

Optimal Skin Care for Aesthetic Patients: Topical Products to Restore and Maintain Healthy Skin

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A daily skin care regimen using topical products is essential for individuals who want to acquire and maintain healthy skin or protect their "investment" after undergoing an aesthetic procedure. Whereas sunscreens function to prevent further damage, cosmeceuticals aim to restore the skin's youthful appearance. Cosmeceuticals often contain potent bioactive ingredients that target cellular components affecting collagen production, pigmentation, erythema, and texture to promote the healthy appearance of skin. When cosmeceuticals are incorporated into a daily skin care regimen, they have the potential to counteract the detrimental effects of UV exposure and other environmental factors, as well as intrinsic factors such as

chronological aging and the cellular production of free radicals. These environmental and intrinsic factors can lead to wrinkle formation, irregular pigmentation, xerosis, reduced elasticity, and coarsened, roughened texture. Telangiectasia and benign and premalignant skin tumors are also frequent findings. Histologic changes in aging skin include degradation of collagen and elastin; decreased numbers of fibroblasts, melanocytes, keratinocytes, Langerhans cells, sweat glands, and hair follicles; and loss of subcutaneous fat. An effective skin care regimen entails application of several multifunctional topical products in the morning and evening to cleanse, hydrate, brighten, smooth, and firm the skin and protect it from photodamage.

A MULTIFUNCTIONAL APPROACH TO ACHIEVING HEALTHY SKIN

A daily skin care regimen using topical products is essential for men and women of all ages who want to acquire and maintain beautiful, healthy skin. Many of the topical skin care products and cosmeceuticals available today perform multiple functions, such as protecting the skin from photodamage (sunscreens), reducing the formation of free radicals (antioxidants), enhancing the skin's lipid barrier (moisturizers), brightening the skin and unifying its color (skin lighteners and antioxidants), and making the skin smoother and firmer while decreasing the appearance of fine lines and wrinkles (retinoids).

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The development of multifunctional products is an important cosmeceutical trend today. To garner maximum patient loyalty and continued use, skin care cosmeceuticals need to be appealing (eg, have a pleasant smell or texture) while providing multiple short-term and long-term aesthetic benefits. Skin care cosmeceuticals combine advancements in the fields of dermatology, pharmacology, and cosmetic science, thereby improving the care of the skin.¹

INTRINSIC AND EXTRINSIC FACTORS IN SKIN CHANGES

The appearance and condition of the skin are affected by both biologic and environmental factors. Biologic factors include heredity (racial and genetic factors) and chronologic aging, which produce various undesirable intrinsic changes in the skin over time. These changes, which occur all over the skin, are marked by a slow, irreversible degeneration of tissue.² Environmental

factors, particularly chronic exposure to UV radiation, produce undesirable extrinsic changes in the skin in areas exposed to sunlight.² Some of the other environmental or exogenous factors that adversely affect the appearance, structure, and function of the skin with repeated exposure and the passage of time are air pollution, smoking, alcohol intake, certain sleeping positions, and repetitive facial expressions.^{3,4} Table 1 lists the major intrinsic and extrinsic changes in the skin that occur with aging.⁵

SKIN CONDITIONS TREATED WITH TOPICAL SKIN CARE PRODUCTS

Topical skin care products are formulated to treat a variety of skin conditions, including skin damage due to normal aging, exposure to UV radiation, and rosacea. Chronic sun exposure leads to such clinical changes in the skin as rhytide (wrinkle) formation, irregular pigmentation or hyperpigmentation (eg, freckling and the formation of lentiginos, commonly called liver spots or age spots), xerosis (dry skin), reduced elasticity, roughening, and coarsened texture.² Cumulative UVB radiation produces damage to the epidermis, whereas cumulative UVA radiation damages the middle layers of the dermis.² Telangiectasia and a variety of benign and premalignant skin tumors, such as seborrheic and actinic keratoses, are also frequent findings in aged skin.²

