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ScienceDirect
Molecular Aspects of Medicine 28 (2007) 646–667
MOLECULAR ASPECTS OF MEDICINE
www.elsevier.com/locate/mam

Review

Vitamin E in human skin: Organ-specific physiology and considerations for its use in dermatology

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Received 14 January 2007; revised 12 June 2007; accepted 12 June 2007

Abstract

Vitamin E has been used for more than 50 years in experimental and clinical dermatology. While a large number of case reports were published in this time, there is still a lack of controlled clinical studies providing a rationale for well defined dosages and clinical indications. In contrast, advances in basic research on the physiology, mechanism of action, penetration, bioconversion and photoprotection of vitamin E in human skin has led to the development of numerous new formulations for use in cosmetics and skin care products. This article reviews basic mechanisms and possible cosmetic as well as clinical implications of the recent advances in cutaneous vitamin E research. Experimental evidence suggests that topical and oral vitamin E has antitumorigenic, photoprotective, and skin barrier stabilizing properties. While the current use of vitamin E is largely limited to cosmetics, controlled clinical studies for indications such as atopic dermatitis or preventions of photocarcinogenesis are needed to evaluate the clinical benefit of vitamin E.

Keywords: Dermatology; Aging; Stratum corneum; Skin surface lipids; Sebum; Vitamin E; Tocopherol; Skin; Cosmetics; Cosmeceuticals; Skin care; Ultraviolet radiation; Surgery

Abbreviations: SC, stratum corneum; SSL, skin surface lipids; SqmOOH, squalene monohydroperoxide; SPT, sebum photo-oxidation test; UV, ultraviolet.

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doi:10.1016/j.mam.2007.06.001

Contents

1. Introduction

As the outermost organ of the body, the skin is frequently and directly exposed to a prooxidative environment, including ultraviolet radiation, drugs, and air pollutants. Besides external inducers of oxidative attack, the skin has to cope with endogenous generation of reactive oxygen species (ROS) and other free radicals, which are continuously produced during physiological cellular metabolism. To counteract the harmful effects of ROS, the various compartments of the skin (stratum corneum/skin barrier, epidermis, dermis, subcutis) are equipped with layer-specific antioxidant systems, which help to maintain an equilibrium between ROS and antioxidants and thus prevent oxidative stress. The antioxidant defense in cutaneous tissues can be overwhelmed by either an increased exposure to exogenous (e.g., UV-exposure) or endogenous (e.g., inflammatory disorders) sources of ROS, or by a primarily depleted antioxidant defense (e.g., by genetic defects or malnutrition) facing a normal level of prooxidative challenge. In skin, the induction of oxidative damage by environmental stimuli such as UVA, UVB, and ozone was demonstrated to occur in lipids (Thiele et al., 1998a; Thiele et al., 1997b,c), proteins (Thiele et al., 1998b), and DNA (Beehler et al., 1992; McVean and Liebler, 1997).

Vitamin E is an essential nutrient that is receiving growing attention in the skin care industry because of its antioxidant properties. While some antioxidants such as glutathione or ubiquinol-10 can be synthesized by humans, levels of cutaneous vitamin E depend on its oral intake or topical delivery. The main natural sources of vitamin E are fresh vegetables, vegetable oils, cereals and nuts. A recently published study analyzing dietary data from almost 10,000 individuals suggests that the majority of men and women in the United States fail to meet the current recommendations for vitamin E intake (Maras et al., 2004).

The aim of this article is to review experimental and clinical data available on the physiology and biological activity of vitamin E in human skin with special emphasis on its antioxidative and photoprotective properties.

2. Prevalence of vitamin E in murine and human skin

As demonstrated in other body tissues, α-tocopherol is the predominant vitamin E homologue in murine and human skin (Shindo et al., 1994; Thiele et al., 1998a; Thiele et al., 1997b). In addition, γ-tocopherol is present in murine and human epidermis, dermis and stratum corneum. The α-tocopherol/γ-tocopherol molar ratio in the human dermis and epidermis is ≈10:1. Notably, a vitamin E gradient has been demonstrated in human upper arm stratum corneum. The highest α-tocopherol levels were found in the lower stratum corneum, whereas the lowest levels were present in the upper layers. The α-tocopherol/γ-tocopherol ratio decreased from about 10:1 in the lower layers to about 3:1 in the upper stratum corneum. The α-tocopherol levels in human dermis and epidermis were several fold higher than in corresponding layers of hairless mouse skin (Shindo et al., 1994, 1993). Consistently, human stratum corneum contains almost 10-fold higher α-tocopherol levels than measured in murine stratum corneum (Thiele et al., 1998a, 1997b) (Table 1). As observed for hydrophilic antioxidants, higher vitamin E levels were found in murine and human epidermis, as compared with dermal levels. It remains to be clarified whether the uptake and transport of α-tocopherol in the epidermis is an unspecific and passive process or, as described for human hepatocytes (Traber and Sies, 1996), is regulated by a mechanism involving a specific binding enzyme (α-tocopherol transfer protein).

Table 1
Physiological levels of α- and γ-tocopherol in cutaneous tissues

Skin layer	Species	Concentration	Authors & year
Total skin	Mouse	200 pmol α-tocopherol/mg protein	Fuchs et al. (1989a,b)
Epidermis	Mouse	4.8 ± 0.5 nmol α-tocopherol/g tissue	Shindo et al. (1993)
Dermis	Mouse	3.3 ± 0.3 nmol α-tocopherol/g tissue	Shindo et al. (1993)
Epidermis	Human	31 ± 3.8 nmol α-tocopherol/g tissue 3.3 ± 1 nmol γ-tocopherol/g tissue	Shindo et al. (1994)
Dermis	Human	16.2 ± 1.1 nmol α-tocopherol/g tissue 1.8 ± 0.2 nmol γ-tocopherol/g tissue	Shindo et al. (1994)
Stratum corneum	Mouse	8.4 ± 1.3 nmol α-tocopherol/g tissue 2.9 ± 0.9 nmol γ-tocopherol/g tissue	Thiele et al. (1997b)
Stratum corneum	Human	33 ± 4 nmol α-tocopherol/g tissue 4.8 ± 0.8 nmol γ-tocopherol/g tissue	Thiele et al. (1998a)
Sebum	Human	76.5 ± 1.5 nmol α-tocopherol/g sebum 8.7 ± 1.8 nmol γ-tocopherol/g sebum	Thiele et al. (1999)

Table was modified from Thiele et al. (2000).

3. Effect of exogenous stressors on cutaneous vitamin E levels

Irradiation of human skin with solar simulated ultraviolet-light (SSUV; UVA and UVB) at doses below those that cause a mild redness of the skin one day after exposure (0.75 minimal erythema dose, MED) deplete human stratum corneum α-tocopherol by almost 50%, and murine stratum corneum α-tocopherol by 85%, both detected directly after exposure (Thiele et al., 1998a). Therefore, α-tocopherol depletion in the stratum corneum is considered a very early and sensitive event of photooxidative damage in skin (Thiele et al., 1998a). The high susceptibility of stratum corneum vitamin E to SSUV may be, at least in part, due to a lack of co-antioxidants in the stratum corneum. Ascorbate, the major hydrophilic co-antioxidant that is capable of recycling photooxidized α-tocopherol (Kagan et al., 1992a; Kitazawa et al., 1997), is present only at very low levels in murine and human stratum corneum, as compared to epidermal and dermal tissue levels (Weber et al., 1999).

