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Review

Modern Approach to Topical Treatment of Aging Skin

Neira Puizina-Ivić[1], Lina Mirić[1], Antoanela Čarija[1], Dobrila Karlica[2] and Dujomir Marasović[1]

[1] Clinic of Dermatovenereology, School of Medicine, Split University and Split University Hospital Center, Split, Croatia
[2] Clinic of Ophthalmology, School of Medicine, Split University and Split University Hospital Center, Split, Croatia

A B S T R A C T

The main processes involved in skin aging are intrinsic and extrinsic. Apart from them, so called stochastic aging connotes cell damage caused by metabolic processes, free radicals and cosmic irradiation. The clinical expression of intrinsic aging include smooth, dry, and thinned skin with accentuated expression lines. It is inevitable and time dependent. Extrinsically aged skin shows signs of photodamage which include appearance of wrinkles, pigmented lesions, actinic keratoses and patchy hypopigmentations. Therapeutic modalities imply photoprotection with sunscreens that prevent sunburns and block ultraviolet irradiation. Other modalities include use of retinoids which regulate gene transcription with subsequent cellular differentiation and proliferation. The topical and peroral administration of »network antioxidants» such as vitamin E and C, coenzyme Q_{10}, alpha-lipoic acid and glutathione, enhance antiaging effect. The other antioxidants such as green tea, dehydroepiandrosterone, melatonin, selenium and resveratrol, have also antiaging and anti-inflammatory effects. Topical bleaching agents such as hydroquinone, kojic acid and azelaic acid can reduce signs of aging. Studies confirm the efficacy of these topical agents in combination with superficial and/or medium depth or deep peeling agents for photodamaged skin treatment. Indications for type of chemical peels according to various clinical diagnosis are done, as well as advantages and disadvantages of differetn types of chemical peels.

Key words: *skin aging, cosmeceuticals, antioxidants, retinoids, chemical peeling, antiaging procedures*

Introduction

More scientific data about antiaging has radically changed in the last decade. New discoveries contribute to efforts for making younger-looking skin. A youthful healthy appearance seems to be very important in modern society. So, many people feel anxiety about visible signs of aging and consequently seek dermatologic advice. These days, American women spend around 5 billion dollars a year on skin care products[1]. This generation of baby boomers have very proactive approach to reduce the signs of aging[2]. Due to better social, economic and healthy conditions, it is estimated that in the next 50 years, about one-third of women will be menopausal[1]. So, anti-aging medicine is of great importance[3]. Many people prefer a more economical or less invasive approach than for example botulinum toxin A, soft tissue augmentation and laser or chemical resurfacing. These less invasive treatments imply so called »cosmeceuticals« which have biologically active ingredients. The cosmeceutical phenomenon has had a deep impact on the beauty industry and also on dermatological practice[2]. From a regulatory perspective, cosmeceuticals do not really exist. It is a term used primarily for marketing purpose by cosmetic producers, because they can not claim drug-like ingredients for their product. Nowdays, cosmeceutical preparations contain a large list of »active ingredients« (Table 1)[2]. Majority of these substances do not fulfil Kligman's definition of efficacy such as proof of penetration, mode of action and evidence of clinical value. The ideal cosmeceutical product would mean that it has immediate and long-lasting results, as well as low side effect, good compliance which include good texture, pigmentation, laxity and easy applicability. It is important to point out that preventive benefits are also of great importance[2].

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Skin aging

All humans experience intrinsic aging. It is the result of accumulation of endogenous reactive oxygen species (ROS) and is time dependent. Reactive oxygen species damage cellular tissue and constituents such as lipid membranes, cellular enzymes and DNA. In the same time, it has strong genetic background and it is also under influence of decreasing sex hormone levels, though, premature facial wrinkling in women does not respond to hormone replacement therapy[3–5]. It seems that telomeres, terminal portion of eukariotic chromosome, which shortens with successive cycles of replication with subsequent progressive erosion, play very important role[3,6].

