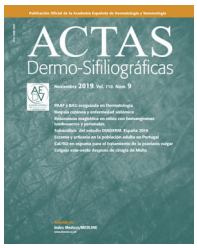
ACTAS Dermo-Sifiliográficas 114 (2023) T114–T124

ACADEMIA ESPAÑOLA DE DERMATOLOGÍA Y VENEREOLOGÍA

ACTAS Dermo-Sifiliográficas

Full English text available at www.actasdermo.org



REVIEW

# [Translated article] Oral Supplementation and Systemic Drugs for Skin Aging: A Narrative Review

D. Morgado-Carrasco[a,*], J. Gil-Lianes[a], E. Jourdain[b], J. Piquero-Casals[c]

[a] *Dermatology Department, Hospital Clínic de Barcelona, Universitat de Barcelona, Spain*
[b] *Innovation and Development, ISDIN, Barcelona, Spain*
[c] *Dermik, Clínica Dermatológica Multidisciplinar, Barcelona, Spain*

Received 12 May 2022; accepted 20 September 2022
Available online 1 December 2022

**KEYWORDS**
Photoaging;
Skin aging;
Oral hydrolyzed collagen;
Hyaluronic acid;
Treatment;
Oral

**Abstract** Skin aging is influenced by intrinsic and extrinsic factors and involves multiple pathogenic mechanisms. The most widely used treatments are topical products and minimally invasive procedures. Evidence on the benefits of systemic therapy is limited for several reasons: reliance on mostly small and predominantly female samples, short study durations, methodologic heterogeneity, and a lack of consensus on which outcome measures are clinically relevant. Furthermore, systemic drugs and oral supplements are not without adverse effects. Oral hydrolyzed collagen and oral hyaluronic acid are well tolerated, and numerous clinical trials show they can mitigate some signs of skin aging. Low-dose oral isotretinoin is another option, but it has a higher risk of adverse effects. Evidence is lacking on the effects of the many dietary supplements on offer, such as vitamins, flavonoids, plant extracts, and trace elements. The future of skin aging management would appear to lie in the use of senolytic and senomorphic agents targeting senescent cells in the skin.


**PALABRAS CLAVE**
Fotoenvejecimiento;
Envejecimiento cutáneo;
Colágeno hidrolizado

## Tratamiento mediante suplementación oral o fármacos sistémicos del envejecimiento cutáneo. Revisión narrativa de la literatura

**Resumen** El envejecimiento cutáneo está influido por factores intrínsecos y extrínsecos y múltiples mecanismos patogénicos están involucrados. Los tratamientos utilizados en la actualidad son sobre todo tópicos o son procedimientos mínimamente invasivos. La evidencia sobre la utilidad de la terapia sistémica es limitada: los estudios son en su mayoría de pequeño

DOI of original article: https://doi.org/10.1016/j.ad.2022.09.014
* Corresponding author.
*E-mail address:* morgadodaniel8@gmail.com (D. Morgado-Carrasco).

https://doi.org/10.1016/j.ad.2022.09.021

oral;
Ácido hialurónico;
Tratamiento;
Oral

tamaño, de reducida duración, incluyen a mujeres de manera mayoritaria, la metodología de evaluación es heterogénea y no hay parámetros consensuados de respuesta clínica relevante. Además, los suplementos o fármacos sistémicos no están exentos de efectos adversos. El colágeno hidrolizado oral y el ácido hialurónico oral son bien tolerados y múltiples ensayos clínicos muestran que pueden mitigar algunos signos de envejecimiento cutáneo. La isotretinoína oral en dosis bajas es otra alternativa, pero con un mayor potencial de efectos adversos. Múltiples suplementos, como vitaminas, flavonoides, diversos extractos de plantas y oligoelementos presentan escasa evidencia clínica. El futuro del manejo del envejecimiento cutáneo parece ser el tratamiento con agentes senolíticos o senomórficos dirigidos específicamente contra células cutáneas senescentes.


## Introduction

Skin aging is characterized by wrinkles, sun spots, an uneven skin tone, decreased elasticity, increased skin fragility and visible capillaries, impaired healing, and an increased incidence of skin cancer and infections.[1] It is influenced by both intrinsic and extrinsic factors involving multiple pathogenic mechanisms (Table 1) (Fig. 1). Extrinsic aging is predominantly influenced by sun exposure (photoaging), although smoking and pollution also play a role.[1] Intrinsic and extrinsic aging overlap in clinical practice.[1] Demand for strategies to mitigate the signs of skin aging is high.[2] Recent studies suggest that regular exercise, apart from improving quality of life and reducing the risk of mortality and chronic disease,[2] might also reduce the thickness of the stratum corneum and improve dermal thickness and collagen content.[3] Diet is also important, with a number of studies highlighting its role in the prevention of aging. Dietary antioxidants such as vitamin C and linoleic acid are considered important.[4] Several studies have shown that calorie-restricted diets (without the loss of essential nutrients) and intermittent fasting have antioxidant and anti-inflammatory effects and associated health benefits. Animal model studies have shown that calorie restriction and fasting might reduce skin aging.[5]

Numerous skin aging treatments exist, and mostly consist of topical products (e.g., retinoids, α-hydroxyacids, broad-spectrum sunscreens, and antioxidant/anti-inflammatory agents, such as preparations containing vitamin C, vitamin E, and niacinamide[6]) and invasive or minimally invasive procedures (e.g., ablative and nonablative laser therapy, intense pulsed light therapy, radiofrequency, dermabrasion, and chemical peels). Consensus is lacking on the use of oral supplements and systemic treatments for skin aging and photoaging. In this article, we review the current evidence on the use of these treatments in the setting of skin aging and photoaging.

Table 1 Molecular Mechanisms of Skin Aging.

| Molecular mechanism | Impact |
|---|---|
| Oxidative stress | Induction of matrix metalloproteinases<br>Increased production of proinflammatory cytokines<br>Indirect DNA damage<br>Mitochondrial damage |
| Telomere shortening | Cellular senescence |
| Altered micro-RNA expression and dysregulated gene expression | Dysregulation of apoptosis<br>Altered collagen gene expression |
| Increased proinflammatory state | Relative immunosuppression<br>Angiogenesis<br>Cell proliferation |
| Apoptosis dysfunction | Cellular senescence<br>Protumor state |
| Direct UVB radiation–induced DNA damage | Formation of mutagenic photoproducts |

## Material and Methods

For this narrative review, we searched for articles published in PubMed and Google Scholar between January 1, 1990 and March 2022 using the keywords *oral*, *systemic treatment*, *treatment*, *therapy*, *skin aging*, *photoaging*, *oral collagen*, *isotretinoin*, *tranexamic acid*, Polypodium leucotomos, *niacinamide*, *antioxidants*, *metformin*, *hormonal replacement therapy*, *melatonin*, *flavonoids*, *vitamin*, *vitamin C*, *vitamin E*, *vitamin D*, *senolytics*, *hyaluronan*, *hyaluronic acid*, *glucosamine*, *coenzyme Q10*, *glutathione*, *marine complex*, *pine bark extract*, *food supplements*, *aloe vera*, and Hydrangea serrata. We included prospective studies and randomized clinical trials (RCTs) published in English or Spanish. No limits were placed on the number of study participants. After screening the abstracts of the articles retrieved, 2 of the authors (DMC and JPC) performed a full-text review to select relevant articles.