Vitamin E may be depleted: (a) directly, by absorption of UVB-radiation, and/or (b) indirectly, by excited-state singlet oxygen or reactive oxygen intermediates that are generated by photosensitizers upon UV-absorption also in the UVA-range. Since both, UVB and UVA alone have been shown to deplete murine α-tocopherol, both mechanisms may be relevant. The absorption maxima of α- and γ-tocopherol fall between 290 and 295 nm (Baxter et al., 1943; Yuen and Halliday, 1997) and thus extend well into the solar UV-spectrum. Interestingly, a large part of terrestrial UVB around 290–300 nm is absorbed in the human stratum corneum. Furthermore, depletion of α-tocopherol by UVR is maximal at wavelengths in the range of its absorption maximum in skin homogenates of hairless mice (Kagan et al., 1992a). This congruency suggests that α-tocopherol is directly destroyed upon short wavelength UVB absorption. Indeed, tocopheroxyl radical formation occurs in UVB irradiated skin homogenates (Kagan et al., 1992a). Direct depletion of α-tocopherol and formation of its radical may also affect other endogenous antioxidant pools. As mentioned previously, α-tocopherol is readily regenerated from its radical at the expense of reductants like ascorbate (Kagan et al., 1992a,b), which itself can be regenerated by glutathione (Martensson and Meister, 1992). In addition to direct depletion by UVB, skin α-tocopherol levels may also be consumed as a consequence of its chain-breaking antioxidant action. The absorption of UVB and UVA photons by endogenous photosensitizers (e.g., porphyrins, riboflavin, quinones, and bilirubin) results in its electronically excited state (Kochevar et al., 1996; Rosenstein et al., 1983). The excited sensitizer subsequently reacts with another substrate (type I reaction) to form radicals or radical ions, or with oxygen (type II reaction) to generate singlet oxygen (Foote, 1991). Photosensitizers, such as melanin, are present in variable amounts in the stratum corneum (Jimbow et al., 1993). Hence, their wavelength-dependent potential to generate or to quench free radicals, and to absorb UVR may modulate α-tocopherol depletion during and after solar exposure.

Another exogenous stressor that was shown to affect cutaneous vitamin E levels is the air pollutant ozone on skin antioxidants: While no depletion of vitamin E was observed when full thickness skin was analyzed (Thiele et al., 1997a), α-tocopherol depletion was detected in the outer epidermis when skin layers were analyzed

separately (Thiele et al., 1997c). It was concluded that ozone itself is too reactive to penetrate deeply into skin and reacts rapidly with skin barrier lipids and proteins (Thiele et al., 1998b). Consequently, it was demonstrated that the stratum corneum is the most susceptible skin layer for ozone induced vitamin E depletion (Thiele et al., 1997b). Furthermore, we have demonstrated that stratum corneum Vitamin E is highly susceptible to topical treatment with benzoyl peroxide (Weber et al., 2003).

4. Use of vitamin E in skin disorders

Despite more than half a century of research, there is still insufficient evidence from controlled studies concerning vitamin E's effectiveness in treating specific dermatologic disorders. In mostly small trials and case reports, oral vitamin E supplementation is recommended in the therapy of yellow nail syndrome, vibration disease, epidermolysis bullosa, cancer prevention, claudication, cutaneous ulcers, and collagen synthesis and wound healing (reviewed in: (Fuchs, 1992; Pehr and Forsey, 1993)). Clearly, with vitamin E not being a pharmaceutical drug, there is a lack of placebo controlled studies for treatment of these conditions. However, in the field of skin care, which includes cosmeceuticals, there is a large body of experimental evidence pointing to photoprotective effects (Table 2). Moreover, recent studies indicate that the use of vitamin E may provide dermatological benefits that surpass the purpose of cosmetics and may extend into an area that has been termed "cosmeceuticals".

Although anecdotal reports support the topical use of vitamin E for scar prevention, the benefit of vitamin E on scar formation remains inconclusive. Two controlled studies failed to show scar prevention by topical vitamin E (Baumann and Spencer, 1999; Jenkins et al., 1986). However, it remains unclear in how far the stability and formulation of topical vitamin E may have affected the outcome of these studies. New evidence from studies on diabetic mouse models point to an involvement of oxidative stress in diabetic wound healing and significantly improved wound healing by topical vitamin E (Altavilla et al., 2001; Galeano et al., 2001).

Recently, Tsoureli-Nikita et al. performed a clinical single blind, placebo controlled study in which 96 atopic dermatitis patients were treated with either placebo or oral vitamin E (400 IE/day) for 8 months. They found an improvement and near remission of atopic dermatitis and a 62% decrease in serum IgE levels in the vitamin E treated group. The correlation between α-tocopherol intake, IgE levels, and the clinical manifestations of atopy suggests that oral vitamin E could be an excellent therapeutic adjunct for atopic dermatitis (Tsoureli-Nikita et al., 2002). Another multi-clinical double-blinded study revealed a significant improvement of chloasma and pigmented contact dermatitis lesions using topical vitamins E and C, with the combination clearly proving superior to the single vitamin treatment groups (Hayakawa et al., 1981). Topical formulations used for depigmentation that contain vitamins C and E, besides the commonly used hydroquinone and sunscreens, appear to be safe and efficient (Guevara and Pandya, 2003). Furthermore, there is evidence that oxidative stress is involved in the pathophysiology of melanoma and

Table 2
Studies on the photoprotective potential of topical vitamin E and its derivatives *in vivo*

Compound(s)	Species	Endpoint(s)	Efficacy	Remarks	Reference
Vitamin E Vitamin E acetate	Rabbit	Erythema (MED)	Vitamin E protective; vitamin E acetate not protective	BHT also protective; Vitamin E also protective when applied after UVR-exposure	Roshchupkin et al. (1979)
Vitamin E	Human	Mechanoelectrical properties of skin	Protection against UVR-, and PUVA-induced damage		Potapenko et al. (1983)
Vitamin E Vitamin E derivatives	Human, rabbit	PUVA-induced erythema and changes in mechanoelectrical properties of skin	Vitamin E and derivatives with shorter hydrocarbon chain protective; vitamin E acetate not protective	No protection of vitamin E and derivatives when applied after UVR-exposure	Potapenko et al. (1984)
Vitamin E	Mouse	Lipid peroxidation	Protective	Vitamin A, BHT, and β-carotene also protective	Khettab et al. (1988)
Vitamin E	Mouse	Skin wrinkling, skin tumor incidence, and histology	Protective		Bissett et al. (1989)
Vitamin E	Human	Erythema (MED)	Protective	SPF-determination	Möller et al. (1989)
Vitamin E Trolox® Vitamin E acetate Vitamin E succinate Vitamin E linoleate Vitamin E nicotinate	Mouse	Skin wrinkling and sagging, skin tumor incidence, and histology	Vitamin E esters not as protective as vitamin E or vitamin E analog Trolox®; no protection against UVA-induced skin sagging	Glutathione, β-carotene, BHT, and mannitol not protective	Bissett et al. (1990)
Vitamin E	Mouse	Skin tumor incidence and immunosuppression	Protective	Prolonged pre-treatment	Gensler and Magdaleno (1991)

(*continued on next page*)

Table 2 (*continued*)

Compound(s)	Species	Endpoint(s)	Efficacy	Remarks	Reference
Vitamin E Vitamin E acetate	Rat	UVA-induced binding of 8-MOP and CPZ to epidermal biomacromolecules	Vitamin E protective after single application; vitamin E acetate only protective after prolonged application	Limited conversion of vitamin E acetate into vitamin E after single application	Schoonderwoerd et al. (1991)
Vitamin E acetate	Mouse	Lipid peroxidation and DNA-synthesis rate	Protective		Record et al. (1991)
Vitamin E	Mouse	Skin wrinkling, skin tumor incidence, and histology	Protective	Additive protection in combination with anti-inflammatory agents	Bissett et al. (1992)
Vitamin E acetate	Mouse	Erythema, edema, and skin sensitivity	Protective	Treatment immediately after UVR-exposure	Trevithick et al. (1992)
Vitamin E acetate	Mouse	Edema and histology	Protective	Delayed treatment after UVR-exposure; increased skin vitamin E concentration	Trevithick et al. (1993)
Vitamin E Vitamin E acetate Vitamin E sorbate	Mouse	Skin wrinkling	Vitamin E and sorbate ester protective; vitamin E acetate ester only modestly protective	Sorbate ester more protective than free vitamin E	Jurkiewicz et al. (1995)
Vitamin E Vitamin E acetate	Human	Erythema (skin color)	Moderate protection of vitamin E and vitamin E acetate when applied occlusively after UVR-exposure	No protection when applied occlusively before UVR-exposure	Montenegro et al. (1995)
Vitamin E Vitamin E acetate	Rat	UVA-induced binding of 8-MOP to epidermal biomacromolecules	Vitamin E protective; vitamin E acetate only protective after prolonged application	Conversion of vitamin E acetate into vitamin E slow	Beijersbergen van Henegouwen et al. (1995)

