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Topical Over-the-Counter Antiaging Agents: An Update and Systematic Review

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Keywords
Antiaging · Cosmeceutical · Targeted ingredients · Rejuvenational capacity

Abstract
Over-the-counter antiaging formulations aim to prevent or minimize the signs of aging skin, and to maintain the benefits obtained from different cosmetic procedures. Even though a huge selection of such products is available on the market, evidence and good clinical practice of the data supporting their use are oftentimes lacking. In this systematic review, the authors reviewed scientific data available in the published literature on the most common ingredients used in antiaging cosmetics, with a particular focus on in vivo studies.

Introduction

During the past years, research on cutaneous aging mechanisms has gained considerable importance. This is due to various reasons – on the one hand, understanding aging mechanisms is crucial for the development of new lifestyle and beauty products, on the other hand, the skin is attracting considerable attention as an indicator of the health status of internal organs [1].

Skin aging is a complex biological process, from birth onwards, though the first signs of skin aging are usually noticeable only in the late twenties. It is based on a complex interplay between proinflammatory factors of the environment, lifestyle, and intra-individual genetics. With aging, cell activity decreases at a molecular level; collagen production reduces, and nonfunctional elastic fibers increase [2, 3].

At the center of this process are the so-called free oxygen radicals, also known as reactive oxygen species (ROS), which promote the aging process of the skin [1]. ROS damage of cellular structures such as the DNA or lipid membranes, which leads to upregulation of matrix metalloproteinases (especially MMP1 and MMP2) in fibroblasts; hence, increased breakdown and reduced build-up of collagen and elastin [4].

While very little is known about the role of genetics in intrinsic skin aging, or about its potential to influence intrinsic factors (apart from healthy nutrition and lifestyle), extrinsic skin aging occurs mainly due to the cumulative exposure to ultraviolet radiation [5]. Therefore, the best prevention from skin aging is apparently optimal sun protection.

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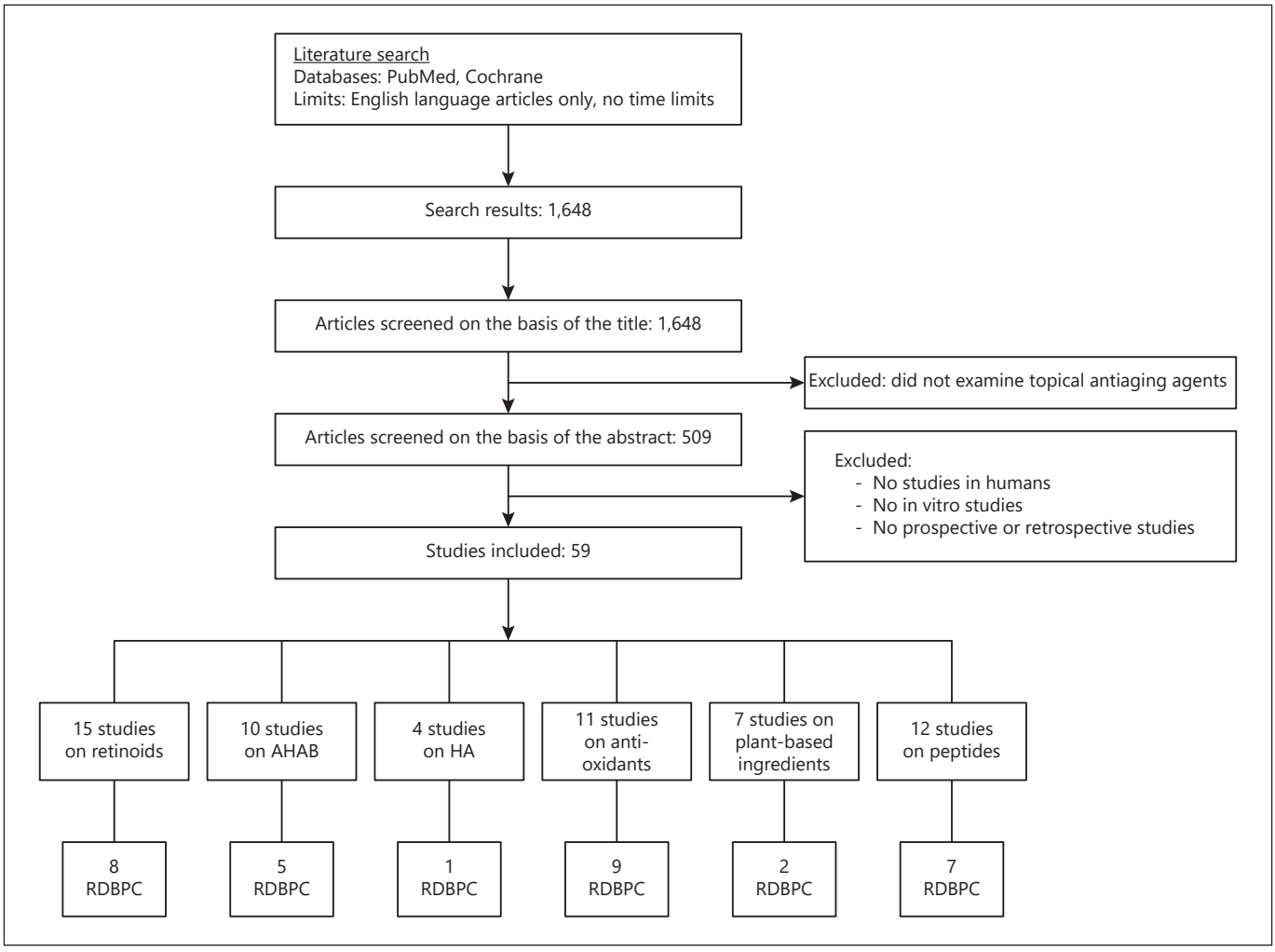

Fig. 1. Flowchart of the Materials and Methods flow diagram of the search and selection process according to Preferred Reporting Items for Systematic Reviews and Meta-Analysis. AHA, α-hydroxy acids; HA, hyaluronic acid; RDBPC, randomized, double-blind, placebo-controlled study.

