REVIEW ARTICLE

Antioxidants in skin ageing – Future of dermatology

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The formation of free radicals is a widely accepted pivotal mechanism leading to skin ageing. Skin ageing is a complex, progressive, time-dependent deterioration caused by intrinsic and extrinsic factors or environmental factors. Skin is equipped with an elaborate antioxidant system that protects it from oxidative damage due to intrinsic and extrinsic factors. However, the natural antioxidant pool can be compromised or overwhelmed by oxidative stress of excess UV exposure, as well as cigarette smoke and other airborne pollutants. Topical antioxidants have been demonstrated to protect the skin from free radical damage and its regular application can actually reverse pervious photodamage. Topical antioxidants are available in over-the-counter skin care products that are aimed at preventing the clinical signs of photoageing. The present review summarises scientific literature regarding efficacy of topical antioxidants and significance of novel delivery systems for topical antioxidant delivery for combating skin ageing.

Key words: Antioxidants, novel drug delivery systems, skin ageing, topical delivery

INTRODUCTION

Age leaves its traces everywhere, as we get older our skin loses its defense against wind, weather, sun, and oxygen deficiency. Environmental aggressors such as UV light may generate free radicals, the major inducers of premature ageing. Antioxidants act as antidote to skin ageing by quenching free radicals formation in skin. So if one is looking for a safe, natural, and significant effect on the skin, it is the antioxidants in which one should put their faith. Thus, the aim of this article was to review importance of antioxidants in skin ageing and novel drug carriers for effective antioxidant delivery.

WHAT IS SKIN AGEING?

Ageing is defined as a progressive deterioration of physiological functions in organisms, eventually leading to senescence and death.[1] It is a continuous time-dependent and multifactorial phenomenon of reduction in size and number of cells and also reduction in the rate of many organic functions both at cellular and molecular levels. The signs of ageing include fine lines and wrinkles, alterations in skin pigmentation, and a thinner appearance of the skin due to epidermal and dermal atrophy.[2] Fortunately, regular application of skin care products containing antioxidants may be of utmost benefit to overcome and correct skin ageing.[3]

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TYPES OF SKIN AGEING

Ageing can be divided into two categories: Intrinsic or chronological ageing and extrinsic or premature ageing.[4]

Intrinsic Ageing

Intrinsic ageing is a natural occurrence in which numerous simultaneous mechanisms occur. Dead skin cells do not shed as quickly, and turnover of new skin cells may decrease slightly. The signs of intrinsic ageing are as follows: Fine wrinkles, thin and transparent skin, loss of underlying fat leading to hollowed cheeks and eye sockets, bones shrink away from the skin due to bone loss resulting in sagging skin, inability to sweat sufficiently to cool the skin, graying hair that eventually turns white, hair loss, unwanted hair, nail plate thins, and ridges develop.[5]

Extrinsic Ageing

Extrinsic ageing is caused by exogenous origin, i.e., smoking, poor nutrition, and solar exposure. These factors are responsible for premature ageing of the skin. Loss in tone and elasticity is observed along with increased skin fragility, benign lesions (keratoses and telangiectases). Histopathology of photoaged skin is characterised by elastosis, epidermal atrophy, and distinct alteration in collagen and elastic fibers.[6]

CHARACTERISTICS OF AGEING SKIN

Changes in Epidermal Layer

Hair graying, skin wrinkling, sagging, and apparent thinning are some of the changes in the clinical

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appearances of the ageing skin.[7] Aged epidermis shows fewer keratohyaline granules at the base as compared to flanks. Decreased elasticity of the skin with age, however, promotes the apparition of a thinner skin due to reduced contractile ability of the epidermis and thus less crowding of epidermal cells.[8]

Changes in Dermal Layer

Although most morphological changes occur in the epidermis, biochemical changes occur in the dermis.[9] Atrophy of the dermis is manifested by changes in the dermal connective tissue. With increasing age, the dermis becomes thinner due to the reduction in the amount and organisation of dermal connective tissue.[10]

Collagen

Collagen degradation is purported to be one of the major contributing factors to ageing of the dermis and leads to some of the major changes that cause the appearance of aged skin.[11] In contrast to dense and compact bundles in young skin, collagen bundles in aged skin are granulated dispersed with separated bundles and fibers.[12]

Elastin

Elastosis, an accumulation of amorphous elastin material, is considered pathogenomonic of photoaged skin. As we age, the reduction of collagen and elastin production together with premature degradation of dermal structure leads to a loss of skin cohesiveness leading to sagging as well as a loss of elasticity.[13]

Glycosaminoglycans

Glycosaminoglycans in skin consist of hyaluronic acid, dermatan sulfate, chondroitin 4-sulfate, and chondroitin 6-sulfate and are responsible for conferring the outward appearance of the skin.[14] Photoaged skin is characterised by reduced levels of hyaluronic acid and elevated levels of chondroitin sulfate proteoglycans.[15]

Melanocytes

With age there is a reduction in formation of melanocytes.[16] The skin of older people is more susceptible to develop sun-induced cancers because melanin that is reduced in the elderly tend to absorb carcinogenic UV radiations.

