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Review article ■

Oxidative Stress, Skin Aging and Antioxidant Therapy

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SUMMARY

Skin aging is a dynamic process that occurs due to chronological and photo-aging caused by the influence of external factors, especially ultraviolet-UV radiation. Cumulative oxidative stress, formation of free radicals and their adverse effects on biological systems in the skin cells is a common mechanism of both skin aging processes. The formed reactive oxygen species-ROS can lead to the oxidation of cell`s building molecules. Lipid peroxidation, membrane protein damage and DNA mutation may lead to many structural, functional and aesthetic changes in the skin and can also initiate development of many diseases.

One of the skin defense mechanisms is antioxidant defense where enzymes and other antioxidant substances react directly with ROS, preventing them from reaching their biological target. Antioxidant substances have the ability to bind free radicals, caused by oxidative stress, and may have significance in prevention and/or therapy of various skin diseases, as well as in slowing the skin aging process. Topical application of antioxidants, such as vitamin C and E, coenzyme Q10 and polyphenolic compounds may provide the strengthening of the skin endogenous protection system and protection from harmful effects of ROS and oxidative damage to the skin.

This article outlines the impact of oxidative stress on the chronological and photo-aging, its mechanism of action, the changes that occur on/in the skin during the aging process. Substances with antioxidant characteristics, which can be used in the prevention of chronological and/or treatment of photo-aging of the skin are shown.

Key words: **oxidative stress, chronological and photo-skin aging, topical antioxidants**

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INTRODUCTION

Skin aging, both intrinsic and extrinsic, is a dinamic process which depends on many endogenous and exogenous factors, and results in a variety of functional and aesthetic skin changes (1). It occurs through two independent, different biological mechanisms: chronological aging and photoaging (2). It has long been believed that photoaging is the accelerated process of chronological aging, leading to clinically visible skin changes. Over time, the difference between internal/chronological aging and photoaging has become evident and the two states were qualitatively and quantitatively separated (3). Chronological aging is genetically determined, while photoaging is a process of serious microscope changes occuring in the stratum corneum (SC) due to chronic and repeated exposure to the ultraviolet (UV) light (4).

UV radiation can induce the production of reactive oxygen species (ROS) leading to the accumulation of oxidative damage and oxidative products, which are markers of oxidative stress (1, 2, 5). Damage caused by ROS is one of the most important mechanisms that leads to skin aging (2). The skin is a very good metabolic tissue and, as the largest organ in the human body, has a protective role (6). Moreover skin is also a major candidate and target of oxidative stress. It is rich in lipids, proteins, carbohydrates, DNA and all of these molecules are highly susceptible to oxidative processes and the effects of ROS caused by oxidative stress (7).

The structure of the skin is quite complex, since it is composed of several layers, each having a specific role and function (8). Each layer is equipped with a large number of defense molecules in order to cope with increased oxidative stress. During the evolution, skin adapted itself in order to cope with the increased concentration of oxygen and oxygen metabolites, since it is constantly exposed to oxidative stress (1). One of the effective skin defense mechanisms is antioxidant defense (6, 8) where enzymes and antioxidant substances react directly with ROS, preventing them from reaching their biological target (6).

Since photoaging is the aging influenced by external factors, mainly by UV radiation, it can be prevented and regulated to maintain the redox balance of cells in the skin. Chronological aging and photoaging are the primary "indicators" for the application of various antioxidants in a variety of skin care products. Antioxidant activity of a large number of vitamins/provitamins, including vitamin E, vitamin C, coenzyme Q10 and phenolic compounds from plant extracts in topical formulations, may reduce the harmful effects of ROS and oxidative stress and prevent or treat clinical signs of skin aging. Cosmeceuticals, with applicable topical antioxidants, play an important role in skin care in the prevention and treatment of skin aging, both chronological aging and especially photoaging of the skin (9).

This review article outlines the chronological aging and photoaging of the skin from the standpoint of oxidation and changes in the skin, as well as possible topical antioxidant therapy applying compounds that may have or already have the potential to prevent or improve the appearance of photoaged skin in different skin care products.