## Results

The results of the most relevant studies analyzing diverse compounds used in the treatment of skin aging are summarized below.

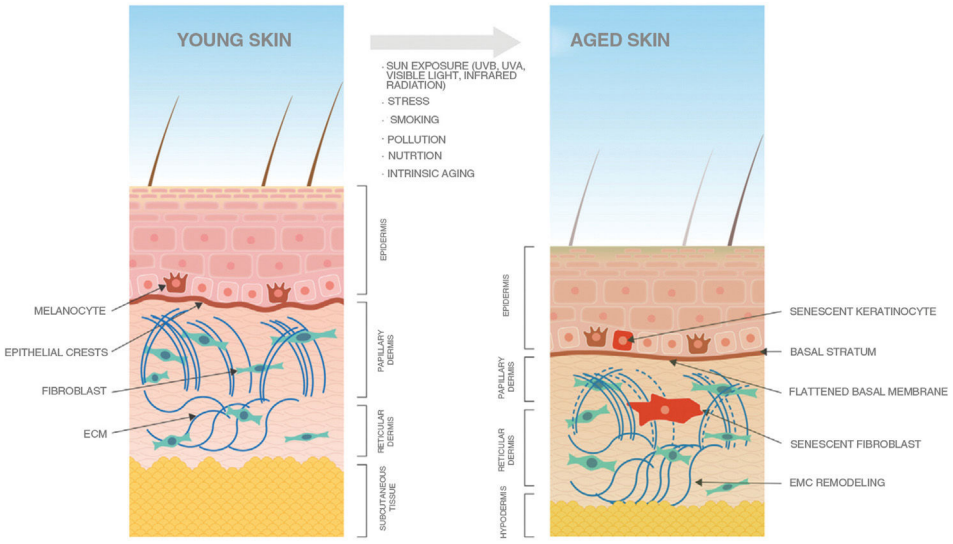



**Figure 1** Skin changes induced by intrinsic and extrinsic aging (exposome). Aged skin is characterized by an atrophic epidermis, with senescent keratinocytes and melanocytes and a flattened basement membrane. Other features include a significantly reduced papillary dermis, senescent fibroblasts, significant extracellular matrix (ECM) remodeling, and subcutaneous tissue thinning.

## Oral Isotretinoin

Isotretinoin is a retinoid widely used in the treatment of acne and many other skin conditions. In addition to its comedolytic, sebum-regulating, and anti-inflammatory properties, it appears capable of inhibiting extracellular matrix metalloproteinases and increasing collagen type I and III production.[7] In a prospective study, 20 individuals were administered oral isotretinoin 20 mg 3 times a week for 12 weeks. Skin biopsies performed before and after treatment and 12 weeks later showed a significant increase in collagen and elastic fiber density. Sixty-five percent of the participants showed histologic improvements in the appearance and distribution of elastic fibers, while they all reported improvements in perceived skin quality.[8]

Two earlier studies had shown both histologic improvements (solar elastosis) and clinical improvements (reduced wrinkle depth and improved skin texture and color).[9,10] No clinical or histologic differences, however, were detected in an RCT ($n = 32$) comparing oral isotretinoin (20 mg 3 times/wk) combined with sunscreen and moisturizer and sunscreen and moisturizer alone.[11] The authors of a more recent systematic review of 6 studies (including 3 RCTs, Table 2) ($n = 251$) concluded that isotretinoin might be a useful treatment for skin aging.[7] There is, however, insufficient evidence to recommend oral isotretinoin over topical treatments. Potential adverse effects, such as mucocutaneous dryness, lipid and liver changes, and teratogenicity, must also be taken into account.

## Oral Supplementation With Hydrolyzed Collagen

Collagen is the main structural protein in the skin, accounting for 75% of the total weight of the extracellular matrix. Hydrolyzed collagen used in oral supplements is obtained through the enzymatic hydrolysis of natural collagen from various sources, such as fish, pork, and chicken.[12] When digested, it is broken down into dipeptides and tripeptides, which are absorbed into the bloodstream through the gastrointestinal tract and largely deposited in the skin. These dipeptides stimulate the metabolism, migration, and proliferation of fibroblasts and generate increased collagen and hyaluronic acid production.[12–14] There is a growing interest in hydrolyzed oral collagen supplements, especially in powder forms.[15] The effects of hydrolyzed collagen supplementation on skin aging were evaluated in a systematic review and meta-analysis of 19 double-blind RCTs[12] involving 1125 individuals. The doses ranged from 372 mg to 12 g a day, and in most of the trials, the participants received a daily dose of 2.5 to 5 g over a period of 8 to 12 weeks. The vast majority of trials showed improved skin elasticity and a reduction in facial wrinkles following treatment. The benefits were maintained for approximately 30 days after the end of treatment, and no adverse effects were observed. Some of the RCTs detected a reduction in skin fragility in hospitalized elderly patients after nursing procedures and improved healing after laser procedures. The meta-analysis showed significant associations between hydrolyzed collagen supplementation and an increase in skin density ($z = 0.48$, $P = .002$), elasticity ($z = 2.31$, $P = .02$), and hydration ($z = 2.58$, $P = .010$) and a significant reduction in facial wrinkles ($z = -1.11$, $P = 009$). The meta-analysis was limited by the heterogeneity of the data pertaining to the collagen supplements used (origin, composition, concentration, formulation, and vehicles [solid vs. liquid]).

A more recent RCT (n = 46) (Table 3) not included in the above meta-analysis showed a significant increase in the echogenicity of the dermis in individuals treated with hydrolyzed collagen for 90 days. Confocal microscopy also showed a reduction in elastosis and improved collagen fiber appearance.[16] In another double-blind RCT ($n = 99$), daily oral supplementation with 1 g or 5 g of collagen was associated with a significant increase in stratum corneum water content in both groups and a reduction in transepidermal water loss in the 5-mg group.[17]