TABLE 1
COMMON AGENTS USED IN COSMETEUTICALS

Category	Ingredients	
Vitamins	Vitamin A (retinoic acid)	Vitamin E(alpha tocopherol)
	Vitamin B	Retinaldehide
	Vitamin B3 (niacinamide)	Retinol
	Niacinamide (nicotinamide) panthenol	Retinyl acetate
	Pro-vitamin B5 (panthenol)	Retinyl esters
	Beta caroten	Retinyl palmitate
	Vitamin C (L-ascorbic acid)	Retinyl propionate
Synthetic vitamins	Adapalene	
	Tazarotene	
	Tretinoin	
Minerals	Copper	
	Selenium	
	Zinc	
Antioxidants	Alpha-lipoic acid (ALA)	Glutathione
	Catalase	Idebenone
	Dimethylaminoethanol (DMAE)	Ubiquinone
Hydroxy acids	Alpha-hydroxy acids (glycolic,lactic,malic acids)	Lanolin
	Beta hydroxy acids (salicylic acid)	4-Oxo-retinoic acid
	Dihydroxyacetone	Polyhydroxy acids (gluconolactone, lactobionic acid)
	4-Hydroxy-retinoic acid	Salicylic acid
Lipids	Glucosylceramide	
Glycosaminoglycans	Hyaluronic acid	
Botanicals	Allantoin	Ginkgo biloba
	Aloe vera	Grape
	Arnica	Green tea
	Bearberry	Lavender
	Bisbolol	Papaya pomegranate
	Black tea	Sylimarin
	Capsaicin	Soy
	Ceramides	Tea tree oil
Botanicals	Chamomile	White tea
	Cinnamate	White wilow
	Ginseng	Witch hazel
Moisturizes	Acylceramide	Petrolatum
	Cholesterolum	Sodium PCA
	Linoleic acid	Squalene
Pigment lightening agents	Azelaic acid	
	Hydroquinone	
	Kojic acid	
Sunscreens	Anthranilate	Padimate O
		p-Aminobenzoic acid
	Padimate A	Tinosorb
	Mexoryl	

During skin aging, modifications of growth factors and hormones that decline, especially sex steroids such as estrogen, testosterone, dehydroepiandrosterone (DHEA) and its sulfate ester (DHEAS), as well as melatonin, insulin, cortisol, thyroxine and growth hormone, occur[3,7–9]. The levels of certain signaling molecules as cytokines and chemokines also diminish as well as the quantity of their receptors, yet the other molecules increase such as transforming growth factor-beta1, which induces fibroblast senescence[10]. These changes lead to different cellular response with subsequent decreased viability to exogenous factors or consecutive cell death[11]. Aged skin shows its characteristic such as dryness, atrophic changes, smoothness and laxicity. The histological appearance reveals no changes in stratum corneum and epidermis, keratinocyte shape and their adhesion. The number of melanocytes and Langerhans cells is decreased[5]. The dermo-epidermal junction is flattened with reduced surface contact between epidermis and dermis. As a result, exchange of nutrients and metabilites is reduced[5,12]. Blood supply is also decreased[13].

Extrinsic aging develops due to long-term ultraviolet (UV) and ionizing radiation, severe physical and psychological stress, alcohol abuse, poor nutrition, over-eating, environmental pollution and other agents. UV radiation shares 80% in extrinsic aging. It is the most important factor in premature aging[4,14].

The most of UVB (290–320 nm) rays are absorbed in the dermo-epidermal level. They damage DNA in keratinocytes and melanocytes. They are responsible for erythema, sunburn, DNA damage, hyperpigmentation, lentigines and occurrence of actinic keratoses and skin cancer. Acronymus for UVB damage is **B** like **b**urn, **b**ad or **b**ronzing.

