Cosmeceuticals: A Review of Their Use for Aging and Photoaged Skin

Anjali Dahiya, MD, PhD; John F. Romano, MD

Cosmeceuticals are popular agents present in many cosmetics that provide beneficial physiologic effects but are not considered true pharmaceuticals. Their sales represent the largest growth segment of the skin care market, with products increasingly available in dermatologists' offices. We review the use of cosmeceuticals in the treatment of aging and photoaged skin. These agents function to reverse clinical signs of aging by serving as antioxidants, targeting extracellular matrix proteins, and modulating cellular signaling pathways involved in the aging process.

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.[1,2] 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),[3-9] while other agents reverse signs of aging skin via regulation of fibroblast proliferation, metalloproteinase activity, and elastotic fiber turnover.

Dr. Dahiya is a dermatology resident and Dr. Romano is Clinical Assistant Professor of Dermatology, Weill Medical College of Cornell University, New York Presbyterian Hospital, New York, New York.

The authors report no actual or potential conflict of interest in relation to this article.

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.[10]

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.[11] Histologically, AHAs in a 25% concentration have been demonstrated to increase collagen density and acid mucopolysaccharides and cause epidermal and papillary dermal thickening.[4] AHAs may be combined with retinoids for the treatment of photoaged skin. In a study by Kligman,[12] women with photoaged skin were treated with

TABLE 1

Cosmeceutical Agents

Cosmeceutical Agent	Examples
α-Hydroxy acids	Citric acid, glycolic acid, lactic acid, salicylic acid, tartaric acid
Retinoids, retinol	Adapalene, retinol, tazarotene, tretinoin
Vitamins	A, B_3 (niacinamide), C, E
Antioxidants	α-Lipoic acid, green tea, kinetin, ubiquinone (coenzyme Q10)
Growth factors	Epidermal growth factor, platelet-derived growth factor, transforming growth factor-β, vascular endothelial growth factor
Peptides	Argireline®, glycyl-L-histidyl-L-lysine, valine-glycine-valine-alanine-proline-glycine
Lightening agents	Aloesin, arbutin, azelaic acid, glabridin, hydroquinone, kojic acid, melatonin, mequinol, niacinamide, paper mulberry extract, soy

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 nicotinamide 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 B_3) 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

TABLE 2

Targets of Cosmeceuticals*[3-9]

Antiaging Target	Cosmeceutical Agent
Collagen turnover	AHAs, growth factors, peptides, retinol, vitamin B_3 (niacinamide)
Antioxidant effect	α-Lipoic acid, green tea, kinetin, ubiquinone (coenzyme Q10), vitamins B_3 (niacinamide), C, and E
Pigmentation	AHAs, aloesin, arbutin, azelaic acid, glabridin, hydroquinone, kojic acid, melatonin, mequinol, paper mulberry extract, retinol, soy, vitamin B3 (niacinamide)

*AHAs indicates α-hydroxy acids.

carcinogenesis and photoimmunosuppression. Recently, Bissett et al[6] reported a double-blind, split-face, randomized trial showing significant improvement in fine lines and wrinkles (*P*=.0005), hyperpigmented areas (*P*=.0006), red blotchiness (*P*=.03), and skin sallowness (*P*=.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.

ANTIOXIDANTS

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*<.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

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.[34] 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.[34] 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.[3]

Elastin-derived peptides consisting of the sequence valine-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.[35] This peptide sequence also has been shown to downregulate elastin expression, suggesting a mechanism for improvement of photodamaged skin.[36] Another peptide found in type I procollagen, lysine-threonine-threonine-lysine-serine, stimulates new collagen synthesis. This peptide has been linked to a lipophilic fatty acid (ie, palmitic acid) to enhance penetration of skin so that studies on human skin can be pursued.