Vasculature

Aged skin is seen to be relatively avascular. Reduced blood flow, depleted nutrient exchange, and inhibited thermoregulation are associated with reduction in vascularity.[17]

Subcutaneous tissue

Site-specific changes, including gains and losses, are known to occur in subcutaneous tissues that also influence the appearance of the elderly and their skin. Subcutaneous fat diminishes in the face, dorsal aspects of the hands, and the shins.

FACTORS CAUSING SKIN AGEING

Various factors contributing to ageing of skin are listed below:

Photodamage

Skin ageing caused by sun exposure can occur even before intrinsic ageing.[18] Changes that are observed due to photoageing are leathery appearance with wrinkle formation, impaired wound healing, appearance of lesions on the skin such as actinic and seborrheic keratoses, cutaneous horns, skin cancer, pigmentary alterations such as lentigens and hyperpigmentation, and the most prominent feature is elastosis. Photoageing or sun damage results in fine lines and wrinkles, discoloration, and textural changes.[19]

Free Radicals and Oxidation

Free radical damage causes skin ageing and wrinkles by activating the metalloproteinases that break down collagen. Oxidative stress plays a major role in the intrinsic and the extrinsic process of skin ageing.[20] UV irradiation continuously bombards the skin with profound oxidising effects, and many other factors such as ozone, cigarette smoke, and environmental pollutants also contribute to the oxidative assault.

Smoking

Chronic smokers have pale, yellowish-grey skin. Cigarette smoking promotes the release of oxidants.[21] Deep lines typically appear radially from the upper and lower lips and laterally from the eyes. There is relative skin thickening between these wrinkles.[22] Oxidants slow the production of new collagen and elastin. Smoking also restricts the blood flow in the epidermis so skin does not get the quantity of nutrients it needs to stay healthy.

Hormones

The most dramatic changes in woman's appearance take place around menopause years, when estrogen drop causes considerable loss of collagen, which is an important protein that makes up most of the skin's supportive structure. As a result, wrinkles appear and skin hangs loosely.[23]

Heredity

Genetic factors dictate the rate at which skin ageing process progresses. If one or both of one's parents had youthful skin well into the old age, chances are one could inherit same characteristics.

Lifestyle

The lifestyle of a person can also contribute to the ageing skin. Factors such as lack of sleep, alcohol consumption, stress, type of exercise, improper diet, and reduced intake of water can all lead to minor signs of ageing.

HOW DO FREE RADICALS CAUSE SKIN AGEING?

Oxygen is a highly reactive atom that is capable of becoming part of potentially damaging molecules commonly called "free radicals," which leads to the signs of ageing. Cell damage caused by free radicals appears to be a major contributor to skin ageing. Free radicals are electrically charged molecules which causes them to seek out and capture electrons from other substances in order to neutralise themselves.[24]

Oxidative stress is caused by an imbalance between the production of and a biological system's ability to readily neutralise the reactive intermediates or easily repair the resulting damage. Free radicals attack collagen and elastin causing the structure to break down.[25] With age, the accumulated free radical effects begin to slow down the cell function therefore reducing the body's self-repair capabilities. Free radical attacks eventually lead to wrinkles, sagging skin, and "age spots." Free radical generation is certainly not the only contributor to the ageing process, but even oxidative damage to cellular and extracellular components is responsible for many of the degenerative changes observed with age.

As the organ with the greatest exposure to such external sources of oxidation, skin has evolved a complex network of endogenous and assimilated antioxidants for protection; however, these are not always sufficient to prevent or repair damage due to reactive oxygen species.[26] Oxygen is a powerful producer of free radicals known as reactive oxygen species. Reactive oxygen species are small, highly reactive, oxygen-containing molecules that are naturally generated in small amounts during the body's metabolic reactions and can react with and damage complex cellular molecules such as fats, proteins, or DNA. Examples of common ROS are superoxide anion ($O_2^{\bullet -}$), hydroxyl radical (•OH), singlet oxygen ($^1O_2$), and nitric oxide (•NO). Reactive oxygen species attack the structure of our cell membranes, creating waste products, including pigments known as lipofuscins. Lipofuscins interfere with the cells ability to repair and reproduce themselves, disturb DNA and RNA synthesis, inhibit protein synthesis, and destroy cellular enzymes.[27]

Oxidation of the phospholipids in cell membranes initiates a chain reaction that results in lipid peroxide formation; these compromise the integrity of the membrane, initiate inflammation, and have also been shown to be involved in the up-regulation of the degradative enzyme, matrix metalloproteinase-1. Oxidative stress also affects the transcription of other genes through mitogen-activated protein kinase (MAPK) pathways. UV irradiation initiates a cascade of events including phosphorylation of protein kinases of the MAPK family and activation of transcription factors such as nuclear factor kB that mediates an inflammatory response. Blocking these pathways with antioxidants is thought to prevent photoageing by preventing the production of collagenase.