PHOTOAGING AND CHRONOLOGICAL AGING OF THE SKIN

The aging process is the subject of many studies, but all the theories could be classified into two groups: genetic and damage theories. In contrast to chronological (intrinsic) aging, which is largely genetically determined, depends on passage of time and is inevitable, photoaging (extrinsic aging) depends on degree of sun exposure and individual skin pigmentation and, and it is avoidable (2).

Many studies of skin photoaging due to oxidation provide much information about the decline of the level of activity of antioxidant enzymes and antioxidant defense capacity, which all together lead to the accumulation of oxidative damage and oxidative products, immunomodulation, stimulation of melanogenesis and carcinogenesis (2). These oxidative products are markers of oxidative stress (5).

Various theories and studies suggest that aging is a result of cumulative oxidative stress caused by free radicals generated in biological systems (9). Photons of UV have enough energy to produce this radicals (10). Products of lipid peroxidation, lipid radicals and other free radicals are present in the skin, and irritated by UV radiation they continue to lead to oxidative stress in the skin (11). Oxidative stress plays an important role in the modulation of the extent of inflammatory response and subsequent tissue damage, and in the appearance of different structural and functional changes in skin proteins, e.g. in collagen and elastin (9).

At the cellular level, UVA radiation mainly causes oxidative stress, in which ROS plays a major role. As a result of this stress, cells respond to UVA damage with modified gene expression, DNA damage, which eventually results in abnormal cell morphology, cell apoptosis or necrosis, and skin aging (12). In addition to direct photochemical reactions, UVB leads also to high levels of ROS in the skin, resulting inphotooxidative damage of the cells and extracellular matrix (13). Some evidence suggests that ROS within cells act as secondary messenger in intracellular signaling cascades that induce and maintain the oncogenic phenotype of cancer cells (14).

MECHANISM OF SKIN AGING

The accumulation of ROS and damage caused by ROS is one of the most important mechanism that leads to cellular aging (2). Important oxygen metabolites, whi-

ch can cause biological damage to the skin or initiate the formation of more reactive metabolites include superoxide radical, hydrogen peroxide, hypochlorous acid, hydroxyl radicals, nitric oxide radicals and singlet oxygen (6, 15).

There are many potential target molecules in the skin layers that may be candidates for oxidative stress, such as lipids, proteins, carbohydrates and DNA (6, 16). A large number of chemical reactions can occur between ROS and these potential target molecules.

The oxidation induced by ROS may result in lipid peroxidation, membrane protein damage and DNA mutations which play an important role in aging and can further initiate or propagate the development of many disease (15). Lipid peroxidation process can lead to the changes in plasma membrane fluidity and molecules leakage, and consequent disruption of their primary roles (6). Recently published results indicate that the process of lipid peroxidation is intensified in the skin epidermis with aging, as well as phospholipase activity which results in the violation of integrity of cell membranes (2). ROS can also directly inactivate enzymes and cause protein degradation (7). Action of ROS on DNA leads to DNA lesions (base loss, base modifications and single and double DNA breakage events), which can all result in various adverse processes and even cancer (6).

Despite the fact that skin epidermis possesses an extremely efficient natural antioxidant defenses, including different types of antioxidant enzymes in the skin, such as peroxidase, catalase and glutathione, the protective effect that these offer may be limited by a high production of ROS, generating cellular oxidative stress as a result of the imbalance between antioxidant and oxidant species of living organisms, and this reduction may be the cause of skin aging. Therefore, antioxidants with free radical scavenging activities may have great significance in the protection and therapeutics of age-related diseases involving free radicals (15-17).