In both photoaged and naturally aged skin, degradation of collagen and elastin weakens dermal connective tissue, causing the epidermis to lose support and the skin to become wrinkled, lax, and fragile.⁶ However, the wrinkles in sun-damaged skin are coarse, and those in chronologically aged skin are finer. Both the dermis and epidermis are thickened in photodamaged skin,⁷ but dermal thinning is characteristic of naturally aged skin.² Although aged skin has fewer melanocytes than younger skin,² overproduction of melanosomes that are distributed unevenly in the skin because of a slowdown in cell turnover causes mottled pigmentation and dark spots, such as lentiginos, to appear.⁶ These spots tend to develop not only on the face but also on other exposed skin surfaces, such as the “V” of the neckline and the dorsum of the hands and arms.⁵

The main functions of the skin are protection, secretion and excretion, absorption, thermoregulation, sensory perception, and regulation of immunologic processes. Once a person reaches middle age, most physiologic functions of the skin are reduced, some of them by as much as 50% to 60%.⁸ These physiologic functions include cell replacement, barrier function, chemical clearance, mechanical protection, immune responsiveness, wound healing, thermoregulation, DNA repair, sweat and sebum production, and vitamin D production.²

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In addition, collagen production is reduced by aging. In aged skin, fragmentation of the dermal collagen matrix by matrix metalloproteinases increases, with the net effect of weakening the dermis.⁹ When the collagen matrix collapses due to fragmentation, the fibroblasts that produce the collagen cannot attach, and even less collagen is produced. Effective antiaging treatments stimulate fibroblast collagen production to break this cycle and slow the aging process. Other cells within the skin that decrease with aging include melanocytes, Langerhans cells, keratinocytes, sweat glands, and hair follicles. The slowing of melanocyte replacement, along with the decrease in collagen production, dermal thinning, and the flattening of the dermoepidermal junction, compromise the mechanical protection of the skin. Flattening of the dermoepidermal junction also contributes to the decline in barrier function of skin. Barrier function is also lessened by reduced lipid synthesis in the stratum corneum, reduced

subcutaneous fat, and dermal thinning. Immunologic function is diminished in part by the decline in the number of Langerhans cells that occurs with aging. This decrease in immunocompetence increases the risk for carcinogenesis due to photoradiation.^{2,8} The skin's function as a thermoregulator declines with age, partly because of a decrease in secretions by sweat and sebaceous glands and loss of subcutaneous fat in certain areas.²

Physiologic alterations in the skin that result from intrinsic aging and from chronic exposure to UV light cause the formation of free radicals, which are unstable, violently reactive atoms or molecules with an unpaired electron. Oxygen-centered free radicals, or oxyradicals, react with proteins, coenzymes, DNA, and lipids, resulting in DNA damage, membrane and collagen damage, and the formation of toxic products, among other harmful effects.^{6,8} The deleterious effects of free radicals can be prevented by small molecules such as α -tocopherol, ascorbic acid, and glutathione, which act as antioxidants or free radical scavengers, and by protective enzymes such as superoxide dismutase, catalase, and glutathione peroxidase. Comparatively low levels of superoxide dismutase and glutathione peroxidase that result from free radical formation may account in part for the susceptibility of the skin to photoaging and carcinogenesis.⁸

Another important skin condition that some topical skin care products are used to treat is the acnelike disorder rosacea. Rosacea may develop in either women or men but is especially common in women, whom it tends to afflict during the menopausal years.⁵ Typical features of rosacea are the presence of facial papules or pustules, telangiectasia, and erythema. The areas of the face most affected by rosacea symptoms are those that receive the most UV light exposure.¹⁰ The pathogenesis of rosacea is unknown, but there is evidence that reactive oxygen species (ROS; superoxide anions, hydrogen peroxide, and hydroxyl radicals) may be an important factor.^{10,11} For example, inflammation is a component of certain subtypes of rosacea, and inflammatory cells mediate their effects partly through ROS release.¹¹ Some of the medications used in the treatment of rosacea act as antioxidants by either decreasing the production of ROS within tissues or scavenging and inactivating existing ROS.¹¹