**Table 2** Randomized Clinical Trials Evaluating the Use of Oral Isotretinoin (ISO) in the Treatment of Skin Aging.

| Author/y | No. of patients | Intervention | Main results |
|---|---|---|---|
| Hernández-Pérez et al., 2000[87] | 120 | Oral ISO 10–20 mg 3 times/wk for 2 mo[a] | Improvement of wrinkles, pore size, and hyperpigmentation. Increased skin thickness, elasticity and tone. |
| Rabello-Fonseca et al., 2009[10] | 30 | Oral SO 10 mg vs. 20 mg 3 times/wk for 3 mo | No significant differences between groups. Good/excellent subjective rating of results by patients and researchers in both groups. Microscopic findings showing an increase in collagen fibers ($P < .05$) and a tendency toward decreased elastosis. |
| Bagatin et al., 2010[11] | 32 | Oral ISO 20 mg 3 times/wk and topical sunscreen for 3 mo vs. topical sunscreen | No clinical or histologic differences (epidermal thickness, number of elastic fibers, and dermal collagen) between groups. Significant reduction in epidermal p53 expression in ISO group. |
| Bagatin et al., 2014[88] | 24 | Oral ISO 20 mg/d vs. topical retinoic acid 0.05% for 6 mo | Improvements in both groups for clinical, histologic (decreased stratum corneum, increased epidermal thickness, and reduced elastosis) and immunohistochemical (reduced p53, increased dermal collagen) findings. Nonsignificant differences ($P > .05$) |
| Ianhez et al., 2019[89] | 61 | ISO 10 mg/d vs. tretinoin 0.05% cream every 48 h for 6 mo | No significant differences between groups. Both groups showed an improvement in number of actinic keratoses, histologic variables (decreased stratum corneum, increased epithelial thickness), and immunohistochemical variables (decreased expression of p53 and bax and increased expression of bcl2) |

[a] Both groups of patients received other treatments for photoaging (peeling, laser, botox, liposuction), but strict control of the distribution of treatments between groups and the statistical analysis was lacking.

**Table 3** Supplementation With Hydrolyzed Collagen for the Treatment of Skin Aging: Randomized Clinical Trials Not Included in or Published After the Meta-analysis by De Miranda et al.[a] (2021).

| Author, y | No. of patients | Intervention | Main results |
|---|---|---|---|
| Kim et al., 2018[80] | 64 | 1 g/d hydrolyzed collagen for 12 wk | Improvement in skin hydration and elasticity. Reduction in periocular wrinkles. |
| Evans et al., 2021[81] | 50 | 10 g/d hydrolyzed collagen (fish) for 12 wk | Decrease in wrinkles (-15%). Increased skin elasticity (+23%), hydration (+14%), and firmness (+25%). |
| Lin et al., 2020[90] | 50 | 5–5.5 g/d hydrolyzed collagen (fish) + 1 g Djulis extract[b] for 8 wk | Improved skin hydration (+17.8%) and brightness (+5.4%). Reduction in periocular wrinkles (-14.9%) and pores (-9.9%). Increased dermal collagen (+22.3%). |
| Miyanaga et al., 2021[17] | 99 | 1 vs. 5 g/d hydrolyzed collagen (fish) for 90 d | Increased stratum corneum water content and reduced transepidermal water loss. Changes maintained for up to 30 days posttreatment. |
| Campos et al., 2021[16] | 46 | 500 mg/d hydrolyzed collagen (fish) for 90 d | Increased dermal echogenicity and reduction in facial wrinkles. Confocal microscopy showed reduction in elastosis and improved morphology of dermal collagen fibers. |

[a] This systematic review analyzed 19 randomized clinical trials.
[b] *Chenopodium formosanum* Koidz.

Table 4 Randomized clinical trials evaluating the use of oral hyaluronic acid (HA) in the treatment of skin aging.

| Author, y | No. of patients | Intervention | Main results |
|---|---|---|---|
| Kawada et al., 2015[22] | 24 | 200 mg/d of HA (300 kDa and 800 KDa) for 6 wk | Increased skin hydration and decreased epithelial thickness. Increased *HAS2* expression. |
| Oe et al., 2017[21] | 60 | 120 mg/d HA (2 kDa or 300 kDa) for 4 wk | Improvement in periocular wrinkles (improvement in sulcus volume, and total wrinkle volume and area). |
| Kalman et al., 2020[26] | 88 | 450 mg/d hydrolyzed eggshell[a] for 12 wk | Reduction in periocular wrinkles. Increased hair growth and thickness. No effect on nail growth. |
| Hsu et al., 2021[20] | 40 | 120 mg/d HA for 12 wk | Reduction in facial wrinkles. Increased stratum corneum water content and skin elasticity and thickness. |
| Michelotti et al., 2021[19] | 60 | 200 mg/d full-spectrum HA for 28 d. | Improved skin hydration and elasticity. Reduction in transepidermal water loss and facial wrinkle volume and depth. |

[a] Hydrolyzed eggshell extract contains HA and collagen peptides.

A recent animal model study showed that hydrolyzed collagen (tripeptide collagen) mixed with galacto-oligosaccharide at a ratio of 1:1 and 3:1 improved clinical photoaging-related parameters and inflammation secondary to UVB exposure.[18]

## Oral Hyaluronic Acid

Hyaluronic acid (HA) is a mucopolysaccharide widely distributed in connective tissue. The skin contains 50% of all HA in the body. HA is synthesized by keratinocytes and fibroblasts, and regulates water balance and maintains the structure of the skin. HA supplements are obtained from animals or bacterial fermentation. Absorption depends on the molecular weight of the acid and can be as high as 93.6%.[19] A recent double-blind RCT (n = 60) showed that oral supplementation with HA 200 mg/d led to significant improvements in skin hydration and elasticity and an objective reduction in transepidermal water loss and facial wrinkles.[19] Sixty-three percent of participants reported a reduction in facial wrinkles and 90% an increase in elasticity. No adverse effects were reported. Another double-blind RCT evaluating the administration of HA 120 mg/d for 12 weeks reported a significant reduction in wrinkles and an increase in stratum corneum water content and skin elasticity and thickness.[20] Similar results had been observed in earlier RCTs (Table 4)[21–23] and prospective studies.[24]

A study of the benefits of an oral eggshell supplement, which contains HA and collagen, showed an improvement in skin elasticity, a reduction in skin pigmentation, and very high patient satisfaction with facial softness, skin hydration, and hair and nail appearance.[25] A double-blind RCT (n = 88) with similar characteristics reported a reduction in periocular wrinkles and improved hair thickness and growth.[26]

## Oral Tranexamic Acid

The plasmin inhibitor tranexamic acid (TA) is a potent anti-inflammatory and depigmenting agent. Numerous RCTs have demonstrated the efficacy of oral TA in the treatment of melasma.[27] Melasma has several features suggestive of a photoaging disorder, such as neovascularization, basement membrane damage, and solar elastosis.[28] TA appears to indirectly decrease metalloproteinase 1 activation and reduce the expression of proinflammatory cytokines, such as interleukin 6 and tumor necrosis factor. It has also been linked to reduced expression of metalloproteinase 9, generation of reactive oxygen species,[29] and increased HA synthesis.[30] It also appears to increase fibroblast proliferation and collagen generation.[31]

Several animal studies of TA have shown a reduction in wrinkles[31] and skin[30] and photoaging[32] signs. Another study found that TA may even be capable of improving the lifespan of mice not exposed to UV radiation.[29]

Oral TA has a good safety profile.[33] In our review of the literature, we found no prospective clinical studies evaluating its effects on skin aging.