Vitamin E acetate Vitamin E succinate	Mouse	Skin tumor incidence and immunosuppression	No protection		Gensler et al. (1996)
Vitamin E	Yorkshire pig	Sunburn cell formation	Protection against UVR-induced damage	Minimal protection in reducing PUVA-induced damage	Darr et al. (1996)
Vitamin E	Mouse	Immunosuppression and lipid peroxidation	Protective	No protection when applied after UVR-exposure	Yuen and Halliday (1997)
Vitamin E	Mouse	Histology (sunburn cell formation and skin thickness)	Protective		Ritter et al. (1997)
Vitamin E Vitamin E acetate Vitamin E methyl ether	Mouse	Formation of DNA-photoadducts	Vitamin E derivatives less protective than vitamin E	Sunscreening properties of vitamin E	McVean and Liebler (1997)
Vitamin E	Mouse	Chemiluminescence after UVA-exposure	Protective	β-Carotene also protective	Evelson et al. (1997)
Vitamin E	Mouse	Formation of DNA-photoadducts in epidermal p53 gene	Protective		Chen et al. (1996)
Vitamin E	Mouse	Lipid peroxidation	Protective	Skin's enzymatic and non-enzymatic antioxidant capacity investigated	Lopez-Torres et al. (1998)

(*continued on next page*)

Table 2 (*continued*)

Compound(s)	Species	Endpoint(s)	Efficacy	Remarks	Reference
Vitamin E	Human	Erythema (skin color and skin blood flow)	Moderate protection	No protection when applied after UVR-exposure; SPF (determined in vitro) = 1	Dreher et al. (1999)
Vitamin E α-Tocopherol γ-Tocopherol Vitamin E acetate Vitamin E methyl ether	Mouse	Formation of DNA-photoadducts	Vitamin E, α-tocopherol and γ-tocopherol protective; vitamin E acetate and vitamin E methyl ether not protective	Application as dispersion in cream	McVean and Liebler (1999)
Vitamin E Vitamin E succinate	Mouse	Erythema, pigmentation, skin tumor incidence	Protective after prolonged application	No sign of toxicity observed for vitamin E and vitamin E succinate	Burke et al. (2000)
Vitamin E	Human	Formation of macrophage metalloelastase mRNA after UV-exposure	Protective with 5% Vitamin E occlusive application for 24 h prior UV-exposure	Pretreatment of skin with 20% NAC also protective	Chung et al. (2002)
Vitamin E	Yorkshire pig	Antioxidant protection factor, erythema, sunburn cells, thymine dimers	1% Vitamin E protective, but stronger protective in combination with 15% vitamin C	Appliction on 4 consecutive days	Lin et al. (2003)

BHT, butylated hydroxytoluene; CPZ, chlorpromazine; MED, minimal erythema dose; 8-MOP, 8-methoxypsoralen; PUVA, 8-methoxypsoralen and UVA-treatment; SPF, sun protection factor.

non-melanoma cancer (Sander et al., 2003), and that vitamin E slows melanoma growth by promoting tumor cell apoptosis and inhibiting VEGF-mediated angiogenesis (Malafa et al., 2002a,b). Despite these and other encouraging results on beneficial clinical effects of vitamin E, further research in form of well-designed controlled trials is needed to clarify the role of vitamin E and its derivatives in the above mentioned and further skin disorders.

5. Rationale for use of vitamin E and co-antioxidants for photoprotection

A series of studies investigating non-enzymatic stratum corneum antioxidants have demonstrated that vitamin E is the predominant physiological barrier antioxidant in human skin (Thiele et al., 2001). When compared to nucleated epidermal layers, there is a lack of important co-antioxidants, such as vitamin C, in the stratum corneum as well as in the dermis. Taken together, these findings suggest that the skin barrier as well as the upper dermis reveal a lack of antioxidant protection. In fact, upon solar UV-exposure, these are the cutaneous sites exhibiting the most pronounced oxidative protein damage (Sander et al., 2002). Accordingly, antioxidant supplementation with vitamin E as well as synergistically active co-antioxidants, such as vitamin C, may enhance the photoprotective strategies of sunscreens.

6. Photoprotection provided by vitamin E

The largest body of scientific evidence for a beneficial role of topical vitamin E exists for photoprotection (Table 2). Numerous topical studies have demonstrated that vitamin E application prior to ultraviolet exposure significantly reduces acute skin responses, such as erythema and edema, sunburn cell formation (Darr et al., 1996; Lin et al., 2003; Ritter et al., 1997), lipid peroxidation (Khettab et al., 1988; Lopez-Torres et al., 1998; Yuen and Halliday, 1997), DNA-adduct formation, immunosuppression (Gensler and Magdaleno, 1991; Yuen and Halliday, 1997), as well as UVA-induced binding of photosensitizers (Beijersbergen van Henegouwen et al., 1995; Schoonderwoerd et al., 1991) and chemiluminescence (Evelson et al., 1997). Chronic skin reactions due to prolonged UVB/UVA-exposure, such as skin wrinkling (Bissett et al., 1990, 1992, 1989; Jurkiewicz et al., 1995), and skin tumor incidence (Bissett et al., 1990, 1992, 1989; Burke et al., 2000; Gensler and Magdaleno, 1991) were also diminished by topical vitamin E formulations. While few studies have demonstrated a significant penetration of topical vitamin E into dermal layers, there is still debate concerning the efficacy of topical vitamin E for protecting dermal components in human skin. Chung et al. demonstrated that a topical, occlusive pretreatment with 5% vitamin E for 24 h protected against UV-induced upregulation of human macrophage metalloelastase in human skin *in vivo* (Chung et al., 2002). Together with other studies (Lopez-Torres et al., 1998), this work suggests that topically applied vitamin E has the potential to penetrate into dermal layers,

where much of oxidative protein oxidation occurs (Sander et al., 2002), and thus protects against photoaging.

Vitamin E esters, particularly vitamin E acetate, were also shown to be promising agents in reducing UV-induced skin damage (Beijersbergen van Henegouwen et al., 1995; Bissett et al., 1990; Burke et al., 2000; Jurkiewicz et al., 1995; Record et al., 1991; Schoonderwoerd et al., 1991; Trevithick et al., 1993, 1992). However, their photoprotective effects appear to be less pronounced as compared to vitamin E; as a result, some studies failed to detect photoprotection provided by vitamin E esters. Since the antioxidant properties of vitamin E are attributed to its free aromatic hydroxyl group, vitamin E esters need to be hydrolyzed during skin absorption to show activity. Vitamin E acetate was shown to be absorbed and penetrate skin (Kamimura and Matsuzawa, 1968; Norkus et al., 1993; Trevithick and Mitton, 1993). For better stability, vitamin E is commonly used as a biologically non-active esterified form, such as vitamin E acetate. Vitamin E esters act as a pro-drug since they are hydrolyzed to the active, free vitamin E (α-tocopherol) upon penetration into skin. However, there is conflicting evidence as to what extent this conversion actually takes place in the SC (Alberts et al., 1996; Baschong et al., 2001; Nabi et al., 2001; Rangarajan and Zatz, 2001b). Most studies suggest that in human stratum corneum, the bioconversion of vitamin E esters into vitamin E is far less than in nucleated epidermal layers. Therefore, α-tocopherol should provide a more efficient antioxidant protection of skin surface lipids and skin barrier constituents than vitamin E esters. In the nucleated epidermis, however, the bioconversion of vitamin E acetate into vitamin E occurs at a much higher rate, but seems to be dependent on formulation (Baschong et al., 2001; Rangarajan and Zatz, 2001a). Some evidence exists suggesting that the bioconversion of vitamin E acetate into vitamin E might be enhanced due to UV-exposure (Kramer-Stickland and Liebler, 1998). UVB-exposure was demonstrated to cause an increase in esterase activity in murine epidermis.