TOPICAL SKIN CARE PRODUCTS: FUNCTIONS AND MECHANISMS OF ACTION

The diligent use of topical skin care products can, to some extent, keep skin healthy by reducing or preventing the adverse effects that aging and the environment have on the skin. However, laboratory or histologic evidence of the efficacy of cosmeceuticals

does not necessarily translate into clinical efficacy,¹² and these products do not have to undergo the rigorous testing that pharmaceuticals do before they can be sold to consumers. In fact, rigorous clinical trials may not be possible for many skin care products. One reason is that their desired effects may constitute subtle changes in the skin that, when measured, do not achieve statistical significance. Complicating the problem of scientifically demonstrating the efficacy of topical products is the fact that distinguishing between the positive effects of their active ingredients and their moisturizing vehicles can be difficult.¹³ Also, in order to exert beneficial effects on the lower layers of the skin, the active ingredients in skin care products must consist of molecules that are small enough to penetrate the epidermis. Finally, if they are to be effective, finished skin care products must be photostable and physically and chemically stable once their containers have been opened. In light of all these considerations, product claims for topical skin care products should be viewed with some degree of skepticism unless convincing evidence of their efficacy is provided.

Topical skin care products may be classified according to their functions as cleansers, moisturizers and conditioners, photoprotective agents, antioxidants, lightening agents, keratolytic agents, and other beneficial agents.

SKIN CLEANSERS

Cleansers are used to remove makeup, dirt, and bacteria from the skin, thereby normalizing the skin biofilm and reducing skin infections. Numerous effective skin cleansers are on the market, including soaps of all kinds, oils, lotions, and creams. The best of these products do a thorough job of cleansing the skin without damaging the skin barrier.

MOISTURIZERS

A healthy stratum corneum consists of approximately 10% to 20% tightly held water. When the stratum corneum is compromised, dry skin results. Dry skin may itch or sting, and it may have evidence of barrier damage, appearing rough, flaky, red, or cracked. Effective moisturizers create an environment to repair the damaged stratum corneum by increasing hydration through decreased water loss, making the skin softer and more hydrated. Many moisturizers contain humectants, skin conditioners, and soothing agents, such as aloe vera or other botanicals. Moisturizers are beneficial, at least temporarily, for barrier-damaged skin with various degrees of photodamage.

SUNSCREENS

Most sunscreen products available today protect the skin from both UVA and UVB radiation. UVB

radiation, with wavelengths between 290 and 320 nm, can cause sunburn and skin cancer. UVA radiation, with wavelengths between 320 and 400 nm, causes premature aging of the skin by penetrating the epidermis and damaging the dermis. Since the 1980s, the harmful effects of UVA radiation have become apparent, including its contribution to the development of skin cancer.

The sun protection factor of a sunscreen is a measure of the protection it affords against UVB radiation. The US Food and Drug Administration is considering introducing new guidelines for labeling of sunscreens that will inform physicians and consumers of the level of UVA protection these agents provide.¹⁴

Chemicals that absorb UVB rays include *p*-aminobenzoic acid derivatives, salicylates, cinnamates, camphor derivatives, and microfine titanium dioxide. UVA rays are absorbed by benzophenones, anthranilates, and dibenzoyl derivatives, such as avobenzene.⁷ Avobenzene, which was introduced in the late 1980s, was the first organic sunscreen to provide some protection against midrange to long-range UVA rays. Although avobenzene is not photostable in all formulations, the newer formulations utilize oxybenzone and octocrylene for photostabilization. Inorganic sunscreens, such as those containing titanium dioxide and zinc oxide, block not only UVA and UVB rays but also some visible light as well.¹⁴

The cosmetic elegance of sunscreen products, as well as their efficacy in protecting the skin from the effects of UV radiation, is important to their acceptance by users and consistent use. Ideally, sunscreens should be invisible when thoroughly massaged into the skin and should not impart a greasy or oily appearance on the skin.

ANTIOXIDANTS

Antioxidants are a heterogeneous class of substances that donate an electron to ROS. These compounds vary in their ability to protect the skin against inflammation, sun damage, and carcinogenesis. Antioxidants produce their effect by neutralizing free radicals and protecting cells from endogenous stress (by-products of cellular metabolism) and exogenous stressors, mainly UV radiation and air pollution.¹³

Skin has an endogenous antioxidant system, which consists of a network of vitamins, specifically vitamins C and E, that intervene in oxidative processes in an attempt to maintain a balance between pro-oxidants and antioxidants.¹⁵

