Seminars in Cutaneous Medicine and Surgery

Cosmeceuticals

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The aging population and a desire to maintain a youthful appearance have propelled the recent surge in the U.S. cosmeceuticals market. The rapidly growing number of products claiming to diminish fine lines and wrinkles, decrease redness, smooth texture, and fade discoloration has lead to much confusion and misinformation among dermatologists and consumers alike. Cosmeceuticals can be a useful adjunct to prescription medications and office procedures. Therefore, it behooves us as dermatologists to understand the science behind these products to better educate ourselves and our patients. We present an update of the following categories of cosmeceuticals: antioxidants, growth factors, peptides, anti-inflammatories/botanicals, polysaccharides, and pigment-lightening agents.
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As Americans are living longer, we are obsessed with diminishing the visible signs of chronological and photoaging. One manifestation of this obsession is that in 2005, the U.S. cosmeceutical market was estimated to be $12.5 billion, with the potential to exceed $16 billion by 2010.[1] Hundreds of products are marketed to diminish fine lines and wrinkles, decrease redness, smooth texture, fade discoloration, and give a more youthful appearance to the skin. Patients are exposed to marketing materials from companies that promise results that rival, or even better than, those of botulinum toxin injections and other rejuvenating procedures. These products are among the heterogeneous group of products collectively referred to as "cosmeceuticals."

What is a cosmeceutical? The term is attributed to Dr. Albert Kligman, who identified a hybrid category of products lying on the spectrum between drugs and cosmetics. It is now commonly used to describe a cosmetic product that exerts a pharmaceutical therapeutic benefit but not necessarily a biologic therapeutic benefit. The difference between a drug and a cosmeceutical is that the former is defined by having a biological effect on living tissue.[2] Another important distinction is that cosmeceuticals are not regulated by the U.S. Food and Drug Administration (FDA) and, thus, are not subject to premarket requirements for proof of safety or efficacy. Cosmeceutical products often are tested through in vitro studies using silicone replicas of skin and, at best, clinical trials are small, open-label studies usually supported by the cosmetic companies themselves. The rigorous testing required for pharmaceuticals is not mandatory for cosmeceutical products.

The recent explosion and fast-paced growth of the cosmeceutical market have left both consumers and dermatologists confused. Patients often receive unregulated information and efficacy claims for products from the internet and the media. Moreover, because many ingredients often are derived from plants, consumers may have a false sense of security that these "all-natural" products do not have potential adverse effects. In some instances, these products may not achieve the results they claim but they offer some benefit to the skin through an emollient effect. Indeed, it is often difficult to separate the effects of the moisturizer vehicle from the effects of the added active ingredient in cosmeceuticals.

It is important for dermatologists to understand the theoretical mechanisms of action of cosmeceuticals. Such information will enable dermatologists to be better equipped to help patients navigate the often muddy waters of the ever-growing sea of products and to manage realistic expectations as they consider adding cosmeceuticals to their skin care regimen. Considerable overlap exists in the purported actions of various products presently on the market. This update will divide cosmeceuticals into the following broad categories: antioxidants, growth factors, peptides, anti-inflammatories/botanicals, polysaccharides, and pigment-lightening agents.

Antioxidants

Oxidative stressors create inflammatory molecules that lead to the formation of free radicals species. These free radicals are highly reactive molecules with unpaired electrons, and they can cause cellular damage to cell membranes, lipids,

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proteins, and DNA. Damage to DNA eventually results in collagen breakdown. Free radicals also play a role in 3 additional detrimental processes: inflammation, photodamage, and carcinogenesis. Antioxidants neutralize damaging free radicals by quenching reactive molecules and, thus, protecting cells from both endogenous stress (byproducts of cellular energy) and exogenous stressors (ultraviolet [UV] light, pollution, cigarette smoke).

Antioxidants comprised a group of diverse molecules including, but not limited to, vitamins (A, B, C, E), alpha lipoic acid (ALA), Coenzyme Q-10 (CoQ-10), idebenone, polyphenols, and kinetin. They vary in their abilities to protect against inflammation, photodamage, and carcinogenesis.