A vast array of cosmeceuticals is available on the market to reduce signs of skin aging. These cosmetic products claim to have biologically active ingredients with medicinal or drug-like benefits. Evidence and good clinical practice of the data supporting their use are often lacking. This article reviews the evidence available in the published literature which supports the use of ingredients most commonly used in cosmeceuticals, with a special focus on in vivo studies.

Materials and Methods

For further details, see the online supplementary material (see www.karger.com/doi/10.1159/000509296; Fig. 1).

Results

Retinoids

Retinoids are natural or synthetic derivates of vitamin A. The naturally occurring vitamin A (retinol) is oxidized reversibly to retinaldehyde, which in turn is oxidized irreversibly to the biologically active form – retinoic acid (tretinoin) [6].

Retinoids have been applied topically and systemically to treat skin diseases – in particular acne vulgaris – since the 1940s. Their antiaging effect has been propagated since the 1980s [7].

The antiaging-specific mechanism of action is based on its interaction with the retinoic acid receptor in the nucleus which leads to an increase in collagen concentra-

Table 1. Human studies on topical retinoids [10, 74–87]

Study	Study design	*n*	Treatment arm(s)	Efficacy
Retinol (vitamin A)				
Pierard-Franchimont et al. [74]	R, DB, PC, PG	120	4 randomized groups of 30 subjects receiving either (1) 0.04% retinol, (2) 1% melibiose + 4% lactose, (3) 0.04% retinol + 1% melibiose + 4% lactose, or (4) 1% salicylic acid	Significant differences in efficacy and lingering activity assessed by Cutometer and image analysis after optical shadowing
Varani et al. [75]	PC, RL	53	1% topical retinol vs. vehicle control	Statistically significant histological improvement on day 7 (increase in fibroblast growth and collagen synthesis and reduction in matrix-degrading matrix metalloproteinase levels)
Kafi et al. [76]	R, DB, PC, RL	36	Topical 0.4% retinol lotion vs. its vehicle up to 3 times/week for 24 weeks	Significant differences between retinol- and vehicle-treated skin in fine wrinkle scores ($p < 0.001$); retinol treatment significantly increased glycosaminoglycan expression ($p = 0.02$) and procollagen I immunostaining ($p = 0.049$)
Kang et al. [77]	R, DB, PG, PC	30	Topical retinol vs. retinoic acid vs. vehicle control	Retinol produced from none to only trace erythema, which was clinically and statistically insignificant, whereas retinoic acid induced a significant 3.7-fold increase in erythema score vs. vehicle ($n = 10$, $p < 0.01$); however, retinol induces epidermal thickening and enhances CRABP II and CRBP mRNA and protein expression
Randhawa et al. [78]	R, DB, PC	62	Retinol formulation vs. its vehicle to full face for 52 weeks	The retinol group showed significant photodamage improvement over vehicle at all time points during the study; after 52 weeks, retinol had improved crow's feet fine lines by 44%, and mottled pigmentation by 84%, with over 50% of subjects showing +2 grades of improvement in many parameters; additionally, at week 52, histochemical data confirmed the clinical results, showing increased expression of type I procollagen, hyaluronan, and Ki67 compared to vehicle
Retinaldehyde				
Saurat et al. [79]	R, PC, RL	229	0.5, 0.1, or 0.05% retinaldehyde for 1–3 months on one forearm and a vehicle control on the other	Significant dose-dependent increase in epidermal thickness/keratin 14 immunoreactivity; at a high concentration (0.5%), the morphological changes noted were similar to those induced by <0.1% topical retinoic acid; improved tolerance with decreasing concentration could be shown
Creidi et al. [10]	MC, DB, PC, PG	125	Topical retinaldehyde (0.05%), retinoic acid (0.05%), or vehicle control for 44 weeks once per day	Retinaldehyde and retinoic acid had similar improvements in profilometric scores at 18 and 44 weeks; retinaldehyde was better tolerated throughout the study period
Tretinoin (retinoic acid)				
Maddin et al. [80]	MC, DB, PC	800	0.1% isotretinoin vs. vehicle cream applied on face, forearms, and hands	Statistically significant clinical improvement in wrinkling, pigmentation, sallowness, and texture on clinical evaluation
Weinstein et al. [81]	MC, R, DB, PC	251	Topical tretinoin at 0.05% or 0.01% vs. vehicle control	Significant improvement in fine wrinkling, mottled hyperpigmentation, roughness, laxity, and epidermal thickness in the group treated with 0.05% tretinoin vs. 0.01% and vehicle groups; dose-dependent responses but no effect on dermal thickness, collagen regeneration, or reversal of keratinocyte atypia
Olsen et al. [82]	MC, R, DB, PC	298	Once daily application of either 0.05% or 0.01% tretinoin emollient cream vs. vehicle cream for a duration of 1 year	Significant improvement in histological and clinical markers in both the 0.05 and 0.01% tretinoin group as compared with vehicle
Leyden et al. [83]	R, DB, PC	?	0.05% tretinoin cream vs. vehicle control once daily in the treatment of photodamaged facial skin for 6 months	Significant amelioration of many signs of photodamage were achieved with minimal side effects; fine and coarse wrinkling, sallowness, looseness, and hyperpigmentation were significantly improved with tretinoin therapy; an objective method based on digital image processing of silicone rubber casts obtained from the crow's-feet area also indicated that the skin surface topography was smoother and less wrinkled in the tretinoin-treated group than the vehicle-control group
Olsen et al. [84]	MC, R, DB, PC	296	Tretinoin at 0.05, 0.01, or 0.001% in an emollient cream formulation vs. vehicle in the treatment of photodamaged facial skin for 24 weeks	Tretinoin emollient cream 0.05% appears to be safe and effective in the treatment of photodamaged skin
Sendagorta et al. [85]	MC, R, PC	776	36 weeks of treatment with either vehicle cream or isotretinoin cream, applied once nightly	Treatment with isotretinoin resulted in statistically significant improvement in overall appearance, fine wrinkling, discrete pigmentation, sallowness, and texture; isotretinoin cream was well tolerated
Ellis et al. [86]	R, SB, PC	30	4 months of treatment with topical tretinoin	Statistically significant improvement in fine and coarse wrinkling and skin texture; the number of discrete lentigines decreased by 71% vs. before therapy; histologically, there was a statistically significant thickening of the epidermis; side effects were limited to a cutaneous retinoid reaction that diminished as therapy proceeded
Kang et al. [87]	MC, R, PC	204	Tretinoin vs. vehicle emollient cream applied to the entire face once a day for up to 2 years	Long-term treatment with tretinoin emollient cream 0.05% is safe and effective in subjects with moderate-to-severe facial photodamage