On the other hand, UVA rays (320–400 nm) are more abundant in the atmosphere than UVB and are absorbed into the deeper part of dermis. So, they damage epidermis and dermis as well. It is well known that UVA radiation plays the most important role in pathogenesis of photoaging, although the mode of action remains unclear. So, the acronymus for UVA damage is ***A*** like **a**ging or **a**llergy[14,15]. Photoaged skin is characterized by alterations in dermal connective tissue such as strengthening and elastin substances accumulation[16–18].

Clinically photodamaged skin presents with coarse and fine wrinkling, motted pigmentary changes, textural roughness, and teleangiectasis. Histological changes of photoaged skin include significant epidermal and dermal alterations with increased or decreased epidermal thickness, loss of polarity of keratinocytes and their atypia. In the dermis elastosis, degeneration of collagen fibriles appear. Blood vessels become dilated. Ultraviolet exposure activates degrading enzyme for collagen and elastic tissue such as matrix metalloproteinases (MMPs). Cytokines are released from keratinocytes, and cumulative effect of these changes is chronic dermal inflammation[15,19,20]. The induction of MMPs can be reached within minutes after UVB radiation. Pretreatment of the skin with tretinoin during autumn, winter and early spring period inhibits activation of MMPs in UVB exposed skin[21].

Smoking is very important factor of premature aging. It activates production of MMPs with subsequently »smoker's face» or »cigarette skin». The skin is characteristically ashen and shows grey colour with increased number of wrinkles[22–24]. Corneal layer is also reduced, as well as quantity of A vitamin[4,25,26]. Chemical compounds such as nitrogen oxides or organic compounds from fuel combustion together with UV irradiation also are responsible for skin damage[27].

In the skin there are also natural protectives such as melanin in lower part of epidermis and the protein-urocanic acid in stratum corneum. They absorb and reflect significant amount of UVB irradiation. It seems that thickness of stratum corneum is more important for photoprotection than pigmentation or total thickness of epidermis[28].

Photoaging affects all races and skin types. The manifestation of photodamage may differ in lighter skin types compared with darker ones. Persons with fair skin and hair (type I, II and III according to Fitzpatrick) will obtain much more degenerative changes than type IV and V, because their melanosomes in higher parts of epidermis and corneal layer more efficiently protect epidermal and dermal structures from UVA and UVB. In contrast to lighter skin types, clinical experience document that persons with dark skin show less wrinkling than lighter-skinned individuals[29–33]. Clinical photodamage in black skin appears to be a subtle phenomenon which manifests as diffuse or patchy hyperpigmentation and texturally rough skin. Also, there is significantly lower incidence of skin cancer among this population[34,35]. Since the number of melanocytes decreases every 10 years for 8–20%, photoprotection is recommended, especially in older persons[3].

The degree of photodamage is classified according to Glogau based on the extent of skin changes. There are four degrees ranging from mild, moderate, advanced and severely photodamaged changes. Depending upon degree of damage, anti-aging treatment can be recommended[3,34,36]. Mild photodamage will respond to topical anti-aging products and superficial chemical peels. Moderate to advance photodamage has excellent response with medium-depth peel. Severe photodamage requires medium-depth or deep peeling procedures in combination with lifting or rhytidectomies[37].

Therapeutic Modalities

Topical therapeutic modalities imply photoprotection, use of retinoids and topical antioxidants such as C vitamin, bleaching agents and peels with alpha-, beta- and polyhydroxy acids. Resurfacing procedures are microdermoabrasion, superficial chemical peeling, medium-depth peeling, ablative and non-ablative laser resurfacing, radio frequency therapy and face lifting procedures (Table 2)[1].

