Cosmeceuticals are becoming increasingly popular as the search for a miracle anti-aging cream intensifies. Cosmeceuticals are agents that exert a pharmaceutical therapeutic benefit but are not classified as drugs because they do not necessarily demonstrate a biologic therapeutic benefit. They are found in diverse forms, ranging from vitamins to botanical extracts to peptides and growth factors (Table 1). It is important to review the studies examining the efficacy of cosmeceuticals, which are becoming popular alternatives to prescription medication because they are perceived to be “natural” products and may have fewer side effects.

Perhaps the area in which cosmeceuticals have shown the most promise is the treatment of aging and photoaged skin. Photoaged skin typically develops coarse wrinkles, uneven pigmentation, atrophy, and a yellowish hue, whereas naturally aged skin is characterized by finer wrinkles. Both types of aging are partially the result of decreased production of new collagen, a target of many cosmeceuticals (Table 2), while other agents reverse signs of aging skin via regulation of fibroblast proliferation, metalloproteinase activity, and elastic fiber turnover.

α- and β-HYDROXY ACIDS

α-Hydroxy acids (AHAs) comprise a group of organic carboxylic acids including citric acid, glycolic acid, lactic acid, and tartaric acid. These agents decrease the thickness of the stratum corneum by reducing corneocyte adhesion in its lower levels. AHAs can cause epidermolysis at higher concentrations, producing exfoliation and improvement of photodamaged skin.

A double-blind randomized clinical trial of glycolic acid and lactic acid creams showed that these agents reduced mottled hyperpigmentation and skin sallowness after 10 weeks of treatment. Subjects treated with AHAs versus vehicle controls noted improvement in fine wrinkles, firmness, age spots, and evenness of color. Histologically, AHAs in a 25% concentration have been demonstrated to increase collagen density and acid mucopolysaccharides and cause epidermal and papillary dermal thickening. AHAs may be combined with retinoids for the treatment of photoaged skin. In a study by Kligman, women with photoaged skin were treated with...
CosmeCeuticals

8% glycolic acid and tretinoin 0.1%. Subjects experienced no additional dryness or erythema from the combination regimen versus tretinoin monotherapy. Fifty percent of subjects reported moderate effacement of wrinkles, and two thirds reported smoother skin, suggesting a possible synergy of these 2 agents.12

Salicylic acid is the most commonly used β-hydroxy acid, with keratolytic effects at concentrations from 2% to 12%. The effectiveness of salicylic acid in aging skin has been debated, but it may be useful in enhancing absorption of other antiaging agents such as vitamin A.

RETINOL AND RETINOIDS

The retinoids tretinoin, adapalene, and tazarotene have been shown to reverse photoaging. Tretinoin 0.05% cream was approved for the treatment of photodamaged skin in the mid 1990s and has been shown to improve fine wrinkles via increased collagen production.13,14 Retinol (vitamin A) is present in many cosmetics and cosmeceuticals at concentrations of 0.08% or less. Although retinol has lower potency than tretinoin, it can improve photodamage and stimulate collagen production without the irritation associated with retinoic acid.5,15 A recent study showed that 4% hydroquinone/0.3% retinol cream more effectively reduced signs of photodamage, including fine wrinkles, dyspigmentation, and tactile roughness, than 0.05% tretinoin cream.16

VITAMINS

In addition to vitamin A, other vitamins including vitamins C, E, and niacinamide have been used to reverse the effects of photoaging. Vitamin C has become popular because of its utility not only as an antioxidant but also as a promoter of collagen synthesis. Furthermore, vitamin C has anti-inflammatory and photoprotective properties.17