DB, double blind; MC, multicenter; *n*, number of participants; PC, placebo controlled; PG, parallel group; R, randomized; RL, right-left comparison; SB, single blind.

tion in the dermis, keratinization of the epidermis, and inhibition of UV-induced MMP production [8]. Additionally, retinoids are able to inhibit tyrosinase, which reduces hyperpigmentation [9].

Various retinoids have been studied for the treatment of aging skin. Table 1 gives an overview of the clinical studies with good evidence of clinical and/or histological improvement in aging skin by retinoids. Precursor forms of tretinoin, such as retinol and retinaldehyde, are commonly used in cosmeceuticals. They were shown to have fewer side effects than tretinoin, the biologically active form. The latter has the best evidence to reduce signs of aging skin (Table 1). Tretinoin is only available on prescription, as it can cause significant side effects such as erythema, xerosis, desquamation, and pruritus. Randomized trials have shown comparable antiaging effects of retinol and retinaldehyde compared to tretinoin [9, 10]. However, as retinol needs to be converted into tretinoin in vivo to become biologically active, it has been speculated that retinol is 20-fold less effective than tretinoin [11]. Additionally, as retinol is extremely unstable and easily gets degraded on exposure to light and air, an appropriate vehicle needs to be used in creams to elicit its efficacy [12].

α-Hydroxy Acids

α-Hydroxy acids (AHAs) are widely used in chemical peeling and cosmetic formulations. There are several AHA types, with the most often used being glycolic, citric, lactic, pyruvic, mandelic, and tartaric acids [13].

Its exact mechanism of action has not yet been fully clarified. According to the literature, they increase the water retention capacity at the epidermal level, cause desquamation and softening, as well as normalization of the differentiation by influencing intracellular ion binding [14, 15]. At the level of the dermis, dose-dependent increases in fibroblast proliferation, collagen production, and glycosaminoglycan synthesis have been described [16].

The beneficial effects were histologically proven in individual studies [17–19]. In these studies, clinical effects included increases in skin firmness and thickness, improvement in skin texture, and reduction in fine wrinkles.

Hyaluronic Acid

Hyaluronic acid (HA), a nonsulfated glycosaminoglycan, is composed of repeating units of polymeric disaccharides of D-glucuronic acid and N-acetyl-D-glucosamine linked by a glucuronidic β (1→3) bond. It is widely used in esthetic medicine. Due to its structure, it has a remarkable water-holding ability. Consequently, it improves tissue hydration. In addition, skin hydration and antioxidant effects of HA promote cell regeneration and stimulate the production of collagen [20].

The percutaneous absorption of HA, across the stratum corneum, is dependent on its molecular weight. Depending on the chain length, it is categorized as small-size HA fragments (HAFs; <50 kDa), intermediate-size HA fragments (HAFi; 50–400 kDa), and large-size HA fragments (HAFl; >400 kDa) [21].

Experimental studies have shown that topically applied HAFs and HAFi are able to penetrate the epidermis, but only HAFi were able to induce cellular proliferation within the epidermal and dermal compartments in vivo [21]. A vehicle-controlled study by Kaya et al. [21] showed histologically an increase in human skin thickness in response to HAFi accompanied by a clear clinical improvement in patients with skin atrophy. In contrast, the same concentration of HAFl and HAFs applied to the same patients had no effect on skin thickness.

In another trial, 76 female patients with periocular wrinkles were administered a 0.1% cream formulation containing HA of different molecular weights twice daily for a period of 60 days. All HA-based creams demonstrated a significant improvement in skin hydration and overall elasticity values when compared to placebo. However, a significant reduction in wrinkle depth was only observed in the women treated with a cream formulation containing low-molecular-weight HA (50 and 130 kDa) [22].

Additional human clinical studies on skin rejuvenation by topically applied HA are listed in Table 2.

Antioxidants

Substances with antioxidant activity find great application in cosmeceuticals. Their effect is based on the neutralization of free radicals (ROS), which are responsible for the degradation of collagen fibers. Most commonly applied antioxidants are vitamins, which are able to penetrate the skin barrier due to their low molecular weight. Table 3 (antioxidants) gives an overview of the most precisely studied substances used in cosmeceuticals with antioxidant properties.