Skin aging involves progressive skin changes. Morphological changes are accelerated with advancing age and the application of oxidative stressors. Histopathologically, there is a loss of epidermal polarity and physiological disorders of keratinocyte maturation (18). Cell population of photoaging dermis changes: fibroblasts become elongated, decayed, hyperplastic and infiltrated by inflammation; elastin quantity decreases with age, even more in the skin exposed to radiation, proportionally to the amount of radiation (3). Photodamage manifests primarily as the disorganization of fibroblast collagen, which forms the connective tissue (1). One study has demonstrated that old fibroblasts are more vulnerable to the accumulation of ROS following oxidative stress and are unable to remove them as efficiently as young fibroblasts (19). Changes in the skin that occur due to aging are shown in Table 1.

SKIN DEFENCE MECHANISMS AGAINST OXIDATIVE STRESS

It is very well known that the skin possesses an antioxidative system for oxidative stress reduction and maintenance of cellular redox balance (20). In order to cope with constant and excess efflux of damaging reactive metabolites, the skin has developed several lines of defense (8). Various defense mechanisms are shown in Table 2.

In defense against oxidative stress, the skin engages all of these four mechanisms: reparation, prevention, stabilization and, as an important defense mechanism, antioxidant defense (6, 8) where enzymes and scavengers react directly with ROS, preventing them from reaching their biological target. The antioxidant defense mechanism is shown in Table 3.

Table 1. *Components of the skin: function and changes with aging (Date from Rabe et al. with modifications (1))*

Cell type/component	Function	Change with age
Keratinocytes	Barrier function, mechanical protection, cytokine production	↓barrier function, ↓proliferation and differentiation
Melanocytes	Synthesize pigment for protection from UV radiation	↓melanocyte number, ↓life span
Fibroblasts	Synthesis and degradation of ECM	↓in number
Collagen	ECM component	↓biosynthesis, ↑stability and resistance to enzymatic degradation
Elastin	ECM component	↓microfibril content, porous, indistinct, and fragmented

ECM (extracellular matrix), UV (ultraviolet)

Table 2. *The defense mechanisms of the skin against oxidative stress (Date from Kohen with modifications (6))*

Defense mechanisms of the skin			
1. Repair systems	2. Prevention mechanisms	3. Physical defenses	4. Antioxidant defenses
DNA repair enzymes	Prevention of the production of ROS (chelating agents)	Stabilization of biological sites (membranes)	Enzymes, „scavengers“

Table 3. *Antioxidant defense systems of living cells (Date from Kohen with modifications (6))*

Antioxidant defense system
Enzymes
- Direct acting enzymes (e.g. SOD, CAT, peroxidase)
- Supporting enzymes (e.g. xanthine oxidase)
LMWA (Law Molecular Weight Antioxidants)
- Direct acting LMWA (scavengers)
• Synthesized by the cell
• Waste products
• Dietary sources (e.g. tocopherols, ascorbic acid, carotene, coenzyme Q10, polyphenols)
- Indirect acting LMWA (chelating agents)

Previous studies have indicated the presence of several important antioxidant enzymes: glutathione-peroxidase (GPx), glutathione-reductase, superoxide-dismutase (SOD) and catalase (CAT) in epidermis. SOD and CAT are the most important antioxidant systems that protect the epidermis (2). SOD converts superoxide anions into hydrogen peroxide, whereas CAT catalyzes the decomposition of hydrogen peroxide to water and oxygen (8).

A highly effective antioxidant system, besides the action of groups of antioxidant enzymes, involves the effects of small molecules that can donate electrons and thus "clean" a reactive oxygen metabolite. A group of small molecules, low molecular weight antioxidants (LMWAs), in the skin is composed of lipophilic and hydrophilic LMWAs. They are situated in all skin layers, including the dermis and epidermis, which indicates their significance and their relative sensitivity to oxidative stress. It has been found that the skin releases LMWAs in certain years in a certain dependent manner. A significant decrease in the levels of secreted LMWAs is found in older skin, which indicates a very low antioxidant activity. This secretion may allow determination of the skin status and its ability to cope with oxidative stress (6).

