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REVIEW

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The role of vitamin E in normal and damaged skin

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Abstract The generation of free oxygen radicals is believed to play an important pathogenic role in the development of various disorders. More than other tissues, the skin is exposed to numerous environmental chemical and physical agents such as ultraviolet light causing oxidative stress. In the skin this results in several short- and long-term adverse effects such as erythema, edema, skin thickening, wrinkling, and an increased incidence of skin cancer or precursor lesions. However, accelerated cutaneous aging under the influence of ultraviolet light, usually termed photoaging, is only one of the harmful effects of continual oxygen radical production in the skin. Others include cutaneous inflammation, autoimmunological processes, keratinization disturbances, and vasculitis. Vitamin E is the major naturally occurring lipid-soluble non-enzymatic antioxidant protecting skin from the adverse effects of oxidative stress including photoaging. Its chemistry and its physiological function as a major antioxidative and anti-inflammatory agent, in particular with respect to its photoprotective, antiphotoaging properties, are described by summarizing animal studies, in vivo tests on human skin and biochemical in vitro investigations. The possible therapeutic use in different cutaneous disorders, and pharmacological and toxicological aspects are discussed. Many studies document that vitamin E occupies a central position as a highly efficient antioxidant, thereby providing possibilities to decrease the frequency and severity of pathological events in the skin. For this purpose increased efforts in developing appropriate systemic and local pharmacological preparations of vitamin E are required.

Key words Vitamin E · Antioxidant · Oxidative stress Photoaging · Radical scavenge

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Introduction

Activated oxygen and oxygen radicals first received mention in UV irradiation damage to skin in the 1950s and 1960s [20, 44, 45, 111, 115]. The opinion that UV-induced cutaneous damage is caused by photoperoxidation (oxidative stress) has been put forward by several experimental studies in the last two decades [14, 17, 25, 57, 106]. These observations were followed by numerous experiments on the benefit of different natural and synthetic agents in protecting cells from the adverse effects of free radical generation. Among these agents vitamin E (α-tocopherol) has proven to function as the major lipid-soluble nonenzymatic defensor against peroxidation of membranes [29, 127, 144]. Although some debate over the protective mechanisms of vitamin E in various kinds of physically or chemically induced skin damage persists, there is no longer doubt over its general use in preventing UV light induced adverse effects.

This review of the literature is aimed at providing insight into the current knowledge of research on vitamin E as a relevant antiphotoaging, antioxidative agent and its possible therapeutic benefit in cutaneous disorders.

Biochemistry of vitamin E

Vitamin E is a ubiquitous, naturally occurring agent derived from plants. The term vitamin E embraces all tocopherols and tocotrienols showing the biological activity of the isomer RRR-α-tocopherol (Fig. 1).

Chemically, tocopherol is a 6-chromanol derivative. It consists of a chromane ring bearing a phenolic OH group at position 6 and a branched side chain with chiral C atoms at the positions 2, 4′, and 8′. There are four tocopherol stereoisomers (α, β, γ, δ) dependent on different substituents at the positions 5 and 7 of the chromane ring (Table 1). RRR-α-tocopherol predominates in the natural vitamin E determining its biological activity. In this stereoisomer all three chiral C atoms show the R configura-

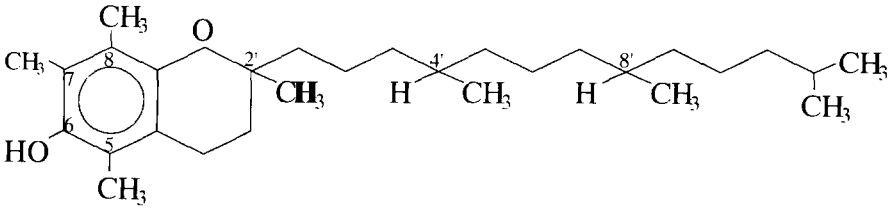

Fig. 1 Configuration of the natural RRR-α-tocopherol stereoisomer

Table 1 Configuration of the naturally occurring tocopherols: substituents at the chromane ring

	Position 5	Position 7
d-α-Tocopherol	CH_3	CH_3
d-β-Tocopherol	CH_3	H
d-γ-Tocopherol	H	CH_3
d-δ-Tocopherol	H	H

Table 2 Relative biological potencies of some tocopherols (modified from [73])