Niacinamide (Vitamin B_3)

Niacinamide, also known as nicotinamide, is part of the niacin coenzymes NAD+, NADP+, and their reduced forms NADH and NADPH. Among others, these coenzymes play a role in DNA synthesis and repair. Surjana et al. [23] demonstrated that niacinamide increases DNA

Table 2. Human studies on α-hydroxy acids and hyaluronic acid [17–19, 21, 88–97]

Study	Study design	*n*	Treatment arm(s)	Efficacy
α-Hydroxy acid: glycolic acid				
Newman et al. [17]	R, DB, PC, RL	41	Glycolic acid (50%) or vehicle was applied topically for 5 min to one side of the face, forearms, and hands, once weekly for 4 weeks; punch biopsies were taken before therapy and at 5 weeks for histologic study	Reduction in fine wrinkles and solar keratosis, improvement in skin texture; histologically reduction in corneal layer, epidermal thickening; some samples show collagen thickening
Thibault et al. [88]	R, DB, PC	75	5% glycolic acid cream vs. the placebo cream to the face and neck for a period of 3 months	Overall, there was a trend toward greater improvement or less worsening in the glycolic acid group for all for photoaging clinically; statistically significant improvement favoring the active cream in general skin texture and discoloration, and a nonsignificant trend favoring glycolic acid in the reduction of wrinkles
α-Hydroxy acid: glycolic acid, lactic acid, citric acid				
Ditre et al. [18]	R, PC, PG, RL	17	Glycolic acid 25% ($n = 5$), lactic acid ($n = 5$), citric acid ($n = 7$) vs. placebo, application on forearms for 6 months	25% increase in skin thickness and reduction in melanin content on the verum side
Stiller et al. [89]	R, DB, PC	74	Glycolic acid, L-lactic acid, or vehicle creams were applied twice daily to the face and outer aspect of the forearms for 22 weeks	More patients in the 8% glycolic acid or 8% L-lactic acid group improved at least 1 grade (on a scale from 0 to 9) in overall photodamage severity on the face than in the vehicle group (76% glycolic acid, 71% lactic acid, and 40% vehicle; $p < 0.05$); on the forearms, after 22 weeks, treatment with glycolic acid was superior to the vehicle in improving the overall severity of photodamage and sallowness ($p < 0.05$); L-lactic acid cream was significantly superior to the vehicle in reducing the overall severity of photodamage ($p < 0.05$), mottled hyperpigmentation ($p < 0.05$), sallowness ($p < 0.05$), and roughness on the forearms ($p < 0.05$) at week 22
Lactic acid				
Smith [19]	OL, PG	24	12% ($n = 14$) or 5% ($n = 10$) lactic acid test solutions twice a day to the full face, except the eyelids for 3 months	Increased firmness and thickness of the epidermis and dermis; clinical improvement in skin texture and the appearance of fine lines and wrinkles
Mandelic acid				
Jacobs et al. [90}	OL, PG	24	Mandelic acid (4 and 6%) applied topically to the face twice a day for 4 weeks	Significant increase in skin firmness and elasticity of the lower eyelid (cutometer); improvement in fine lines of the lower eyelid (subjectively)
α-Lipoic acid (ALA)				
El-Komy et al. [91]	SB, PC, RL	20	5% ALA on right half of the face and placebo gel on left half, twice daily for 6 months	Mean epidermal thickness significantly increased on the verum side; mean dermal thickness increased more (nonsignificant) on the verum side vs. the placebo side
Beitner [92]	R, PC, DB, RL	33	Half of the face treated with 5% ALA cream and other half with control cream, twice daily for 12 weeks	Statistically significant improvement in photoaging on the ALA-treated half of the face
Perricone [93]	OL	15	5% ALA on the face twice daily for 12 weeks	Overall, 50% reduction in facial lines; marked improvement in fine lines; improved texture and decreased discoloration
Sherif et al. [94]	R, DB, PC, RL	12	5% ALA on the right half of the face and a placebo gel on the left half twice daily for 3 months	Visible reduction in the depth of fine periorbital lines and fine vertical lines on the upper lip; deeper periorbital lines appeared shallow; increase in dermal density (ultrasound)
Hyaluronic acid (HA)				
Pavicic et al. [95]	R, DB, PC, RL	76	HA cream 0.1% (w/w) (50, 130, 300, 800, and 2,000 kDa, respectively) twice daily on periocular wrinkles for 60 days	Significant improvement in skin hydration level; remarkable improvement in skin elasticity; significant reduction in wrinkle depth due to better penetration abilities of low-molecular-weight HA
Jegasothy et al. [96]	R, SB	33	Nano-hyaluronic acid in a cream, serum, and lotion; 8 weeks of treatment in the periorbital region	Significant improvement in moisturizing effect of the product range and skin elasticity; skin roughness improved remarkably
Kaya et al. [21]	PC	6 P 17 C	Daily topical application to the forearm of a 1% preparation of intermediate-size HA fragments for 1 month	None of the control participants revealed a measurable increase in skin thickness; by contrast, all 6 patients with skin atrophy (either age-related or associated with corticosteroid therapy) developed marked skin thickening following topical application of intermediate-size HA fragments
Poetschke et al. [97]	OL, PG	20	Four groups, each with a different anti-wrinkle cream containing HA (Balea, Nivea, Lancôme, Chanel), daily use, 3-month trial	Significant reduction in perioral and orbital wrinkle depth and remarkable increase in skin tightness in all groups; minimal significant changes in skin elasticity in individual groups

C, control participants; DB, double blind; *n*, number of participants; OL, open label; PC, placebo controlled; P, patients with atrophic skin lesions; PG, parallel group; R, randomized; RL, right-left comparison; SB, single blind.

