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Aesthetic aspects of skin aging, prevention, and local treatment☆

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Abstract Skin aging is a complex biologic process influenced by a combination of intrinsic and extrinsic factors. Aging skin shows wrinkles, uneven tone, loss of elasticity, and thinning. Skin health is considered one of the principal factors representing overall well-being and the perception of health in humans; therefore, anti-aging strategies to combat aging signs and dysfunction have been developed over the last decades. Understanding the mechanism behind skin aging is required for elucidation of the mechanism of action and, hence, the potential benefits of the claimed anti-aging products. In this review, preventive measurements, cosmetologic strategies, and photoprotection (systemic antioxidants, ultraviolet and filters), as well as the mechanisms of action and the effectiveness of topical pharmaceutical agents, such as antioxidants (vitamins, polyphenols, and flavonoids) and cell regulators (retinols, peptides, hormones, and botanicals), are presented.

Introduction

Skin suffers progressive morphologic and physiologic decrement with increasing age and provides the first obvious evidence of the aging process. Skin aging can be classified into exogenous aging (chronic light exposure, pollution, ionizing radiation, chemicals, or toxins) and endogenous aging.[1] The latter occurs in nonexposed areas, which are not in direct contact with environmental factors such as ultraviolet (UV) and infrared irradiation (eg, the inner side of the upper arm), and is mainly attributed to genetic factors and alterations of the endocrine environment.[2] In contrast to photoaging, endogenously aged skin reflects degradation processes of the entire organism.[3]

Skin aging is a part of a natural human "aging mosaic," which becomes evident and follows different trajectories in different organs, tissues, and cells with time. Whereas the aging signs of internal organs are masked from ambient "eyes," the skin provides the first obvious marks of the passing time.[3] Skin aging is a complex biologic process, leading to cumulative structural and physiologic alterations and progressive changes in each skin layer, as well as changes in skin appearance, especially on the light-exposed skin areas (Fig. 1).[1,4,5]

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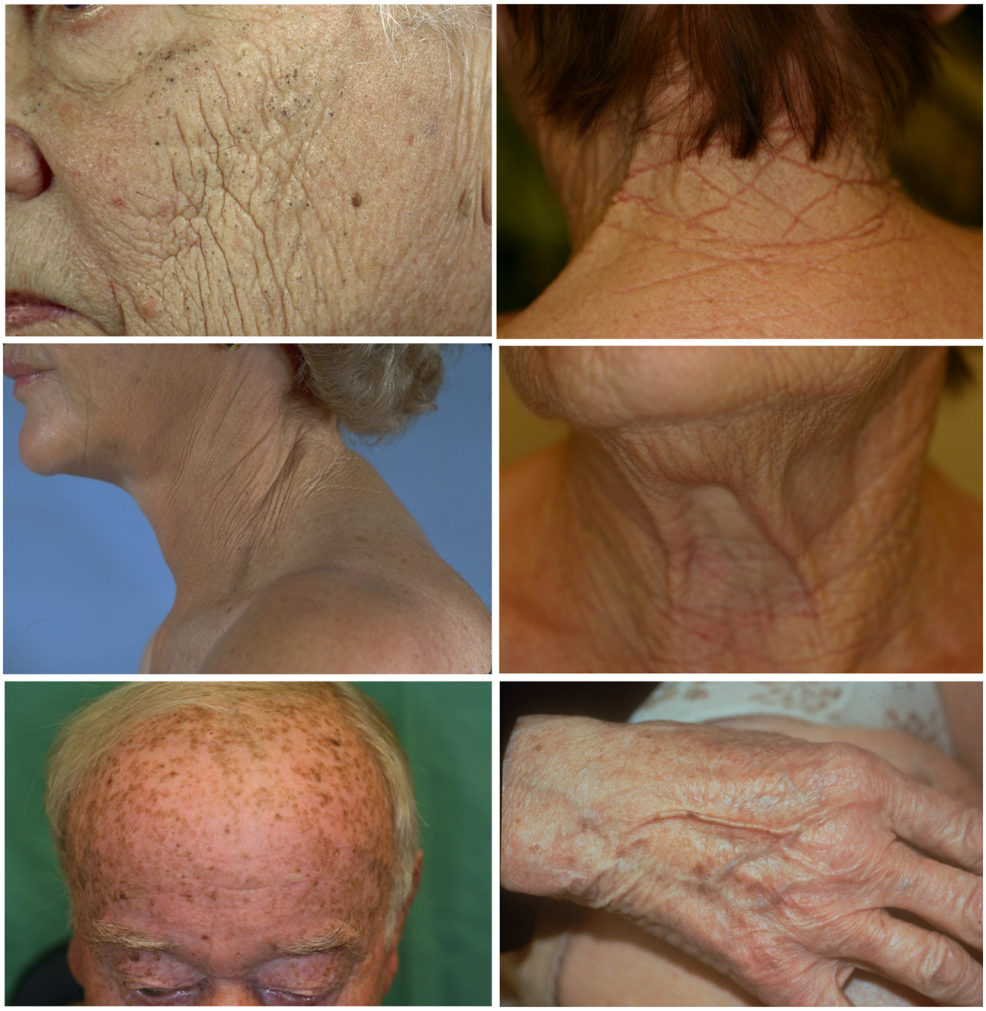