WHAT ARE ANTIOXIDANTS?

Antioxidants are substances that offer protection to cell membranes and prevent oxidative stress to the tissues of the body by neutralising toxic oxygen molecules and free radicals.[28] Collagen and elastin are what keep skin looking fresh and tight; as we get older, collagen and elastin slow in production, which leads to sagging and wrinkles. Antioxidants actively counter free radical attacks on the supple elasticity of the skin.[29] Found naturally in the body and in plants, antioxidants can be ingested orally or applied topically. There are generally three categories of antioxidants (1) Antioxidant enzymes, (2) Chain breaking antioxidants and (3) Preventive antioxidants

Antioxidant Enzymes

Antioxidant enzymes catalyse reactions involved in the conversion of free radicals to oxygen and water. They include catalase, glutathione peroxidase, and superoxide dismutase.

Chain Breaking Antioxidants

Chain breaking antioxidants prevent propagation of oxidative chain reactions by terminating free radicals or the reactive products of molecules that have been damaged by free radicals. They include vitamin E, beta carotene, vitamin A, flavonoids, vitamin C, uric acid, bilirubin bound to albumin, and the thiol groups of plasma proteins such as albumin.

Preventive Antioxidants

Preventive antioxidants are the metal binding proteins that function to sequester free iron or copper to prevent production of the hydroxyl radical from other free radicals. These include ferritin, transferrin, lactoferrin, and ceruloplasmin.

ROLE OF TOPICAL ANTIOXIDANTS AGAINST SKIN AGEING

The reason that antioxidants are important as part of an antiageing skin support program is because antioxidants help protect the skin from the toxic effects of free radicals

that would otherwise damage and destroy healthy skin cells. As free radicals are neutralised by one component of the skin's antioxidant system, that component becomes oxidised and inactivated. As one component becomes inactivated, other components of the skin's antioxidant system interact in a complex fashion to recycle the inactive components back to an active state to restore the antioxidant capability.[30]

Both water-soluble and fat-soluble antioxidants are naturally present in human skin. Vitamin C and glutathione are the most important water-soluble antioxidants that protect the cytoplasm of the cells and along with hyaluronic acid these antioxidants also protect the extracellular matrix that surrounds the cells.[31] The antioxidant activity of vitamin E protects the polyunsaturated fatty acids in cell membranes from oxidation and so protects cell membranes from destruction by free oxygen radicals.[32] Other antioxidants such as green tea extract, glutathione, and vitamin C have synergistic antioxidant effects. Alpha-tocopherol along with vitamin C and glutathione protects the skin from oxidative damage that occurs by exposure to UV light from the sun and chemical toxins.[33]

The use of topical cosmetics that contain tocopherol and alpha-tocopherol acetate can substantially increase the vitamin E content of the skin more effectively than even dietary supplementation. Ascorbate regenerates the oxidised form of vitamin E and the oxidised forms of ascorbate and vitamin E in turn are recycled by glutathione. Vitamin C along with glutathione helps recycle oxidised vitamin E back to its active protective form. In addition, maintaining tocopherol levels in the skin by topical formulas helps maintain the active forms of vitamin C and glutathione in the skin.[34,35]

ANTIOXIDANTS USED IN ANTI-AGEING PRODUCTS

Antioxidants clearly play an important role in the prevention of ageing. Many antioxidants are now available in oral and topical preparations. Combinations of various antioxidants may have synergistic effects, yielding formulations with greater efficacy than any of the individual antioxidant compounds used alone. Each antioxidant is endowed with various properties that distinguish it from other antioxidants. Various antioxidant actives used in antiageing formulations are as follows:

Retinoids

Topical retinoids include retinol and derivatives of retinol and retinaldehyde used frequently in cosmetic products (for example retinol and retinyl palmitate). Vitamin A is a naturally occurring antioxidant in the skin. The biologically active form of vitamin A is all-*trans* retinoic acid or tretinoin (Retin-A). Retinoic acid aids in epidermal proliferation, keratinisation, and peeling.[36] It also modifies keratin synthesis, fibroblastic proliferation, and collagen metabolism. Vitamin A esters also appear to be protective against the carcinogenic effect of UV radiation. Vitamin A increases the blood flow, stimulates the skin, and protects against sunburn, thus promoting skin elasticity.[37]

Alpha Lipoic Acid

It is the most potent antioxidant in the market today. It enhances the skin cell metabolism and helps repair aged skin while preventing future damage. With age, glutathione levels naturally decline, making elder person more susceptible to both free radicals and other environmental toxins but lipoic acid tends to restore levels of glutathione, a protective antioxidant, and detoxification compound, to near normal.[38]

Vitamin C

Vitamin C (L-ascorbic acid) is a highly water-soluble, sugar-like, low-molecular weight ketolactone. It is a proven anti-wrinkle treatment that works as both a "free radical scavenger" and antioxidant.[34] It occurs in two forms:

(a) L-ascorbic acid—water-soluble antioxidant, high active vitamin C.
(b) L-ascorbic palmitate—fat-soluble antioxidant, high stable vitamin C.