TABLE 2
THERAPEUTIC APPROACH FOR TREATMENT OF PHOTODAMAGE

Topical agent	Sunscreens of broad spectrum
	Retinoids
	Tretinoin
	Tazarotene
	Retinol
	Vitamin C, Alpha hydroxy acids, Beta hydroxy acids, Polyhydroxy acids
	Bleaching agents
	Hydoquinone
	Kojic acid
	Azelaic acid
	Arbutin
	Licorice
Resurfacing procedure	Microdermabrasion
	Superficial chemical peeling
	Medium-depth peeling
	Deep peeling
	Ablative laser resurfacing
	Nonablative laser resurfacing
	Radio frequency
	Facial lifting procedures

Photoprotection

Photoprotection means avoidance of sun exposure when it is possible by wearing protective clothing, glasses and daily use of sunscreens[3,4,38–41]. Sunscreens are the gold standard for skin protection from UV rays. They were initially synthesized to prevent UVB induced sunburns. But in the last 10–15 years, agents have been formulated that can absorb and/or block UVA irradiation[39]. Sun-protecting agents are classified as organic or physical blocking agents. Organics agents protect by absorbing UVA and/or UVB rays. Chemical ingredients in sunscreens are: octyl-dimethyl-PABA (UVB), 2-ethylhexyl-p-methoxycinnamate (UVB), octocrylene (UVA/UVB), octyl salycilate (UVB), benzophenones (UVA/UVB), and methyl anthranilate (UVA). Avobenzone or Parsol 1789 block UVA, but can induce photoallergic reaction. Many producers combine ingredients in order to maximize photoprotection[1,39]. Their combination in the same product renders the whole filter system photo-unstable which means that UV exposure causes photochemical reactions that generate ROS with subsequent phototoxic and photoallergic reactions[1,3]. The great efforsts have been made to stabilize molecules in UV filters[1,3]. The sunscreen ingredients should absorb or reflect and scatter during the period of photo-protection, and thus should remain stable photochemically. Many chemical filters have some photoreactivity, leading to formation of photoproducts that might act as a light filters. Photostability depends on the filter itself, on the presence of other filters in the product and on solvents or vehicle. Many UV filters such as avobenzone octinoxate and octyl dimethyl PABA, are photolabile. Other UV filters are frequently used in the sunscreens as they are known to increase the photostability of the final product. These agents are zinc and titanium oxide, the salicylates and methylbenzylidene camphor. There are some new agents that are photostable such as terephthalylidene dicamphor sulphonic acid (Mexoryl SX) drometriazole trisiloxane (Mexoryl XL), methylenebis-benzotriazoyl tetramethylbutylphenol (Tinosorb M) and bis-ethyl-exyloxyphenol methoxyphenol triazine (Tinosorb S)[39]. Mexoryl is the most efficient chemical blocking agent for UVA[38,39]. They reflect UVA and UVB. Applied on the skin, they induce white or ashen color, so called »ghost« effect which is for the most patients unacceptable[3,4,42]. Nowdays, micronized formulations of these agents are available with subsequent much more better compliance by the patient. Sunscreens must be used weeks before and months after chemical peeling procedures[4].

Retinoids

Initially, the definition of retinoid was a compound whose structure and action resembled the parent compound, vitamin A. Last several decades, chemists made extensive modifications of the molecule that resulted in the development of three generations of retinoids (Table 3)[4]. There are over 125 distinct dermatologic disorders for which there is credible evidence of retinoid efficacy[43]. The latest retinoids bear little structural resemblance to retinol but they are qualified as retinoids because they share one or more functions with the parent compound. Retinoids mediate cellular response through regulating gene transcription and affecting activities such as cellular differentiation and proliferation[4]. They activate two types of nuclear retinoid receptors: the retinoic acid receptors (RARs), and retinoid X receptors (RXRs). Each of them contain three subtypes: alpha, beta and gamma[4,44,45]. All of these receptors are members of a large superfamily called nuclear hormone superfamily receptors which includes receptors for vitamin D, estradiol, glucocorticoids and thyroid hormone. Ninety percent of the RARs in the epidermis are RARγ, which are receptors responsible for terminal differentiation. So, they are target used in dermatology[4]. Recent evidence suggest that aside of its therapeutic role, retinoids also prevent photoaging because of