Fig. 1 Phenotypes of extrinsic aging-associated skin changes.

In contrast to thin and atrophic, finely wrinkled and dry intrinsically aged skin, photoaged skin typically shows a thickened epidermis, mottled discoloration, deep wrinkles, laxity, dullness, and roughness.[2,6–8] Gradual loss of skin elasticity leads to the phenomenon of sagging.

Slowing of the epidermal turnover rate and cell cycle lengthening coincides with a slower wound healing and less effective desquamation in older adults. This fact is important when aesthetic procedures are scheduled.[9] Many of these features are targets for product application or procedures to accelerate the cell cycle, in the belief that a faster turnover rate will yield improvement in skin appearance and will speed wound healing.

Because skin health and beauty are considered among the principal factors representing overall well-being and the perception of health in humans, several anti-aging strategies have been developed during the last few years, namely, preventive measurements, cosmetologic strategies, topical and systemic therapeutic agents, and invasive procedures.[9]

Molecular aspects of skin aging

A marked loss of fibrillin-positive structures, as well as a reduced content of collagen type VII, may contribute to wrinkles by weakening the bond between the dermis and epidermis of extrinsically age skin.[10,11] Sun-exposed aged skin is characterized by solar elastosis. The sparse distribution and decrease in collagen content in photoaged skin can be due to increased collagen degradation by various matrix metalloproteinases, serine, and other proteases irrespective of the same collagen production.[11,12] In older skin, collagen looks irregular and disorganized, and the ratio of collagen III to collagen I has been shown to increase due mostly to a loss of collagen I. The overall collagen content per unit area of the skin surface is known to decline approximately 1% per year.

Glycosaminoglycans are among the primary dermal skin matrix constituents that assist in binding water. In photoaged skin, glycosaminoglycans may be associated with abnormal elastotic material and thus be unable to function effectively. In

the dermis of intrinsically aging skin, the total hyaluronic acid level remains stable over life, while epidermal hyaluronic acid level diminishes markedly.

Aging of the entire face is associated with gravity impact, muscles action, loss of volume, diminishing and redistribution of superficial and deep fat, and loss of bony skeleton support. These taken which together lead to the face sagging and changes in its shape and contour.

Asian skin responds differently to sun exposure than Caucasian skin.[13] Asian skin tends to tan more and burn less, which means that chronic UV exposure tends to produce more pigmentation-related problems. Asians recognize melasma, freckles, and lentigines as more common phenotypic characteristics of skin aging than fine wrinkles, which appear as the first signs of aging among the Caucasian population.