In view of the vast experimental evidence for the photoprotective properties of antioxidants, it was suggested that the addition of synergistic co-antioxidants, such as vitamins C and E, may increase the photoprotective potential of modern sunscreen formulations (Thiele et al., 2000). Indeed, recent reports suggests that currently available broad-spectrum sunscreen formulations, while efficient in preventing erythema formation, poorly protect against UVA-induced free radical formation in human skin (Haywood et al., 2003). Importantly, vitamin E acetate, as well as sodium ascorbyl phosophatate have been shown to be bioconverted to the vitamins E and C, and thus to significantly improve photoprotection of sunscreens against free radical formation in viable epidermal layers (Hanson and Clegg, 2003).

7. Dosage and practical use in skin care products

While numerous topical skin care products claim to contain "vitamin E", these products may actually contain very different concentrations and formulations including active vitamin E, its several esters and many other derivatives. Product for-

mulation data submitted by the Food and Drug Administration (FDA) in 1998 reported that α-tocopherol was present in a total of 1072 cosmetic formulations, tocopheryl acetate in 1322, tocopherol linoleate in 279, tocopherol nicotinate in 3, tocopherol succinate in 4, potassium ascorbyl tocopheryl phosphate in 15, and tocophersolan in 2 formulations (FDA, 1998). While topical α-tocopherol is mostly used at concentrations of 5% or less, products with concentrations of 0.0001% and more than 20% vitamin E/vitamin E esters have been developed and marketed in Europe and the USA. According to data submitted to the Cosmetic, Toiletry, and Fragrance Association (CFTA), vitamin E acetate was used at concentrations $\leqslant$36%, tocopherol linoleate and – nicotinate at $\leqslant$2% (the latter recommended at 0.1–1%), dioleyl tocopheryl methylsilanol at 3–6%, potassium ascorbyl tocopheryl phosphate at 0.02%, and tocophersolan at $\leqslant$0.2% (Zondlo Fiume, 2002) (Table 3).

Notably, there is a striking lack of published data on dose–response studies defining the optimal dosage of vitamin E. This could certainly be due to limited efficacy control requirements for non-pharmaceuticals, such as vitamin E. Furthermore, it may also be attributed to ill-defined study endpoints as well as to the difficulty of measuring oxidative stress *in vivo*. Recent advances in biophysical (e.g., ultra weak photon emission; near-infrared/Raman spectroscopy; electron paramagnetic resonance (Fuchs et al., 2002)) and biochemical research (e.g., the recent identification of highly sensitive and specific skin surface lipid photo-oxidation products/SqmOOH (Ekanayake-Mudiyanselage et al., 2003)) have led to the development of non-invasive assays (e.g., the "sebum photo-oxidation test" (Ekanayake-Mudiyanselage et al., 2002)) that will help to better define relevant dose–response curves of antioxidants such as vitamin E.

Using this approach, we have recently demonstrated that even the use of rinse off products containing α-tocopherol in concentrations of less than 0.2% leads to significantly increased levels of vitamin E in the stratum corneum of human skin and protects against lipid peroxidation *in vivo* (Ekanayake-Mudiyanselage et al., 2005). Therefore, topical formulations containing α-tocopherol at concentrations ranging from 0.1% to 1% are likely to be effective skin care measures to enhance antioxidant protection of the skin barrier. According to the antioxidant network theory, combinations with co-antioxidants such as vitamin C may help to enhance antioxidant effects and the stability of vitamin E.

8. Special dermatologic considerations, contraindications and adverse effects

8.1. Allergic contact dermatitis

Although vitamin E and its derivatives are widely used in many topical cosmetic products, reports of side effects such as allergic or irritant skin reactions are rare. In clinical studies, tocopherol and tocopherol acetate were found to be safe for use in topical skin formulations since irritant or sensitizing reactions were found only in very small percentages. With respect to oral supplementation, reproductive and developmental toxicity tests in animals using tocopherol and many of its derivatives

Table 3
Concentration of use, function and product formulation data of vitamin E and its derivatives

Compound	Concentration of use (%)	Antioxidant function	Function as skin-conditioning agent
Tocopherol	Baby products: 1 Bath products/shampoo/rinse off products: 0.01–0.8 Deodorants: 0.05 Hair products: 0.01–0.6 After shave lotion: 0.2 Moisturizing preparations, creams, lotions, body/hand ointments: 0.05–2 sun tan gels and creams: 0.001–0.3 Make up preparations (e.g., liquids, eye shadows, lipsticks, face powders, blushers, foundations): 0.001–0.9	Antioxidant; humectant; skin protectant	Occlusive; humectant; emollient; miscellaneous
Tocopheryl acetate	Baby products: 0.001–1 Bath products/shampoo/rinse off products: 0.0001–25 Deodorants: 0.2 Hair products: 0.001–0.3 After shave lotion: 0.2 Moisturizing preparations, creams, lotions, body/hand ointments: 0.001–25 suntan gels and creams: 0.05–1 Cosmetics (e.g., make up liquids, eye shadows, lipsticks, face powders, blushers, foundations): 0.02–0.8	Antioxidant; humectant; skin protectant	Humectant; emollient; miscellaneous
Tocopheryl linoleate	Shaving cream: 2	Antioxidant	Miscellaneous
Tocopheryl linoleate/oleate	Moisturizing preparations, creams, lotions, body/hand ointments: 0.1–2 suntan gels and creams: 2 Cosmetics (e.g., make up liquids, eye shadows, lipsticks, face powders, blushers, foundations): 0.1–2	Antioxidant	Emollient; miscellaneous

Tocopheryl nicotinate	Shampoo/rinse off products: 0.0001–1 Hair conditioner: 0.1–1 After shave lotion: 0.2 Moisturizing preparations, creams, lotions, body/hand ointments: 0.1 Make up preparations (e.g., liquids, eye shadows, lipsticks, face powders, blushers, foundations): 0.1	Antioxidant	Miscellaneous;
Potassium ascorbyl tocopheryl phosphate	Moisturizing preparations, creams, lotions, body/hand ointments: 0.02 suntan gels and creams: 0.02 make up preparations (e.g., liquids, eye shadows, lipsticks, face powders, blushers, foundations): 0.02	Antioxidant	Anti-dandruff agent
Tocophersolan	Moisturizing preparations, creams, lotions, body/hand ointments: 0.2 ski freshener: 0.05	Antioxidant	
Tocopheryl succinate	Use in food supplementation; 1 mg D-α-tocopheryl succinate = 1.21 IU α-tocopherol	Antioxidant; humectant; skin protectant	Humectant; emollient;

According to data compiled by the cosmetic, toiletry, and fragrance association (CFTA); modified from Zondlo Fiume (2002).

were overwhelmingly negative or even showed some effect of reducing toxicity (reviewed in Zondlo Fiume, 2002). In case reports, however, clinical side effects have been described after topical application of vitamin E containing products, e.g., local and generalized contact dermatitis, contact urticaria, and erythema-multiforme-like eruptions (Brodkin and Bleiberg, 1965). In 1992, an "epidemic outbreak" of about 1000 cases of allergic papular and follicular contact dermatitis caused by α-tocopherol linoleate in a cosmetic line was reported in Switzerland (Perrenoud et al., 1994). The authors found that this compound was easily oxidized under the storage condition used. Therefore, secondary or tertiary oxidation products of α-tocopherol linoleate, rather than the reduced vitamin E ester are likely to have caused irritation or even the oxidation of proteins and subsequent hapten formation. Positive patch test reactions were also reported in several cases after application of α-tocopherol acetate (De Groot et al., 1991; Manzano et al., 1994). In general, however, positive patch test results due to α-tocopherol are rare and need to be critically reviewed. Some authors of case reports have used the oil of vitamin E capsules for patch testing assuming to test "pure vitamin E" without evaluating the containing tocopherol derivatives, source or further components of these capsules (Fisher, 1991; Harris and Taylor, 1997). After correspondence with the manufacturer, some authors could not exclude that the symptoms of their patients could be caused from soybean oil, glycerin or gelatin, all also present in the accused topical applied vitamin E capsules (Harris and Taylor, 1997). Some animal studies even suggest that topical vitamin E at a concentration of 20% suppressed allergic and irritant contact dermatitis, exerting a comparable effect to that of a 0.5% prednisolone ointment. Furthermore, this vitamin E formulation protected efficiently from contact dermatitis induced loss of skin barrier function (Kuriyama et al., 2002).