## Hormone Replacement Therapy

Women can lose up to 30% of skin collagen in the first 5 years of menopause[34] and may also experience a 0.55% loss of skin elasticity each year.[35] A double-blind RCT evaluating the effects of hormone replacement therapy (HRT) (2 mg 17B estradiol/10 mg dydrogesterone) on the skin of 40 postmenopausal women found an increase in skin thickness, hydration, and elasticity after 7 months of treatment.[36] Another study (n = 55) showed that postmenopausal women on HRT with estrogen and testosterone had 48% higher collagen content in the skin.[37] A similar study (n = 25) reported significantly higher type III collagen content in women treated with estradiol and testosterone

implants.[38] Likewise, a large prospective study involving 176 women found a 5.2% increase in skin elasticity after 12 months of HRT.[35]

Other authors have also reported a significant increase in skin viscoelasticity (n = 200) in women on HRT.[39] Nonetheless, a large RCT (n = 485) detected no differences in facial wrinkles or skin laxity between postmenopausal women treated with HRT and those treated with placebo.[40]

Elderly individuals may show low levels of growth hormones and also experience a dramatic decrease in skin thickness.[41] Two studies have reported increased epidermal and dermal thickness in individuals with deficient growth hormone levels treated with growth hormone therapy.[41,42] Potential adverse effects include gynecomastia and carpal tunnel syndrome.

## Oral Polypodium Leucotomos

*Polipodium leucotomos* is a fern with anti-inflammatory and antioxidant properties native to Central and South America. Clinical studies have shown that it can reduce erythema induced by UV radiation and DNA damage and is also a useful adjuvant in the treatment of photoinduced and photoaggravated skin conditions and pigmentation disorders, such as vitiligo and melasma.[43,44] It has an excellent safety profile. The findings of numerous in vitro studies using animal and human models suggest that *P. leucotomos* might be able to mitigate photoaging induced by UV radiation and visible light.[43]

A recent double-blind RCT ($n = 30$) found a significant increase in minimal erythema dose and skin antioxidant capacity and skin hydration, in addition to improvements in skin appearance and elasticity following oral supplementation with a dietary product containing *P. leucotomos*, green tea, and other antioxidants.[45]

## Oral Coenzyme Q10

Coenzyme Q10 has both antioxidative and anti-inflammatory properties. A double-blind RCT (n = 33) evaluating the effects of oral coenzyme Q10 on the skin found improvements in wrinkles and skin smoothness, but no changes in skin hydration, dermal thickness, or minimal erythema dose.[46] Another double-blind RCT ($n = 34$) found that a dietary supplement containing coenzyme Q10, oral collagen, vitamin C, vitamin A, and biotin for 12 weeks reduced facial wrinkles and increased dermal density, but had no impact on skin hydration or thickness.[47]

## Oral Glucosamine

Oral glucosamine sulfate is widely used in osteoarthritis. It is essential for the synthesis of glycoproteins, glycolipids, glycosaminoglycans, and proteoglycans. A clinical study involving 8 participants showed that 250 mg of glucosamine administered for 8 weeks increased the expression of type I and III collagen and hyaluronan synthase.[48] In a blinded RCT (n = 53), a dietary supplement containing glucosamine, minerals, and antioxidants significantly decreased the number of facial wrinkles and fine lines.[49]

## Systemic Glutathione

Glutathione has antioxidative, antitumor, antiviral, and antimelanogenic properties.[50] Oral and intravenous formulations have been used to decrease skin pigmentation and photoaging, but 2 recent systematic reviews of the literature, including 3 RCTs, did not find sufficient evidence to recommend their use in this setting.[50,51]

A more recent RCT (n = 124), not included in the above systematic reviews, showed that 250 mg of glutathione combined with 500 mg of L-cystine for 12 weeks significantly reduced solar lentigines and hyperpigmented macules in Asian women. Glutathione 250 mg alone, however, was not significantly superior to placebo.[52] Another recent RCT (n = 46) reported decreased skin pigmentation following an 8-week regimen of 600 mg of glutathione, 50 mg of $\alpha$-lipoic acid, and 4 mg of zinc.[53] Even better results were observed for oral glutathione combined with topical 2% glutathione. A multicenter RCT (n = 83), however, found no significant differences between glutathione supplementation and placebo.[54]

## Oral Melatonin

Melatonin is a hormone secreted by the pineal gland, but it is also synthesized and metabolized in the skin. It has powerful antioxidant, anti-inflammatory, immunomodulatory, and antitumor properties.[55] In vivo and in vitro studies have shown that it can attenuate the deleterious effects of UV radiation and increase the antioxidant capacity of the skin.[55] In our review of the literature, we found no clinical studies analyzing its effect on skin aging.

## Oral Metformin

Metformin is a promising drug widely used in the treatment of type 2 diabetes mellitus. Multiple studies have shown that it can reduce the incidence of age-related diseases, such as cardiovascular and neurological diseases and cancer, as well as overall mortality[56] in both diabetic and nondiabetic individuals.[57] Animal studies have also shown an increase in lifespan.[58] The ongoing Targeting Aging with Metformin (TAME) trial is a large multicenter trial evaluating the effects of metformin on human aging.[59] We did not find any clinical studies analyzing its use in skin aging.

## French Maritime Pine Bark Extract

French maritime pine bark extract is a blend of bioflavonoids, which are powerful antioxidants and anti-inflammatory agents. Clinical studies have shown that it has several antiaging and cardio- and neuro-protective properties, and can also alleviate osteoarticular, urologic, and menopause-related discomfort.[60] The extract has also been found to have a photoprotective, modulating effect on skin pigmentation.[61] Several RCTs evaluating the use of French maritime pine bark extract have shown a significant reduction in signs of facial aging, such as wrinkles and solar lentigines,[62,63] and increased levels of hyaluronan synthase and type I collagen.[64] Another RCT (n = 76) showed increased

skin elasticity and hydration and decreased skin darkening in Asians working in highly polluted areas after treatment for 12 weeks.[65] No relevant adverse effects were reported.

## Other Agents

Administration of 210 mg of a marine complex combined with vitamin C, zinc, and other antioxidants led to improved facial appearance in 2 RCTs led by the same group of authors (n = 152[66] and n = 72[67]). Similar findings were reported in prospective clinical studies.[68,69] A large multicenter RCT (n = 194), however, found no significant differences with placebo.[70] A meta-analysis of the above findings for a total of 480 patients showed a favorable effect on facial appearance.[70]

Multiple oral antioxidants and anti-inflammatory agents, such as vitamins A, C, D, and E, green tea polyphenols, niacinamide, and trace elements such as zinc may help mitigate signs of skin aging. Many of the studies evaluating different combinations of antioxidants, however, have used different methodologies, impeding replication.[71] There is insufficient clinical evidence to recommend the use of dietary supplements in the management of skin aging, and some authors urge caution when it comes to recommending vitamins or dietary supplements to well-nourished individuals.[72] Promising results have been observed with extracts from plants such as *Aloe vera*, *Citrus paradisi*, *Rosmarinus officinalis*, *Cyclopia intermedia*, and *Hydrangea serrata*,[73] but clinical evidence is lacking.