	Synonym	Relative potency[a]
d-α-Tocopherol 1 mg	RRR-α-Tocopherol	1.49
d-α-Tocopheryl acetate 1 mg	RRR-α-Tocopheryl acetate	1.36
dl-α-Tocopherol 1 mg	all-rac-α-Tocopherol	1.10
dl-α-Tocopheryl acetate 1 mg	all-rac-α-Tocopheryl acetate	1.00[b]

[a] In USP units (United States Pharmacopoea XXI)
[b] Taken as reference today

tion, and the substituents at position 5 and 7 of the chromane ring are CH_3. Due to its slight dextrorotation RRR-α-tocopherol is frequently called *d*-α-tocopherol.

The relative biological potencies of the tocopherols have been examined in several studies. In 1984 Machlin [90] assessed the activities of different tocopherols using three animal models: fetal resorption in the rat, hemolysis in the rat, and muscle dystrophy in the chicken. He found that α-tocopherol is by far the most efficacious agent (relatively, 100%), followed by β- (12–40%), γ- (1–20%) and δ-tocopherol (0–3%). A different scale is obtained when protection against UV light is compared in terms of skin thickness measurements [120]. Again, natural α-tocopherol is the most effective agent. However, γ-tocopherol also provides good photoprotection (relatively, 72%), and even the effects of β- and δ-tocopherol are not negligible (40%).

There also is a synthetic vitamin E product derived from phytol usually termed all-rac-α-tocopherol (or *dl*-α-tocopherol). All-rac-α-tocopherol, which is the active ingredient in many approved vitamin E preparations, consists of equal amounts of all eight possible stereoisomers of α-tocopherol. It shows a significantly lower biological activity, as compared with the natural RRR-α-tocopherol [21, 22]. Highly reduced biological activities were also found in the 2S epimer (2S, 4′R, 8′R), as compared with the 2R epimer (2R, 4′R, 8′R) of α-tocopherol, indicating that the position 2 is determining the biological efficacy of vitamin E [153]. Thus, the mixture of the 2R, 4′R, 8′R and 2S, 4′R, 8′R epimers (also called 2-ambo-tocopherol) which can also be produced synthetically, shows a biological activity comparable only to that of all-rac-α-tocopherol, but significantly lower than naturally occurring RRR-α-tocopherol [73].

The relative activity of vitamin E is usually referred to *dl*-α-tocopheryl acetate, which is taken as the standard today [134]: 1 mg *dl*-α-tocopheryl acetate is defined as 1 USP unit (= 1 IU; Table 2) [147].

Antioxidative properties of vitamin E

Today vitamin E is believed to be the most important naturally occurring nonenzymatic, lipid-soluble antioxidative agent in human tissue [29, 58, 59, 134].

Reactive oxygen radicals (superoxide anion, hydroxyl radical, peroxyl radical, singlet oxygen) are generated in numerous physiological and pathological processes [138]. These include inflammation [51, 54, 58, 59, 86, 134, 138], excessive physical activity [37, 113, 136], nutritional imbalance [49, 62], hereditary disorders such as fat malabsorption syndromes [65, 123] and congenital hemolytic anemia [10, 105], neoplasias [33, 64, 121, 122, 131], arteriosclerosis and other vascular diseases [49, 58, 60, 88], as well as chemically or physically caused damages. Among the latter, preferentially intoxications, for example, by alcohol, CCl_4, paraquat and cigarette smoke, and radiation have been associated with the harmful effects of reactive oxygen [24, 31, 87, 124, 139, 142, 154].

Many studies indicate that antioxidant inadequacy by depleted dietary vitamin E is linked with an increase in reactive oxygen species, cell injuries, and subsequent disorders in the affected tissues, including inflammation, actinic changes, and accelerated aging of the skin [16, 18, 27, 56, 62, 97, 116–118, 130, 135, 137, 149].