Vitamin A, or retinol, is an antioxidant member of the retinoid family, which includes tretinoin. It has been studied extensively for treatment of photodamage and acne. Available by prescription, tretinoin improves fine wrinkles by increasing collagen production. Retinol is a cosmeceutical with less biological activity than tretinoin that is also is less potentially irritating. Application of retinol can increase epidermal water content, epidermal hyperplasia, and cell renewal while enhancing collagen synthesis.[3] Retinol also interferes with melanogenesis and inhibits matrix metalloproteinases (MMPs), which are involved in collagen breakdown. The clinical benefits include a reduction in the appearance of fine lines and wrinkles and lightening of lentigines. Retinol can be less irritating than the prescription retinoids so for patients who might not tolerate a prescription retinoid, they might be able to tolerate an over-the-counter retinol. The over-the-counter retinol will be better tolerated for those who might be sensitive and will still be helpful but not as efficacious as a prescription.

The vitamin B complex includes niacinamide (Vitamin B_3) and panthenol (provitamin B_5). Topical B vitamins have been studied for treatment of acne, wounds, and bullous pemphigoid and for preventing photocarcinogenesis. The mechanisms of action for these vitamins have not been completely elucidated. Niacinamide is a precursor of NAD(P) as well as its reduced form NAD(P)H, which are potent antioxidants. Topical niacinamide has been shown to have antitumor activity on keratinocytes and to suppress UVB-induced photocarcinogenesis in vitro.[4] Niacinamide improves the lipid barrier component of the epidermis by increasing ceramide and free fatty acids, as well as the epidermal barrier proteins such as keratin, filaggrin, and involucrin. This results in a decrease in transepidermal water loss. Like Vitamin A, niacinamide is thought to stimulate collagen synthesis by fibroblasts. It can inhibit melanosome transfer from melanocytes to keratinocytes and subsequently reduce melanin content in the skin. Another benefit is the reduction of skin yellowing or sallowness by preventing oxidative glycation of proteins. Overall, the use of niacinimide results in improvements in skin tone and texture, decreases of fine lines and wrinkles, and diminished hyperpigmentation. Topical niacinamide is well tolerated and typically does not induce skin irritation responses.[5]

Panthenol is a water-soluble cosmeceutical that easily penetrates the stratum corneum and is a humectant. It is a precursor to pantothenic acid, a cofactor in lipid biosynthesis, and it promotes lipid synthesis to improve the barrier function of the skin. Panthenol also promotes fibroblast proliferation and epidermal re- epithelialization to promote wound healing. Finally, it has anti-inflammatory and antipruritic effects.[6]

Vitamin C (ascorbic acid) is a water-soluble antioxidant that is essential for collagen biosynthesis. It confers both photoprotective and antioxidant effects. Various clinical studies have investigated its use to improve the signs of photodamage.[7] In a double-blind placebo-controlled split-face trial using a formulation of 10% L-ascorbic acid and 7% tetrahexyodecyl ascorbate versus an inactive polysilicone gel, Fitzpatrick and Rostan[8] showed a statistically significant decrease in photoaging on cheeks and perioral skin. Skin biopsies showed an increase in grenz zone collagen and increased mRNA for type I collagen. The necessary role of vitamin C in collagen biosynthesis makes it important for wound healing. In addition, vitamin C may inhibit elastin biosynthesis by fibroblasts, which may reduce solar elastosis of photoaged skin.[9] Vitamin C also has anti-inflammatory properties. Finally, it inhibits tyrosinase and decreases melanogenesis, which may contribute to clinical lightening of melasma and lentigines.[7]

Vitamin E (α-tocopherol) is lipid soluble and, when taken orally, it protects membrane lipids from peroxidation. In the skin, it has been shown to decrease sunburn cells after UV exposure, neutralize free radicals, and also act as a humectant. There is substantial evidence that combining topical Vitamins C and E enhances their individual antioxidant as well as photoprotective effects.[10]

Alpha lipoic acid (ALA) is a lipoamide synthesized in the mitochondria of plants and animals. It is a scavenger of reactive oxygen species and a metal chelator. ALA regenerates endogenous antioxidants such as Vitamins C and E, glutathione, and ubiquinol. ALA is both water and lipid soluble, allowing it to penetrate lipophilic cell membranes and enter the aqueous intracellular matrix. The molecule prevents lipid peroxidation, has anti-inflammatory properties, and acts as an exfoliant. In a split face study, topical 5% ALA applied twice daily for 12 weeks decreased skin roughness, lentigines, and fine wrinkles.[11] Notably, ALA does not protect against UV-induced erythema or reduce the number of sunburn cells.