Almonds contain high levels of vitamin E. Two RCTs (n = 91 and n = 31) showed that participants who consumed almonds as 20% of their daily energy intake experienced a significant reduction in wrinkles and facial pigmentation.[74,75] Another RCT (n = 36) found that eating 85 g of mango a day reduced the depth of facial wrinkles. Consumption, however, of 250 g a day was associated with an increase in wrinkle length and depth.[76] In a large cohort study (n = 4025), beneficial effects were observed for a higher intake of vitamin C (decreased likelihood of facial wrinkles and dry skin) and consumption of linoleic acid (less atrophy and dry skin). By contrast, a 17-g increase in fat intake and a 50-g increase in carbohydrate intake was associated with a higher likelihood of wrinkles and skin atrophy.[4]

## Discussion

Demand for skin antiaging therapies is high and expected to increase.[15] The use of oral supplements and systemic drugs to fight skin aging is an attractive option, as it would eliminate or reduce the need for topical treatments or invasive or minimally invasive procedures, which can be costly and are not without adverse effects. Multivitamin and dietary supplements have many uses and are popular among the general population, and demand for antiaging supplements is on the rise.[15] It is estimated that more than 50% of adults in the United States take vitamin supplements, and this percentage is expected to increase in coming years.[77] Vitamins and other supplements are perceived as natural and safe,[77] but the evidence supporting their effectiveness is weak. According to a recent systematic review, supplementation with vitamin A, C, $B_{12}$, $B_3$, $B_6$, and D (with or without calcium), multivitamins, selenium, and calcium does not reduce the risk of overall or cardiovascular mortality.[78] The US Preventive Services Task Force does not recommend the use of vitamins or multivitamins to prevent cardiovascular disease or cancer.[78] Indeed, it advises against beta-carotene supplementation, as there is evidence that it might increase the risk of lung cancer and overall and cardiovascular mortality. It also advises against vitamin E for the prevention of cardiovascular disease and cancer, and warns of the potential risks of vitamin or mineral supplementation in general, recommending instead a healthy, balanced diet.[78]

The risks and benefits of systemic skin aging treatments must be carefully weighed up, as their purpose is to reverse or slow down a natural process rather than treat a particular disease. It is very difficult to make recommendations or draw valid conclusions on the effectiveness of oral supplements and systemic drugs in the treatment of skin aging, as most of the evidence is based on small, single-center studies with short follow-up periods (mostly 2–4 months), predominantly female samples, and use of heterogeneous methodologies and evaluation criteria. In addition, some of the confirmatory studies have been performed by the same researchers. Agreement on clinically relevant outcome measures is also lacking,[71] and many studies have clear conflicts of interest.

In our review of the literature, we did not find any prospective clinical studies with sufficient evidence to support the use of metformin, melatonin, tranexamic acid, vitamins A, C, D, E, niacinamide, or zinc in the treatment of skin aging. Evidence on isotretinoin is also lacking, and caution must be exerted before recommending its use due to potential safety issues. More evidence is also needed on the effects of HRT on skin aging, and careful consideration must be given to the risk of cardiovascular disease and breast cancer before prescribing this treatment.[79] We also found insufficient evidence to recommend glucosamine, glutathione, or coenzyme Q10.

Oral supplementation with hydrolyzed collagen, analyzed by 24 RCTs, has the strongest evidence in favor of its use for the mitigation of skin aging.[12,16,17,26,80,81] It is inexpensive, has a good safety profile, and may also work in synergy with other antioxidants and anti-inflammatory agents. Oral HA is another novel, well-tolerated treatment that could help mitigate the effects of skin aging.[19–22,26] Optimal doses, molecular weights, and duration of treatment remain to be determined for both collagen and HA supplements. Other promising compounds are French maritime pine bark extract[62,63] and marine complexes.[70]

## The Future of Systemic Treatments for Skin Aging

Cellular senescence, which is characterized by cell cycle arrest and changes in the epigenome, transcriptome, proteome, and secretome, is attracting increasing attention in the setting of skin aging. Markers of cellular senescence include increased intracellular levels of damaged and fragmented double-stranded DNA, lipofuscin, cell cycle inhibitors such as p16 and p21, and a proinflammatory secretory phenotype. The long-term presence of senescent cells has been linked to aging and skin diseases.[82] Animal studies

have shown that the destruction of senescent cells may prolong survival and reduce carcinogenesis and the incidence of age-related diseases.[83]

Selective agents targeting senescent cells in the dermis hold promise as a treatment for aging. Questions, however, remain about potential adverse effects, as, paradoxically, the transient presence of senescent cells could be beneficial during embryogenesis and wound healing.[82]

A more conservative approach involves the use of molecules with senomorphic effects capable of modulating the counterproductive nature of senescent cells and restarting cell proliferation. One such molecule is rapamycin, an mTOR inhibitor. Acute use of this drug in animal models has been seen to reverse several characteristics of senescent fibroblasts,[84] protect against UV radiation damage,[85] and reinitiate fibroblast proliferation.[84]

Metformin has also shown senomorphic effects in lung fibroblasts.[86] Flavonoids and plant extracts such as *Solidago virgaurea* extracts, are capable of modulating cellular senescence.[82]

Senolytics and senomorphics are promising new agents in the field of human aging, but clinical studies are needed to evaluate their true effectiveness and safety.

## Limitations

One limitation of this study is that it is a narrative rather than a systematic review. In addition, most of the studies analyzed were small prospective studies or clinical trials with heterogeneous methodologies.

## Conclusions

A number of systemic drugs and dietary supplements may be useful for the treatment of skin aging. Clinical evidence, however, is largely lacking. Potential risks and benefits must be carefully weighed up before recommending any treatments. Oral supplementation with hydrolyzed collagen and HA has a good safety profile and is supported by the strongest evidence.

## Conflicts of Interest

Industry groups had no role in the design or conduct of this study, in the collection, analysis, or interpretation of data, or in the preparation, review, or approval of this manuscript.