Photoaging may result in suboptimal protection against cumulative stress from free radicals during chronic and repeated UV radiation and it is necessary for the skin to provide additional topical therapy using various non-enzymatic antioxidants in various cosmetic products (9). Presence of bioactive natural compounds that maintain the balance in biological systems plays an important role in prevention of age- and oxidative stress-related diseases, such as skin aging. Some of these compounds are water or fat soluble vitamins and a huge variety of polyphenols is associated with the antioxidant activity (16).

FEATURES OF CHRONOLOGICAL AGING AND PHOTOAGING OF THE SKIN - FUNCTIONAL AND COSMETIC CHANGES

Skin aging is a complex, biological phenomenon consisting of two components; intrinsic (chronological) aging, which is largely genetically determined and extrinsic aging caused by external factors, mostly chronic exposure to UV radiation (premature photoaging), as already noted above (2, 18, 21).

In chronological aging, skin is smooth and without any evident spots (hyper- and hypopigmentation), with normal topography, mostly with distinct mimic wrinkles and lines. Histologically, there is atrophy of the epidermis and dermis, reducing the number of fibroblasts and mast cell, and increase of collagen fibers and relationship between collagen III and collagen I (22).

Skin that is chronically exposed to sunlight (face, neck, chest, exposed hand skin) is characterized by a large number of signs of photoaged skin, such as pigmented lesions (lentigo), loss of muscle tone and elasticity, increased fragility, weakness of the blood capillaries - visible telangiectasias and keratosis. Histopathologically, elastosis can be observed in the dermis, as well as atrophy of the epidermis, clear changes in the appearance of collagen, and elastic fiber fragmentation (higher content of collagen and soluble collagen). Elastic fibers are also fragmented, irregularly meshed and calcified (22).

Considering the intensity of changes and age, the Glogau scale was created that presented four photoaged skin types, Table 4.

Table 4. *Glogau types of photoaged skin*
(Date from Baumann with modifications (22))

Type of skin	Visible changes	Keratoses	Wrinkles	Make-up	Age
Type I "no wrinkles" Early photoaging	mild pigment changes	no	minimal	minimal, or no	20-30 years of age
Type II "wrinkles in motion - mimic" Early to moderate photoaging	early senile lentigo	palpable but not visible	parallel smile lines beginning to appear side of the mouth	usually carry a base for make-up	late 30's or 40's
Type III "wrinkles at rest" Advanced stage photoaging	dishromation obvious	visible	at rest	always wear heavy make-up	at the age of 50 and older persons
Type IV "just struggle" Expressed photoaging	yellow-green color	precedes malignant skin lesions	a fully lined, has normal skin	can not wear, "cakes and cracks,"	the 6^{th} or 7^{th} decade

POSSIBLE STRATEGY FOR ANTIOXIDANT THERAPY

In order to survive the injury and damage after exposure to sunlight, the skin has developed several defense mechanisms, including different types of antioxidants, such as vitamin C, vitamin E, coenzyme Q10, phenolic compounds as well as SOD and glutathione-peroxidase-reductase enzyme system in the epidermis (9).

Many antioxidants have the ability to prevent or treat clinical signs of photoaging of the skin, which are associated with oxidative stress and the appearance of ROS. Secondary prevention and treatment of chronologically and photoaged skin involves the application of different cosmetic products containing a variety of cosmetic active substances with antioxidant activity (21).

Dominant antioxidants in topical cosmetic formulation are non-enzymatic antioxidants, such as vitamin E and its derivatives, vitamin C and its derivatives, coenzyme Q10 and phenolic compounds, as well as various combinations of these, and their antioxidant activity may reduce the harmful effects of free radicals and contribute to the prevention and treatment of skin photoaging (1, 21). Scientific evidence has shown that, in addition to their specific functions, some vitamins are useful in topical prevention and treatment of skin aging (23). In modern formulations of cosmetic products, which belong to very different groups regarding their form and purpose, the most used vitamins are vitamin E and C (and their derivatives), as well as various combinations of these vitamins. A particular problem in the formulation of cosmetic products is the stabilization of unstable forms of vitamin E and C, which is solved by proper selection of ingredients, using colloidal carriers (liposomes, niosomes, nanoparticles) or by using appropriate packaging and special production techniques (24). Cosmetic products containing substances with antioxidative activities could exert appropriate action if the substance is used in adequate concentrations, and if suitable vehiculum/foundation is selected that will ensure their stability and release from the preparation and transition to the skin (21).