The earliest cosmeceuticals contained L-ascorbic acid, the active form of vitamin C, but this agent was noted to be unstable in solution. Subsequently, more stable esterified forms were derived, including ascorbyl-6-palmitate and magnesium ascorbyl phosphate. Several clinical studies have demonstrated the benefits of topical vitamin C. In a 3-month double-blind, randomized vehicle-controlled study, topical ascorbic acid 10% was shown to significantly improve fine wrinkling (P=.002), tactile roughness (P=.04), coarse rhytides (P=.01), as well as skin tone and sallowness (P=.03).18 Other studies also have shown reversal of photoaging with vitamin C creams, including histologic evidence of elastic tissue repair and increased Grenz zone collagen, as well as increased type I collagen messenger RNA.19,20

Niacinamide (vitamin B₃) is a precursor to nicotinamide adenine dinucleotide and nicotinamide adenine dinucleotide phosphate, both important in many cellular metabolic enzyme reactions. The reduced forms of these cofactors are antioxidants.6 Several studies have shown the effectiveness of topical niacinamide in reversing signs of photoaging.21-23 Improvement of facial dyspigmentation associated with aging skin by this vitamin is likely mediated by suppression of melanosome transfer from melanocytes to keratinocytes.21 Topical preparations of niacinamide are well tolerated and have been shown to reduce UV-induced
carcinogenesis and photoimmunosuppression. Recently, Bissett et al reported a double-blind, split-face, randomized trial showing significant improvement in fine lines and wrinkles ($P=0.0005$), hyperpigmented areas ($P=0.0006$), red blotchiness ($P=0.03$), and skin sallowness ($P=0.0004$) with niacinamide use for 12 weeks. In vitro, niacinamide increases collagen production in fibroblast culture.23

Vitamin E is an important lipophilic antioxidant that has shown photoprotective effects in many animal studies. However, there are no placebo-controlled studies investigating the effects of vitamin E on aging skin.24 Further studies are needed before it can be recommended as a cosmeceutical agent for the treatment of photoaging.

**ANTI-OXIDANTS**

Antioxidants include the vitamins discussed previously in this article as well as α-lipoic acid, ubiquinone (coenzyme Q10), green tea, and kinetin. α-Lipoic acid is a potent lipid- and water-soluble antioxidant that scavenges reactive oxygen species. Lipoic acid 5% cream was evaluated in a split-face, randomized, placebo-controlled, double-blind study of 33 women.25 Topical 5% lipoic acid cream was applied twice daily for 12 weeks and significantly decreased skin roughness, lentigines, and fine wrinkles ($P<0.001$).

Ubiquinone, or coenzyme Q10, is an antioxidant present in all cells that functions in energy transduction.7 Topical ubiquinone can penetrate the viable epidermis and reduce wrinkle depth. It is also effective against UVA-mediated oxidative stress in human keratinocytes and can significantly suppress the expression of collagenase in human dermal fibroblasts following UVA irradiation.26 The use of 0.3% ubiquinol cream once daily for 6 months resulted in a 27% reduction in wrinkle depth, analyzed by laser profilometry.27

Green tea polyphenols have both antioxidant and anti-inflammatory properties. Although green tea has been shown to protect against UV-induced carcinogenesis in mice, there are few studies examining its effects on human skin.28 In a double-blind, placebo-controlled trial of 40 women with moderate photoaging, 8 weeks of a combination of 10% green tea cream and twice-daily green tea oral supplements (300 mg) resulted in histologic improvement in elastic tissue content versus placebo, though no clinically significant changes could be detected.29 Further studies are needed before green tea can be established as an inhibitor of photodamage in human skin.

Kinetin, or N6-furfuryladenine, is a plant growth factor that has significant antioxidant properties. The addition of kinetin to human fibroblasts in culture delays the onset and decreases the extent of many characteristic changes of aging seen in cultured fibroblasts.30 Initial studies suggest that kinetin lotion applied twice daily for 24 weeks can improve skin roughness, mottled hyperpigmentation, and facial wrinkling.31 Genistein, an isoflavone isolated from soy, is another useful antioxidant. Animal studies have demonstrated anticarcinogenic effects of oral genistein, which may function through inhibition of tyrosine protein kinases.32 Topical genistein inhibited UVB-induced skin tumors in mice and blocked UVB-induced acute skin burns and cutaneous wrinkling. Topical genistein also can inhibit UVB-induced erythema in human skin.33