## References


1. Lee H, Hong Y, Kim M. Structural and functional changes and possible molecular mechanisms in aged skin. Int J Mol Sci. 2021;22:12489.
2. Sreekantaswamy SA, Butler DC, Shah AA. Reframing aging in dermatology: the role of the dermatologist in healthy aging. Int J Womens Dermatol. 2021;7:529–32.
3. Crane JD, MacNeil LG, Lally JS, Ford RJ, Bujak AL, Brar IK, et al. Exercise-stimulated interleukin-15 is controlled by AMPK and regulates skin metabolism and aging. Aging Cell. 2015;14:625–34.
4. Cosgrove MC, Franco OH, Granger SP, Murray PG, Mayes AE. Dietary nutrient intakes and skin-aging appearance among middle-aged American women. Am J Clin Nutr. 2007;86:1225–31.
5. Bragazzi NL, Sellami M, Salem I, Conic R, Kimak M, Pigatto PDM, et al. Fasting and its impact on skin anatomy physiology, and physiopathology: a comprehensive review of the literature. Nutrients. 2019;11:249.
6. Guan LL, Lim HW, Mohammad TF. Sunscreens and photoaging: a review of current literature. Am J Clin Dermatol. 2021;22:819–28.
7. Honeybrook A, Bernstein E. Oral isotretinoin and photoaging: a review. J Cosmet Dermatol. 2020;19:1548–54.
8. Bravo BS, Azulay DR, Luiz RR, Mandarim-de-Lacerda CA, Cuzzi T, Azulay MM. Oral isotretinoin in photoaging: objective histological evidence of efficacy and durability. An Bras Dermatol. 2015;90:479–86.
9. Kalil CL, Fachinello FZ, Lamb FM, Comunello LN. Use of oral isotretinoin in photoaging therapy. Skinmed. 2008;7:10–4.
10. Rabello-Fonseca RM, Azulay DR, Luiz RR, Mandarim-de-Lacerda CA, Cuzzi T, Manela-Azulay M. Oral isotretinoin in photoaging: clinical and histopathological evidence of efficacy of an off-label indication. J Eur Acad Dermatol Venereol. 2009;23:115–23.
11. Bagatin E, Parada MO, Miot HA, Hassun KM, Michalany N, Talarico S. A randomized and controlled trial about the use of oral isotretinoin for photoaging. Int J Dermatol. 2010;49:207–14.
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;60:1449–61.
13. Zague V, de Freitas V, da Costa Rosa M, de Castro GÁ, Jaeger RG, Machado-Santelli GM. Collagen hydrolysate intake increases skin collagen expression and suppresses matrix metalloproteinase 2 activity. J Med Food. 2011;14:618–24.
14. Ohara H, Ichikawa S, Matsumoto H, Akiyama M, Fujimoto N, Kobayashi T, et al. Collagen-derived dipeptide, proline-hydroxyproline, stimulates cell proliferation and hyaluronic acid synthesis in cultured human dermal fibroblasts. J Dermatol. 2010;37:330–8.
15. Albornoz CA, Shah S, Murgia RD, Wang JV, Saedi N. Understanding aesthetic interest in oral collagen peptides: a 5-year national assessment. J Cosmet Dermatol. 2021;20:566–8.
16. Maia Campos PM, Franco RS, Kakuda L, Cadioli GF, Costa GM, Bouvret E. Oral supplementation with hydrolyzed fish cartilage improves the morphological and structural characteristics of the skin: a double-blind placebo-controlled clinical study. Molecules. 2021;26:4880.
17. Miyanaga M, Uchiyama T, Motoyama A, Ochiai N, Ueda O, Ogo M. Oral supplementation of collagen peptides improves skin hydration by increasing the natural moisturizing factor content in the stratum corneum: a randomized, double-blind placebo-controlled clinical trial. Skin Pharmacol Physiol. 2021;34:115–27.
18. Han K, Hong K-B, Ahn Y, Jo K, Jung J, Suh HJ. Effects of collagen-tripeptide and galacto-oligosaccharide mixture on skin photoaging inhibition in UVB-exposed hairless mice. Photochem Photobiol. 2022, http://dx.doi.org/10.1111/php.13618. Epub ahead of print.
19. Michelotti A, Cestone E, De Ponti I, Pisati M, Sparta E, Tursi F. Oral intake of a new full-spectrum hyaluronan improves skin profilometry and ageing: a randomized, double-blind, placebo-controlled clinical trial. Eur J Dermatol. 2021;31:798–805.
20. Hsu T-F, Su Z-R, Hsieh Y-H, Wang M-F, Oe M, Matsuoka R, et al. Oral hyaluronan relieves wrinkles and improves dry skin: a 12-week double-blinded placebo-controlled study. Nutrients. 2021;13:2220.