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-glutaminyl-arginyl-arginylamide, a recently synthesized hexapeptide (known as *Argireline®*), inhibits neurotransmitter release in vitro.[37] 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.[38]

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.[39,40]

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.[41] 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 melasma.[41]

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.[42] Mequinol, or 4-hydroxyanisole, is a substrate of the tyrosinase enzyme and acts to inhibit melanogenesis.[43] 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.[9] 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

1. Kligman D. Cosmeceuticals. *Dermatol Clin.* 2000;18:609-615.
2. Brody HJ. Relevance of cosmeceuticals to the dermatologic surgeon. *Dermatol Surg.* 2005;31:796-798.
3. Lupo MP. Peptides and proteins. In: Draelos ZD, ed. *Cosmeceuticals.* 1st ed. Philadelphia, Pa: Elsevier Saunders; 2005:119-124.
4. Ditre CM, Griffin TD, Murphy GF, et al. Effects of alpha hydroxy acids on photoaged skin: a pilot clinical, histologic, and ultrastructural study. *J Am Acad Dermatol.* 1996;34:187-195.
5. Varani J, Warner RL, Gharaee-Kermani M, et al. Vitamin A antagonizes decreased cell growth and elevated collagen-degrading matrix metalloproteinases and stimulates collagen accumulation in naturally aged human skin. *J Invest Dermatol.* 2000;114:480-486.
6. Bissett DL, Oblong JE, Berge CA. Niacinamide: a B vitamin that improves aging facial skin appearance. *Dermatol Surg.* 2005;31: 860-865.
7. Burke KE. Nutritional antioxidants. In: Draelos ZD, ed. *Cosmeceuticals.* 1st ed. Philadelphia, Pa: Elsevier Saunders; 2005:125-132.
8. Fitzpatrick RE. Endogenous growth factors as cosmeceuticals. *Dermatol Surg.* 2005;31:827-831.
9. Rendon MI, Gaviria JI. Review of skin-lightening agents. *Dermatol Surg.* 2005;31:886-889.
10. Ditre CM. Exfoliants: AHAs and BHAs. In: Draelos ZD, ed. *Cosmeceuticals.* 1st ed. Philadelphia, Pa: Elsevier Saunders; 2005:111-118.
11. Corcuff P, Fiat F, Gracia AM, et al. Hydroxy acid induced desquamation of the human stratum corneum: a comparative ultrastructural study. Presented at: 19th International Federation Society of Chemists Congress; October, 1996; Sydney, Australia.
12. Kligman AM. The compatibility of combinations of GA and tretinoin in acne and in photoaged facial skin. *J Geriatr Dermatol.* 1995;3:25A-28A.
13. Woodley DT, Zelickson AS, Briggaman RA, et al. Treatment of photoaged skin with topical tretinoin increases epidermal-dermal anchoring fibrils. a preliminary report. *JAMA.* 1990;263:3057-3059.
14. Olsen EA, Katz I, Levine N, et al. Tretinoin emollient cream: a new therapy for photodamaged skin. *J Am Acad Dermatol.* 1992;26:215-224.
15. Kang S, Duell EA, Fisher GJ, et al. Application of retinol to human skin in vivo induces epidermal hyperplasia and cellular retinoid binding proteins characteristic of retinoic acid but without measurable retinoic acid levels or irritation. *J Invest Dermatol.* 1995;105:549-556.
16. Draelos ZD. Novel approach to the treatment of hyperpigmented photodamaged skin: 4% hydroquinone/0.3% retinol versus tretinoin 0.05% emollient cream. *Dermatol Surg.* 2005;31:799-804.
17. Farris PK. Topical vitamin C: a useful agent for treating photoaging and other dermatologic conditions. *Dermatol Surg.* 2005;31:814-817.
18. Traikovich SS. Use of topical ascorbic acid and its effects on photodamaged skin topography. *Arch Otolaryngol Head Neck Surg.* 1999;125:1091-1098.
19. Humbert PG, Haftek M, Creidi P, et al. Topical ascorbic acid on photoaged skin. clinical, topographical and ultrastructural evaluation: double-blind study vs. placebo. *Exp Dermatol.* 2003;12:237-244.
20. Fitzpatrick RE, Rostan EF. Double blind, half-face study comparing topical vitamin C and vehicle for rejuvenation of photodamage. *Dermatol Surg.* 2002;28:231-236.
21. Hakozaki T, Minwalla L, Zhuang J, et al. The effect of niacinamide on reducing cutaneous pigmentation and suppression of melanosome transfer. *Br J Dermatol.* 2002;147:20-31.
22. Bissett DL, Oblong JE, Saud A, et al. Topical niacinamide provides skin aging appearance benefits while enhancing barrier function. *J Clin Dermatol.* 2003;32:S9-S18.
23. Matts PJ, Oblong JE, Bissett DL. A review of the range of effects of niacinamide in human skin. *Int Fed Soc Cosmet Chem Mag.* 2002;5:285-289.
24. Thiele JJ, Hsieh SN, Ekanayake-Mudiyanselage S. Vitamin E: critical review of its current use in cosmetic and clinical dermatology. *Dermatol Surg.* 2005;31:805-813.
25. Beitner H. Randomized, placebo-controlled, double blind study on the clinical efficacy of a cream containing 5% alpha-lipoic acid related to photoaging of facial skin. *Br J Dermatol.* 2003;149:841-849.
26. Hoppe U, Bergemann J, Diembeck W, et al. Coenzyme Q10, a cutaneous antioxidant and energizer. *Biofactors.* 1999;9:371-378.
27. Wrinkle reduction study 2003. In: Eucerin Q10 Product Compendium. Wilton, Conn: Beiersdorf Inc; 2003:11.
28. Hsu S. Green tea and the skin. *J Am Acad Dermatol.* 2005;52: 1049-1059.
29. Chiu AE, Chan JL, Kern DG, et al. Double-blinded, placebo-controlled trial of green tea extracts in the clinical and histologic appearance of photoaging skin. *Dermatol Surg.* 2005;31:855-860.
30. Rattan SI, Clark BF. Kinetin delays the onset of aging characteristics in human fibroblasts. *Biochem Biophys Res Commun.* 1994;201:665-672.
31. McCullough JL, Weinstein GD. Clinical study of safety and efficacy of using Kinetin 0.1% (Kinerase®) to treat photodamaged skin. *Cosmet Dermatol.* September 2002;15:29-32.