Anti-aging strategies

The three primary structural components of the dermis—collagen, elastin, and glycosaminoglycans—have been the subjects of most anti-aging research and efforts for aesthetic anti-aging strategies pertaining to the skin, from "anti-wrinkle creams" to various filling agents.[9]

Regardless of the fact that aging is a biologically inevitable process and not a pathologic condition, it is correlated with various skin and body pathologies, including degenerative disorders and benign and malignant neoplasms.[14,15] The "successful aging" paradigm focuses on health and active participation in life, counters traditional conceptualizations of aging as a disease of time, and is increasingly equated with minimizing age signs on the skin, face, and body. From this perspective, preventative aesthetic dermatology might supplement the request for healthy aging, treating, or preventing certain cutaneous disorders, notably skin cancer, and delay skin aging by combining local and systemic methods of therapy, instrumental devices, and invasive procedures.[9] The mainspring of any skin anti-aging therapy is to achieve a healthy, smooth, blemish-free, translucent, and resilient skin.

In clinical practice, "to look better" does not mean to "look younger." That is why it is so important to understand patients' wishes and to orientate them to the treatment modality that will provide the most satisfying results and know all available treatment techniques. Age, previous procedures or surgery, general health status, type of skin, lifestyle, and many other factors should be taken into consideration before choosing a strategy for an individual patient. The desired therapeutic anti-aging effect of the skin is a continuous, step-by-step process that combines various methods of skin biorevitalization and rejuvenation, augmentation, restoration of each skin layer individually. May factors may play a role, altering lifestyle according to the immune, genetic, emotional, and health status in general.

Skin anti-aging strategies that attempt to reverse the dermal and epidermal signs of extrinsic and intrinsic aging can be grouped in the approaches listed in Table 1.

Prevention of skin aging

The healthy and functioning skin barrier is an important protector against dehydration and penetration of various microorganisms, allergens, irritants, reactive oxygen species,

Table 1 Skin anti-aging approaches

Cosmetologic care	Daily skin care
	Correct sun protection
	Esthetic noninvasive procedures
Topical medical agents	Antioxidants
	Cell regulators
Invasive procedures	Chemical peelings
	Visible light devices
	Intense pulsed light (iPL)
	Ablative and nonablative laser photo-rejuvenation
	Radiofrequency (rF)
	Injectable skin biostimulation and rejuvenation
	Prevention of dynamic wrinkles
	Correction of static, anatomic wrinkles
	Restoration (redistribution) of fat and volume loss, skin augmentation, and contouring
Systemic agents	Hormone replacement therapy
	Antioxidants
Preventive medicine (avoiding of exogenous factors of aging, correction of lifestyle and habits)	Smoking
	Pollution
	Solar UV irradiation
	Stress
	Nutrition, diet restriction, and alimentary supplementation
	Physical activity
	Control of general health

and radiation. The skin barrier may be specifically adjusted to allow penetration. For this reason, daily skin care may increase skin regeneration, elasticity, and smoothness and thus temporarily change the skin's condition[9]; however, it is necessary to stop the degradation of the skin's primary structural constituents—collagen and elastin—to prevent the formation of wrinkles. Although the technology required to suitably deliver these molecules into the skin has not yet been developed, some products do promote the natural synthesis of these substances except elastin enhancing.

Another integral approach preventing wrinkle formation is the reduction of inflammation by topical or systemic antioxidants, which should be used in combination with sunscreens and retinoids to enhance their protective effects.

Photoprotection and systemic antioxidants

Chronic photodamage of the skin manifests itself as extrinsic skin aging (photoaging). DNA photodamage and UV-generated reactive oxygen species are the initial molecular events that lead to most of the typical histologic and clinical manifestations of chronic photodamage of the skin.[8–11] Wrinkling and pigmentary changes are directly associated with premature photoaging and are considered the most important cutaneous manifestations. The strategies aimed at preventing photo-aging include sun avoidance; sun protection using sunscreens to block or reduce skin exposure to UV radiation; retinoids in order to inhibit collagenase synthesis and promote collagen production; and use of antioxidants, particularly in combination, to reduce and neutralize free radicals.