21. Oe M, Sakai S, Yoshida H, Okado N, Kaneda H, Masuda Y, et al. Oral hyaluronan relieves wrinkles: a double-blinded, placebo-controlled study over a 12-week period. Clin Cosmet Investig Dermatol. 2017;10:267–73.
22. Kawada C, Yoshida T, Yoshida H, Sakamoto W, Odanaka W, Sato T, et al. Ingestion of hyaluronans (molecular weights 800 k and 300 k) improves dry skin conditions: a randomized, double blind, controlled study. J Clin Biochem Nutr. 2015;56:66–73.
23. Kawada C, Yoshida T, Yoshida H, Matsuoka R, Sakamoto W, Odanaka W, et al. Ingested hyaluronan moisturizes dry skin. Nutr J. 2014;13:70.
24. Göllner I, Voss W, von Hehn U, Kammerer S. Ingestion of an oral hyaluronan solution improves skin hydration, wrinkle reduction elasticity, and skin roughness: results of a clinical study. J Evid Based Complement Altern Med. 2017;22:816–23.
25. Aguirre A, Gil-Quintana E, Fenaux M, Erdozain S, Sarria I. Beneficial effects of oral supplementation with ovoderm on human skin physiology: two pilot studies. J Diet Suppl. 2017;14:706–14.
26. Kalman DS, Hewlings S. The effect of oral hydrolyzed eggshell membrane on the appearance of hair, skin, and nails in healthy middle-aged adults: a randomized double-blind placebo-controlled clinical trial. J Cosmet Dermatol. 2020;19: 1463–72.
27. Kim HJ, Moon SH, Cho SH, Lee JD, Kim HS. Efficacy and safety of tranexamic acid in melasma: a meta-analysis and systematic review. Acta Derm Venereol. 2017;97: 776–81.
28. Passeron T, Picardo M. Melasma, a photoaging disorder. Pigment Cell Melanoma Res. 2018;31:461–5.
29. Hiramoto K, Yamate Y, Sugiyama D, Matsuda K, Iizuka Y, Yamaguchi T. Effect of tranexamic acid in improving the lifespan of naturally aging mice. Inflammopharmacology. 2019;27:1319–23.
30. Hiramoto K, Yamate Y, Sugiyama D, Matsuda K, Iizuka Y, Yamaguchi T. Ameliorative effect of tranexamic acid on physiological skin aging and its sex difference in mice. Arch Dermatol Res. 2019;311:545–53.
31. Hiramoto K, Sugiyama D, Takahashi Y, Mafune E. The amelioration effect of tranexamic acid in wrinkles induced by skin dryness. Biomed Pharmacother. 2016;80:16–22.
32. Hiramoto K, Yamate Y, Sugiyama D, Matsuda K, Iizuka Y, Yamaguchi T. Tranexamic acid inhibits the plasma and non-irradiated skin markers of photoaging induced by long-term UVA eye irradiation in female mice. Biomed Pharmacother. 2018; 107:54–8.
33. Zhang L, Tan W-Q, Fang Q-Q, Zhao W-Y, Zhao Q-M, Gao J, et al. Tranexamic acid for adults with melasma: a systematic review and meta-analysis. Biomed Res Int. 2018; 2018:1683414.
34. Majidian M, Kolli H, Moy RL. Management of skin thinning and aging: review of therapies for neocollagenesis; hormones and energy devices. Int J Dermatol. 2021;60: 1481–7.
35. Sumino H, Ichikawa S, Abe M, Endo Y, Ishikawa O, Kurabayashi M. Effects of aging, menopause, and hormone replacement therapy on forearm skin elasticity in women. J Am Geriatr Soc. 2004;52:945–9.
36. Sator P-G, Sator MO, Schmidt JB, Nahavandi H, Radakovic S, Huber JC, et al. A prospective, randomized, double-blind, placebo-controlled study on the influence of a hormone replacement therapy on skin aging in postmenopausal women. Climacteric. 2007;10:320–34.
37. Brincat M, Moniz CF, Studd JW, Darby AJ, Magos A, Cooper D. Sex hormones and skin collagen content in postmenopausal women. Br Med J (Clin Res Ed). 1983;287:1337–8.
38. Savvas M, Bishop J, Laurent G, Watson N, Studd J. Type III collagen content in the skin of postmenopausal women receiving oestradiol and testosterone implants. Br J Obstet Gynaecol. 1993;100:154–6.
39. Piérard GE, Hermanns-Lê T, Paquet P, Piérard-Franchimont C. Skin viscoelasticity during hormone replacement therapy for climacteric ageing. Int J Cosmet Sci. 2014;36: 88–92.
40. Phillips TJ, Symons J, Menon S, HT Study Group. Does hormone therapy improve age-related skin changes in postmenopausal women? A randomized, double-blind, double-dummy, placebo-controlled multicenter study assessing the effects of norethindrone acetate and ethinyl estradiol in the improvement of mild to moderate age-related skin changes in postmenopausal women. J Am Acad Dermatol. 2008;59: 397–404, e3.
41. Rudman D, Feller AG, Cohn L, Shetty KR, Rudman IW, Draper MW. Effects of human growth hormone on body composition in elderly men. Horm Res. 1991;36:73–81.
42. Rudman D, Feller AG, Nagraj HS, Gergans GA, Lalitha PY, Goldberg AF, et al. Effects of human growth hormone in men over 60 years old. N Engl J Med. 1990;323:1–6.
43. Pourang A, Tisack A, Ezekwe N, Torres AE, Kohli I, Hamzavi IH, et al. Effects of visible light on mechanisms of skin photoaging. Photodermatol Photoimmunol Photomed. 2022;38:191–6.
44. Segars K, McCarver V, Miller RA. Dermatologic applications of polypodium leucotomos: a literature review. J Clin Aesthet Dermatol. 2021;14:50–60.
45. Granger C, Aladren S, Delgado J, Garre A, Trullas C, Gilaberte Y. Prospective evaluation of the efficacy of a food supplement in increasing photoprotection and improving selective markers related to skin photo-ageing. Dermatol Ther (Heidelb). 2020;10:163–78.
46. Žmitek K, Pogačnik T, Mervic L, Žmitek J, Pravst I. The effect of dietary intake of coenzyme Q10 on skin parameters and condition: results of a randomised, placebo-controlled, double-blind study. Biofactors. 2017;43:132–40.
47. 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: E618.
48. Gueniche A, Castiel-Higounenc I. Efficacy of glucosamine sulphate in skin ageing: results from an ex vivo anti-ageing model and a clinical trial. Skin Pharmacol Physiol. 2017;30: 36–41.
49. Murad H, Tabibian MP. The effect of an oral supplement containing glucosamine, amino acids, minerals, and antioxidants on cutaneous aging: a preliminary study. J Dermatol Treat. 2001;12:47–51.
50. Sitohang IB, Ninditya S. Systemic glutathione as a skin-whitening agent in adult. Dermatol Res Pract. 2020;2020 :8547960.
51. Dilokthornsakul W, Dhippayom T, Dilokthornsakul P. The clinical effect of glutathione on skin color and other related skin conditions: a systematic review. J Cosmet Dermatol. 2019;18: 728–37.
52. Duperray J, Sergheraert R, Chalothorn K, Tachalerdmanee P, Perin F. The effects of the oral supplementation of L-cystine associated with reduced L-glutathione-GSH on human skin pigmentation: a randomized, double-blinded, benchmark- and placebo-controlled clinical trial. J Cosmet Dermatol. 2022;21:802–13.
53. Wahab S, Anwar AI, Zainuddin AN, Hutabarat EN, Anwar AA, Kurniadi I. Combination of topical and oral glutathione as a skin-whitening agent: a double-blind randomized controlled clinical trial. Int J Dermatol. 2021;60:1013–8.
54. Sitohang IB, Anwar AI, Jusuf NK, Arimuko A, Norawati L, Veronica S. Evaluating oral glutathione plus ascorbic acid, alpha-lipoic