32. Akiyama T, Ishida J, Nakagawa S, et al. Genistein, a specific inhibitor of tyrosine-specific protein kinases. *J Biol Chem.* 1987; 262:5592-5595.
33. Wei H, Saladi R, Lu Y, et al. Isoflavone genistein: photoprotection and clinical implications in dermatology. *J Nutr.* 2003(11 suppl 1);133:3811S-3819S.
34. Fitzpatrick RE, Rostan EF. Reversal of photodamage with topical growth factors: a pilot study. *J Cosmet Laser Ther.* 2003;5:25-34.
35. Kamoun A, Landeau JM, Godeau G, et al. Growth stimulation of human skin fibroblasts by elastin-derived peptides. *Cell Adhes Commun.* 1995;3:273-281.
36. Tajima S, Wachi H, Uemera Y, et al. Modulation by elastin peptide VGVAPG of cell proliferation and elastin expression in human skin fibroblasts. *Arch Dermatol Res.* 1997;289:489-492.
37. Blanes-Mira C, Clemente J, Jodas G, et al. A synthetic hexapeptide (Argireline) with antiwrinkle activity. *Int J Cosmet Sci.* 2002;24:303.
38. Piamphongsant T. Treatment of melasma: a review with personal experience. *Int J Dermatol.* 1998;37:897-903.
39. Balina LM, Graupe K. The treatment of melasma. 20% azelaic acid versus 4% hydroquinone cream. *Int J Dermatol.* 1991;30: 893-895.
40. Sarkar R, Bhalla MA, Kanwar AJ. A comparative study of 20% azelaic acid cream monotherapy versus a sequential therapy in the treatment of melasma in dark-skinned patients. *Dermatology.* 2002;205:249-254.
41. Lim JT. Treatment of melasma using kojic acid in a gel containing hydroquinone and glycolic acid. *Dermatol Surg.* 1999;25: 282-284.
42. Holloway VL. Ethnic cosmetic products. *Dermatol Clin.* 2003; 21:743-749.
43. Riley PA. Mechanism of pigment cell toxicity produced by hydroxyanisole. *J Pathol.* 1970;101:163-169. ■