TABLE 3
THREE GENERATIONS OF RETINOIDS FOR THE TOPICAL TREATMENT OF AGING SKIN

I generation	tretinoin
	retinal
	isotretinoin
II generation	etretinate
	acitretin
III generation	adapalene
	arotenoid
	tazarotene
	alitretinoin

its inhibitory effects on MMPs. Pretreatment of the skin with topical retinoids was shown to inhibit loss of procollagen synthesis[4]. Among commonly prescribed drugs retinoids, such as tretinoin activates the RARs (α, β and γ) directly, and RXRs indirectly. On the other hand, tazarotenic acid, the tazarotene metabolite, binds selectively to RARs (β and γ), and is unable to directly or indirectly activate RXRs[46,47]. Consequently, it is likely to be less irritating than tretinoin[48]. The difference in their activity can explain the varying efficacy of different retinoids in topical dermatologic therapy. It is also important to emphasize that retinoids increase the depth and penetration of peeling agent[38]. Several studies documented the efficacy and safety of tretinoin in treatment of photodamage[49–51]. There are two concentrations: 0.1% and 0.025%, and there is no difference in these two formulations concerning the improvement of skin aging, but 0.1% produces higher degree of irritation[38]. Skin treated with 0.1% tretinoin showed increase in type I collagen formation in comparison with skin treated with vechicle. With colorimetric analysis, significant lightening of hyperpigmentation after tretinoin treatment was demonstrated[38]. Tazarotene is synthetic retinoid, pro-drug of tazarotenic acid which is effective for photodamaged skin. It improves wrinkling, lentigines, elastosis, irregular depigmentation and roughness like tretinoin does[44]. Retinoids are also well tolerated in dark pigmented skin, but they may cause post-inflammatory hyperpigmentation, although hyperpigmentation can occur after treatments with retinoids without evidence of irritation[38].

Retinol is also a first generation retinoid, that must be converted to retinaldehyde and then to all-trans re-

TABLE 4
ADVANTAGES AND DISADVANTAGES OF DIFFERENT TYPES OF CHEMICAL PEELS

Type of peeling agent	Advanatage	Disadvanatage
Glycolic acid	– very mild erythema – mild desquamation – short post–operative period	– neutralization is mandatory – burning sensation and erythema during application – no uniformity of application – necrotic ulceration depend upon the time of application – cautions in patients with active acne
Jessner's solution	– excellent safety profile – all skin types (III and IV) – enhance penetration of TCA	– resorcinol toxicity (thyroid dysfunction) – manufacturing variations – instability with exposure to light and air – increased exfoliation in some patients, scarring
Pyruvic acid	– very mild erythema – mild desquamation – short post-operative period – all skin types (III and IV)	– neutralization is mandatory – intense burning sensation during application – irritating vapors for upper respiratory mucosa
Resorcinol	– easy to perform – uniformity of application – uniformity of penetration – useful in acne, melasma – useful against postinflammatory hyperpigmentation – not painful	– desquamation is aesthetically unacceptable – unsafe in dark skin type – is not used in summer – might be a sensitizing and toxic agent
Salicylic acid	– safety profile for types I–VI – excellent for acne patients – white precipitation – an anesthetic effect – subsequent better tolerance	– limited depth of peeling – minimal efficacy in significant photodamage – scaling
Tricloracetic acid	– low-cost procedure – uniformity of application – uniformity of penetration – easy modulable	– burning and stinging sensation during application – high concentrations not good in skin types V and VI – hypo/hyperpigmentation can occur – scaring – no neutralisation possible
Phenol	– useful in severe photodamage – useful for deep wrinkles – useful for atrophic acne scars – for facial rejuvenation – the strongest option	– cardiotoxicity, nephrotoxicity – hypopigmentation after repeated procedures – stand-by anaesthesist – demarcation lines