The most popular antioxidants for use in skin care are flavonoids and vitamins A, C, and E.⁵ At present, the only topical therapy that has been approved by the US Food and Drug Administration for the treatment of photodamaged skin is tretinoin 0.05% emollient cream.⁵ A total of 12 trials have provided

evidence suggesting that topical tretinoin cream, in concentrations of 0.02% or higher, is beneficial in treating mild to severe photodamage on the face and forearms. The main disadvantage of tretinoin is that it tends to cause adverse effects such as erythema, scaling, dryness, stinging, or irritation during the first few weeks of treatment.¹⁶ Although the cosmeceutical retinol has less biologic activity than tretinoin, it is also potentially less irritating.¹³

Vitamin C, a water-soluble antioxidant, is necessary for collagen biosynthesis and has photoprotective, antioxidant, and anti-inflammatory effects.¹³ Vitamin E, the most active form of which is α -tocopherol, is a lipid-soluble antioxidant that decreases UV-induced erythema, neutralizes free radicals, and serves as an emollient.¹³

Flavonoids are a subgroup of plant-derived antioxidants called polyphenols. These compounds, which have anti-inflammatory, photoprotective, and anticarcinogenic properties, include grape seed extract, green tea extracts, and soy isoflavones.¹³

Niacinamide (vitamin B₃), a member of the vitamin B complex, is thought to perform several important functions in maintaining healthy skin, including improving the lipid barrier component of the epidermis and reducing melanin content in the skin by inhibiting melanosome transfer from melanocytes to keratinocytes. These functions result in improved skin tone and texture, diminished fine lines and wrinkles, and reduced hyperpigmentation.¹³

One of the newer antioxidants to be used in topical skin care products is the crushed, processed fruit of the *Coffea arabica* plant, CoffeeBerry extract. This extract contains high concentrations of several natural polyphenolic antioxidants, including chlorogenic acid, ferulic acid, quinic acid, and condensed proanthocyanidins.⁶ The dermatologic benefits of an antiaging skin care system (cleanser, day cream, and night cream) containing up to 1% CoffeeBerry extract were examined in a 12-week, double-blind, randomized, controlled trial in 50 women with mild to moderate facial photoaging. Results of the study indicated that the CoffeeBerry extract system produced significantly greater improvement ($P \leq .05$) than the control regimen in a global assessment of the subjects' skin, as well as in skin roughness, texture, and scaling.¹⁷ Two other recent studies evaluated the efficacy of the CoffeeBerry extract skin care system in women with mild to moderate facial photoaging.^{17,18} The 17 subjects who completed a 6-week, full-face trial of the CoffeeBerry extract system exhibited a mean improvement of 25% in facial pigmentation, as judged by a dermatologist blinded to treatment regimen.¹⁷ The 10 subjects who completed a 6-week, split-face trial (CoffeeBerry extract system on one side of the face and matching vehicle without CoffeeBerry extract on the other) showed a moderate improvement in

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pigmentation (15% for CoffeeBerry extract versus 5% for vehicle; $P=.055$).¹⁸ Photographs of the subjects' skin taken with specialized software indicated reductions in erythema after using the CoffeeBerry extract system.¹⁸

There are several other antioxidants worth briefly mentioning. The novel antioxidant idebenone, a potent synthetic analogue of coenzyme Q10, may be a powerful agent in topical protection of the skin.¹³ Kinetin is a synthetic growth hormone derived from plants, which may have antioxidant and photoprotective properties.¹³

The lipamide α -lipoic acid is water soluble and lipid soluble, with anti-inflammatory and exfoliant

properties. In addition to scavenging ROS, α -lipoic acid regenerates endogenous antioxidants, including vitamins C and E.¹³

A list of many of the antioxidants commonly used in topical skin care products is given in Table 2.

PIGMENT LIGHTENERS

The purpose of pigment-lightening agents is to even skin tone by reducing hyperpigmented spots or patches on the skin, such as those due to freckles and lentigines.¹³ Lightening agents work by inhibiting or degrading tyrosinase, the essential enzyme in the biosynthesis of melanin; by decreasing melanin