8.2. Vitamin E intake during pregnancy

Oral vitamin E doses between 50 IU and 1000 IU per day have been tolerated in humans with no or minimal side effects. Vitamin E supplements for pregnancy usually contain only small doses of vitamin E, although adverse effects have not been observed even at higher doses (Brigelius-Flohe et al., 2002). Theoretically, however, due to the involvement of the cytochrome P450 system in the metabolism of orally supplemented *RRR*-α-tocopherol, drug interactions have to be taken into account when supra nutritional dosages of vitamin E are provided. To the best of our knowledge, there is no published report documenting adverse fetal effects due to use of topical vitamin E products.

8.3. Oral vitamin E intake and dermatologic surgery

In order to assess the risk of bleeding complications associated with dermatological surgery, many patient questionnaires and consent forms used in the US ask not only for intake of medicated anticoagulants, such as Coumadin® and Aspirin®, but also for oral vitamin E intake. The latter is based on studies investigating the influence of tocopherols and their derivatives on platelet aggregation, adhesion, and vas-

cular thrombosis (Freedman et al., 1996; Steiner, 1999). While various *in vivo* and *in vitro* human and animal data suggest an inhibitory effect of oral vitamin E on platelet aggregation and adhesion at various concentrations of tocopherol and its derivatives; other human studies have refuted this anti-platelet aggregation theory (Dereska et al., 2006; Freedman et al., 1996; Freedman and Keaney, 2001; Saldeen et al., 1999; Steiner, 1983; Steiner, 1999).

In a recent study by Dereska et al. 40 healthy volunteers were supplemented with a dosage of 800 IU dl-α-tocopherol acetate for 14 days (Dereska et al., 2006). Whole blood was analyzed for platelet aggregation, coagulation profile, and simulated bleeding time. Moderate dosage of α-tocopherol did not appear to have a significant impact on any parameter when comparing pre- and post-supplementation in whole blood *in vivo*. However, the power of the performed test was below the desired value of 0.8, and these negative findings should be interpreted with caution. In addition, larger volume, prospectively controlled trials are necessary to make a definitive conclusion (Dereska et al., 2006). General recommendations in many outpatient surgery settings are to discontinue anti-platelet agents such as aspirin 5–7 days prior to surgery. However, little is known to date regarding bleeding complications in surgical patients due to oral Vitamin E intake. Liede et al. demonstrated differences in bleeding tendency in patients using Vitamin E, as well as a combination of Vitamin E and aspirin (Liede et al., 1998). Male subjects, all smokers, were enlisted from a controlled clinical trial (A-Tocopherol, Beta-Carotene Cancer Prevention Study). Gingival bleeding was assessed with the use of a dental probe in 191 men on 50 mg/day of α-tocopherol and 30 men on α-tocopherol and aspirin. Bleeding was reported as a percentage of bleeding sites, and α-tocopherol was found to increase gingival bleeding compared to men on no supplementation. In combination with aspirin, α-tocopherol significantly increased gingival bleeding compared to those who refrained from aspirin and Vitamin E (33.4% versus 25.8%) (Liede et al., 1998). Recently, Marsh and Coombes showed that dietary supplementation of vitamin E and α -lipoic acid prolongs clotting time via inhibition of an intrinsic coagulation pathway (Marsh and Coombes, 2006). In healthy rats, activated partial thromboplastin time was significantly prolonged following supplementation of vitamin E and α-lipoic acid while prothrombin time (PT) remained unchanged. Therefore, while the role of tocopherols and their oxidation products in inhibit platelet aggregation and bleeding time remains controversial, simultaneous supplementation of anticoagulants and vitamin E is not recommended (Brigelius-Flohe et al., 2002; Marsh and Coombes, 2006). Given the growing popularity of food supplements, it appears justified to screen candidates for dermatological surgery not only for medicated anticoagulants but also for high doses, prolonged use, and simultaneous intake of high doses of dietary supplements, such as vitamin E and α-lipoic acid.

9. Outlook

As indicated above, topical strategies alone may not be sufficient to bolster the skin's antioxidative defense in the dermis and thus prevent or lessen photoaging in

this skin compartment. Therefore, current research on vitamin E focuses on systemic delivery of vitamin E to the various compartments of human skin. It was recently discovered that human sebum contains high amounts of α-tocopherol and that sebaceous gland secretion is a relevant physiological delivery pathway of α-tocopherol to sebaceous gland-rich skin regions, such as facial skin (Thiele et al., 1999). Similarly, orally administered drugs have been reported to be transported to the skin surface and stratum corneum by the sebaceous gland secretion route (Faergemann et al., 1995). A randomized human vitamin E supplementation trial with daily intake of either 400 mg RRR-α-tocopheryl acetate (RRR-α-toc) or 400 mg all-rac-α-tocopheryl acetate (all-rac-α-toc) for 14 days investigated possible increases in cutaneous vitamin E. Fasting blood samples, facial sebum samples, and lower-arm skin surface lipids (SSL) were taken at time-points between 0 and 21 days. Remarkably, while unchanged until day 14, α-tocopherol sebum levels were increased on day 21 in both the RRR-α-toc and the all-rac-α-toc group by 87% and 92%, respectively. With respect to dietary supplementation of vitamin E and its bioavailability in human skin, these results suggested that (1) sebaceous gland secretion is a relevant delivery mechanism; (2) the bioavailabilities of RRR-α-toc and the all-rac-α-toc are similar; and (3) significant accumulation requires a daily supplementation period of at least 2–3 weeks (Ekanayake-Mudiyanselage et al., 2004). Thus, oral supplementation of vitamin combined with topical application may have implications for conditions of sebostatic, dry skin (e.g., atopic dermatitis) as well as for the skin of pre-pubertal children, who have a low activity of sebaceous glands (Ekanayake-Mudiyanselage et al., 2005; Ekanayake-Mudiyanselage and Thiele, 2006).

Animal and human studies have convincingly demonstrated significant photoprotective effects of natural and synthetic vitamin E when applied topically before UVA and UVB-exposure. However, particularly with respect to UVB-induced skin damage, the photoprotective effects of most antioxidants were modest, as compared to sunscreens. Regarding photoprotective effects against UVA-induced skin alterations, which are largely determined by oxidative processes, topical administration of antioxidant mixtures containing vitamin E might be particularly promising as adjuncts to modern sunscreen formulations. A better knowledge of the unique skin-specific physiology of vitamin E, including its percutaneous penetration, skin barrier interactions, bioconversion of vitamin E esters, and cutaneous delivery pathways of oral vitamin E could help to develop more efficacious skin care products and to better evaluate indications and dosage regimen for prevention and treatment of acute and chronic skin disorders.

References

Alberts, D.S., Goldman, R., Xu, M.J., Dorr, R.T., Quinn, J., Welch, K., Guillen-Rodriguez, J., Aickin, M., Peng, Y.M., Loescher, L., Gensler, H., 1996. Disposition and metabolism of topically administered α-tocopherol acetate: a common ingredient of commercially available sunscreens and cosmetics. Nutr. Cancer 26, 193–201.

Altavilla, D., Saitta, A., Cucinotta, D., Galeano, M., Deodato, B., Colonna, M., Torre, V., Russo, G., Sardella, A., Urna, G., Campo, G.M., Cavallari, V., Squadrito, G., Squadrito, F., 2001. Inhibition of

lipid peroxidation restores impaired vascular endothelial growth factor expression and stimulates wound healing and angiogenesis in the genetically diabetic mouse. Diabetes 50, 667–674.

Baschong, W., Artmann, C., Hueglin, D., Roeding, J., 2001. Direct evidence for bioconversion of vitamin E acetate into vitamin E: an ex vivo study in viable human skin. J. Cosmet. Sci. 52, 155–161.

Baumann, L.S., Spencer, J., 1999. The effects of topical vitamin E on the cosmetic appearance of scars. Dermatol. Surg. 25, 311–315.

Baxter, J.G., Robeson, C.D., Taylor, J.D., Lehman, R.W., 1943. Natural alpha, beta, and gamma-tocopherols and certain esters of physiological interest. J. Am. Chem. Soc. 65, 918–924.