Vitamin C improves skin elasticity by enhanced collagen production. Vitamin C stimulates the skin to produce collagen while reducing the action of collagenase.[31]

Vitamin E

Vitamin E (tocopherol) is a lipid-soluble antioxidant that is present in the skin and found in various foods such as vegetables, seeds, and meat. The lipophilic nature of vitamin E makes it attractive for application to and absorption into skin. It helps skin repair itself, protects it from harmful bacteria, and also creates a moisture barrier so that the epidermis is less likely to dry out.[39] The free hydroxyl group in this molecule is responsible for antioxidant activity. Deficiency of vitamin E leads to an increase in lipid peroxidation in skin, a key mediator of oxidative damage highlighting its importance as a skin antioxidant.[40]

Coenzyme Q10

Coenzyme Q10 or ubiquinone is a fat-soluble compound naturally occurring antioxidant found in fish, shellfish, spinach, and nuts. Coenzyme Q10 is a potent antioxidant with anti-ageing and -wrinkle properties and is a potent moisturiser and prevents damage to collagen and elastin production process and helps to avoid wrinkles.[41]

Lycopene

Lycopene is a bright red carotenoid antioxidant. As an antioxidant, lycopene is a powerful carotenoid quencher of free radicals.[42] Lycopene provides antioxidant protection

from environmental damage, shielding skin from premature ageing. Lycopene strengthens skin by enhancing its ability to produce collagen and reducing wrinkles.

Tea Polyphenols

Green tea is a very popular beverage and an antioxidant that is extracted from the plant *Camellia sinensis*. Green tea contains predominantly monomeric catechins including epicatechin, epicatechin-3-gallate, epigallocatechin, and epigallocatechin-3-gallate. Topical application of green tea extracts helps maintain the levels of both glutathione and glutathione recycling enzymes in the skin after exposure to ultraviolet light and reduces depletion of protective antioxidant enzymes in the skin.[43]

Silymarin

Silymarin is a naturally occurring polyphenolic flavonolignans antioxidant derived from the seeds of the milk thistle plant *Silybum marianu*. Its main component silybin (silibinin) is considered to be the most biologically active with strong antioxidant properties.[44] It possesses antioxidant, anti-inflammatory, and immunomodulatory properties that may help prevent skin cancer and photoageing.

Coffea Arabica Extract

C. arabica extract is an antioxidant extracted from the fruit of coffee plant *C. arabica* containing polyphenols and is a more potent antioxidant than green tea, pomegranate extract, and vitamins C and E. In 2007, a product containing CoffeeBerry® polyphenols 1% (Revaleskin™, Stiefel Laboratories) was launched showing reduction of hyperpigmentation, fine lines, wrinkles, and overall appearance.

Grape Seed Extract

Grape seed extract is extracted from *Vitis vinifera* and is rich in proanthocyanidins, which belong to the flavonoid family and are potent antioxidants with strong free radical scavenging activities than vitamins C and E.[45] It is included in topical cosmetic formulations for antiageing purposes.

Pomegranate Extract

Pomegranate extracts can be obtained from various parts of the fruit *Punica granatum*, such as the juice, seed, and peel. In particular, the phenolic components have potent antioxidant activity. Topical application of fruit extract has been shown to ameliorate ultraviolet-A- and -B-mediated skin damages *in vitro*.[46]

Pycnogenol

Pycnogenol can be extracted from French maritime pine (*Pinus pinaster*) plant, which is rich in proanthocyanidins. It contains flavonoids and phenolic compounds, which act as potent free radical scavengers. Immunosuppression and a reduction of the inflammatory sunburn reaction were observed in mice after topical application of pycnogenol (0.05%-0.2%).[47]

Niacinamide

Niacinamide, or nicotinamide, is a water-soluble component of the vitamin B complex group. Besides its antioxidant activity, it has also been shown to exhibit anti-inflammatory, depigmenting, and immunomodulant properties. The use of niacinamide has been shown to improve texture and tone of the skin and reduce fine lines, wrinkles, and hyperpigmentation.

TOPICAL ANTIOXIDANT DELIVERY SYSTEMS

Recently, research-based focus is on usage of natural antioxidants for obliterating the free radicals mediated skin damage. Because most antioxidant molecules are inherently unstable in nature, it makes them difficult to formulate in an acceptable, stable aesthetic product for cosmetic use. Further, the use of conventional delivery systems (e.g., creams and lotions) in several cases showed a little or no improvement in antioxidant profile. These observations facilitate the significance of novel delivery systems in the development of antioxidant formulations.[48] Some of the commercially available antiageing products which have antioxidants as their major components are listed in Table 1.