TABLE 3

Selected Skin Lighteners Used in Topical Skin Care Products^{4,13}

Skin Lightener	Source
α -hydroxy acids	Derivatives of certain dairy products, fruits, or sugar cane ⁵
Arbutin and arbutin derivatives	Leaves of cranberry, blueberry, and other shrubs
CoffeeBerry extract ¹⁸	Subripe fruit of the <i>Coffea arabica</i> plant ⁶
Coriander seed oil	<i>Coriandrum sativa</i>
Hydroquinone	Synthesized in laboratory and available in over-the-counter formulations in 2% concentration
Kojic acid	Natural substance produced by fungi or bacteria
Licorice extract	<i>Glycyrrhiza glabra</i>
Linoleic acid	Naturally occurring fatty acid
Niacinamide (vitamin B ₃)	Naturally occurring vitamin
Pomegranate extract	Pomegranate rind
Pycnogenol	Extract of the French maritime pine bark tree, <i>Pinus pinaster</i>
Topical retinoids	Derivatives of vitamin A
Vitamins C and E	Naturally occurring vitamins
Zinc- α -2-glycoprotein	Endogenous substance produced by epidermal keratinocytes

content in melanocytes; or by inhibiting the transfer of melanosomes to epidermal keratinocytes.¹³ Table 3 lists some commonly used skin-lightening ingredients in topical skin care products.

KERATOLYTICS

Keratolytic agents diminish corneocyte adhesion in the lower part of the stratum corneum, permitting exfoliation of the skin and the exposure of younger skin cells to improve the appearance of the skin.²⁰ Glycolic acid (from grapes), lactic acid (from milk), malic acid (from apples), and citric acid (from citrus fruits) are among the α -hydroxy acids that are popular keratolytic ingredients in skin care products. In addition to inducing desquamation and promoting cell renewal, α -hydroxy acids stimulate collagen synthesis at the dermal level, thereby increasing the thickness of the dermis.³

OTHER TYPES OF COSMECEUTICALS

Among the other products used to enhance the appearance of the skin are growth factors, cytokines, small peptides, and anti-inflammatory agents. Growth factors and cytokines are regulatory proteins that attach to receptors on cell surfaces, mediating signaling pathways. Use of growth factors in wound healing may induce the formation of new collagen, elastin, and glycosaminoglycans (moisture-holding proteins). One of the human growth factors present in some cosmeceuticals is called transforming growth factor β 1. It is derived from cultured fibroblasts harvested from neonatal foreskin.¹³ Clinical and histologic evaluation of skin cream containing a mixture of human growth factors and cytokines showed improved appearance and structural changes consistent with new collagen formation.²¹

Short chains of amino acid sequences, called peptides, are relatively new ingredients in some cosmeceuticals

designed to reduce facial lines and wrinkles. To be effective in improving the clinical appearance of the skin, peptides in skin care products must be stabilized and absorbed into the dermis, where the stimulation of collagen and extracellular matrix production occurs.²² Although naturally occurring peptides play key roles in collagen production, the efficacy of topically applied peptides is still under investigation.

Numerous botanical cosmeceuticals that may be effective in treating sensitive or inflamed skin, the redness of rosacea, and damage from UV radiation have been identified. This lengthy list of botanicals includes allantoin, chamomile, aloe vera, curcumin, feverfew, lycopene, *Pinus pinaster*, and silymarin, to name a few. Allantoin, which is derived from comfrey root, is an anti-inflammatory agent as well as an antioxidant and a soothing keratolytic. The soothing, anti-inflammatory properties of chamomile and aloe vera are widely known. Curcumin comes from the herb turmeric and has anti-inflammatory, antioxidant, anticarcinogenic, and antimicrobial effects. Feverfew is an old folk remedy for fevers and inflammation that has demonstrated efficacy as an antioxidant and anti-inflammatory booster. The carotenoid lycopene has potential antioxidant and anticarcinogenic effects. *P. pinaster* has several biologic effects, including the ability to reduce the vitamin C radical, thus regenerating vitamin E and recycling the endogenous antioxidant enzyme system. Silymarin, which is derived from the milk thistle plant, is purported to be effective in reducing the erythema of rosacea. Silymarin also has anticarcinogenic properties.¹³

ASSESSING SKIN AND SKIN IMPROVEMENTS

During normal aging, the skin undergoes histologic and physiologic changes as well as alterations in its clinical appearance and characteristics. Many of these changes were described previously in this article.