Interventional studies indicate that it is possible to delay skin aging and to improve skin conditions through administration of selected nutritional supplements.[16] Nutritional antioxidants act through different mechanisms and in different compartments, but they are mainly free radical scavengers:

- they directly neutralize free radicals,
- they reduce the peroxide concentrations and repair oxidized membranes,
- they quench iron to decrease reactive oxygen species production,
- via lipid metabolism, short-chain free fatty acids and cholesteryl esters neutralize reactive oxygen species.

Endogenous antioxidant defenses are both nonenzymatic (eg, uric acid, glutathione, bilirubin, thiols, albumin, and nutritional factors, including vitamins and phenols) and enzymatic (eg, superoxide dismutases, glutathione peroxidases [GSHPx], and catalase). The most important source of antioxidants is provided by nutrition. The most known systemic antioxidants are vitamin C, vitamin E, carotenoids, and trace elements copper and selenium.[16,17] There are also studies demonstrating that vitamins C and E combined with ferulic acid impart both a sunscreen and an antioxidant effect.

Photoprotection and UV filters

Because exposure to UV radiation plays a crucial role in skin aging, its reduction is the foremost measure in the prevention of photoaging. The reduction of skin exposure to UV radiation is accomplished by UV filters and depends on its composition in a sunscreen or day cream. The performance of a sunscreen can be calculated with the help of a simulation tool that is accessible on the Internet for free (www.basf.com/sunscreen-simulator). From a sunscreen manufacturer's point of view, the basic requirements for all UV filters used in sunscreens are:

- efficacy,
- safety,
- registration
- freedom-to-operate according to the status of intellectual property.[18]

The development of efficient molecules is a prerequisite before other aspects come into play. UV filters are classified into inorganic and organic, and most modern sunscreens contain a mixture of both (Table 2). The safety and efficacy of these products are mainly defined by:

- the type and concentration of the filters employed
- the formulation of the product.

Efficacy indicates that there is good absorbance in the spectral range of most interest for sunscreens, 290 to 400 nm. It also means that it is possible to incorporate the substance in sufficient amounts into cosmetic formulations.[18]

At present, all organic UV absorbers used in sunscreens possess aromatic moieties. The substitutions at the aromatic ring are of great importance for the UV spectroscopic properties.[19] The most frequently used inorganic UV filters are zinc oxide or titanium dioxide; they protect against UVB and UVA radiation and are photostable and water-resistant. There are micropigments with particle diameters in the range of 10 to 100 nm.[18] Topically applied micropigments should not pass the intact skin barrier and thus have a low potential to exert toxic effects. They are often used in combination with organic filters to achieve higher sun protection factors and a broader spectrum of protectionas well as to reduce the need for organic filters.

A major disadvantage of micropigments is their reflection of visible light, creating a "whitening" effect, which is cosmetically unfavorable. From the Galenic point of view, formulation of micropigments has a strong tendency to conglomerate, which greatly decreases its efficacy. Titanium dioxide and zinc oxide are also used at larger (>100 nm) particle sizes, which provide skin protection through both reflection and diffusion of visible light.

