supplementation, and topical treatment.

Inclusion criteria included studies published in any language between 2011 and 2021. Excluded studies included those published outside of the designated time period, duplicates, studies with focus outside the scope of this review, studies on experimental animals, in vitro studies and other reviews.

The articles were analyzed based on the research question: *What topical and oral treatments, either used in combination or separately, have been demonstrated to be effective for the prevention and treatment of skin aging, based on clinical studies conducted on human subjects?*

RESULTS

The initial search resulted in 4543 articles, and after applying inclusion and exclusion criteria, a final sample of 24 articles was selected for analysis, as presented in Figure 1 and Table 1.

Figure 1. Flowchart of identification of studies via database¹³.

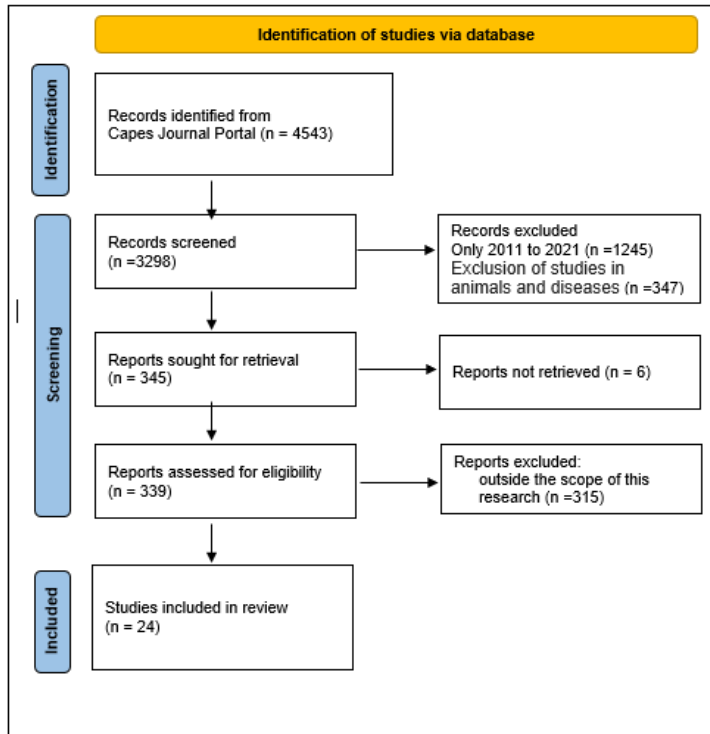


Table 1. Studies included in this review.

	Year	Studied compounds	Study type
<i>Djawad;</i> <i>Anggraini</i>	2021	oral superoxide dismutase	Clinical study
<i>Laing et al,</i>	2020	collagen peptides	Clinical study
<i>Ryu et al.</i>	2020	coenzyme Q10-loaded microemulsion	Experimental study
<i>Evans et al.</i>	2020	freshwater marine collagen	Clinical study
<i>Myung et al.</i>	2020	<i>Hydrangea serrata</i> (thunb.) Ser. Leaves extract	Clinical study
<i>Granger et al.</i>	2020	food supplement	Clinical study
<i>Bolke et al.</i>	2019	collagen supplement	Clinical study

<i>Bolke et al.</i>	2019	collagen supplement	Clinical study
<i>Campos, Melo, César</i>	2019	peptides	Clinical study
<i>Guaitolini et al.</i>	2019	hyaluronic acid, l-carnosine, and methylsulfonylmethane	Clinical study
<i>Egoumenides, et al.</i>	2018	melon concentrate	Clinical study
<i>Kim, et al.</i>	2018	collagen peptide	<i>In vitro</i>
<i>Shibuya, et al.</i>	2017	trisodium ascorbyl 6-palmitate 2-phosphate	<i>In vitro</i>
<i>Göllner, et al.</i>	2017	hyaluronan solution	Clinical study
<i>Ghafarzadeha, Eatemadi</i>	2017	liposome-encapsulated aloe vera	Clinical study
<i>Weschawalit, et al.</i>	2017	glutathione	Clinical study
<i>Lademann et al.</i>	2016	antioxidants	Clinical study
<i>Costa et al.</i>	2015	marine protein, vitamin c, grape seed extract, zinc, and tomato extract	Clinical study
<i>Knott et al.</i>	2015	coenzyme Q10	Clinical study
<i>Boucetta et al.</i>	2015	argan oil	Clinical study
<i>Borumand, Sibilla</i>	2015	collagen peptides	Clinical study
<i>Fanian, et al.</i>	2013	micronutrient	Clinical study
<i>Morganti, et al.</i>	2012	chitin complexes	Clinical study

DISCUSSION

Our systematic review identified 24 articles reporting on clinical studies examining the effectiveness of oral and/or topical active substances for skin disorders or skin aging (Figure 1 and Table 1).