CoQ-10, or ubiquinone, is a fat-soluble antioxidant located in the inner mitochondrial membrane of nearly all living cells that is necessary for steps in adenosine triphosphate (ATP) production for cellular energy. It acts by downregulating MMPs. CoQ-10 also inhibits lipid peroxidation in plasma cell membranes.[12] There is good in vitro evidence that CoQ-10 can decrease periorbital wrinkles.[13]

Idebenone is a more potent synthetic analog of CoQ-10 that is a powerful antioxidant. In an in vitro comparison of antioxidants (including idebenone, tocopherol, kinetin, ubiquinone, ascorbic acid, and lipoic acid) idebenone scored highest using 5 different assays to measure anti-inflammatory properties, photoprotective effects, and prevention of UV immunosuppression.[14] It may repair mitochondrial DNA and decrease nuclear thymine dimer photoproducts. Like other antioxidants, idebenone downregulates MMP expression. Overall, it may improve roughness, dryness and fine lines, and increase hydration.[15]

Polyphenols are plant-derived antioxidants that have anti-inflammatory, photoprotective, and anticarcinogenic properties. Flavonoids are a subgroup of polyphenols that are popular ingredients in many cosmeceuticals. They include grape seed extract, green tea extracts, and soy isoflavones. Grape seed extract can induce vascular endothelial growth factor expression on keratinocytes to enhance dermal wound healing.[16] Green tea extracts such as epigallocatechin 3-allate have been shown to decrease levels of UVB damage, DNA damage, sunburn, and erythema. In one study, epigallocatechin 3-allate increased epidermal thickness by inducing proliferation of keratinocytes. However, a recent double-blinded, placebo-controlled trial testing a combination regimen of 10% green tea cream and 300 mg twice-daily green tea oral supplementation for 8 weeks detected no significant clinical changes.[17] Soy isoflavones include genistein and daidzein. These are antioxidants with anti-inflammatory and anticarcinogenic properties. Isoflavones function as phytoestrogens, which increase skin thickness through an estrogenic effect.[10] Fresh soy milk contains 2 serine protease inhibitors: soybean trypsin inhibitor (STI) and Bowman-Birk inhibitor (BBI). STI inhibits melanosome transfer to keratinocytes, which can lighten the skin. BBI inhibits hair growth presumably as an inhibitor of ornithine decarboxylase. Other flavonoids will be discussed with the botanicals.

Kinetin, or N^6-furfuryladenine, is a plant- derived synthetic growth hormone that may have significant antioxidant properties and photoprotective effects. In an open-label 24-week study, topical application of 0.1% kinetin improved the appearance of fine wrinkles, color, texture, and blotchiness.[18]

Growth Factors

Growth factors comprise a large group of regulatory proteins that attach to cell surface receptors to mediate inter- and intracellular signaling pathways. Wound healing relies on a complex interaction of various cytokines and growth factors. Growth factors relevant to wound healing may induce new collagen, elastin, and glycosaminoglycan formation and mediate angiogenesis. Fitzpatrick and coworkers[19] studied the effect of a mixture of growth factors applied to photodamaged skin for 60 days. In this study, 11 of the 14 patients (68.6%) showed clinical improvement in wrinkle scores. Microscopic evaluation revealed that 37% showed new collagen formation in the grenz zone, and 27% showed epidermal thickening. One human growth factor presently used in cosmeceuticals is transforming growth factor-β1, which is derived from cultured fibroblasts harvested from neonatal foreskin. Advances in biotechnology have lead to further products such as processed skin cell proteins (PSP™) harvested from fetal cell lines.[20] Other growth factors include placental extract, recombinant epidermal growth factor, and platelet- derived growth factor.

Peptides

Peptides are short amino acid sequences that are components of larger proteins, such as collagen. The theoretical benefits of applying peptides to the skin were discovered during wound healing research.

Copper is a metal that enhances wound healing and angiogenesis. It is an essential cofactor for collagen and elastin formation, downregulates MMPs, and reduces the activity of collagenase. Copper is a required cofactor for the enzyme superoxide dismutase, a powerful antioxidant. Peptides may be used to stabilize and deliver copper into cells. For example, the tripeptide glycyl-L-histidyl-L-lysine-copper complex is used as a copper vehicle. As a cosmeceutical, copper peptide is thought to improve skin firmness and texture, fine lines, and hyperpigmentation.[21]

Amino peptides are produced during wound healing. Pal-KTTKS is a procollagen pentapeptide fragment that stimulates collagens I and III and fibronectin production by fibroblasts in vitro.[22] Conjugation of palmitic acid to pal-KTTKS (Palmitoyl-Pal-KTTKS) imparts lipophilic properties that facilitate stratum corneum penetration. In a double- blind, vehicle- controlled study of 49 women, Pal-KTTKS (3 ppm) application twice daily for 4 months was shown to decrease skin roughness by 13%, wrinkle volume by 36%, and wrinkle depth by 27%.[23]