There is strong evidence supporting the potential role of vitamin E, vitamin C, coenzyme Q10 and phenolic compounds in the prevention and modification of the process of photoaging. In vitro studies have shown that vitamins have strong antioxidant capacity and may play an important role in skin reparation. For this reason, the possible benefits of the use of vitamins and phenolic compounds in topical formulations have been widely investigated (16, 25).

VITAMIN E AND DERIVATES

Vitamin E is an important antioxidant in skin therapy. Numerous data indicate that the antioxidant function of vitamin E is supplemented and linked to many enzymatic and non-enzymatic antioxidant systems (26).

Vitamin E is a collective name for all tocopherols which exhibit the biological activity of natural *d* α-tocopherol. Alpha-tocopherol is the stabilizer of cellular, mitochondrial, and lisosomereticulocyte membranes. Membrane stabilization is achieved via the interaction between vitamin E and poly-unsaturated fatty acids that constitute the membrane lipids (21). It has a direct antioxidant activity, because it donates a free electron to oxygen and superoxide anion (27).

Vitamin E is a lipophilic non-enzymatic antioxidant located at specific sites of cell membranes and cell organelles. Oxidation of unsaturated fatty acids present in phospholipids of cell membranes, produces lipid peroxides which react with structural and functional elements of biological membranes and cause their damage. Owing to a specific structure (the presence of phenolic hydroxyl group), vitamin E has the ability to "clean" ("catches", "neutralizes") lipid peroxides and deposited excited oxygen atoms. In this way it protects cell membranes from peroxidative damage, phospholipase A activity, and action of free fatty acid peroxides and lisophospholipids (21).

Alcohol form of vitamin E (dl or d α-tocopherol) is susceptible to oxidation. Therefore, in the preparations for local application its esters are commonly used for the purpose of stability: *d* and *dl* α-tocopheryl-acetate, linoleate, succinate, or nicotinate. Which form of vitamin E is used in a preparation and in which concentration depends on the effects to be achieved in the product or on the skin. Of all the ester forms, vitamin E acetate, due to its efficiency, stability, good compatibility (does not cause skin sensitization and allergies) and relatively low cost, is mainly used in the products intended for skin care and protection. In cosmetic products, it is recommended that vitamin E acetate should be used at a concentration of 1-10%, although the results of other authors have shown that the best effect in the skin is achieved with 5% concentration (21).

Topical applications of 1% solution of vitamin E have been shown to be effective in protecting the epidermis from early UV damage. The reactions of the skin after UVB irradiation are significantly reduced by topical application of tocopherol acetate, even after exposure (21). It is known that the application of topical formulations of 0.2% α-tocopherol leads to increased levels of vitamin E in the SC and the reduction of lipid peroxidation in vivo (25).

Under the influence of UV radiation vitamin E is consumed from the skin, and since vitamin C with coenzyme Q10 reduces the oxidized form of vitamin E, their concentration in the skin is reduced. After local application, alcohol and acetate form of vitamin E are absorbed directly through the epidermis or the hair follicle, where 6-24h after application a reservoir of vitamin E acetate is formed in the epidermis and dermis in

particular, from where if necessary, the body converts the ester into active form - *d* α-tocopherol (21).

The literature describes that vitamin E acetate protects the skin from the effects of UV rays, exerts anti-inflammatory effects, "moisturizes" and soothes the skin, "prevents" the appearance of new wrinkles and improves microcirculation. In cosmetic productions, α-tocopherol should be added at a temperature below 40°C, because at higher temperatures it may lose color. For the production of cosmetic product stocopheryl acetate is used as being more stable (21).