Liposomes as an Antioxidant Delivery System

Liposomes are uniquely suited for delivery of cosmeceuticals because of their ability to deliver water-soluble compounds in the same particle as water-insoluble compounds.[49] First liposomal cosmetic product to appear in market was antiageing cream "Capture" launched by Dior in 1986. Marinosomes® are liposomes based on a natural marine lipid extract containing a high polyunsaturated fatty acid ratio.[50] The characterisation studies showed Marinosomes® as promising candidates for topical application in view of the prevention and treatment of skin diseases.

Niosomes as an Antioxidant Delivery System

Niosomes are essentially non-ionic surfactant-based multilamellar or unilamellar vesicles in which an aqueous solution of solute is entirely enclosed by a membrane resulting from the organisation of surfactant macromolecules as bilayers. Niosomes appear to have application in topical products containing both hydrophilic and hydrophobic drugs.[51] The first product "Niosome" was introduced in 1987 by Lancome, L'Oreal company. Manconi *et al*. evaluated the potential of niosomal formulations as topical delivery systems capable of improving the stability of photosensitive drugs, such as tretinoin.[52]

Table 1: Commercially available antiageing products containing antioxidants

Active ingredients/delivery system	Trade name	Manufacturer	Use
Ascorbyl palmitate, Tocopherol, Retinol/Liposomes	Rovisome® ACE Plus	Rovi Cosmetics International GmbH	Anti-ageing, wrinkle reduction
Vitamin E/Nanotopes	Tinoderm® E	Ciba Specialty Chemicals	Anti-inflammatory, anti-ageing
Coenzyme Q10, Niacinamide/ Liposomes	Ageless Facelift™ cream	I-Wen Naturals	Anti-ageing, anti-oxidative, wrinkle reduction
Micro-encapsulated Vitamin C (5%)	Ultimate Anti-Aging Serum®	Provin Cosmeceuticals	Anti-ageing, wrinkle reduction
Coenzyme Q10, Vitamin E acetate/Nanoemulsion	Nano-Lipobelle™ H-EQ10 cream	Mibelle Biochemistry, Switzerland	Anti-ageing, anti-inflammatory
Pro-Retinol A/Nanoparticles	Revitalift®	L'Oreal	Anti-wrinkle, anti-ageing
Coenzyme Q10/Nanostructured lipid carriers	Cutanova Nano Repair® Q10 Cream	Dr. Rimpler GmbH	Revitalising, anti-ageing
Black currant seed oil/ Nanostructured lipid carriers	Nanolipid Restore CLR™	CLR Chemisches Laboratorium Dr. Kurt Richter GmbH	Revitalising, anti-ageing
Vitamins A, E, C/Nanoemulsion	Nano-Lipobelle™ H-AECL	Mibelle Biochemistry, Switzerland	Revitalising, anti-ageing
Vitamin E, Panthenol/Nanocapsules	Lancome Soleil Soft-Touch Anti-Wrinkle Sun® Cream SPF 15	L'Oreal	Anti-wrinkle, anti-ageing
Grape seed extract, Vitamin E, Green tea extract/Fullerenes	Sircuit Addict Firming Antioxidant® Serum	Sircuit Skin Cosmeceuticals Inc.	Revitalising, anti-ageing

Solid Lipid Nanoparticles and Nanostructured Lipid Carriers as an Antioxidant Delivery System

Solid lipid nanoparticles (SLNs) are novel colloidal delivery systems with many cosmetic and dermatological features, such as enhanced skin hydration, protection against degradation, active penetration enhancement, and controlled-release properties.[53] Curcuminoids loaded SLN cream enhanced the anti-ageing properties of curcuminoids when compared with conventional cream base, with no signs of skin irritation. Nanostructured lipid carriers (NLC) are mixtures of solid and fluid lipids, in which the fluid lipid phase is embedded into the solid lipid matrix.[54] Commercially available products, NanoRepair Q10® cream and NanoRepair Q10® serum (Germany), which were introduced to the cosmetic market in October 2005 epitomises the success of NLCs.

Phytosomes as an Antioxidant Delivery System

Phytosomes are complexes between a pure phospholipid and pure active principles from the chemical perspective, containing high percentages of natural triglycerides for emolliency and skin moisturising.[55] Grape Seed Phytosome provides superior antioxidant activity for healthy skin integrity and skin ageing. Opextan® is an innovative Ecocert validated olive fruit extract. Opextan® has been demonstrated to reduce skin sensitivity to UV irradiation, lipid peroxidation, and oxidative stress.

Multiple Emulsions and Nanoemulsions as an Antioxidant Delivery System

Multiple emulsions are a type of polydisperse systems allowing controlled release of active entrapped compounds. They are of two types: w/o/w type and o/w/o type.[56] Ascorbic acid and vitamin A have been successfully formulated showing improved stability and release profile.[57] Nanoemulsions are fine oil-in-water dispersions, having droplet diameter smaller than 100 nm with aesthetic properties suitable for application in cosmetics.[58] But, in comparison with microemulsions, they are in a metastable state and are very fragile systems. Procter and Gamble's Olay™ brand was designed with nanoemulsion technology in 2005.