TABLE 5
INDICATIONS OF CHEMICAL PEELS ACCORDING TO VARIOUS DIAGNOSIS

Diagnosis	Type of chemica peel
Photoaging	Mild to moderate:
	– glycolic acid 50–70%
	– trichloracetic acid 50%
	– salicylic acid 20–30%
	– salicylic acid 25% + trichloracetic acid >25% gel
	Severe:
	– glycolic acid 70% + trichloracetic acid 35%
	– Jessner's solution + trichloracetic acid 35%
	– pyruvic acid 60–70%
	– phenol 45–80%
Solar lentigines	– trichloracetic acid >25%
	– salicylic acid 25% + trichloracetic acid 25–30% gel
	– pyruvic acid 50–70%
	– phenol 45–80%
Actinic keratoses	– trichloracetic acid >30%
	– pyruvic acid 50–60%
	– salicylic acid 25% + trichloracetic acid 25–30% gel
Melasma	– salicylic acid 25%
	– salicylic acid 25% + trichloracetic acid 10% gel
	– trichloracetic acid 15–20%
	– pyruvic acid 40–50%
	– glycolic acid 50–70%
	– resorcinol
Post-inflammatory pigmentation	– salicylic acid 20–30%
	– glycolic acid 70%
	– Jessner's solution
	– pyruvic acid 40%
Rosacea	Erythrosis:
	– salicylic acid 15–25–30%
	Papulo-pustular rosacea:
	– salicylic acid 25–30%

tinoic acid within keratinocytes to become active[52]. Today it is classified as a cosmetic substance rather than drug. It is now found in many over-the-counter formulations[53]. Patients treated with retinol products were said to have significant improvements in skin texture, clarity and hyperpigmentation. Application of retinol produces histologic and molecular alteration that is very similar with results after retinoic acid application[53].

Antioxidants

In cosmetic industry there are lot of antioxidants, which are used for protective role enhancing antiaging effect, but the most currently used in cosmetic industry are »network antioxidants«. They are used because they work synergistically and regenerate and enhance the power of each other[54]. The five network antioxidants known at this time are vitamins C and E (tocopherol), glutathione, lipoic acid and coenzyme Q10 (ubiquinone). Vitamin C or coenzyme Q10 can recycle vitamin E, donating electrons to vitamin E to return the compound to its antioxidant state. Vitamin C and glutathione are recycled by lipoic acid or vitamin C[4]. Antioxidants are divided in three groups: fat-soluble, water-soluble and fat- and water-soluble antioxidants[55].

Fat-soluble antioxidants are found in the lipophilic portion of the cell membrane and include vitamin E and coenzyme Q10. Vitamin E is found in vegetables, oils, seeds, nuts, corn, soy, whole wheat flour, margarine and some meat and dairy products. Protective effect of orally administered vitamin E is achieved with 22–400 IU daily. The potency of vitamin E is increased through combination with other antioxidants. Side effects of topically applied vitamin E are contact dermatitis, papular and follicular lesions, contact urticaria, eczematous dermatitis and erythema multiforme-like reactions. Vitamin E has a blood-thinning effect, and patients on anticoagulant therapy should avoid high doses of vitamin E[55]. Coenzyme Q10 is found in fish and shellfish. The current recommended oral dose is 90–150 mg daily. Oral Q10 supplementation is associated with caffeine-like side effects and may cause nervousness, diarrhea and insomnia. So, it is recommended that Q10 should not to be taken at night[56].

The antioxidant known to be soluble in water and fat is lipoic acid (formerly called thioctic acid). It is essential co-factor in mitochondrial dehydrogeneses[57]. It is a potent antioxidant and systemically administered influences in the glucose control preventing chronic hyperglycemia-associated complications such as diabetes mellitus, Alzheimer disease, cataracts, HIV activation and radiation injury[4,59]. It is suggested to use 25–500 mg daily[4,58,59].