We have specifically focused on those studies which were conducted on human participants, regardless of the type or number of active substances used. The studies examined collagen peptides, vitamins, minerals, antioxidants, and herbal compounds,

and we observed that some evaluated the effects of a combination of topical and oral treatments on skin properties, while others examined only one type of treatment. For the purposes of discussion, we have grouped our findings according to the compounds under study.

Collagen Peptides

The biomechanical properties of the dermis are primarily determined by its structural components, which include collagen, elastin, and ground substance. Collagen, in particular, is essential for skin firmness¹⁴, which may explain why numerous studies have examined the cutaneous effects of oral collagen supplementation. Collagen peptides are classified as nutraceuticals and are believed to contribute to increased skin firmness, thereby making them suitable for use in anti-aging treatments¹⁵.

Hydrolyzed collagen is commonly used in cosmetic applications due to its high biocompatibility, ease of biodegradability, and low antigenicity. It is a safe biomaterial that possesses antioxidant properties and has been shown to effectively moisturize the skin¹⁶.

In this context, a study examined the clinical efficacy of a dermocosmetic formulation containing di and tripeptides, as well as the effects of an oral supplementation based on hydrolyzed collagen in women aged 40 to 50 years old¹⁷. The topical formulation produced a significant increase in the stratum corneum water content and skin elasticity after 28 days, while oral supplementation improved skin elasticity and had a more pronounced effect on the echogenicity of the dermis, resulting in reduced skin pores after 90 days. The authors of this study considered the results of oral supplementation and topical application to be complementary in improving the overall condition of the skin, acting on different mechanisms.

A similar outcome was observed in a randomized, placebo-controlled study involving women over 35 years of age. The study revealed that oral supplementation of collagen peptides, along with other nutrients, improved skin hydration and elasticity, reduced wrinkles, and increased skin density for at least three months. In this double-blind, randomized, placebo-controlled trial, a mixture of 2.5g of collagen peptides, acerola fruit extract, vitamin C, zinc, biotin, and a vitamin E complex was administered, resulting in increased skin hydration, improved elasticity, wrinkle reduction, and increased skin density¹⁸. Another double-blind, randomized, placebo-controlled study

evaluated the effect of low-molecular-weight collagen peptides on 64 participants who were administered the supplement daily for three months. The study concluded that these peptides can be used as a functional ingredient to improve skin hydration, elasticity, and wrinkles in humans¹⁹.

The randomized, double-blind, placebo-controlled crossover trial conducted on 59 female volunteers who received amino acid supplementation for six weeks, allowed for the conclusion that there was a significant increase in the improvement of skin texture and body composition. The consumption of hydrolyzed collagen powder derived from *Pangasius hypophthalmus* by 45 volunteers daily for 12 weeks resulted in improvements in facial wrinkles, skin hydration, brightness, and firmness. It is worth noting that a randomized, double-blind, placebo-controlled study evaluated the effects of oral supplementation with hydrolyzed collagen and a combination of vitamins and minerals in women aged 35-60 years. The results showed significant improvements in skin hydration, elasticity, and firmness after 12 weeks of treatment, suggesting that the combination of collagen and micronutrients can be effective in promoting skin health²⁰⁻²².

In summary, clinical studies have shown that oral collagen supplementation, in combination with other active substances such as vitamins, minerals and antioxidants, can have a positive impact on the biomechanical properties of the skin, including hydration, elasticity, firmness and the reduction of wrinkles. The use of hydrolyzed collagen has been highlighted as a safe and effective option for improving skin health.

Antioxidants

Antioxidant compounds were also prominent in the eligible studies for this review. One randomized clinical trial evaluated the oral supplementation of superoxide dismutase, an essential enzyme in antioxidant defense, for a period of 60 days. The study found a significant increase in total antioxidant status, a reduction in transepidermal water loss (TEWL), and an improvement in skin with reduced dryness²³.

Oral antioxidant supplementation has been shown to have skin benefits, particularly in terms of increased photoprotection, with botanical compounds and vitamins demonstrating photoprotective effects²⁴. In a study of Caucasian individuals aged 18 to 50 years, the effects of oral supplementation and topical administration of a concentrate obtained from melon were evaluated, and it was found that the use of this



concentrate both orally and topically in combination resulted in an increase in the minimal erythema dose. The melon juice concentrate is rich in superoxide dismutase, which is responsible for the observed activity²⁵.