Table 3. Human studies on topical antioxidants [24–26, 29–33, 35, 36, 39]

Study	Study design	*n*	Treatment arm(s)	Efficacy
Niacinamide (B_3)				
Kawada et al. [24]	R, DB, PC, RL	30	Nicotinamide 4% cream vs. placebo for 8 weeks	Significant improvement in skin wrinkles ($p < 0.001$) and skin texture ($p < 0.05$)
Bissett et al. [25]	R, DB, PC, RL	50	Nicotinamide cream 5% vs. placebo for 12 weeks	Skin improvement overall and improvement in skin elasticity in the nicotinamide group
Bissett et al. [26]	R, DB, PC, RL	50	Moisturizer control product vs. the same moisturizer product containing 5% niacinamide for 12 weeks	Niacinamide significantly improved fine lines/wrinkles, hyperpigmentation spots, texture, and red blotchiness vs. control
L-Ascorbic acid (vitamin C)				
Humbert et al. [33]	R, DB, PC	20	5% vitamin C cream vs. vehicle for 6 months	Significant increase in the density of skin microrelief and a decrease in deep furrows; ultrastructural evidence of elastic tissue repair
Nusgens et al. [29]	R, DB, PC, RL	10	5% L-ascorbic acid in glycerol vs. glycerol alone for 6 months daily (right vs. left arm)	Collagen type I and III mRNAs were increased to a similar extent by vitamin C in skin biopsies
Raschke et al. [30]	R, DB, PC, RL	23	3% vitamin C cream and placebo cream each on one half of the face (split-face design) twice daily for 12 weeks	After 1 month, a significant increase in the number of dermal papillae was demonstrated by confocal laser scanning microscope; significant reduction in facial wrinkles after 12 weeks
Fitzpatrick and Rostan [31]	R, DB, PC, RL	10	Vitamin C complex having 10% ascorbic acid (water soluble) and 7% tetrahexyldecyl ascorbate (lipid soluble) in an anhydrous polysilicone gel base to one-half of the face and the inactive polysilicone gel base to the opposite side for 12 weeks	Biopsies showed increased grenz zone collagen, as well as increased staining for collagen type I mRNA; significant improvement in the vitamin C-treated side was seen in the decreased photoaging scores of the cheeks ($p = 0.006$) and peri-oral area ($p = 0.01$).
Haftek et al. [32]	R, DB, RL	20	5% stabilized vitamin C and 0.1% madecassoside (Remederm) vs. Toleriane for 6 months twice daily half	Significant improvement in the clinical score for deep and superficial wrinkles, suppleness, firmness, roughness, and skin hydration; in 2/3 of the subjects, re-appearance of a normally structured elastic fiber network in skin biopsy
Vitamin E				
Murray et al. [35]	R, PC, DB, RL	9	15% vitamin C, 1% vitamin E, and ferulic acid and its vehicle vs. vehicle only were applied to separate patches of normal-appearing human skin for 4 days; each patch was irradiated with solar-simulated UV, 2–10 minimal erythema doses; 1 day later, the skin was evaluated for erythema and sunburn cells, and immuno-histochemically for thymine dimers and p53	Significant and meaningful photoprotection; particularly effective for reducing thymine dimer mutations known to be associated with skin cancer
Lin et al. [36]	Not further specified		Aliquots of vehicle; 0.5% *trans*-ferulic acid; 15% L-ascorbic acid, 1% DL-α-tocopherol, and 15% L-ascorbic acid, 1% DL-α-tocopherol, and 0.5% *trans*-ferulic acid were applied to patches of back skin daily for 4 days; a 1,000-W solar simulator delivered UV radiation to the skin surface; evaluation was carried out 24 h later	Doubled photoprotection to solar-simulated skin irradiation from 4- to approximately 8-fold measured by both erythema and sunburn cell formation; inhibition of apoptosis was associated with reduced induction of caspase-3 and caspase-7
CoQ10				
Inui et al. [39]	R, DB, PC	31 f	1% CoQ_{10} cream or placebo cream twice daily for 3 months	Reduction in the wrinkle score in the 1% CoQ_{10} group after 5 months vs. no reduction in the control

DB, double blind; *n*, number of participants; PC, placebo controlled; R, randomized; RL, right-left comparison.

excision repair and enhances repair of UVB radiation-induced cyclobutane pyrimidine dimers and UVA radiation-induced 8-oxo-7,8-dihydro-2′-deoxyguanosine. Multiple randomized, placebo-controlled trials have shown clinical improvement in skin texture, elasticity, and wrinkles after 12 weeks of daily application of cream containing 5% niacinamide [24–26]. However, clinical trials with more participants need to be conducted to determine its applicability as a definitive treatment for photoaging.

L-Ascorbic Acid (Vitamin C)

Vitamin C, also known as ascorbic acid, plays a critical role in collagen and elastin synthesis as it is a cofactor for

both prolyl and lysyl hydroxylases, which catalyze the formation of hydroxyproline and hydroxylysine [27]. The hydroxylation of proline and lysine facilitates the excretion of procollagen from fibroblasts. Its effect as antioxidant in the skin is based on the modulation of the UV-induced ROS damage [28].

Effectiveness of vitamin C in concentrations of up to 15% was shown in several double-blind, placebo-controlled studies [29–33]. The increase in collagens I and III was also observed histologically after use of vitamin C [29]. However, the clinical studies conducted so far included low participant numbers; thus, placebo-controlled trials with higher numbers of participants are necessary to confirm the promising clinical results seen in earlier studies.

Ascorbic acid requires an acidic environment for optimal absorption and oxidizes very quickly when exposed to light and air. This problem has been partially overcome by chemically modifying ascorbic acid by esterification of its hydroxyl group.

D-α-Tocopherol (Vitamin E)

D-α-Tocopherol is the synthetic form of vitamin E which is found in commercial preparations. It acts as antioxidant within cell membranes where it protects polyunsaturated fatty acids from free radicals. Vitamin E also works as a direct antioxidant by donating electrons to singlet oxygen and superoxide anions. Ascorbic acid and glutathione are both essential for the sustained action of vitamin E as they donate necessary hydrogen ions when the tocopherol radical is formed. In vitro experiments have shown a reduction in MMP-1 transcription after fibroblasts from older individuals were incubated with D-α-tocopherol. MMP-1 is normally elevated in older persons compared with younger individuals [34]. Increase in MMP-1 levels leads to collagen breakdown and the destruction of supportive matrix [4]. In vivo, vitamin E has been studied as a sun protectant [35, 36]. Pretreatment of hairless mice skin with 5% tocopherol before UVB exposure resulted in a 75% decrease in the severity of skin wrinkling and a significant decrease in skin tumor formation [37].