Water soluble antioxidants are found in hydrophobic areas of the cell and the serum. They are vitamin C (ascorbic acid) and glutathione. Glutathione is the most abundant antioxidant in the »network«. It is produced from aminoacids as glutamic acid, cysteine and glycine. Oral glutathione is not well absorbed in the body, and supplementation is difficult and not available. The other antioxidant vitamin C is well known. Oral vitamin C is associated with decreasing risk of certain cancers, cardiovascular disease and cataracts and with improving wound healing and immune modulation[60]. Unfortunately, there are no studies that demonstrate that ingestion of oral C vitamin increase the levels of vitamin C in the skin[4]. Topically administered vitamin C prevents some effects of sun damage and is applied for the treatment of melasma and reduction of postoperative erythema in laser patients[61]. But it must be stressed that topical vitamin C products must be formulated properly and stored in light-resistant containers to be effective. Ascorbic acid can be formulated into water- or lipid-soluble forms. A lipid form of topical ascorbyl palmitate, is nonirritating and anti-inflammatory, but many available topical preparations are unable to penetrate the stratum corneum due

to lipophobic nature of vitamin C[4]. The problem with vitamin C is also lack of stability after opening of container and contact with air and UV radiation, so, the most of preparations become inactive within hours of opening the bottle[4]. Oral supplements are superior. As vitamin C improves existing wrinkles, the mechanism must be rather its effect on collagen synthesis than its antioxidant effects[4,62].

In the group of other antioxidants, there are green tea, dehydroepiandrosterone (DHEA), melatonin, selenium and resveratrol. Green tea is a popular beverage in Asian countries. The antioxidant effects of green tea are due of the polyphenolic compounds contained. They are known as epicatechins. Polyphenols are molecules with two adjacent hydroxyl groups on a benzol ring. They are found in numerous foods like white and red wine, black or the before mentioned green tea, fruits (extract from grape seeds) and vegetables[1]. Topically or orally administered they inhibit chemical carcinogens or UV induced skin carcinogenesis and have anti-inflammatory effects[63,64]. DHEA is belived to be the potent antioxidant, but its antioxidant abilities still have to be proven. It stimulates the immune system. Secretion of DHEA and its sulfate ester decrease with age. Patients treated with DHEA experienced increase sebum production, skin surface hydration, epidermal thickness and decreased facial pigmentation. Because it is a new product among the antiaging treatment options, little is known about the effects of long term use. Endogenous DHEA concentrations reach peak at age 20 to 30 years. So, use of DHEA in the age under 35-year has some risk. A manic episode in a young man is recorded[4]. Melatonin is hormone, which is secreted by the pineal gland. It is a free radical scavenger and increases the efficacy of other antioxidants. It protects membrane lipids and nuclear DNA from ROS oxidative damage. It is available in an oral form, but not topically[62,4]. Resveratrol is a polyphenolic phytoalexin compound found in the skin and seeds of grapes, peanuts, berries and red wine. It exists in two isomeric forms: trans-resveratrol, that is more stable form, and cis-resveratrol. It has antiproliferative and anti-inflammatory properties against various cancers, including skin cancer. It has inhibitory effect on events associated with tumor initiation, promotion and progression by triggering apoptosis in tumor cells[4]. It seems that data and clinical evidence are promising to regard resveratrol in various products such as emollients, patches, sunscreens and other skin care products[4].

Bleaching agents

Topical bleaching agents include hydroquinone, kojic acid, azelaic acid, and agents that are added to cosmeceuticals such as arbutin, licorice, soy extract, ellagic acid, resveratrol and unsaturated fatty acids[65].

Hydroquinone is a very effective bleaching agent used in the tretment of post-inflammatory hyperpigmentaion, melasma, photoaging, freckles and lentiginosis. It is often used in combination with retinoids and chemical peeling agents in order to reverse signs of photoaging[38]. It inhibits tyrosinase and prevents conversion of tyrosine to DOPA[66,67]. Long-lasting repeated application can damage melanosomes as well as melanocytes[66]. It is usually well tolerated in concentrations of 2%. In Europe it is rarely sold in concentration of 4% without prescription[68]. A very potent formulation based on combination of 4% hydroquinone, 0.05% tretinoin and 0.01% fluocinolone improves signs of photoaging and post-inflammatory hyperpigmentation[4]. Side effects of hydroquinone treatment might be acute or chronic. Acute reactions are allergic contact and irritant dermatitis with subsequent temporary post-inflammatory hyperpigmentation. A chronic side effect is ochronosis in dark skinned patients characterized by reticulated hyperpigmentation of the face. It is often permanent[69].