In a clinical study, the efficacy of topically applied coenzyme Q10 (ubiquinone) was evaluated in 73 volunteers aged 20 to 66 years old, who used it at different concentrations for 2 weeks. The results showed that coenzyme Q10 can penetrate the skin, be metabolically transformed, and exert an antioxidant effect, supporting the maintenance of cellular energy levels. This effect can not only benefit the elderly population suffering from coenzyme Q10 deficit but also replenish the levels in the skin for people of all ages. The authors of the study suggest that regular treatment with formulas containing coenzyme Q10 can more effectively deal with short-term damage inflicted by UV irradiation and stress, while promoting long-term anti-aging effects on the skin²⁶. Additionally, microemulsions containing coenzyme Q10 were developed and evaluated using an in vitro method to verify skin permeation, and they showed very satisfactory results, indicating their safe application²⁷.

Carotenoids, such as beta-carotene, lycopene, astaxanthin, and lutein, have been found to have free radical scavenging effects that are crucial for combating skin aging. They can be utilized as nutraceuticals, cosmeceuticals, and photoprotectors due to their antioxidant, anti-inflammatory, and immunomodulatory properties, which increase protection against ultraviolet radiation and contribute to the skin's youthful and healthy appearance. A diet rich in fruits and vegetables provides numerous benefits to public health, including disease prevention, and the use of nanotechnology to deliver these active compounds in the body is a critical area for developing new delivery systems that should be extensively explored in the future²⁸.

Authors have also evaluated the effects of vitamin C derivatives such as Trisodium Ascorbyl 6-Palmitate 2-Phosphate (APPS) through topical application in some studies²⁹. These studies assessed the conversion of APPS to ascorbic acid in skin cells and the redox regulation associated with oxidative stress. The results were positive, showing that APPS effectively restores the ascorbic acid level and normalizes the redox balance in skin cells. Thus, this topical treatment can be a beneficial strategy to deliver ascorbic acid and improve the physiology of damaged skin²⁹.

Antioxidants have been shown to have potential benefits in the gut-skin axis, as demonstrated in various studies³⁰. An 8-week double-blind study³⁰ was conducted on women aged 20 to 73 years to evaluate the influence of systemic and combined topical antioxidant treatment on the barrier properties of human skin. The study involved the use of cream and tablets containing vitamin E acetate, plant-derived vitamin C acetate, plant extracts (green tea, green coffee, pongamia, pinnata seed, and angelica), and 0.2% of the carotenoids β -carotene and lycopene at the same concentrations. The results of this study³¹ showed that the stratum corneum can be saturated with topically used antioxidants, and oral supplementation would not interfere. However, oral supplementation may have a longer-lasting effect, while the topical application of antioxidants should be carried out continuously to obtain the benefits³¹.

Another double-blind placebo-controlled study was conducted on 18 volunteers, where the test product was a fruit-based drink containing vitamin C, vitamin E, hydrolyzed collagen, and other ingredients. The study demonstrated that daily consumption of the test product in its current formulation was able to induce a clinically measurable improvement in the depth of facial wrinkles, skin elasticity, and hydration³².

A 12-week open, prospective, monocentric clinical trial with 30 volunteers was conducted to evaluate photoprotective efficacy. The test group consumed a supplement, one capsule daily for 12 weeks, containing vitamin C, vitamin E, vitamin D3, selenium, vitamin A, lycopene, lutein, extract of *Vitis vinifera*, extract of *Camellia sinensis*, and *Polypodium leucotomos*. The evaluated supplement was found to be effective and well-tolerated in increasing the minimal erythema dose, skin antioxidant capacity, and other parameters related to skin aging. The authors attribute these effects to the increase in antioxidant capacity promoted by oral ingestion of the supplement³³.

An oral antioxidant supplement containing marine protein, vitamin C, grape seed extract, zinc, and tomato extract was evaluated in another study. This 210-day study involved 47 volunteers. The results showed an increase in dermis density, facial hydration, and a reduction in pH, as well as an increase in collagen and elastin fibers, indicating excellent results for skin anti-aging³⁴.

In addition to antioxidants, protecting mitochondrial DNA is important in preventing skin aging. Substances such as vitamins C and E, coenzyme Q10, as well as anti-inflammatory ingredients like argan oil, caffeine, chamomile, feverfew, green tea,

licorice extract, aloe, linoleic acid, and niacinamide have shown significant effects against ultraviolet radiation³⁵. Oral administration of glutathione at a dose of 250mg/day for 12 weeks has also been shown to reduce wrinkles and increase skin elasticity³⁶.

Ghafarzadeha and Eatemadi³⁷ conducted a study on the effects of topical application of aloe vera microencapsulated in liposomes in improving melasma in pregnant women. The results suggested that the antioxidant action of aloe vera, which contains minerals, vitamins, amino acids, and vitamins A, B, C, D, and E, may have contributed to the observed improvement.