acid, and zinc aspartate as a skin-lightening agent: an Indonesian multicenter randomized, controlled trial. J Clin Aesthet Dermatol. 2021;14:E53–8.
55. Bocheva G, Slominski RM, Janjetovic Z, Kim T-K, Böhm M, Steinbrink K, et al. Protective role of melatonin and its metabolites in skin aging. Int J Mol Sci. 2022;23:1238.
56. Campbell JM, Bellman SM, Stephenson MD, Lisy K. Metformin reduces all-cause mortality and diseases of ageing independent of its effect on diabetes control: a systematic review and meta-analysis. Ageing Res Rev. 2017;40:31–44.
57. Chen S, Gan D, Lin S, Zhong Y, Chen M, Zou X, et al. Metformin in aging and aging-related diseases: clinical applications and relevant mechanisms. Theranostics. 2022;12:2722–40.
58. Martin-Montalvo A, Mercken EM, Mitchell SJ, Palacios HH, Mote PL, Scheibye-Knudsen M, et al. Metformin improves healthspan and lifespan in mice. Nat Commun. 2013;4:2192.
59. Justice JN, Niedernhofer L, Robbins PD, Aroda VR, Espeland MA, Kritchevsky SB, et al. Development of clinical trials to extend healthy lifespan. Cardiovasc Endocrinol Metab. 2018;7:80–3.
60. Rohdewald P. Pleiotropic effects of French maritime pine bark extract to promote healthy aging. Rejuvenat Res. 2019;22:210–7.
61. Grether-Beck S, Marini A, Jaenicke T, Krutmann J. French maritime pine bark extract (Pycnogenol®) effects on human skin: clinical and molecular evidence. Skin Pharmacol Physiol. 2016;29:13–7.
62. Furumura M, Sato N, Kusaba N, Takagaki K, Nakayama J. Oral administration of French maritime pine bark extract (Flavangenol(®)) improves clinical symptoms in photoaged facial skin. Clin Interv Aging. 2012;7:275–86.
63. Thom E. A randomized, double-blind, placebo-controlled study on the clinical efficacy of oral treatment with DermaVite on ageing symptoms of the skin. J Int Med Res. 2005;33:267–72.
64. Marini A, Grether-Beck S, Jaenicke T, Weber M, Burki C, Formann P, et al. Pycnogenol® effects on skin elasticity and hydration coincide with increased gene expressions of collagen type I and hyaluronic acid synthase in women. Skin Pharmacol Physiol. 2012;25:86–92.
65. Zhao H, Wu J, Wang N, Grether-Beck S, Krutmann J, Wei L. Oral Pycnogenol® intake benefits the skin in urban chinese outdoor workers: a randomized, placebo-controlled double-blind, and crossover intervention study. Skin Pharmacol Physiol. 2021;34:135–45.
66. Stephens TJ, Sigler ML, Hino PD, Moigne AL, Dispensa L. A randomized, double-blind placebo-controlled clinical trial evaluating an oral anti-aging skin care supplement for treating photodamaged skin. J Clin Aesthet Dermatol. 2016;9:25–32.
67. Stephens TJ, Sigler ML, Herndon JH, Dispensa L, Le Moigne A. A placebo-controlled, double-blind clinical trial to evaluate the efficacy of Imedeen(®) Time Perfection(®) for improving the appearance of photodamaged skin. Clin Cosmet Investig Dermatol. 2016;9:63–70.
68. Costa A, Pegas Pereira ES, Assumpção EC, Calixto dos Santos FB, Ota FS, de Oliveira Pereira M, et al. Assessment of clinical effects and safety of an oral supplement based on marine protein, vitamin C, grape seed extract, zinc, and tomato extract in the improvement of visible signs of skin aging in men. Clin Cosmet Investig Dermatol. 2015;8:319–28.
69. Skovgaard GR, Jensen AS, Sigler ML. Effect of a novel dietary supplement on skin aging in post-menopausal women. Eur J Clin Nutr. 2006;60:1201–6.
70. Birnbaum JE, McDaniel DH, Hickman J, Dispensa L, Le Moigne A, Buchner L. A multicenter, placebo-controlled, double-blind clinical trial assessing the effects of a multicomponent nutritional supplement for treating photoaged skin in healthy women. J Cosmet Dermatol. 2017;16:120–31.
71. Birnbaum J, Le Moigne A, Dispensa L, Buchner L. A review of clinical trials conducted with oral multicomponent dietary supplements for improving Photoaged Skin. J Drugs Dermatol. 2015;14:1453–61.
72. Zhang S, Duan E. Fighting against skin aging: the way from bench to bedside. Cell Transplant. 2018;27:729–38.
73. Myung D-B, Lee J-H, Han H-S, Lee K-Y, Ahn HS, Shin Y-K, et al. Oral intake of *Hydrangea serrata* (thunb.) *ser*. leaves extract improves wrinkles, hydration, elasticity, texture, and roughness in human skin: a randomized double-blind, placebo-controlled study. Nutrients. 2020;12:E1588.
74. Rybak I, Carrington AE, Dhaliwal S, Hasan A, Wu H, Burney W, et al. Prospective randomized controlled trial on the effects of almonds on facial wrinkles and pigmentation. Nutrients. 2021;13:785.
75. Foolad N, Vaughn AR, Rybak I, Burney WA, Chodur GM, Newman JW, et al. Prospective randomized controlled pilot study on the effects of almond consumption on skin lipids and wrinkles. Phytother Res. 2019;33:3212–7.
76. Fam VW, Holt RR, Keen CL, Sivamani RK, Hackman RM. Prospective evaluation of mango fruit intake on facial wrinkles and erythema in postmenopausal women: a randomized clinical pilot study. Nutrients. 2020;12:E3381.
77. Ubel PA. Why too many vitamins feels just about right. JAMA Intern Med. 2022;182:791–2.
78. Mangione CM, Barry MJ, Nicholson WK, Cabana M, Chelmow D, Coker TR, et al. Vitamin mineral, and multivitamin supplementation to prevent cardiovascular disease and cancer: US Preventive Services Task Force recommendation statement. JAMA. 2022;327:2326–33.
79. Rozenberg S, Di Pietrantonio V, Vandromme J, Gilles C. Menopausal hormone therapy and breast cancer risk. Best Pract Res Clin Endocrinol Metab. 2021;35:101577.
80. 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:E826.
81. Evans M, Lewis ED, Zakaria N, Pelipyagina T, Guthrie N. A randomized, triple-blind, placebo-controlled, parallel study to evaluate the efficacy of a freshwater marine collagen on skin wrinkles and elasticity. J Cosmet Dermatol. 2021;20:825–34.
82. Pils V, Ring N, Valdivieso K, Lämmermann I, Gruber F, Schosserer M, et al. Promises and challenges of senolytics in skin regeneration, pathology and ageing. Mech Ageing Dev. 2021;200:111588.
83. Baker DJ, Childs BG, Durik M, Wijers ME, Sieben CJ, Zhong J, et al. Naturally occurring p16(Ink4a)-positive cells shorten healthy lifespan. Nature. 2016;530:184–9.
84. Walters HE, Deneka-Hannemann S, Cox LS. Reversal of phenotypes of cellular senescence by pan-mTOR inhibition. Aging (Albany NY). 2016;8:231–44.
85. Bai G-L, Wang P, Huang X, Wang Z-Y, Cao D, Liu C, et al. Rapamycin protects skin fibroblasts from UVA-induced photoaging by inhibition of p53 and phosphorylated HSP27. Front Cell Dev Biol. 2021;9:633331.
86. Noren Hooten N, Martin-Montalvo A, Dluzen DF, Zhang Y, Bernier M, Zonderman AB, et al. Metformin-mediated increase in DICER1 regulates microRNA expression and cellular senescence. Aging Cell. 2016;15:572–81.
87. Hernández-Pérez E, Khawaja HA, Álvarez TY. Oral isotretinoin as part of the treatment of cutaneous aging. Dermatol Surg. 2000;26:649–52.
88. Bagatin E, Guadanhim LR, Enokihara MM, Sanudo A, Talarico S, Miot HA, et al. Low-dose oral isotretinoin versus topical retinoic

acid for photoaging: a randomized, comparative study. Int J Dermatol. 2014;53:114–22.
89. Ianhez M, Pinto SA, Miot HA, Bagatin E. A randomized, open, controlled trial of tretinoin 0.05% cream vs. low-dose oral isotretinoin for the treatment of field cancerization. Int J Dermatol. 2019;58:365–73.
90. Lin P, Alexander RA, Liang C-H, Liu C, Lin Y-H, Lin Y-H, et al. Collagen formula with Djulis for improvement of skin hydration, brightness, texture, crow's feet, and collagen content: a double-blind, randomized, placebo-controlled trial. J Cosmet Dermatol. 2021;20:188–94.