VITAMIN C AND DERIVATES

Vitamin C (ascorbic acid) is hydrophilic vitamin that plays an important role in preventing and protecting the skin from oxidative stress, doing so in the hydrophilic part of the electron donating cells, neutralizing free radicals and protecting intracellular structures against oxidative stress. It is important in dermatology, because many studies show significant benefits from the use of vitamin C (23).

The functions of ascorbic acid, as a biological cofactor and antioxidant, can be significantly reduced after UV irradiation due to the reduction of levels of vitamin C in the skin. It has been shown that vitamin C protects skin from UVA-mediated phototoxic reactions and prevents common degenerative cellular changes associated with lipid peroxidation (28).

Vitamin C is in a reduced form as *l*-ascorbic acid or in the oxidized form as *l*-dehydroaskorbic acid in the body. This biological redox system is important for metabolic processes that occur in the connective tissue. Vitamin C affects the activity of fibroblasts and thus participates in the synthesis of collagen. It is known that the lack of *l*-ascorbic acid reduces the synthesis of collagen, which decreases skin tone (21).

Since it is essential for the synthesis of collagen and elastin, vitamin C as a cofactor can neutralize negative effects of UV radiation on the skin (25). In a double-blind clinical study, the topical effect of 5% *l*-ascorbic acid formulations on the forearm and neck was investigated for six months and fine wrinkles, skin hydration, tactile roughness, visual dryness, laxity/tone, pigmentation, keratoses were observed. After three months, significant improvement of the observed characteristics was recorded, which continued even after six months (29).

The stability of vitamin C in formulations that contain water has long been problematic for cosmetologists. It is sensitive to light, elevated temperature, heavy metals and can change the color of preparation (cream) into brownish. Therefore, in cosmetic formulations, stable vitamin C derivatives such as sodium-ascorbyl-phosphate and magnesium-ascorbyl-phosphate are usually used. These derivatives of vitamin C can penetrate into the skin and under the influence of the phosphatase enzyme they release active ascorbic acid that exerts its effects (21).

In cosmetic formulations, sodium-ascorbyl-phosphate is often used in various concentrations: in sunscreen preparations at 0.2-2%, and in preparations for bleaching the skin pigmentation at 3-5% (21).

The combination of vitamins C and E provides very good protection against UVB radiation. Vitamin E and vitamin C may have a prophylactic role in defending the skin from a large number of serious light-induced conditions that mediate in photooxidative damage of cell membrane (9). However, it was shown that vitamin C provides much better protection than vitamin E when it comes to the phototoxic effect of UVA rays on the skin (21).

Vitamin C, in addition to its role in the skin, plays a role in the stabilization of vitamin E in the formulation against UV degradation (30). Due to the important role of vitamin C in maintaining the active form of vitamin E, some studies have examined the combination of vitamins C and E (31).

COMBINATION OF VITAMINS IN ANTIOXIDANT THERAPY

Alpha-tocopherol has a synergistic role with vitamin A (retinol) and vitamin C in the combined products, providing a noticeable photoprotection and antioxidant activity, which indicates the potential effects of photoprotection against skin photoaging (32).

Some studies have analyzed an exciting new formulation of tocopherol-acetate, retinyl-palmitate, ascorbyl-tetra-izopalmitat and biflavonoids from the plant Ginkgo biloba. The authors of this formulation present it as "a biological filter" against UV damage (33). They demonstrated that this formulation has a high in vitro antioxidant activity, due to the "cleansing" of free radicals (almost 100% inhibition of free radical production), using these components. The authors concluded that this result is probably related to the formulation vehicle, which affects skin penetration. This combination is very unstable and it is very important to achieve an excellent chemical stability so that best possible effects could be obtained with these formulations (23).

A new study was conducted and a powerful herbal antioxidant ferulic acid was added to the solution formulation of 15% vitamin C and 1% vitamin E. It turned out that topical application of antioxidant stable formulations of 15% vitamin C and vitamin E 1% with 0.5% ferulic acid (CEFer) can protect human skin in vivo from substantial amounts of UV radiation. It was noticed that the effect of such a photoprotective formulation doubled compared to the previous formulation of the free acid. By its mechanism, which differs from the action of preparations for sun protection (*sunscreens* formulations), this formulation may be a complement to sunscreens formulations and the skin defense mechanisms to protect skin from the sun (34).