As ascorbic acid is needed to maintain active vitamin E stores, the combined effect of vitamins C and E has also been studied. The topical use of vitamins C and E combined before UV irradiation decreased erythema, cytokine production, thymine dimer formation, and p53 upregulation [35]. Additionally, it was shown that ferulic acid (a botanical agent) could reduce the oxidative stress 4-fold when added to formulations containing vitamins C and E [36]. Data supporting any effect of vitamin E in topical therapies by improvements in skin wrinkling, discoloration, or texture, however, are still lacking.

Coenzyme Q10

Coenzyme Q (CoQ_{10}) was discovered in 1957 by Frederick Crane. The name coenzyme Q10 derives from its chemical structure, a benzoquinone ring with a side chain composed of 10 isoprene units. The structure is similar to some vitamins (e.g., vitamin K); however, CoQ_{10} is not a vitamin since it is synthesized in the body, whereas vitamins must be obtained from the diet.

It has a fundamental role in cellular bioenergetics as a cofactor for mitochondrial enzyme complexes involved in the oxidative phosphorylation and production of adenosine triphosphate (ATP). Beside this, CoQ_{10} serves as an antioxidant or free radical scavenger, and is able to stimulate collagen production [38]. Its application in different illnesses is being discussed but not yet established. So far, one placebo-controlled double-blind study could show wrinkle improvement after application of 1% CoQ_{10} cream [39]. Furthermore, it was shown in vitro that it reduces MMP activity [39].

Plant-Based Ingredients

Phenols

Phenols are aromatic organic compounds found in many plants (e.g., black, white, or green tea, soja, grapes, and berries). The naturally occurring phenols are referred to as flavonoids and procyanides. Several studies have shown the antioxidant activity of phenols, which is associated with their chemical structure [40]. Thring et al. [41] assessed 23 plant extracts for their antiaging properties as anti-elastase and anti-collagenase activities, and antioxidant activity along with their phenolic content. The *white tea* showed the highest anti-elastase and anti-collagenase activities as well as the highest antioxidant activity and phenolic content. Elmets et al. [42] demonstrated in an in vivo study that the topical application of *green tea extracts* results in a dose-dependent inhibition of the erythema response evoked by UV radiation. Histologically, skin treated with green tea extracts reduced the number of sunburn cells and protected epidermal Langerhans cells from UV damage. Few randomized placebo-controlled clinical trials with green tea extracts (listed in Table 4) have shown improvement in elastin content on skin biopsies and improvement in skin texture [43].

Mohammad et al. [44] showed in a preliminary experiment that *Prosopis cineraria* bark extract has a significant amount of phenolic compounds. In an in vivo

Table 4. Human studies on plant-based ingredients [35, 42–44, 50, 98, 99]

Study	Study design	*n*	Treatment arm(s)	Efficacy
Grean tea extracts				
Elmets et al. [42]	Not further specified	6	Areas of normal skin were treated with an extract of green tea; 30 min later, the treated sites were exposed to 2-MED solar-simulated radiation; UV-treated skin was examined clinically for UV-induced erythema, histologically for the presence of sunburn cell or Langerhans cell distribution	Dose-dependent inhibition of the erythema response evoked by UV radiation; on histologic examination, skin treated with green tea extract reduced the number of sunburn cells and protected epidermal Langerhans cells from UV damage
Chiu et al. [43]	R, DB, PC	40	Combination regimen of 10% green tea cream and 300 mg green tea oral supplementation twice daily vs. a placebo regimen for 8 weeks	No significant differences were noted between groups on any of the dermatologist-rated parameters; significantly greater improvement in elastin content of skin biopsies in the treatment group compared with controls ($p < 0.05$)
Syed [98, P25]	R, DB, PC	60	2% epigallocatechin gallate (found in green tea) in a hydrophilic gel vs. placebo gel b.i.d. for 4 weeks	Marked improvement in skin texture noted in 46.7% of subjects: 83.3% of experimental group and 10.0% of the control group improved
2% Prosopis cineraria bark				
Mohammad et al. [44]	R, SB, PC, RL	9	2% *Prosopis cineraria* bark extract loaded emulsion formulation vs. base formulation applied for 8 weeks	The formulation decreased the skin melanin, erythema, and sebum contents up to 79%, but increased skin hydration and elasticity up to 2×
Ferulic acid				
Murray et al. [35]	R, PC, RL	9	Solution of 15% L-ascorbic acid, 1% DL-α-tocopherol, and 0.5% trans ferulic acid (CEF) vs. vehicle only applied daily for 4 days to separate patches; on day 4 skin irradiation with solar-simulated UV radiation	CEF provided substantial protection against UV-induced erythema, apoptosis, and DNA mutation vs. vehicle-treated skin
Salja et al. [99]	PG	6	Caffeic or ferulic acid solution immediately applied to UV-B irradiated sites on the forearm	Caffeic acid and ferulic acid proved a significant protection to the skin against UVB-induced erythema vs. controls
Oresajo et al. [50]	PG, PC	10	Vitamin C, ferulic acid, and phloretin (CFerPhlor) or vehicle alone (control) were applied to back skin daily for 4 days; skin was irradiated with solar-simulated UV 1–5 times MED	CferPhlor-treated site showed statistically significant reduction in erythema compared to the vehicle-treated control site ($^*p < 0.01$) at all MEDs tested

DB, double-blind; *n*, number of participants; MED, minimal erythema dose; PC, placebo controlled; PG, parallel group; R, randomized; RL, right-left comparison; SB, single blind.

study with 9 volunteers, they measured an increase in hydration and elasticity compared to the base formulation.

Resveratrol, which is also a phenol, is another promising active ingredient. It is contained in various plants (including grapes, grapefruits, and nuts). Just like a low-calorie diet, resveratrol promotes the expression of sirtuin genes, leading to longer cell survival [45]. Resveratrol effectively prevented UVB-induced skin edema in a preclinical study [46].