Beehler, B.C., Przybyszewski, J., Box, H.B., Kulesz-Martin, M.F., 1992. Formation of 8 hydroxydeoxyguanosine within DNA of mouse keratinocytes exposed in culture to UV-B and hydrogen peroxide. Carcinogenesis 13, 2003–2007.

Beijersbergen van Henegouwen, G.M.J., Junginger, H.E., de Vries, H., 1995. Hydrolysis of RRR-α-tocopheryl acetate (vitamin E acetate) in the skin and its UV protecting activity (an in vivo study with the rat). J. Photochem. Photobiol. B: Biol. 29, 45–51.

Bissett, D.L., Hillebrand, G.G., Hannon, D.P., 1989. The hairless mouse as a model of skin photoaging: its use to evaluate photoprotective materials. Photodermatology 6, 228–233.

Bissett, D.L., Chatterjee, R., Hannon, D.P., 1990. Photoprotective effect of superoxide-scavenging antioxidants against ultraviolet radiation-induced chronic skin damage in the hairless mouse. Photodermatol. Photoimmunol. Photomed. 7, 56–62.

Bissett, D.L., Chatterjee, R., Hannon, D.P., 1992. Protective effect of a topically applied anti-oxidant plus an anti-inflammatory agent against ultraviolet radiation-induced chronic skin damage in the hairless mouse. J. Soc. Cosmet. Chem. 43, 85–92.

Brigelius-Flohe, R., Kelly, F.J., Salonen, J.T., Neuzil, J., Zingg, J.M., Azzi, A., 2002. The European perspective on vitamin E: current knowledge and future research. Am. J. Clin. Nutr. 76, 703–716.

Brodkin, R.H., Bleiberg, J., 1965. Sensitivity to topically applied vitamin E. Arch. Dermatol. 92, 76–77.

Burke, K.E., Clive, J., Combs Jr., G.F., Commisso, J., Keen, C.L., RM, N., 2000. Effects of topical and oral vitamin E on pigmentation and skin cancer induced by ultraviolet irradiation in Skh: 2 hairless mice. Nutr. Cancer 38, 87–97.

Chen, X., Gresham, A., Morrison, A., Pentland, A.P., 1996. Oxidative stress mediates synthesis of cytosolic phospholipase A-2 after UVB injury. Biochim. Biophys. Acta 1299, 23–33.

Chung, J.H., Seo, J.Y., Lee, M.K., Eun, H.C., Lee, J.H., Kang, S., Fisher, G.J., Voorhees, J.J., 2002. Ultraviolet modulation of human macrophage metalloelastase in human skin in vivo. J. Invest. Dermatol. 119, 507–512.

Darr, D., Dunston, S., Faust, H., Pinnell, S., 1996. Effectiveness of antioxidants (vitamin C and E) with and without sunscreens as topical photoprotectants. Acta Dermatol. Venereol. 76, 264–268.

De Groot, A.C., Berretty, P.J., van Ginkel, C.J., den Hengst, C.W., van Ulsen, J., Weyland, J.W., 1991. Allergic contact dermatitis from tocopheryl acetate in cosmetic creams. Contact. Dermatitis 25, 302–304.

Dereska, N.H., McLemore, E.C., Tessier, D.J., Bash, D.S., Brophy, C.M., 2006. Short-term, moderate dosage vitamin E supplementation may have no effect on platelet aggregation, coagulation profile, and bleeding time in healthy individuals. J. Surg. Res. 132, 121–129.

Dreher, F., Denig, N., Gabard, B., Schwindt, D.A., Maibach, H.I., 1999. Effect of topical antioxidants on UV-induced erythema formation when administered after exposure. Dermatology 198, 52–55.

Ekanayake-Mudiyanselage, S., Thiele, J.J., 2006. Sebaceous glands as transporters of vitamin E. Hautarzt 57, 291–296.

Ekanayake-Mudiyanselage, S., Elsner, P., Thiele, J.J., 2002. UVA and UVB induce depletion of vitamin E and generation of a highly sensitive lipid photooxidation product in human sebum: basis for a new phototoxicity test: SPT. J. Invest. Dermatol. 119, 331 A.

Ekanayake-Mudiyanselage, S., Hamburger, M., Elsner, P., Thiele, J.J., 2003. Ultraviolet A induces generation of squalene monohydroperoxide isomers in human sebum and skin surface lipids in vitro and in vivo. J. Invest. Dermatol. 120, 915–922.

Ekanayake-Mudiyanselage, S., Kraemer, K., Thiele, J.J., 2004. Oral supplementation with all-Rac- and RRR-α-tocopherol increases vitamin E levels in human sebum after a latency period of 14–21 days. Ann. N.Y. Acad. Sci. 1031, 184–194.

Ekanayake-Mudiyanselage, S., Tavakkol, A., Polefka, T.G., Nabi, Z., Elsner, P., Thiele, J.J., 2005. Vitamin E delivery to human skin by a rinse-off product: penetration of α-tocopherol versus wash-out effects of skin surface lipids. Skin Pharma. Skin Physiol. 18, 20–26.

Ekanayake-Mudiyanselage, S., Seefluth, R., Mancini, A., Paller, A., Thiele, J., 2005. The α-tocopherol/squalene ratio in human sebum is age-dependent and reaches lowest levels in adolescence. J. Invest. Dermatol. 124 (S4), A67.

Evelson, P., Ordóñez, C.P., Llesuy, S., Boveris, A., 1997. Oxidative stress and in vivo chemiluminescence in mouse skin exposed to UVA radiation. J. Photochem. Photobiol. B: Biol. 38, 215–219.

Faergemann, J., Godleski, J., Laufen, H., Liss, R.H., 1995. Intracutaneous transport of orally administered fluconazole to the stratum corneum. Acta Derm. Venereol. (Stockh.) 75, 361–363.

FDA, 1998. Frequency of Use of Cosmetic Ingredients. FDA, Washington, DC.

Fisher, A.A., 1991. Three faces of vitamin E topical allergy. Cutis 48, 272–274.

Foote, C.S., 1991. Definition of type I and type II photosensitized oxidation. Photochem. Photobiol. 54.

Freedman, J.E., Keaney Jr., J.F., 2001. Vitamin E inhibition of platelet aggregation is independent of antioxidant activity. J. Nutr. 131, 374S–377S.

Freedman, J.E., Farhat, J.H., Loscalzo, J., Keaney Jr., J.F., 1996. α-Tocopherol inhibits aggregation of human platelets by a protein kinase C-dependent mechanism. Circulation 94, 2434–2440.

Fuchs, J., 1992. Oxidative Injury in Dermatopathology. Springer, Berlin, Heidelberg, New York, 360 pp.

Fuchs, J., Huflejt, M.E., Rothfuss, L.M., Wilson, D.S., Carcamo, G., Packer, L., 1989a. Acute effects of near ultraviolet and visible light on the cutaneous antioxidant defense system. Photochem. Photobiol. 50, 739–744.

Fuchs, J., Huflejt, M.E., Rothfuss, L.M., Wilson, D.S., Carcamo, G., Packer, L., 1989b. Impairment of enzymic and nonenzymic antioxidants in skin by UVB irradiation. J. Invest. Dermatol. 93, 769–773.

Fuchs, J., Groth, N., Herrling, T., 2002. In vivo measurement of oxidative stress status in human skin. Methods Enzymol. 352, 333–339.

Galeano, M., Torre, V., Deodato, B., Campo, G.M., Colonna, M., Sturiale, A., Squadrito, F., Cavallari, V., Cucinotta, D., Buemi, M., Altavilla, D., 2001. Raxofelast, a hydrophilic vitamin E-like antioxidant, stimulates wound healing in genetically diabetic mice. Surgery 129, 467–477.

Gensler, H.L., Magdaleno, M., 1991. Topical vitamin E inhibition of immunosuppression and tumorigenesis induced by ultraviolet radiation. Nutr. Cancer 15, 97–106.

Gensler, H.L., Aickin, M., Peng, Y.M., Xu, M., 1996. Importance of the form of topical vitamin E for prevention of photocarcinogenesis. Nutr. Cancer 26, 183–191.

Guevara, I.L., Pandya, A.G., 2003. Safety and efficacy of 4% hydroquinone combined with 10% glycolic acid, antioxidants, and sunscreen in the treatment of melasma. Int. J. Dermatol. 42, 966–972.