Transfersomes and Ethosomes as an Antioxidant Delivery System

Transfersomes are specially designed vesicular particles, composed of phospholipids, with 10–25% percent surfactant and 3-10% ethanol.[59] They significantly improve photostability and skin deposition of α-tocopherol. Ethosomes are noninvasive delivery carriers composed mainly of phospholipids, with 20-50% ethanol and water, which enable drugs to reach the deep skin layers.[60] These are soft, malleable vesicles tailored for enhanced delivery of active agents. The *in vitro* release rate of azelaic acid was more rapid from ethosomal systems than from liposomal systems.

Cubosomes and Nanospheres as an Antioxidant Delivery System

Cubosomes are discrete, sub-micron, nanostructured particles of bicontinuous cubic liquid crystalline phase.[61] They offer a large surface area, low viscosity, high heat stability, and are capable of carrying hydrophilic and hydrophobic molecules. L'Oreal has patented the use of cubosome particles as oil-in-water emulsion stabilisers and pollutant absorbents in cosmetics.

Nanospheres are microscopic fragments used to deliver active ingredients into the deep layers of the skin. This

advanced technology plays a very beneficial role in protecting against actinic ageing, which is 90% of the ageing of our skin. Nanosphere technology is incorporated into some of Arbonne's anti-ageing skin care (RE9 NutriMinC) and hair care products.

Nanotopes and Nanocrystals as an Antioxidant Delivery System

Nanotopes™ are particles, which comprises of membrane having well-defined ratio of a phospholipid and a cosurfactant. Nanotopes delivery system enables efficient penetration of vitamin E acetate and bioconversion to its active form, vitamin E, where its action is needed inside skin. Nanocrystals are aggregates comprising several hundred to thousands of atoms that combine into a cluster, used for the delivery of poorly soluble actives.[62] Rutin and hesperidin are two poorly soluble, plant glycoside antioxidants formulated as nanocrystals with enhanced antioxidant effect.

CONCLUSION

We all can truly "look as young as we feel" by applying topical antioxidants. Because even once-daily application of correct formulations of topical antioxidants provides a long-lasting reservoir in the skin for protection not only against post UV-induced erythema, hyperpigmentation, photoageing, and skin cancer but also against other free radical damage. They are indeed a valuable adjunct to frequent sunscreen application. This protection over time not only protects the skin but also reverses the unattractive appearance of previous photodamage by directly enhancing collagen synthesis and elastic tissue repair. Novel drug delivery systems reviewed here possess the potential to incorporate antioxidants which will augment their stability and hence enhance the performance as cosmetic ingredients against skin ageing.