Another important active ingredient of the phenol family is *ferulic acid* (*4-hydroxy-3-methoxycinnamic acid*), which is widely present in the cell walls of numerous plants, including fruits, vegetables, and grains [47, 48]. Today, it is mainly used as a photoprotective agent in skin products. Its photoprotective effect has been demonstrated in several studies [35, 49, 50]. The synergistic effect of ferulic acid with vitamins C, E, and β-carotene is another promising and interesting aspect [35, 50]. Lin et al. [36] demonstrated that the addition of ferulic acid to a solution containing vitamins C and E doubled the skin-protective capacity of the formulation, from 4- to 8-fold.

Ectoine

Ectoine is an organic molecule of low molecular weight occurring in halophilic bacteria [51]. These bacteria grow under extreme conditions (dryness, high temperatures, and intensive UV irradiation) and protect themselves against these stressors by synthesizing ectoine.

Pretreatment with ectoine before sun exposure prevents the UV-induced reduction in Langerhans cells [52]. Furthermore, it was shown that ectoine protects the skin from the effects of UVA-induced cell damage in different ways; it prevents the formation of ceramide by singlet-oxygen-quenching properties, and it prevents mutations

Table 5. Human studies on peptides [58–61, 68–73]

Peptide	Study	Study design	*n*	Treatment arm(s)	Efficacy
Signal peptides: modulator of dermal extracellular matrix					
Lysine-threonine-threonine-lysine-serine (KTTS)	Robinson et al. [58]	R, DB, PC, RL	93	Pal-KTTKS O/W moisturizer vs. placebo O/W moisturizer for 12 weeks	Significant improvement vs. placebo control for reduction in wrinkles/fine lines
	Lintner [59]	Not further specified	16	pal-KTTS vs. retinol	Similar wrinkle reduction and increase in skin thickness in both groups
	Fu [60]	R, PG	196	5% niacinamide, pal-KTTS, antioxidant, retinyl propionate vs. 0.02% tretinoin for 8 weeks	Significantly improved wrinkles relative to the tretinoin regimen
Gly-Glu-Lys-Gly (GEKG)	Farwick et al. {61]	R, DB, PC	10	GEGK vs. placebo cream for 8 weeks	Histochemical analyses indicate increased formation of procollagen, hyaluronic acid, and fibronectin; significant improvement in skin physiological and clinical parameters such as skin wrinkles and skin roughness
	Farwick et al. [61]	R, DB, PC	30	GEGK vs. placebo-cream for 8 weeks	Improvement in skin physiological and clinical parameters such as skin wrinkles and skin roughness
Carrier peptide: stimulates collagen and elastin synthesis					
Glycil-L-histidyl-L-lysine (GHK)	Finkley et al. [68]	R, DB, PG, PC	67	GHK-Cu vs. placebo creams	Significant improvement in skin laxity and clarity with decreased wrinkles
	Leyden J et al. [69, P69]	R, DB, PC	41	GHK-Cu vs. placebo and vitamin K cream around the eyes	Reduction in lines and wrinkles, increase in skin density and thickness around the eyes
	Leyden et al. [69, P68]	R, DB, PC	71	GHK-Cu vs. placebo creams	Significant improvement in skin texture after 12 weeks
	Abdulghani and Gottlieb [73]	Non-R, AC, PG, WP	20	Topical tretinoin, topical vitamin C, topical GHK-Cu, topical melatonin; application on thigh skin for 12 weeks	Increase in procollagen synthesis: 4/10, 5/10, 5/10, and 7/10 of patients showed response to tretinoin, vitamin C, melatonin, and GHK-Cu, respectively
Neurotransmitter inhibitor peptides: modulates acetylcholine transmission					
Acetyl hexapeptide – 3 (Ac-Glu-Glu-Met-Gln-Arg-Arg-NH_2)	Raikou et al. [71]	R, PG	24	Acetyl hexapeptide-3 with tripeptide-10 citrulline (group G1), tripeptide-10 citrulline (group, G2), acetyl hexapeptide-3 (group G3), or neither peptide (group G4) for 60 days	Significant reduction in wrinkles (up to 30%)
	Blanes-Mira et al. [70]	PC, OL	10	O/W emulsion containing 10% acetyl hexapeptide-3 solution vs. placebo creams for 30 days	27% in depth of wrinkles after 30 days (10% reduction in placebo group)
	Wang et al. [72]	R, DB, PC, PG	60	Acetyl hexapeptide-3 vs. placebo at a 3:1 ratio twice daily for 4 weeks	Significant reduction in depth of wrinkles

AC, active controlled; DB, double-blind; *n*, number of participants; OL, open label; PC, placebo controlled; PG, parallel group; R, randomized; RL, right-left comparison; SB, single-blind; WP, within patient.

in the mitochondrial DNA in dermal fibroblasts [53]. In an in vivo study with 104 volunteers, Heinrich et al. [54] demonstrated that a formulation containing 2% ectoine was more effective in terms of skin hydration, skin elasticity, and skin surface structure than vehicle-only treatment.

Bioactive Peptides

Peptides are formed from short amino acid sequences and confer a diverse range of biological effects [55]. Active sequences of these peptides can be isolated and synthetically modified to further enhance their biological activities [56].

Along with health benefits demonstrated in areas such as inflammation, wound healing, angiogenesis, and antimicrobial defense, bioactive peptides are also being explored for their use in cosmeceuticals [56].

These topical peptides can be categorized into 4 groups:
- signal peptides;
- carrier peptides;
- neurotransmitter inhibitor peptides; and
- enzyme inhibitor peptides

The first 3 groups have the most data on skin rejuvenation (Table 5). The peptides with the highest evidence are explained in more detail below.