Hanson, K.M., Clegg, R.M., 2003. Bioconvertible vitamin antioxidants improve sunscreen photoprotection against UV-induced reactive oxygen species. J. Cosmet. Sci. 54, 589–598.

Harris, B.D., Taylor, J.S., 1997. Contact allergy to vitamin E capsules: false negative patch tests to vitamin E. Contact. Dermatitis 36, 273.

Hayakawa, R., Ueda, H., Nozaki, T., Izawa, Y., Yokotake, J., Yazaki, K., Azumi, T., Okada, Y., Kobayashi, M., Usuda, T., Ishida, J., Kondo, T., Adachi, A., Kawase, A., Matsunaga, K., 1981. Effects of combination treatment with vitamins E and C on chloasma and pigmented contact dermatitis. A double blind controlled clinical trial. Acta Vitaminol. Enzymol. 3, 31–38.

Haywood, R., Wardman, P., Sanders, R., Linge, C., 2003. Sunscreens inadequately protect against ultraviolet-A-induced free radicals in skin: implications for skin aging and melanoma? J. Invest. Dermatol. 121, 862–868.

Jenkins, M., Alexander, J.W., MacMillan, B.G., Waymack, J.P., Kopcha, R., 1986. Failure of topical steroids and vitamin E to reduce postoperative scar formation following reconstructive surgery. J. Burn Care Rehabil. 7, 309–312.

Jimbow, K., Fitzpatrick, T.B., Wick, M.M., 1993. Biochemistry and physiology of melanin pigmentation. In: Goldsmith, L.A. (Ed.), Physiology, Biochemistry, and Molecular Biology of the Skin. Oxford University Press, New York, pp. 873–909.

Jurkiewicz, B.A., Bissett, D.L., Buettner, G.R., 1995. Effect of topically applied tocopherol on ultraviolet radiation-mediated free radical damage in skin. J. Invest. Dermatol. 104, 484–488.

Kagan, V., Witt, E., Goldman, R., Scita, G., Packer, L., 1992a. Ultraviolet light-induced generation of vitamin E radicals and their recycling. A possible photosensitizing effect of vitamin E in skin. Free Radical Res. Commun. 16, 51–64.

Kagan, V.E., Serbinova, E.A., Forte, T., Scita, G., Packer, L., 1992b. Recycling of vitamin E in human low density lipoproteins. J. Lipid Res. 33, 385–397.

Kamimura, M., Matsuzawa, T., 1968. Percutaneous absorption of α-tocopheryl acetate. J. Vitaminol. 14, 151–159.

Khettab, N., Amory, M.C., Briand, G., Bousquet, B., Combre, A., Forlot, P., Barey, M., 1988. Photoprotective effect of vitamins A and E on polyamine and oxygenated free radical metabolism in hairless mouse epidermis. Biochimie 70, 1709–1713.

Kitazawa, M., Podda, M., Thiele, J.J., Traber, M.G., Iwasaki, K., Sakamoto, K., Packer, L., 1997. Interactions between vitamin E homologues and ascorbate free radicals in murine skin homogenates irradiated with ultraviolet light. Photochem. Photobiol., 355–365.

Kochevar, I.E., Lambert, C.R., Lynch, M.C., Tedesco, A.C., 1996. Comparison of photosensitized plasma membrane damage caused by singlet oxygen and free radicals. Biochim. Biophys. Acta 1280, 223–230.

Kramer-Stickland, K., Liebler, D.C., 1998. Effect of UVB on hydrolysis of α-tocopherol acetate to α-tocopherol in mouse skin. J. Invest. Dermatol. 111, 302–307.

Kuriyama, K., Shimizu, T., Horiguchi, T., Watabe, M., Abe, Y., 2002. Vitamin E ointment at high dose levels suppresses contact dermatitis in rats by stabilizing keratinocytes. Inflamm. Res. 51, 483–489.

Liede, K.E., Haukka, J.K., Saxen, L.M., Heinonen, O.P., 1998. Increased tendency towards gingival bleeding caused by joint effect of α-tocopherol supplementation and acetylsalicylic acid. Ann. Med. 30, 542–546.

Lin, J.Y., Selim, M.A., Shea, C.R., Grichnik, J.M., Omar, M.M., Monteiro-Riviere, N.A., Pinnell, S.R., 2003. UV photoprotection by combination topical antioxidants vitamin C and vitamin E. J. Am. Acad. Dermatol. 48, 866–874.

Lopez-Torres, M., Thiele, J.J., Shindo, Y., Han, D., Packer, L., 1998. Topical application of α-tocopherol modulates the antioxidant network and diminishes ultraviolet-induced oxidative damage in murine skin. Brit. J. Dermatol. 138, 207–215.

Malafa, M.P., Fokum, F.D., Mowlavi, A., Abusief, M., King, M., 2002a. Vitamin E inhibits melanoma growth in mice. Surgery 131, 85–91.

Malafa, M.P., Fokum, F.D., Smith, L., Louis, A., 2002b. Inhibition of angiogenesis and promotion of melanoma dormancy by vitamin E succinate. Ann. Surg. Oncol. 9, 1023–1032.

Manzano, D., Aguirre, A., Gardeazabal, J., Eizaguirre, X., Diaz Perez, J.L., 1994. Allergic contact dermatitis from tocopheryl acetate (vitamin E) and retinol palmitate (vitamin A) in a moisturizing cream. Contact. Dermatitis 31, 324.

Maras, J.E., Bermudez, O.I., Qiao, N., Bakun, P.J., Boody-Alter, E.L., Tucker, K.L., 2004. Intake of α-tocopherol is limited among US adults. J. Am. Diet. Assoc. 104, 567–575.

Marsh, S.A., Coombes, J.S., 2006. Vitamin E and a-lipoic acid supplementation increase bleeding tendency via an intrinsic coagulation pathway. Clin. Appl. Thromb./Hem. 12 (2), 169–173.

Martensson, J., Meister, A., 1992. Glutathione deficiency increases hepatic ascorbic acid synthesis in adult mice. Proc. Natl. Acad. Sci. U.S.A. 89, 11566–11568.

McVean, M., Liebler, D.C., 1997. Inhibition of UVB induced DNA photodamage in mouse epidermis by topically applied α-tocopherol. Carcinogenesis 18, 1617–1622.

McVean, M., Liebler, D.C., 1999. Prevention of DNA photodamage by vitamin E compounds and sunscreens: roles of ultraviolet absorbance and cellular uptake. Mol. Carcinogen. 24, 169–176.

Möller, H., Ansmann, A., Wallat, S., 1989. Wirkungen von Vitamin E auf die Haut bei topischer Anwendung. Fat. Sci. Technol. 91, 295–305.

Montenegro, L., Bonina, F., Rigano, L., Giogilli, S., Sirigu, S., 1995. Protective effect evaluation of free radical scavengers on UVB induced human cutaneous erythema by skin reflectance spectrophotometry. Int. J. Cosmet. Sci. 17, 91–103.

Nabi, Z., Tavakkol, A., Dobke, M., Polefka, T.G., 2001. Bioconversion of vitamin E acetate in human skin. Curr. Probl. Dermatol. 29, 175–186.

Norkus, E.P., Bryce, G.F., Bhagavan, H.N., 1993. Uptake and bioconversion of α-tocopheryl acetate to α-tocopherol in skin of hairless mice. Photochem. Photobiol. 57, 613–615.

Pehr, K., Forsey, R.R., 1993. Why don't we use vitamin E in dermatology? Can. Med. Assoc. J. 149, 1247–1253.

Perrenoud, D., Homberger, H.P., Auderset, P.C., Emmenegger, R., Frenk, E., Saurt, J.H., Hauser, C.Hauser Swiss Contact Dermatitis Res G, 1994. An epidemic outbreak of papular and follicular contact dermatitis to tocopheryl linoleate in cosmetics. Dermatology (Basel) 189, 225–233.

Potapenko, A.J., Piszov, M.J., Abijev, G.A., Pliquett, F., 1983. α-Tokopherol, ein Inhibitor von durch UV-Strahlung induzierten Veranderungen mechanoelektrischer Hauteigenschaften. Dermatologische Monatsschrift 169, 300–304.