Morganti et al.³⁸ conducted a study to evaluate the effects of a complex composed of melatonin, vitamin E, and beta-glucan complexed with chitin nanocrystals on skin properties when administered topically and orally for 12 weeks on 70 volunteers. The study showed significant results in reducing wrinkles, improving skin appearance, and overall well-being. The complex is believed to work through the antioxidant properties of vitamin E and melatonin, as well as the ability of beta-glucan to stimulate collagen production and the use of chitin nanocrystals to enhance delivery of the active ingredients.

In summary, prescribed treatments target the physiological processes of skin aging and have been clinically proven to effectively modify the skin's structure and appearance³⁹.

Skin Hydration

Supplementing with hyaluronic acid has been shown to be useful for skin hydration⁴⁰. In one clinical study, a supplement containing hyaluronic acid, biotin, vitamin C, copper, and zinc was administered to women aged 45 to 60 with healthy skin once daily for 40 days. Results showed a significant increase in skin elasticity and hydration, as well as a significant decrease in roughness and depth of wrinkles. The supplement was well-tolerated with no observed side effects throughout the study⁴¹. Another study evaluated a combination of 200mg hyaluronic acid, 500mg L-carnosine, and 400mg methylsulfonylmethane, or a placebo, in 50 women aged 40 to 65 with photoaging for 60 days. The combination supplement showed significant improvement in reducing the periorcular region⁴².

Regarding topical use, a study evaluated the effect of dietary and/or cosmetic argan oil on postmenopausal skin elasticity. Thirty participants were divided into two groups, where one group received argan oil in their diet and applied cosmetic argan oil to the left volar forearm, while the control group received only olive oil in their diet and applied no topical treatment. After a 60-day period, the group that consumed and/or applied argan oil showed a significant increase in skin elasticity compared to the control group⁴³.

Regarding topical applications, Nilforoushzhadeh et al.⁴⁴ discussed the use of facial masks to improve skin health. The authors mentioned the use of moisturizers, vitamins, antioxidants, herbal compounds, minerals, proteins, and exfoliants. Face masks are an important tool for skin enhancement, and it is crucial to choose a mask that is appropriate for one's skin type and specific needs.

Another randomized, placebo-controlled, double-blind study was conducted on 80 volunteers between the ages of 35 and 55 who received micronutrient supplementation for four months. The product analyzed contained a complex composition of B-complex vitamins, vitamin A, vitamin D, vitamin C, biotin, magnesium, zinc, copper, manganese, selenium, chromium, marine collagen, green tea extract, lycopene, coenzyme Q10, beta-carotene, and two plant extracts. The study concluded that this supplement can reduce or eliminate the negative effects of intense winter months on the skin, especially in exposed areas⁴⁵.

A randomized, placebo-controlled double-blind study conducted by Myung et al.⁴⁶ evaluated the effect of oral supplementation with hot water extract of *Hydrangea serrata* leaves on skin wrinkles. The study found that wrinkles were significantly reduced after 8 and 12 weeks of supplementation. Additionally, the supplementation resulted in increased skin hydration, suggesting its potential as a protective supplement against skin aging in healthy functional foods by targeting systemic factors and regulating skin appearance.

Lifestyle

Several authors have highlighted the role of lifestyle and nutrition in the aging process. Factors such as healthy lifestyle habits, including moderate eating, having a life purpose, social support, physical activity, and specific nutritional habits such as consuming teas and red wine, as well as spirituality and maintaining a healthy body mass, have been found to contribute to advanced human longevity, as seen in



centenarians. The foundations for a long life are multifactorial, and while genetics play a strong role, they are not the only factors⁴⁷. Microbial changes in the gut have also been linked to age-related diseases and immune response, emphasizing the importance of ingesting probiotics and maintaining a healthy diet for the gut microbiota. Nutrition plays a crucial role in healthy aging and can impact the prevention of aging-related diseases, including sarcopenia and cognitive decline⁴⁸.

Upon conducting a comprehensive evaluation of the results obtained in the reviewed studies, it is evident that the majority of them demonstrate a high level of scientific evidence as they are randomized, double-blind, and placebo-controlled. Furthermore, these studies involved middle-aged and elderly adults, who are the population groups that would benefit the most from the proposed interventions. As a result, the combination of topical treatments containing antioxidant compounds, along with oral administration of collagen peptides, diverse antioxidants, and botanical compounds may be a promising approach for improving the structure of human skin. These interventions may also have a positive impact on self-esteem and quality of life.

FINAL CONSIDERATIONS

Several clinical studies have demonstrated the effectiveness of both topical and oral treatments in preventing skin aging and improving skin conditions. Collagen peptides and various antioxidants, administered topically and orally, have been extensively studied and their efficacy in improving human skin has been proven, with increased firmness, elasticity, skin hydration, and antioxidant protection. As such, young adults can benefit from their use to maintain healthy skin and slow the aging process, particularly if they combine these treatments with a healthy lifestyle.

Conflicts of Interest: The authors declare no conflict of interest.

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