Kojic acid is a fungal derivative that inactivates tyrosinase by chelation of copper, but it is less effective than hydroquinone. It is often used in concentration of 2 to 4%. It can be used in combination with retinoids and glycolic acid usually in patients who do not tolerate hydroquinone, or after longterm teatment with hydroquinone[38].

Azelaic acid was created for acne treatment, but it showed quite mild therapeutic effect in treatment of hyperpigmentation, freckles and lentigines. Its effect is probably mediated by inhibition of mitochondrial oxydoreductase activity and DNA synthesis as well as by disturbing of tyrosinase synthesis. It might be used in patients sensitive to hydroquinone[4].

Chemical peels

According to the degree of photoaging, several agents can be utilized to obtain superficial, medium-depth or deep peeling of the skin.

Mild to moderate photodamaged skin is treated with several superficial peeling agents such as alpha hydroxy acids (AHA) in concentrations of 50–70%, or 50% thrichloracetic acid (TCA). They stimulate collagen production. Salicylic acid 20–30% and pyruvic acid 40–70% also showed beneficial results in treatment of advanced photodamage of the neck and chest. Only irritation of upper respiratory mucosa due to vapors of pyruvic acid and intense stinging are reported disadvantages[70,71].

TCA and phenol are used in the treatment of advanced photodamage. TCA in concentrations above 35% has sometimes doubtful result as is quite unpredictable. On the other hand, phenol peeling can cause serious cardiac arrhythmias[38]. Combination of various agents are recommended to enhance the efficacy of each other. So, AHA 70% or Jessner solution with prior TCA 35% damages epidermal layer and enhance penetration of TCA in deeper part of skin. So, combinations of AHA and TCA 35% is superior for the treatment of actinic keratosis in comparison with Jessner solution and TCA 35%[72]. Histological specimens revealed decreased elastic fibers, increased activity of fibroblasts and better collagen fibrile organization. Also, 5% fluorouracil might be combined with Jessner solution and TCA in severely UV-damaged skin with actinic keratoses[73]. Advanatages and disadvan-

tages of commonly used peels in practice are presented in the Table 4, as well as instructions about the type of chemical peels according to diagnosis and indication (Table 5)[1].

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N. Puizina-Ivić

Clinic of Dermatovenerology, Split University Hospital Center, Šoltanska 1, 21 000 Split, Croatia
e-mail: neira.puizina@kbsplit.hr; neira@radogost.com

SUVREMENI NAČINI LIJEČENJA STARENJA KOŽE

S A Ž E T A K

Temeljni procesi uključeni u starenje kože su posljedica djelovanja čimbenika iz okoliša te nasljeđenih činitelja. Pored toga, tzv. stohastičko starenje dovodi do staničnog oštećenja uzrokovanim metaboličkim procesima, slobodnim radikalima i kozmičkim zračenjem. Klinička slika starenja kože uzrokovanog nasljeđem ili protokom vremena, uključuje glatku i tanku kožu s naglašenim linijama boranja. Starenje kože zbog djelovanja čimbenika iz okoliša uključuje znakove fotooštećenja kože kao što su pojava bora, pigmentiranih lezija, aktiničkih keratoza i mrljastih hipopigmentacija. Zaštita od ultravioletnog (UV) zračenja te upotreba antioksidansa kao što su vitamin E i C, koenzim Q_{10}, alfa lipoična kiselina i glutation, mogu reducirati znakove starenja kože. Brojne studije potvrđuju učinkovitost primjene topičkih agensa u kombinaciji s površnim i/ili srednje dubokih i dubokih peelinga u prevenciji fotooštećenja kože.