COENZYME Q10-CoQ10

Ubiquinone - Coenzyme Q10 is a good antioxidant in subcellular membranes. CoQ10 protects against UVA-induced collagen degradation. Together with tocopherol,it inhibits the production and expression of fibroblast collagenase. It is also important for the regeneration of tocopherol. There is in vitro evidence that CoQ10 protects tocopherol from the photooxidation by recyclable mechanism (35).

The concentration of CoQ10 in the skin is quite low, and arranged so that CoQ10 levels are ten times higher in the epidermis than in dermis; epidermis thus may have potential benefit of topical applications of Co Q10. It turned out that CoQ10 was absorbable after topical applications. Topical use of aethanol solution of CoQ10 in the pig's skin showed a 20% penetration in the epidermis and 27% into dermis (36).

The antioxidant activity of CoQ10 has been confirmed in many studies. After topical applications of 0.3% CoQ10, for one week two times a day on the skin previously exposed to UVA radiation, causing a drop in antioxidant activity of the skin, there was a significant improvement in antioxidant activity. The efficiency of Co Q10 in photoaging was studied clinically. In one half of the volunteers, facial 0.3% CoQ10 cream was applied for six months, while for the other half a placebo preparation was used. Wrinkle reduction of 27% was noticed (36). Another study examined photoaging skin by changing the size of SC cells. It is known that corneocytes become elongated over time. By topical application of CoQ10 cream for six months, the size of corneocytes reduced equivalent to 20 years' rejuvenation (36).

A study have shown that CoQ10 in the formulation of nano structure of lipid carriers (NLC-CoQ10) has a higher antioxidant capacity and topical penetration through the skin-emulsion of CoQ10. The formulation is made as a "drug delivery system" to improve the efficiency of antioxidant CoQ10. The new formulation of Co Q10-NLC, mainly lipophilic in structure, shows a high solubility of substances, high stability, good penetration through the SC and low skin irritation (12).

CoQ10, as a very effective antioxidant in the protection of the dermal matrix and photoaging and chronological aging of the skin, is an important cosmetic agent (36).

POLYPHENOLIC COMPOUNDS

Many plant extracts are used in cosmetic formulations as additives or are used due to their functional properties (emollient, anti-irritant, moisturizing, anti-aging). Plants are affluent source of free radical scavenging molecules, such as vitamins, terpenoids, phenolic compounds, lignins, tannins, which are rich in antioxidant activity (37). Therefore, antioxidants from natural products present novel possibilities for the treatment and prevention of oxidative stress-mediated skin diseases and they have been used successfully in the prevention and treatment of photoaging (38).

Polyphenolic compounds are the most important natural antioxidants for topical application (39). Typical plant polyphenols include tannins, galloylglucoses, flavonoids and phenolic acids. Plant tannins can be classified as proanthocyanidins or hydrolysable tannins that include both gallotannins and ellagitannins (40).

Phenolics are a class of low- molecular- weight secondary metabolites found in most land plants. Phenolics protect plants against UV radiation, pathogens, and herbivores. Flavonoids, secondary plant metabolites, contribute to both fruit color and human health. Flavonoids are widely believed to possess antioxidative, antimicrobial, antimutagenic and anticarcinogenic properties (41).

The biological activity of polyphenols is interesting because of the double-edged character of reactivity. Polyphenols can act as antioxidants in their reduced form (through radical scavenging) or prooxidants in the oxidized form (through the generation of reactive phenoxyl radicals or quinone/quinone methide intermediates) depending on the environment (40). The phenolic compounds act as antioxidants due to their redox properties, allowing them to act as reducing agents, hydrogen donors, free radical scavengers and metal chelators and they have been shown to be more effective antioxidants than vitamins E and vitamin C (42, 43).