Table 2 European Commission–approved UV filters

Chemical name / International Nomenclature for Cosmetic Ingredients	Personal Care Europe (COLIPA) denomination	Maximum concentration in ready for use preparations in Europe, %	UV protection type	
			Broad spectrum and UVAI (340-400 nm)	UVB (290-320 nm) and UVAII (320-340 nm)
1-(4-tert-Butylphenyl)-3-(4-methoxyphenyl) propane-1,3-Dione / Butyl methoxydibenzoyl methane	S 66	5	+	–
3,3'-(1,4-Phenylenedimethylene) bis (7,7-dimethyl-2-oxobicyclo-[2.2.1] hept-1-ylmethanesulfonic acid) and its salts / Terephthalylidene dicamphor sulfonic acid	S 71	10 (as acid)	+	–
Phenol, 2-(2 H-Benzotriazol-2-yl)-4-Methyl-6-(2-Methyl-3-(1,3,3,3-Tetramethyl-1-(Trimethylsilyl)Oxy)-Disiloxanyl)Propyl / Drometrizole trisiloxane	S 73	15	+	–
2,2'-Methylene bis(6-(2 H-benzotriazol-2-yl)-4-(1,1,3,3-tetra-methylbutyl)phenol) / Methylene bis-benzotriazolyl tetramethylbutylphenol	S 79	10	+	–
Sodium salt of 2,2'-bis(1,4-phenylene)-1 H-benzimidazole-4,6-disulfonic acid / Disodium phenyl dibenzimidazole tetrasulfonate	S 80	10 (as acid)	+	–
2,2'-(6-(4-Methoxyphenyl)-1,3,5-triazine-2,4-diyl)bis(5-((2-ethyl-hexyl)oxy)phenol) / Bis-ethylhexyloxyphenol methoxyphenyl triazine	S 81	10	+	–
Benzoic acid, 2-[4-(diethylamino)-2-hydroxybenzoyl]-,hexylester / Diethylamino hydroxybenzoyl hexyl benzoate	S 83	10	+	–
2-Ethylhexyl 4-(dimethylamino)benzoate / Ethylhexyl dimethyl PABA	S 08	8	–	+
Benzoic acid, 2-hydroxy-, 3,3,5-trimethylcyclohexyl ester / Homomenthyl salicylate	S 12	10	–	+
2-Ethylhexyl salicylate / Ethylexyl salicylate	S 13	5	–	+
3-Methylbutyl (2 *E*)-3-(4-methoxyphenyl) acrylate / Isoamyl *P*-methoxycinnamate	S 27	10	–	+
2-Ethylhexyl 4-methoxycinnamate / Ethylhexyl MethoxycinnamateOctinoxate	S 28	10	–	+
2-ethylhexyl 2-cyano-3,3-Diphenyl-2-propenoate / Octoceylene	S 32	10	–	+
2-Hydroxy-4-methoxybenzophenone / Benzophenone-3	S 38	10	–	+
4-Hydroxy-2-methoxy-5-(oxo-phenylmethyl)benzenesulfonic acid / Benzophenone-4	S 40	5 (as acid)	–	+
2-Phenylbenzimidazole-5-sulphonic acid and its potassium, sodium and triethanolamine salts / Phenylbenzimidazole sulfonic acid Ensulizole	S 45	8 (as acid)	–	+
3-(4'-Methylbenzylidene)-dL-camphor / 4-Methylbenzylidene camphor Enzacamene	S 60	4	–	+
2,4,6-Trianilino-(*P*-carbo-2'-ethylhexyl-1'-oxy)-1,3,5-triazine / Ethylhexyl triazone	S 69	5	–	+
Dimethicodiethylbenzalmalonate / Polysilicone-15	S 74	10	–	+
Titanium dioxide	S 75	25	–	+
Benzoic acid, 4,4-{[6-[[[(1,1-dimethylethyl)amino]carbonyl]phe-nyl]amino]-1,3-5-triazine-2,4-diyl]diimino}bis-, bis(2-ethylhexyl) ester / Diethylhexyl Butamido Triazone	S 78	10	–	+

ZnO is not yet listed as a UV filter in Europe.
UV, ultraviolet.
Information is from http://ec.europa.eu/consumers/cosmetics/cosing/index.cfm?fuseaction=search.results&annex_v2=VI&search modified) and from Osterwalder et al.[18])

The two most frequently used chemical filters are ethylhexyl-methoxycinnamate and butyl-methoxydibenzoylmethane[18]; however, the combination of these filter molecules in the same product makes the filter system photounstable. Exposure to UV radiation causes photochemical reactions that generate reactive oxygen species, plus subsequent phototoxic and photoallergic skin reactions.

In recent years, considerable progress has been made in developing strategies that allow the photostabilization of UV filters. The last development in UV protection concerns organic UV filters, which have been approved for use in cosmetic products by the European Commission (Table 2, eg, S71, S73, S79, S80, S81, S83). They provide significant protection against UVA radiation.[18]

Topical pharmacologic agents with anti-aging properties

There are two main groups of agents that can be used as anti-aging cream components, antioxidants and cell regulators.[20,21] Antioxidants, such as vitamins, polyphenols, and flavonoids, reduce collagen degradation by reducing the concentration of free radicals in the tissues. Cell regulators, such as retinols, peptides, hormones (including growth factors), and botanicals except polyphenols, act directly on collagen metabolism and stimulate the production of collagen and elastic fibers.