The mode of action of vitamin E as an antioxidant is chemically mediated by the phenolic OH group of the chromane ring. Due to its incorporation in biological membranes, α-tocopherol is localized close to the polyunsaturated fatty acids of the membranic phospholipids. Initiated by reactive oxygen species, these fatty acids undergo peroxidation [70]. Briefly the chemical process can be described as follows. A lipid with double bonds reacts with oxygen radicals forming a lipid radical. The lipid radical is transformed to a lipid peroxyl radical in the presence of molecular oxygen. The lipid peroxyl radical is again able to attack unsaturated lipids with double

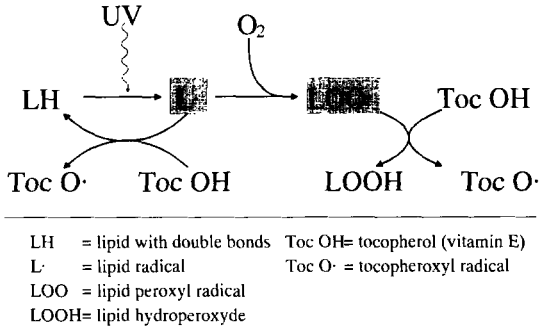

Fig. 2 Interruption of the lipid radical chain reaction by vitamin E. *LH*, Lipid with double bounds; *L*, lipid radical; *LOO*, lipid peroxyl radical; *LOOH*, lipid hydroperoxide; *Toc OH*, tocopherol; *Toc O·*, tocopheroxyl radical

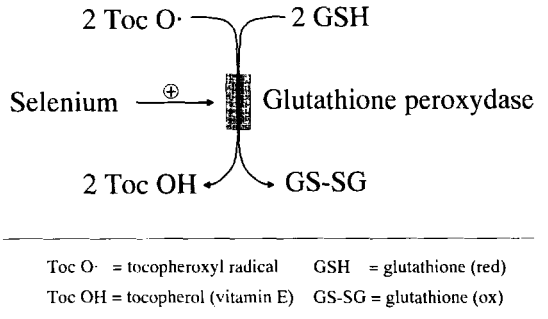

Fig. 3 Reoxygenation of α-tocopherol (*Toc OH*) in the presence of glutathione and selenium. *Toc O·*, Tocopheroxyl radical; *GSH*, glutathione, reduced; *GS-SG*, glutathione, oxidized

bonds thereby forming another lipid radical and lipid hydroperoxide. The whole procedure is termed radical chain reaction [70, 95]. α-Tocopherol interrupts the chain reaction by donating hydrogen either to the lipid or to the lipid peroxyl radical (Fig. 2) emerging in the stable low-energy tocopheroxyl radical which does not act as a further radical-forming agent. Aside from this, α-tocopherol also functions as a direct antioxidant towards singlet oxygen and superoxide anion without involvement of lipid radicals [53, 96, 160].

The antioxidative properties of α-tocopherol are closely linked with its continual regeneration by other micronutrients and biological agents, such as glutathione and ascorbic acid [29, 108]. Glutathione and ascorbic acid act as the main biological cofactors of vitamin E in the protection of skin from oxidative damage [26, 91, 107, 108, 133, 143, 151]. Both agents spare the oxidative degradation of vitamin E by donating a hydrogen ion to the tocopheroxyl radical [108, 151]. Much attention has also been paid to the cofactorial function of selenium in the regeneration of vitamin E [28, 62, 103]. Selenium represents an integral part of the enzyme glutathione peroxydase which enables the reoxygenation of α-tocopherol while oxidated glutathione is generated as shown in Fig. 3. Thus, selenium deficiency syndromes may mimic vitamin E depletion-correlated symptoms [28, 62]. Other vitamin E regenerating agents also exist, such as the naturally occurring ubiquinols (ubiquinones) [71].

Vitamin E is the most important biological supplement of the (water-soluble) enzymatic antioxidant systems (superoxide dismutase, glutathione peroxydase, catalase). Whereas β-carotene may represent the most important liposoluble agent for the quenching of singlet oxygen, the role of vitamin E as the major membrane-linked radical scavenger in lipid environment is thought to be unique [29, 103, 134].

Other biological functions of vitamin E

Aside from its antioxidative properties, further biological effects of α-tocopherol are under discussion.

The metabolism of arachidonic acid is obviously biased by α-tocopherol [4, 66]. The complex interactions with the eicosanoid system appear to result in an inhibition of prostaglandin synthesis [41, 101]. Vitamin E depresses the biosynthesis of prostaglandin E_2 [150] possibly by preventing the release of arachidonic acid by phospholipase A_2 [43]. The lipo-oxygenase function in thrombocytes is depressed [114], as well as the generation of thromboxane A_2 and B_2 [35, 68, 114]. In contrast, lipo-oxygenase function in neutrophil granulocytes, and the biosynthesis of prostacyclins are enhanced by vitamin E (66,114). The cyclo-oxygenase activity is modulated in a dose-dependent manner by α-tocopherol: low concentrations lead to inhibition and high ones to activation of the enzyme [61, 85].