SUMMARY

A wide array of topical skin care products exists in today's market. Most of these products contain multiple ingredients that help restore and maintain the health and beauty of the skin and protect it from the damaging effects of natural aging, UV radiation, free radicals, ill health, emotional stress, smoking, air pollution, and other environmental insults. Clinical studies have demonstrated that cosmeceuticals have the potential to improve the appearance of rhytides, hyperpigmentation and erythema, and skin texture. This is an exciting period in the development of innovative cosmeceuticals, marked by the constant introduction of new topical products with the

potential to provide multiple short-term and long-term aesthetic benefits.

REFERENCES

1. Draelos ZD. Cosmeceutical trends: the multifunctional cosmetic. *Cosmet Dermatol.* 2004;17:735-736.
2. Norman RA, ed. *Diagnosis of Aging Skin Diseases.* London, England: Springer-Verlag London Ltd; 2008.
3. Rona C, Vailati F, Berardesca E. The cosmetic treatment of wrinkles. *J Cosmet Dermatol.* 2004;3:26-34.
4. Gao XH, Zhang L, Wei H, et al. Efficacy and safety of innovative cosmeceuticals. *Clin Dermatol.* 2008;26:367-374.
5. Bergfeld WF. A lifetime of healthy skin: implications for women. *Int J Fertil Womens Med.* 1999;44:83-95.
6. Lupo MP, Draelos ZD, Farris PK, et al. *CoffeeBerry*: a new, natural antioxidant in professional antiaging skin care. *Cosmet Dermatol.* 2007;20(suppl 4):2-9.
7. Pillai S, Oresajo C, Hayward J. Ultraviolet radiation and skin aging: roles of reactive oxygen species, inflammation and protease activation, and strategies for prevention of inflammation-induced matrix degradation—a review. *Int J Cosmet Sci.* 2005;27:17-34.
8. Cerimele D, Celleno L, Serri F. Physiological changes in ageing skin. *Br J Dermatol.* 1990;122(suppl 35):13-20.
9. Fisher GJ, Varani J, Voorhees JJ. Looking older: fibroblast collapse and therapeutic implications. *Arch Dermatol.* 2008;144:666-672.
10. Bakar Ö, Demirçay Z, Yuksel M, et al. The effect of azithromycin on reactive oxygen species in rosacea. *Clin Exp Dermatol.* 2007;32:197-200.
11. Jones D. Reactive oxygen species and rosacea. *Cutis.* 2004;74(suppl 3):17-20, 32-34.
12. McDaniel DH, Neudecker BA, Dinardo JC, et al. Idebenone: a new antioxidant—part I. relative assessment of oxidative stress protection capacity compared to commonly known antioxidants. *J Cosmet Dermatol.* 2005;4:10-17.
13. Choi CM, Berson DS. Cosmeceuticals. *Semin Cutan Med Surg.* 2006;25:163-168.
14. Bissonnette R. Update on sunscreens. *Skin Therapy Lett.* 2008;13:5-7.
15. Dreher F, Maibach H. Protective effects of topical antioxidants in humans. *Curr Probl Dermatol.* 2001;29:157-164.
16. Samuel M, Brooke RC, Hollis S, et al. Interventions for photodamaged skin. *Cochrane Database Syst Rev.* 2005;Jan 25: CD001782.
17. Draelos Z. A double-blind, randomized clinical trial evaluating the dermatologic benefits of coffee berry extract. Poster presented at: 66th Annual Meeting of the American Academy of Dermatology; February 1-5, 2008; San Antonio, TX.
18. McDaniel H, Mazur CJ. Coffee Berry extract skin care system: results from clinical trials and gene expression analyses. Poster presented at: 66th Annual Meeting of the American Academy of Dermatology; February 1-5, 2008; San Antonio, TX.
19. Dreher F, Gabard B, Schwindt DA, et al. Topical melatonin in combination with vitamins E and C protects skin from ultraviolet-induced erythema: a human study in vivo. *Br J Dermatol.* 1998;139:332-339.
20. Van Scott EJ, Yu RJ. Hyperkeratinization, corneocyte cohesion, and alpha hydroxy acids. *J Am Acad Dermatol.* 1984;11:867-879.
21. Hussain M, Phelps R, Goldberg DJ. Clinical, histologic, and ultrastructural changes after use of human growth factor and cytokine skin cream for the treatment of skin rejuvenation. *J Cosmet Laser Ther.* 2008;10:104-109.
22. Lupo MP. Cosmeceutical peptides. *Dermatol Surg.* 2005;31: 832-836. ■