REFERENCES

1. Wlaschek M, Tantcheva-Poor I, Naderi L, Ma W, Schneider LA, Razi-Wolf Z, *et al*. Solar UV irradiation and dermal photoaging. J Photochem Photobiol 2001;63:41-51.
2. Chui A, Kimball AB. Topical vitamins, minerals, and botanical ingredients as modulators of environmental and chronological skin damage. Br J Dermatol 2003;149:681-91.
3. Dreher F, Maibach H. Protective effects of topical antioxidants in humans. Curr Probl Dermatol 2001;29:157-64.
4. Rabe JH, Mamelak AJ, McElgunn PJ, Morison WL, Sauder DN. Photoaging, mechanisms and repair. J Am Acad Dermatol 2006;55:1-19.
5. Holtkötter O, Schlotmann K, Hofheinz H, Olbrisch RR, Petersohn D. Unveiling the molecular basis of intrinsic skin aging. Int J Cosmet Sci 2005;27:263-9.
6. Südel KM, Venzke K, Mielke H, Breitenbach U, Mundt C, Jaspers S, *et al*. Novel aspects of intrinsic and extrinsic aging human skin: Beneficial effects of soy extract. J Photochem Photobiol 2005;18:581-7.
7. Elias PM, Ghadially R. The aged epidermal permeability barrier: Basis for functional abnormalities. Clin Geriatr Med 2002;18:103-20.
8. Wilhelm KP, Cua AB, Maibach HI. Skin aging. Effect on transepidermal water loss, stratum corneum hydration, skin surface pH, and casual sebum content. Arch Dermatol 1991;127:1806-9.
9. Kurban RS, Bhawan J. Histologic changes in skin associated with aging. J Dermatol Surg Oncol 1990;16:908-14
10. Rhie G, Shin MH, Seo JY, Choi WW, Cho KH, Kim KH, *et al*. Aging and photoaging dependent changes of enzymic and nonenzymic antioxidants in the epidermis and dermis of human skin *in vivo*. J Invest Dermatol 2001;117:1212-7.
11. Chung JH, Seo JY, Choi HR, Lee MK, Youn CS, Rhie G, *et al*. Modulation of skin collagen metabolism in aged and photoaged human skin *in vivo*. J Invest Dermatol 2001;117:1218-24.
12. Varani J, Dame MK, Rittie L, Fligiel SE, Kang S, Fisher GJ, *et al*. Decreased collagen production in chronologically aged skin: Roles of age-dependent alteration in fibroblast function and defective mechanical stimulation. Am J Patho 2006;168:1861-8.
13. Ohnishi Y, Tajima S, Akiyama M, Ishibashi A, Kobayashi R, Horii I. Expression of elastin-related proteins and matrix metalloproteinases in actinic elastosis of sun-damaged skin. Arch Dermatol Res 2000;292:27-31.
14. Waller JM, Maibach HI. Age and skin structure and function, a quantitative approach (II): Protein, glycosaminoglycans, water, and lipid content and structure. Skin Res Technol 2006;12:145-54.
15. Fleischmajer R, Perlish JS, Bashey RI. Human dermal glycosaminoglycans and aging. Biochim Biophys Acta 1972;279:265-75.
16. Gilchrest BA, Blog FB, Szabo G. Effects of aging and chronic sun exposure on melanocytes in human skin. J Invest Dermatol 1979;73:141-3.
17. Kelly RI, Pearse R, Bull RH, Leveque JL, de Rigal J, Mortimer PS. The effects of aging on the cutaneous microvasculature. J Am Acad Dermatol 1995;33:749-56.
18. Gniadecka M, Jemec GB. Quantitative evaluation of chronological aging and photoaging *in vivo:* Studies on skin echogenciity and thickness. Br J Dermatol 1998;139:815-21.
19. Rijken F, Kiekens RC, van den Worm E, Lee PL, van Weelden H, Bruijnzeel PL. Pathophysiology of photoaging of human skin: Focus on neutrophils. Photochem Photobiol Sci 2006;5:184-9.
20. Rikans LE, Hornbrook KR. Lipid peroxidation, antioxidant protection and aging. Biochim Biophys Acta 1997;1362:116-27.
21. Smith JB, Fenske NA. Cutaneous manifestations and consequences of smoking. J Am Acad Dermatol 1966;34:717-32.
22. Kadunce DP, Burr R, Gress R, Kanner R, Lyon JL, Zone JJ. Cigarette smoking: Risk factor for premature facial wrinkling. Ann Intern Med 1991;114:840-4.
23. Schmidt JB, Binder M, Demschik G, Bieglmayer C, Reiner A. Treatment of skin aging with topical estrogens. Int J Dermatol 1996;35:669-74.
24. Junqueira V, Barros S, Chan S, Rodrigues L, Giavarotti L, Abud R, *et al*. Aging and oxidative stress. Mol Aspects Med 2005;25:5-16.
25. Podda M, Traber MG, Weber C, Yan LJ, Packer L. UV-irradiation depletes antioxidants and causes oxidative damage in a model of human skin. Free Radic Bio Med 1998;24:55-65.
26. Sander CS, Chang H, Hamm F, Elsner P, Thiele JJ. Role of oxidative stress and the antioxidant network in cutaneous carcinogenesis. Int J Dermatol 2004;43:326-35.
27. Nishigori C, Hattori Y, Toyokuni S. Role of reactive oxygen species in skin carcinogenesis. Antioxid Redox Signal 2004;6:561-70.
28. Stone WL, Smith M. Therapeutic uses of antioxidant liposomes. Mol Biotech 2004;27:217-30.
29. Shindo Y, Witt E, Packer L. Antioxidant defense mechanisms in murine epidermis and dermis and their response to ultraviolet light. J Invest Dermatol 1993;100:260-5.