Topical application of polyphenols has proven to be effective in protecting the skin against age-related diseases and ultraviolet-mediated oxidative damage and provides a straightforward way to strengthen the endogenous protection system (37).

CONCLUSION

Despite quantitative and qualitative differences between photoaging and chronological aging, it can be said that oxidative stress and formation of free radicals is the main and common cause of aging. It is generally known that one of the most important sources of oxidative stress, UV radiation, can induce the production of ROS leading to oxidative damage and thus skin aging. Oxidative stress leads to the formation of free radicals that can react with a large number of potential target molecules in the skin, and that can lead to the variety of structural and functional injuries to the skin. Cumulative photodamage of the skin contributes to photoaging of the skin, which can result in falling levels of antioxidant enzymes and antioxidant defense capacity, all leading to the accumulation of oxidative damage and products, which are the markers of oxidative stress.

Extensive UV radiation can be harmful to the skin, and it is necessary to minimize or prevent adverse effects of UV light on the skin with extra artificial defense. Topical application of antioxidant substances, such as tocopherol, ascorbic acid, coenzyme Q10, plant extracts with phenolics, as well as various combinations of these

compounds, produces high concentrations of these compounds in the skin, as a skin antioxidant reservoir, so antioxidant skin defense increases, thus reducing the harmful effects of free radicals and oxidative stress and improving prevention and treatment of photoaging and chronological aging of the skin.

Understanding the relationship of UV radiation, which can induce the production of ROS and oxidative stress with skin aging and decreased antioxidant capacity of the skin, is very important for determining adequate antioxidant therapy in the fight against age- and oxidative stress-related skin diseases. Cosmeceutics with aplicable topical antioxidants and their further development have a very important place in dermatology and cosmetology and represent an important antioxidant strategy in reducing oxidative stress caused by skin exposure to UV radiation in the prevention and treatment of skin aging.

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OKSIDACIONI STRES, STARENJE KOŽE I ANTIOKSIDACIONA TERAPIJA

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Sažetak

Starenje kože je dinamičan proces koji se dešava usled hronološkog starenja i foto-starenja izazvanog izlaganjem delovanju faktora spoljašnje sredine, pre svega UV (eng. ultraviolet) zračenja. Kumulativni oksidacioni stres, formiranje slobodnih radikala i njihov nepovoljan uticaj na biološke sisteme u ćelijama kože, predstavljju čest i zajednički mehanizam oba procesa starenja kože. Formirane reaktivne kiseonične vrste (eng. reactive oxygen species-ROS) mogu dovesti do oksidacije gradivnih molekula ćelija. Peroksida-

cija lipida, oštećenje membranskih proteina i DNK mutacije mogu dovesti do pojave strukturnih, funkcionalnih, kao i estetskih promena na koži, a takođe mogu pokrenuti razvoj mnogih bolesti.

Jedan od odbrambenih mehanizama kože je antioksidaciona odbrana, gde enzimi i druge antioksidacione supstance direktno reaguju sa ROS-om, sprečavajući ih da dopru do bioloških meta u koži. Antioksidacione supstance imaju sposobnost da vežu slobodne radikale nastale usled oksidacionog stresa, pa mogu biti značajne u prevenciji i/ili terapiji mnogih bolesti kože, kao i u usporavanju procesa starenja kože. Lokalna aplikacija antioksidanasa, kao što su vitamin E i C, koenzim Q10 i polifenolna jedinjenja, može da omogući jačanje endogenog zaštitnog sistema kože i predstavlja jedan od načina zaštite kože od štetnih efekata ROS-a i oksidacionog oštećenja kože u procesu starenja kože.

U ovom radu je prikazan uticaj oksidacionog stresa na hronološko i foto-starenje kože, mehanizam njegovog delovanja, promene koje nastaju na/u koži u toku procesa starenja. Dat je prikaz supstanci sa antioksidacionim delovanjem koje mogu da se koriste u prevenciji hronološkog i/ili tretmanu foto-starenja kože.

Ključne reči: **oksidacioni stres, hronološko i foto-starenje kože, topikalni antioksidansi**