Potapenko, A.Y., Abijev, G.A., Pistsov, M.Y., Roshchupkin, D.I., Vladimirov, Y.A., Pliquett, F., Ermolayev, A.V., Sarycheva, I.K., Evstigneeva, R.P., 1984. PUVA-induced erythema and changes in mechanoelectrical properties of skin. Inhibition by tocopherols. Arch. Dermatol. Res. 276, 12–16.

Rangarajan, M., Zatz, J.L., 2001a. Effect of formulation on the delivery and metabolism of α-tocopheryl acetate. J. Cosmet. Sci. 52, 225–236.

Rangarajan, M., Zatz, J.L., 2001b. Kinetics of permeation and metabolism of α-tocopherol and α-tocopheryl acetate in micro-Yucatan pig sin. J. Cosmet. Sci. 52, 35–50.

Record, I.R., Dreosti, I.E., Konstantinopoulos, M., Buckley, R.A., 1991. The influence of topical and systemic vitamin E on ultraviolet light-induced skin damage in hairless mice. Nutr. Cancer 16, 219–226.

Ritter, E.F., Axelrod, M., Minn, K.W., Eades, E., Rudner, A.M., Sarafin, D., Klitzman, B., 1997. Modulation of ultraviolet light-induced epidermal damage: beneficial effects of tocopherol. Plast. Reconstr. Surg. 100, 973–980.

Rosenstein, B.S., Ducore, J.M., Cummings, S.W., 1983. The mechanism of bilirubin-photosensitized DNA strand breakage in human cells exposed to phototherapy light. Mutat. Res. 112, 397–406.

Roshchupkin, D.I., Pistsov, M.Y., Potapenko, A.Y., 1979. Inhibition of ultraviolet light-induced erythema by antioxidants. Arch. Dermatol. Res. 266, 91–94.

Saldeen, T., Li, D., Mehta, J.L., 1999. Differential effects of alpha- and gamma-tocopherol on low-density lipoprotein oxidation, superoxide activity, platelet aggregation and arterial thrombogenesis. J. Am. Coll. Cardiol. 34, 1208–1215.

Sander, C.S., Chang, H., Salzmann, S., Muller, C.S., Ekanayake-Mudiyanselage, S., Elsner, P., Thiele, J.J., 2002. Photoaging is associated with protein oxidation in human skin in vivo. J. Invest. Dermatol. 118, 618–625.

Sander, C.S., Hamm, F., Elsner, P., Thiele, J.J., 2003. Oxidative stress in malignant melanoma and non-melanoma skin cancer. Brit. J. Dermatol. 148, 913–922.

Schoonderwoerd, S.A., Beijersbergen van Henegouwen, G.M.J., Persons, K.C.M., 1991. Effect of α-tocopherol and di-butyl-hydroxytoluene (BHT) on UV-A-induced photobinding of 8-methoxypsoralen to Wistar rat epidermal biomacromolecules in vivo. Arch. Toxicol. 65, 490–494.

Shindo, Y., Witt, E., Packer, L., 1993. Antioxidant defense mechanisms in murine epidermis and dermis and their responses to ultraviolet light. J. Invest. Dermatol. 100, 260–265.

Shindo, Y., Witt, E., Han, D., Epstein, W., Packer, L., 1994. Enzymic and non-enzymic antioxidants in epidermis and dermis of human skin. J. Invest. Dermatol. 102, 122–124.

Steiner, M., 1983. Effect of α-tocopherol administration on platelet function in man. Thromb. Haemost. 49, 73–77.

Steiner, M., 1999. Vitamin E, a modifier of platelet function: rationale and use in cardiovascular and cerebrovascular disease. Nutr. Rev. 57, 306–309.

Thiele, J.J., Traber, M.G., Podda, M., Tsang, K., Cross, C.E., Packer, L., 1997a. Ozone depletes tocopherols and tocotrienols topically applied to murine skin. FEBS Lett. 401, 167–170.

Thiele, J.J., Traber, M.G., Polefka, T.G., Cross, C.E., Packer, L., 1997b. Ozone-exposure depletes vitamin E and induces lipid peroxidation in murine stratum corneum. J. Invest. Dermatol. 108, 753–757.

Thiele, J.J., Traber, M.G., Tsang, K., Cross, C.E., Packer, L., 1997c. In vivo exposure to ozone depletes vitamins C and E and induces lipid peroxidation in epidermal layers of murine skin. Free Radical Biol. Med. 23, 385–391.

Thiele, J.J., Traber, M.G., Packer, L., 1998a. Depletion of human stratum corneum vitamin E: an early and sensitive in vivo marker of UV induced photo-oxidation. J. Invest. Dermatol. 110, 756–761.

Thiele, J.J., Traber, M.G., Re, R., Espuno, N., Yan, L.J., Cross, C.E., Packer, L., 1998b. Macromolecular carbonyls in human stratum corneum: a biomarker for environmental oxidant exposure? FEBS Lett. 422, 403–406.

Thiele, J.J., Weber, S.U., Packer, L., 1999. Sebaceous gland secretion is a major physiologic route of vitamin E delivery to skin. J. Invest. Dermatol. 113, 1006–1010.

Thiele, J.J., Dreher, F., Packer, L., 2000. Antioxidant defense systems in skin. In: Elsner, P., Maibach, H. (Eds.), Drugs vs. Cosmetics: Cosmeceuticals? Marcel Dekker, New York, pp. 145–188.

Thiele, J.J., Schroeter, C., Hsieh, S.N., Podda, M., Packer, L., 2001. The antioxidant network of the stratum corneum. Curr. Probl. Dermatol. 29, 26–42.

Traber, M.G., Sies, H., 1996. Vitamin E in humans: demand and delivery. Annu. Rev. Nutr. 16, 321–347.

Trevithick, J.R., Mitton, K.P., 1993. Topical application and uptake of vitamin E acetate by the skin conversion to free vitamin E. Biochem. Mol. Biol. Int. 31, 869–878.

Trevithick, J.R., Xiong, H., Lee, S., Shum, D.T., Sanford, S.E., Karlik, S.J., Norley, C., Dilworth, G.R., 1992. Topical tocopherol acetate reduces post-UVB, sunburn-associated erythema, edema, and skin sensitivity in hairless mice. Arch. Biochem. Biophys. 296, 575–582.

Trevithick, J.R., Shum, D.T., Redae, S., Mitton, K.P., Norley, C., Karlik, S.J., Groom, A.C., Schmidt, E.E., 1993. Reduction of sunburn damage to skin by topical application of vitamin E acetate following exposure to ultraviolet B radiation: effect of delaying application or of reducing concentration of vitamin E acetate applied. Scanning. Microsc. 7, 1269–1281.

Tsoureli-Nikita, E., Hercogova, J., Lotti, T., Menchini, G., 2002. Evaluation of dietary intake of vitamin E in the treatment of atopic dermatitis: a study of the clinical course and evaluation of the immunoglobulin E serum levels. Int. J. Dermatol. 41, 146–150.

Weber, S.U., Thiele, J.J., Cross, C.E., Packer, L., 1999. Vitamin C, uric acid and glutathione gradients in murine stratum corneum and their susceptibility to ozone exposure. J. Invest. Dermatol. 113, 1128–1132.

Weber, S.U., Thiele, J.J., Han, N., Luu, C., Valacchi, G., Weber, S., Packer, L., 2003. Topical α-tocotrienol supplementation inhibits lipid peroxidation but fails to mitigate increased transepidermal water loss after benzoyl peroxide treatment of human skin. Free Radical Biol. Med. 34, 170–176.

Yuen, K.S., Halliday, G.M., 1997. A-Tocopherol, an inhibitor of epidermal lipid peroxidation, prevents ultraviolet radiation from suppressing the skin immune system. Photochem. Photobiol. 65, 587–592.

Zondlo Fiume, M., 2002. Final report on the safety assessment of tocopherol, tocopheryl acetate, tocopheryl linoleate, tocopheryl linoleate/oleate, tocopheryl nicotinate, tocopheryl succinate, dioleyl tocopheryl methylsilanol, potassium ascorbyl tocopheryl phosphate, and tocophersolan. Int. J. Toxicol. 21 (Suppl 3), 51–116.