30. De Rios G, Chan JT, Black HS, Rudolph AH, Knox JM. Systemic protection by antioxidants against UVL-induced erythema. J Invest Dermatol 1978;70:123-5.
31. Lin JY, Selim MA, Shea CR, Grichnik JM, Omar MM, Monteiro-Riviere NA, *et al*. UV photoprotection by combination topical antioxidants vitamin C and vitamin E. J Am Acad Dermatol 2003;48:866-74.
32. Panin G, Strumia R, Ursini F. Topical alpha-tocopherol acetate in the bulk phase: Eight years of experience in skin treatment. Ann N Y Acad Sci 2004;1031:443-7.
33. Wefers H, Sies H. The protection by ascorbate and glutathione against microsomal lipid peroxidation is dependent on vitamin E. Eur J Biochem 1988;174:353-7.
34. Colven RM, Pinnell SR. Topical vitamin C in aging. Clin Derma 1996;14:227-34.
35. Lopez-Torres M, Thiele JJ, Shindo Y, Han D, Packer L. Topical application of alpha-tocopherol modulates the antioxidant network and diminishes ultraviolet-induced oxidative damage in murine skin. Br J Derma 1998;138:207-15.
36. Lever I, Kumar P, Marks R. Topical retinoic acid for treatment of solar damage. Br J Derma 1990;122:91-8.
37. Kligman LH, Duo CH, Kligman AM. Topical retinoic acid enhances the repair of ultraviolet damaged dermal connective tissue. Connect Tissue Res 1984;12:139-50.
38. Suh J, Wang H, Liu R, Liu J, Hagen T. (R)-α-lipoic acid reverses the age-related loss in Glutathione redox status in post-mitotic tissue: Evidence for increased cysteine requirement for Glutathione synthesis. Arch Biochem Biophys 2004;423:126-35.
39. Thiele JJ, Hsieh SN, Ekanayake-Mudiyanselage S. Vitamin E: Critical review of its current use in cosmetic and clinical dermatology. Dermatol Surg 2005;31:805-13.
40. Mayer P, Pittermann W, Wallat S. The effects of vitamin E on the skin. Cosmet Toil 1993;108:99-109.
41. Hoppe U, Bergemann J, Diembeck W, Ennen J, Gohla S, Harris I, *et al*. Coenzyme Q10, a cutaneous antioxidant and energizer. Biofactors 1999;9:371-8.
42. Srinivasan M, Sudheer AR, Pillai KR, Kumar PR, Sudhakaran PR, Menon VP. Lycopene as a natural protector against gamma-radiation induced DNA damage, lipid peroxidation, and antioxidant status in primary culture of isolated rat hepatocytes *in vitro*. Biochim Biophys Act 2007;1770:659-65.
43. Vayalil PK, Elmets CA, Katiyar SK. Treatment of green tea polyphenols in hydrophilic cream prevent UVB-induced oxidation of lipids and proteins, depletion of antioxidant enzymes and phosphorylation of MAPK proteins in SKH-1 hairless mouse skin. Carcinogenesis 2003;24:927-36.
44. Meeran SM, Katiyar S, Elmets CA, Katiyar SK. Silymarin inhibits UV radiation-induced immunosuppression through augmentation of interleukin-12 in mice. Mol Cancer Ther 2006;5:1660-8.
45. Mantena SK, Katiyar SK. Grape seed proanthocyanidins inhibit UV-radiation-induced oxidative stress and activation of MAPK and NF-kappaB signaling in human epidermal keratinocytes. Free Radic Biol Med 2006;40:1603-14.
46. Aslam MN, Lansky EP, Varani J. Pomegranate as a cosmeceutical source: Pomegranate fractions promote proliferation and procollagen synthesis and inhibit matrix metalloproteinase-1 production in human skin cells. J Ethnopharmacol 2006;103: 311-8.
47. Sime S, Reeve V. Protection from inflammation, immunosuppression, and carcinogenesis induced by UV radiation in mice by topical Pycnogenol. Photochem Photobiol 2004;79:193-8.
48. Souto E, Muller R. Nanoparticulate Drug Delivery Systems. Inform Healthc 2007;166:213-34.
49. Samad A, Sultana Y, Aqil M. Liposomal drug delivery systems: An update review. Curr Drug Deliv 2007;4:297-305.
50. Moussaoui N, Cansell M, Denizot A. Marinosomes, marine lipid-based liposomes: Physical characterization and potential application in cosmetics. Int J Pharm 2002;242:361-5.
51. Uchegbua I, Vyas S. Non-ionic surfactant based vesicles in drug delivery. Int J Pharm 1998;172:33-70.
52. Manconi M, Valenti D, Sinico C, Lai F, Loy G, Fadda AM. Niosomes as carriers for tretinoin: Influence of vesicular incorporation on tretinoin photostability. Int J Pharm 2003;260:261-72.
53. Müller RH, Radtke M, Wissing SA. Solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC) in cosmetic and dermatological preparations. Adv Drug Deliv Rev 2002;54 Suppl 1: S131-55.
54. Müller RH, Petersen RD, Hommoss A, Pardeike J. Nanostructured lipid carriers (NLC) in cosmetic dermal products. Adv Drug Deliv Rev 2007;59:522-30.
55. Bombardelli E, Curri S, Della R. Complexes between phospholipids and vegetal derivatives of biological interest. Fitoterapia 1989;90:1-9.
56. Laugel C, Baillet A, Youenang P, Marty J, Ferrier D. Oil-water-oil multiple emulsions for prolonged delivery of hydrocortisone after topical application, Comparison with simple emulsions. Int J Pharm 1998;160:109-17.
57. Siva M, Contente D, Filho P. Ascorbic acid liberation from o/w/o multiple emulsions. Cosmet Toil 1997;112:85-7.
58. Sonneville-Aubrun O, Simonnet JT, L'Alloret F. Nanoemulsions: A new vehicle for skincare products. Adv Colloid Interface Sci 2004;108-9:145-9.
59. Cevc G, Blume G. New, highly efficient formulation of diclofenac for transdermal administration in ultradeformable drug carriers, Transfersomes. Biochim Biophys Acta 2001;1514:191-205.
60. Dayan N, Touitou E. Carriers for skin delivery of trihexyphenidyl HCl: Ethosomes vs liposomes. Biomaterials 2000;21:1879-85.
61. Garg G, Saraf S, Saraf S. Cubosomes: An overview. Biol Pharm Bull 2007;30:350-3.
62. Keck C, Muller RH. Drug nanocrystals of poorly soluble drugs produced by high pressure homogenisation. Eur J Pharm Biopharm 2006;62:3-16.

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