**GROWTH FACTORS**

Growth factors regulate intra- and intercellular signaling critical in wound healing. Hundreds of different growth factors assist in wound healing by mediating angiogenesis, regulating matrix proteins such as collagen and proteoglycans, and inducing mitosis of fibroblasts, endothelial cells, keratinocytes, and hematopoietic cells.8 The

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**Table 2**

<table>
<thead>
<tr>
<th>Antiaging Target</th>
<th>Cosmeceutical Agent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Collagen turnover</td>
<td>AHAs, growth factors, peptides, retinol, vitamin B3 (niacinamide)</td>
</tr>
<tr>
<td>Antioxidant effect</td>
<td>α-Lipoic acid, green tea, kinetin, ubiquinone (coenzyme Q10), vitamins B3 (niacinamide), C, and E</td>
</tr>
<tr>
<td>Pigmentation</td>
<td>AHAs, aloesin, arbutin, azelaic acid, glabridin, hydroquinone, kojic acid, melatonin, mequinol, paper mulberry extract, retinol, soy, vitamin B3 (niacinamide)</td>
</tr>
</tbody>
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*AHAs indicates α-hydroxy acids.
interaction of many growth factors is felt to determine the outcome of wound healing. Growth factors represent a group of cosmeceutical agents potentially effective in reducing signs of photoaging because repair of photodamaged skin requires tissue remodeling similar to that of a chronic wound.

A pilot study was conducted in which a mix of several growth factors derived from human fibroblast cultures was applied twice daily for 60 days to the skin of 14 subjects with photodamaged skin.\(^3^4\) Eleven of the 14 subjects (79%) had clinical improvement in wrinkle scores at the study’s end. Biopsy results revealed a 37% increase in new collagen formation in the Grenz zone and 27% increase in epidermal thickening.\(^3^4\) Double-blind placebo-controlled studies are needed to further establish the role of growth factors in reversing photodamage and to elucidate which growth factors are most effective.

**PEPTIDES**

The 3 types of peptides used in cosmeceuticals are (1) signal peptides, which can stimulate production of new collagen and elastin; (2) carrier peptides, which function as carriers of cofactors for enzymatic steps in collagen production; and (3) neurotransmitter blocking peptides.

Elastin-derived peptides consisting of the sequence glycine-valine-alanine-proline-glycine were shown to stimulate the growth of human skin fibroblasts in vitro, presumably through binding of a plasmalemmal receptor on the fibroblasts.\(^3^5\) This peptide sequence also has been shown to downregulate elastin expression, suggesting a mechanism for improvement of photodamaged skin.\(^3^6\) Another peptide found in type I procollagen, lysinethreonine-threonine-lysine-serine, stimulates new collagen synthesis. This peptide has been linked to a lipophilic fatty acid (ie, palmitic acid) to enhance penetration of topical skin-lightening agents by removal of superficial layers of the epidermis.\(^4^1\) Peptides can also stabilize metals such as copper, which itself has antiaging benefits. For example, the tripeptide glycyl-L-histidyl-L-lysine, found on the α-II chain of human collagen, is thought to facilitate the uptake of copper by cells.

Copper is a cofactor for superoxide dismutase, an important antioxidant, and regulates lysyl oxidase, thereby influencing collagen and elastin production.\(^3^\)

Acetyl-glutamyl-glutamyl-methoxyl-glutamyl-arginyl-arginylamide, a recently synthesized hexapeptide (known as Argireline\(^\text{®}\)), inhibits neurotransmitter release in vitro.\(^3^7\) This peptide has been incorporated into cosmeceutical products because it is presumed that inhibition of neurotransmitter signaling will raise the threshold of muscle activity required to produce dynamic facial wrinkles.