Vitamins

Vitamins C, B3, and E are the most important antioxidants due to their ability to penetrate the skin through their small molecular weight.[22] The water-soluble, heat-labile local L-ascorbic acid (vitamin C) in concentrations ranging from 5% and 15% has a skin anti-aging effect that induces the production of collagen I and collagen III, plus enzymes important to the production of collagen and inhibitors of metalloprotease-1.[23] Clinical studies have proven that the antioxidative protection is higher with the combination of vitamins C and E than with vitamin C or E alone.[24] Niacinamide (vitamin B3) regulates cell metabolism and regeneration, and it is used in 5% concentration as an anti-aging agent.[22]

In some studies, improvement of skin elasticity, erythema, and pigmentations after 3 months of topical treatment has been observed. Vitamin E (α-tocopherol), used as a component of skin products, has antiinflammatory and antiproliferative effects in concentrations ranging from 2% to 20%. It acts by smoothing the skin and increasing the ability of the stratum corneum to maintain its humidity, to accelerate the epithelialization, and to contribute to the photoprotection of the skin. The effects are not as strong as with vitamins C or B.[25]

Polyphenols

The topical application of green tea polyphenols, such as epigallocatechin gallate, before UV exposure leads to an increase of the minimal erythema dose, decreases the number of Langerhans cells, and reduces DNA damage to the skin.[26] Other polyphenols that act as antioxidants are the isoflavones from soya[27] and α-lipoic acid.

α-Lipoic acid functions as an essential cofactor of the mitochondrial multienzyme complex and thus plays an important role in energy metabolism. It has a very sensitive chemical structure, rendering it vulnerable to UV radiation. Topically applied α-lipoic acid could achieve a reduction in facial lines, almost complete resolution of fine lines in the periorbital region and upper lip area, and overall improvement in skin color and texture.[28] This is achieved through enhancing type I collagen synthesis in the fibroblasts by activation of tumor growth factor-β; it also facilitates the expression of a collagen-processing enzyme, prolyl-4-hydroxylase.

In diabetic wounds, the application of antioxidants, such as epigallocatechin gallate, α-lipoic acid, and gold nanoparticles, reduces the receptor of advanced glycation end product protein expression in fibroblasts, increases the vascular endothelial growth factor, and decreases the CD68 expression, hence achieving angiogenesis, antiinflammatory effect, and antioxidant effects. This combination could accelerate the diabetic wound's healing.[29] α-Lipoic acid is also an effective coantioxidant agent for the stabilization of epigallocatechin gallate.[30]

Retinols

Vitamin A (retinol) and its derivatives (retinaldehyde and tretinoin) are a group of agents that also have antioxidant effects. They can induce the biosynthesis of collagen and reduce the expression of metalloprotease-1. Retinol is, at the moment, the substance that is most often used as an anti-aging compound and, compared with tretinoin, causes less skin irritation.[31] Retinol has positive effects on not only extrinsic but also intrinsic skin aging and has a strong positive effect on collagen metabolism. Tretinoin, a nonaromatic, first-generation retinoid, is approved in the United States for application as an anti-aging treatment in a concentration of 0.05%. It is able to reduce the signs of UV-induced early skin aging, such as wrinkles, loss of skin elasticity, and pigmentation.

Peptides

Polypeptides or oligopeptides are composed of amino acids and can imitate a peptide sequence of molecules, such as collagen or elastin. Through topical application, polypeptides have the ability to stimulate collagen synthesis and activate dermal metabolism.[32]

Idebenone is an organic compound of the quinone family. It is also promoted commercially as a synthetic analog of coenzyme Q_{10}. Clinically, it could reduce skin roughness and fine lines. Immunohistochemical investigations showed a decrease in interleukin-1β, interleukin-6, and MMP-1 and an increase in collagen I after 6-week topical application at concentrations of 0.5% and 1%.[33] Idebenone has a higher oxidative stress protection compared with α-lipoic acid and ascorbic acid. Allergic contact dermatitis is a limiting complication for its use.