Acetyl hexapeptide-3 (argireline) is a synthetic peptide that inhibits SNARE complex formation, which is involved in synaptic vesicle exocytosis in vitro.[24] One open-label trial of 5% argireline cream applied twice daily on 10 women demonstrated a 27% improvement in periorbital rhytides after 30 days as measured by silicone replica analysis.[25] Theoretically, argireline may mimic the effects of botulinum toxin injections. Although a promising idea, it has yet to be proven whether this topically applied agent can penetrate to the level of the neuromuscular junction.

Dimethylaminoethanol is a membrane stabilizer that purportedly improves facial muscle tone by releasing acetylcholine. It has been used as a homeopathic oral supplement to enhance mental and physical performance and is found in high concentration in salmon. A multicenter placebo-controlled trial of 156 patients with moderate photodamage applying 3% topical dimethylaminoethanol gel for 16 weeks showed some evidence of skin firming in perioral, periorbital, and cheek skin.[26]

Antiinflammatories/Botanicals

Numerous cosmeceuticals have been researched to treat sensitive skin, skin affected by rosacea, and photodamage to reduce the redness associated with inflammation.

Licochalcone A, from the licorice plant *Glycyrrhiza inflata,* has anti-inflammatory properties. The mechanism of action is thought to be dual inhibition of cyclo-oxygenase and lipoxygenase, thereby reducing proinflammatory cytokines and UVB-induced prostaglandin E_2 release by keratinocytes.[27] One clinical study of 62 adults with mild-to-moderate erythematotelangiectactic rosacea who used topical licochalcone A products daily for 8 weeks showed statistically significant decreases in erythema and improvements in Quality of Life Index scores.[28] Licochalcone A is not an antioxidant and therefore is not used for antiaging.

Lycopene is a carotenoid that gives tomatoes their characteristic red color. It has potential antioxidant and anti carcinogenic effects both orally and topically. Lycopene is thought to prevent prostate cancer when ingested orally.[29] On the skin, it is protective against UVB photodamage by preventing UVB-induced apoptosis.[30]

Pycnogenol is an extract of the French maritime pine bark tree, *Pinus pinaster*. It has multiple biological effects, including antimicrobial,[31]anti-inflammatory, antioxidant, and anticarcinogenic properties.[32] Pycnogenol may accelerate wound healing and reduce scar formation,[33] as well as stabilize elastin fibers.[34] It decreases erythema after UV radiation[35] and improves UV-induced pigmentation.[36] In addition, it reduces the vitamin C radical which, in turn, regenerates vitamin E, thus recycling the endogenous antioxidant enzyme system.

Silymarin is found in the milk thistle plant, *Silbum marianum*, and is touted to decrease the erythema of rosacea. It is a polyphenolic flavonoid that inhibits UVB-induced sunburn, apoptotic cell formation, and edema.[37] Its anti- inflammatory effect is caused by the inhibition of COX-2 and IL-1α. Silymarin also has anticarcinogenic effects and has been shown to reduce pyrimidine dimer formation in murine models.[38]

Quercetin is a flavonoid found in many common fruits and vegetables that is thought to have antioxidant, anti- inflammatory,[39] and anticarcinogenic effects.[40] It counters inflammation by inhibiting lipoxygenase and COX-2. In addition, quercetin is an antihistamine that inhibits histamine release from basophils and mast cells.

Allantoin is derived from the comfrey root and is now commercially manufactured by the alkaline oxidation of uric acid in a cold environment.[41] This botanical has a number of touted effects on the skin. It is an antioxidant, anti-inflammatory agent, and a soothing keratolytic. Allantoin also induces cell proliferation, promotes repair of photodamage, and reduces UV-induced inflammation.[42]

Chamomile and aloe vera are botanicals that inhibit cyclooxygenase and lipoxygenase and are soothing anti-inflammatory agents. In a clinical study, topical chamomile cream was found to be superior to 0.5% hydrocortisone in the treatment of dermatitis and sunburn by significantly decreasing wound area and healing time.[43] Aloe vera is purported to reduce inflammation and enhance wound healing.[41] It also has antibacterial, antifungal, and viricidal properties.[42]