**LIGHTENING AGENTS**

Hydroquinone, an inhibitor of tyrosinase activity, is the most widely used skin-lightening agent. The maximum concentration approved by the US Food and Drug Administration for use in cosmetics is 2%, with higher strengths available by prescription. This phenolic compound is found naturally in many plants as well as in coffee, tea, beer, and wine.\(^9\) However, hydroquinone can cause contact dermatitis and, rarely, exogenous ochronosis, resulting in hyperpigmentation in the treated area that is difficult to reverse. Other natural lightening agents are being studied as alternatives to hydroquinone. These include aloesin, a natural derivative of aloe vera that inhibits tyrosinase activity, as well as arbutin and methylarbutin, skin-lightening glucosides found in the bearberry fruit. Manufacturers of arbutin claim that a 1% concentration is effective for depigmentation, though further studies are needed. According to one report, arbutin appears to be less effective than kojic acid.\(^3^8\)

Azelaic acid, a naturally occurring dicarboxylic acid derived from *Pityrosporum ovale*, inhibits tyrosinase and mitochondrial oxidoreductase activation and DNA synthesis. Topical azelaic acid, available in strengths of 15% and 20%, is used twice daily for 3 to 12 months to improve hyperpigmentation. Some studies report a superior beneficial effect to that of hydroquinone for the treatment of melasma, while others have found no significant difference.\(^3^9,4^0\)

Glycolic acid peels in concentrations of 30% to 70% can enhance penetration of topical skin-lightening agents by removal of superficial layers of the epidermis.\(^5^1\) Kojic acid, a tyrosinase inhibitor isolated from fungi, is used widely in Asia as a skin-lightening agent. A topical steroid can be combined with kojic acid to reduce the irritation often seen with this agent. In one study, the use of 0.05% hydroquinone, 10% glycolic acid, and 2% kojic acid was more effective than the combination of 2% hydroquinone and 10% glycolic acid in treating patients with epidermal melanoma.\(^4^2\)

Glabridin is a potent skin-lightening agent present in licorice extract. The depigmenting effect seen with glabridin is 16 times greater than that of hydroquinone, and its effects are evident after 7 days of use.\(^4^3\) Mequinol, or 4-hydroxyanisole, is a substrate of the tyrosinase enzyme and acts to inhibit melanogenesis.\(^4^3\) The combination of 2% mequinol and 0.01% retinoic acid is used for the treatment of solar lentigines.

Other agents that improve hyperpigmentation include melatonin, which can inhibit melanogenesis in a dose-related manner, and niacinamide, which inhibits transfer of melanosomes to the epidermal keratinocytes. Paper
mulberry extract from the roots of the *Broussonetia papyrifera* tree inhibits tyrosinase activity even at concentrations as low as 0.396%, comparable to 5.5% hydroquinone and 10% kojic acid. Paper mulberry extract is used widely in Europe and South America. Soy has been shown to reduce melanin transfer and improve mottled hyperpigmentation and solar lentigines after 12 weeks of twice-daily application. Although controlled studies are needed to establish the role of many of these naturally occurring agents in skin lightening, they represent promising alternatives to hydroquinone, which may be irritating or ineffective in some patients.

**CONCLUSION**

Cosmeceuticals show much promise for the treatment of both aging and photoaged skin. The biologic activity of many of these agents has been elucidated, providing plausible mechanisms for how cosmeceuticals may protect skin against aging. However, many of the clinical trials performed thus far are not controlled and have been conducted by manufacturers of the cosmetic products containing these agents. Further randomized, placebo-controlled, double-blind studies are needed to substantiate many of the claims made about cosmeceuticals.

Because the practice of combining cosmeceutical agents with prescription drugs and/or laser treatments to enhance efficacy in the treatment of aging skin will likely increase in the future, it is important to understand how these agents work. Furthermore, elucidating the diverse pathways targeted by different cosmeceuticals highlights the need to study combinations of several classes of cosmeceuticals, which will likely reveal synergistic effects on reversing signs of aging.

**REFERENCES**

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