Hormones

Aging-related decline in hormonal and vitamin levels raises hormone substitution as a therapeutic concept in the treatment of skin aging. Postmenopausal hormone substitution leads to improvement of the skin barrier and skin quality through preservation of the dermal collagen content and by improving cutaneous circulation and hair quality. Postmenopausal women respond well to hormone substitution when substitution is administered from the beginning of

menopause. In recent decades, not only systemic hormonal and vitamin substitution but also the topical use of hormones contributed as anti-aging agents.[34]

Estradiol

The role of estradiol as a systemic hormone replacement therapy on skin aging has been well-documented. Since the mid-1990s, the topical use of estradiol has been discussed.[35] Topical estradiol increases skin thickness and keratinocyte proliferation. It improves skin moisture through the induction of mucopolysaccharide and hyaluronic acid production; it also improves the skin's surface texture, skin microcirculation, and hair quality. 17-β-Estradiol was used in a 0.01% concentration and could increase the epidermal thickness, number of dermal papillae, fibroblasts, and vessels after 24 weeks of application. Although topical estradiol could induce collagen production in the sun-protected skin and counteract the chronologic skin aging, it failed in counteracting the effect of photoaging, as it neither induced collagen production nor reduced the production of metalloprotease-1 in photoaged skin.[36] Topical estradiol also improved functional skin aging, as it accelerated wound healing in humans of both sexes through estrogen-induced increase in latent tumor growth factor–β1 secretion by dermal fibroblasts.[37]

Progesterone

Progesterone 2% cream improves the elastic skin properties measured by skin elasticity parameters, counteracting different signs of aging in the skin of perimenopausal and postmenopausal women. It also reduces wrinkle counts and wrinkle depth and increases skin firmness. This is achieved by increasing the collagen I levels and reduction of metalloprotease-1 activity.[38] Progesterone, however, is highly absorbed in tissues; therefore, it is likely that the effects of topical application are systemic ones.

Dehydroepiandrosterone

Age-related changes in the circulating androgen levels influence the morphology as well as the key functions of the skin, such as epidermal barrier homeostasis, wound healing, sebaceous gland growth and differentiation, and hair growth. Androgen treatment has been proposed to be an effective way to reverse the age-associated deterioration of the skin functions. The local application of dehydroepiandrosterone markedly increased the expression of the androgen receptor, procollagen 1 and 3 mRNA, and heat hock protein 47—a molecule reported to affect procollagen—both on the protein and mRNA levels.[39] On the gene level, dehydroepiandrosterone modulated the genes involved in the proliferation and differentiation of keratinocytes, and it increased the expression of *collagen-1*, *b-collagen-3*, and *collagen-5* as well as the genes required for normal maturation and deposition of collagen fibers (*SPARC*). It also reduced the expression of genes associated with terminal differentiation and cornification of keratinocytes. The collagen-promoting ability of dehydroepiandrosterone is magnified by inhibition of UV-induced metalloprotease synthesis and stimulation of tissue metalloprotease inhibitor.

Other botanicals

Boswellic acids are pentacyclic triterpenes extracted from the gum resins of the tropical tree *Boswellia serrata*, which grows in Africa and India. They have well-known antiinflammatory and immunomodulatory activities as well as stimulatory effects on fibroblasts. A base cream containing 0.5% boswellic acid was found effective in treatment of clinical manifestations of photoaging of facial skin and in improving the extensibility firmness of the skin.[40]

Conclusions

Although natural aging is genetically determined, extrinsic aging can be prevented. Esthetic dermatology should contribute to healthy aging not only through cosmetic means by trying to erase time vestiges on the skin but also by playing a significant part in prevention, regeneration, and delay of skin aging, both by instrumental devices and invasive procedures and by combining knowledge of possible local therapy. Filling this particular lack of scientific investigations may become—with molecular knowledge and the detection of biomarkers—one of the important focuses of research on aging.[41–44]

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