Feverfew, a botanical folk remedy for fevers and inflammation, is an antioxidant/anti-inflammatory booster that inhibits nuclear factor-κB-dependent gene transcription in a manner similar to that of corticosteroids. In a randomized double-blind study evaluating twice-daily application of a moisturizer containing feverfew in 31 women with sensitive skin, significant improvements in erythema, tactile roughness, and overall irritation were reported during the 3-week study duration.[44]

Curcumin is derived from the herb turmeric (*Curcuma domestica*), which is used to flavor and color curry in foods. It has antioxidant, anticarcinogenic, antimicrobial, and anti-inflammatory effects. Studies show that curcumin's anti-inflammatory effects are mediated through the inhibition of lipoxygenase and cyclo-oxygenase, prostaglandins, and various proinflammatory cytokines. Curcumin can also inhibit collagease, elastase, and hylauronidase. Whether application of topical curcumin may improve the signs of photoaging is yet to be determined in clinical studies.[42]

Polysaccharides

Polysaccharides include the family of hydroxy acids: alpha hydroxy acids (AHA), beta hydroxyl acids (BHA), and polyhydroxy acids (PHA). The AHAs include glycolic acid (grapes), lactic acid (milk), malic acid (apples), and citric acid (citrus fruits) among others. They are considered to be keratolytics because they diminish corneocyte adhesion in the lower levels of the stratum corneum, allowing exfoliation and improvement in skin dullness. They also function as humectants, possibly by increasing dermal glycosaminoglycans,[45] as well as improve stratum corneum barrier function.[46] The exact mechanism of action of AHAs is not known.

BHAs, such as beta-lipohydroxyacid and tropic acid, are exfoliants appropriate for acne prone and oily skin. Salicylic acid was once thought to be a BHA, but it is structurally a phenolic aromatic acid. Its lipophilic structure allows it to penetrate into the sebaceous follicles, thus making it useful for patients with oily skin. Salicylic acid is available in a wide range of concentrations.

PHAs can hydrate, moisturize, as well as exfoliate the skin. They include gluconolactone, which may protect against UV radiation in vitro,[47] and lactobionic acid, which is both an antioxidant and a humectant. Because of their large size, PHAs do not penetrate the skin as easily and are therefore less irritating to sensitive skin.[48]

Pigment Lightening

The popularity of pigment-lightening cosmeceuticals stems from the desire to not only fade pigmentation but also to even out skin tone. Perhaps the most commonly use pigment-lightening agent is hydroquinone, which works by inhibiting tyrosinase activity. Tyrosinase is the rate-limiting, essential enzyme in the biosynthesis of melanin. It is available both in over-the-counter and in prescription strengths, and it is often combined with other agents such as retinol, AHAs, vitamin C, and topical steroids.[49] Side effects include an irritant contact dermatitis and, more rarely, exogenous ochronosis.

Kojic acid is a fungal derivative commonly used in Japan that has been shown to decrease melanin content via tyrosinase inhibition in vitro. It also decreases melanin content in melanocytes and is an antioxidant.[50] One disadvantage is that it can be irritating and is known to cause true hypersensitivity.[51] Like hydroquinone, it is often combined with other cosmeceutical agents or with topical steroids to reduce irritation.

Glabridin is the main active ingredient in licorice extract and can inhibit tyrosinase activity.[49] In addition, glabridin has anti- inflammatory properties attributed to cyclooxygenase inhibition.[52]

Ellagic acid is a polyphenol widely found in plants such as

pomegranates, which inhibits tyrosinase by chelating copper at the active center of this enzyme. It may selectively inhibit melanin synthesis only in UV-activated melanocytes. Fatty acids such as linoleic acid act by tyrosinase degradation without toxic effects on melanocytes.[53]

Many of the cosmeceuticals already described also have pigment-lightening effects. Vitamins C and E decrease tyrosinase activity. Pycnogenol decreases UV-induced pigmentation. Niacinamide (B_3) inhibits transfer of melanosomes to epidermal keratinocytes. Finally, the 2 serine protease inhibitors found in soy, BBI and STI, can reduce melanin transfer.

Conclusion/Future Directions

Consumer-driven demand has lead to development of products to counteract the signs of aging skin, to decrease erythema, and to even out tone and pigmentation. These cosmeceuticals can help protect the skin from photodamage and in some ways repair it through stimulation of new collagen production. Using them in conjunction with sunscreens and prescription retinoids may enhance results when used as an adjunct to rejuvenating procedures. They can also help to increase tolerability of retinoids by improving the epidermal barrier. With different cosmeceuticals being touted to impart different effects, an upcoming trend will be the multifunctional cosmetic.[54] Future research in wound healing and biotechnology will serve to expand this field.

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