Signal peptides increase matrix cell activities and stimulate protein production in general and collagen synthesis in specific. Substances with most existing data are the procollagen-I-derived pentamer lysine-threonine-threonine-lysine-serine (KTTS), which stimulates the production of collagens I and III and fibronectin in vitro in a time- and dose-dependent manner, and the copper tripeptide glycil-L-histidyl-L-lysine (GHK) [57]. The latter also acts as a carrier peptide.

To overcome permeability issues, palmitoyl is added to the peptide fragments.

Several clinical published studies have shown that topical formulations containing palmitoyl-KTTS have the capacity to reduce fine lines, wrinkles, and improve skin texture significantly [58, 59]. However, most of reported clinical benefits were obtained by using a formulation containing palmitoyl-KTTKS and other active ingredients (e.g., niacinamide and vitamin E), or at least in the presence of a basic moisturizer, suggesting that the observed benefits may not be solely produced by the conjugated peptide. Furthermore, study design and data evaluation are not described in detail in all studies, except for the studies by Robinson et al. [58] and Fu et al. [60].

A more recent signal peptide is the tetrapeptide GEKG (Gly-Glu-Lys-Gly), represented as a sequence in several extracellular matrix proteins. When applied to human dermal fibroblasts in vitro, the peptide caused up-regulation of fibronectin, HA synthase, and pro-collagen I mRNA [61]. Tested topically on 10 persons in a double-blind, randomized, placebo-controlled trial over 8 weeks, GEKG led to increased levels of collagen I mRNA and increased formation of procollagen I, HA, and fibronectin. Significant improvements in the elasticity of skin (measured by resilient distension) were claimed in further clinical studies [61].

The tripeptide-1 glycyl-L-histidyl-L-lysine (GHK) is primarily known as *carrier peptide*. This kind of peptide facilitates the transportation of important substances. The major application of GHK is to deliver important trace elements [62]. GHK is a fragment of the α_2-chain of collagen I and exhibits a high affinity for copper (I) ions, forming spontaneously a tripeptide-copper complex (GHK-Cu) [63, 64].

Originally, GHK-Cu was studied in the skin for its ability to promote wound healing [65, 66]. It was further shown to be able to restore the function of irradiated fibroblasts. Consequently, it also has to have effects on DNA repair [67]. A few placebo-controlled clinical studies claimed GHK-Cu improves skin quality in women [68, 69].

Neurotransmitter inhibitor peptides mimic the action of botulinum toxin by emulating the amino acid sequence of the synaptic protein, SNAP-25. They inhibit acetylcholine release at the neuromuscular junction and have curare-like effects [62].

Acetyl hexapeptide-3 is one of the best-studied peptides in this group. A clinical vehicle-controlled study by Blanes-Mira et al. [70] showed that 10% acetyl hexapeptide-3 reduced the depth of periorbital wrinkles up to 30% (vs. 10%) after 30 days of use. A more recent prospective, randomized, controlled study on 24 female volunteers with a mean age of 45 years found similar results [71]. Yet, these results should be interpreted with caution due to the small number of patients per group. In another randomized trial, acetyl hexapeptide-3 or placebo was applied to periorbital wrinkles of 60 Chinese subjects twice daily for 4 weeks. In the objective evaluation, silicone replicas of the skin at the application area were made before and after the treatment, which were analyzed by a wrinkle analysis apparatus. Analysis showed a significant reduction in the depth of wrinkles in the treatment arm [72].

Combinations

Recent studies suggest that the combination of antioxidants and cell regulators may multiply the antiaging effects. Fu et al. [60] compared the combination of niacinamide/pentapeptide/retinyl propionate to a formulation with 0.02% retinoic acid in a vehicle-controlled, randomized, in vivo study with 196 patients. The combination of niacinamide/pentapeptide/retinyl propionate led to a significant reduction in wrinkles after 8 weeks, whereas similar results with the retinoic acid formulation could only be achieved after 24 weeks.

Conclusion

Cosmetic products with targeted ingredients are increasingly used to prevent skin aging and to maintain results after skin rejuvenation procedures. Meanwhile, there is a large number of products, marketed as cosmeceuticals, which claim that their ingredients actively improve skin health and have rejuvenation capabilities. However, most products available on the market lack evidence of clinical benefits from use of sufficiently high concentrations of these ingredients. Additionally, clinical trial data for their clinical efficacy are meagre due to various factors including permeability with regard to the skin barrier and stability upon light exposure.

The best evidence (level A, randomized, double-blind, placebo-controlled studies) for the effectiveness of active substances in local therapeutics so far is available for vitamins B_3, C, and A, and their derivatives; as well as for various α-hydroxy acids such as glycolic or α-lipoic acid. Furthermore, some peptides are relatively well investigated. Several scientific studies indicate that palmitoyl-KTTS has a capacity to significantly reduce signs of skin aging on the face [58–60]. In vivo synergistic activity of cell regulators and antioxidants, as observed in some studies [60, 73], makes the combination of differently acting active substances promising for cosmetic and dermatological applications.

A major shortcoming in published studies is that most industry-driven studies do not meet the standards required for a scientific publication yet. Placebo-controlled, double-blind studies, the standard in medical research, are still too rare for cosmetic products. Most of the existing scientific investigations were carried out on very small number of subjects, mainly female volunteers, with a wide age range. Good clinical practice was often lacking in the protocols.

The product manufacturers and universities ought to work together in this field and generate more data on safety and efficacy, with the aim of improving the benefit for patients.

Qualitatively, evidenced studies would also justify high market prices for well-studied cosmetic products.

Key Message

Scientific evidence is still scarce for many topical antiaging products.

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Statement of Ethics

This research did not involve human participants or animals as this was a review of existing publications, and no primary data were collected. Written informed consent was, therefore, not obtained, and ethical approval was not sought.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Author Contributions

L.I. and D.L. take responsibility for the integrity of the data and the accuracy of the data analysis. L.I. designed the study and critically revised the manuscript for important intellectual content.

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