The various effects on the eicosanoid system result in a visible anti-inflammatory effect. There is no evidence as to whether this effect is due only to the antioxidative properties or is mediated by other functions which are not yet known in detail [134].

Photoprotective properties of vitamin E in animal models

The role of reactive oxygen species in UV light induced damage to skin, as well as the protection by antioxidants, has been a major subject of investigations in recent decades [15, 32, 36, 38, 44, 47, 55, 57, 63, 99, 100, 101, 126, 141, 148]. A large and steadily growing number of experiments suggests that vitamin E exerts a decisive function as free radical-quenching photoprotective agent in the skin, thereby possibly preventing it from UV mediated diseases [12, 81]. The hairless mouse is an accepted model for UV damage studies by reliably mimicking UV effects on human skin [11, 82, 158]. Chronic skin damages occurring shortly after UV irradiation in unprotected hairless mice include elastosis, wrinkling, increased skin thickness, sagging and histological changes, dermal vessel damages, and tumorigenesis. These changes are also observed in human skin, however only after decades [82]. In addition, acute UV effects can be easily and reproducibly studied in hairless mice.

In a study by Möller et al. [101] topical vitamin E preparations significantly reduced UV edema, regardless

of whether applied before or after irradiation. Similarily, Trevithick and colleagues [143] found that post-UVB, sunburn-associated erythema, edema, and skin sensitivity in hairless mice is significantly decreased after topical application of *d*-α-tocopherol acetate. Bisset et al. [11, 12] evaluated the protective property of 5% tocopherol using the same model separately for UVB and UVA. After UVB exposure a 75% reduction of the severity of skin wrinkling, a significant increase in tumor latency, and a decrease of the average number of cutaneous tumors per mouse was reported [12]. However, tocopherol did not provide significant protection against UVA-induced skin sagging [12].

Black and coworkers [17] evaluated that UVB-irradiated hairless mice showed enhanced photocarcinogenesis with respect to both tumor delay and multiplicity approximately due to the level of unsaturated fatty acids in dietary lipid. In a further study [18] they found that supplementation of the polyunsaturated fatty acid rich diet with antioxidants containing 0.2% *dl*-α-tocopheryl acetate produces a significant inhibitory effect against photocarcinogenesis.

Fuchs et al. [55, 56] observed a 50% reduction in the vitamin E concentration in the skin of hairless mice after UV irradiation which was equivalent to a 5-h natural sunlight exposure, and an impairment of cutaneous tocopherol after near UVA and visible light exposure. They hypothesized that vitamin E consumption is closely associated with its free radical scavenging function. Further experiments in hairless mice show that the recycling of vitamin E by other antioxidants such as ascorbate or glutathione is accompanied by reduced photodamage [91].

Combinations of α-tocopherol and anti-inflammatory agents such as hydrocortisone have been supposed to provide synergistic protection against photodamage events. Bisset et al. [13] reported on hairless mice which showed a delayed onset, decreased number of wrinkles, and decreased occurrence of UVB-associated skin tumors after topical administration of 5% α-tocopherol plus hydrocortisone and subsequent irradiation with suberythemogenous doses of UVB, compared with control groups only receiving a single agent.

Record and coworkers [127] evaluated the damaging effects of a single UV irradiation equivalent to one minimal erythema dose in hairless mice under the influence of vitamin E. Mice were fed diets with varying levels of vitamin E or received it topically before irradiation. The degree of epidermal damage was indicated by the suppression of thymidine incorporation into DNA and the lipid peroxidation in the skin. The incorporation of thymidine in vitamin E treated animals was comparable to that of unirradiated mice. Lipid peroxidation was not affected by the diet but was significantly reduced in the topically treated group [127].

Roshchupkin and coworkers [130] reported an up to 50% inhibition of UV light induced erythema in hairless mice when they applied tocopherol onto the skin 60 min before or shortly after UV irradiation.

Ohzawa et al. [112] tested the influence of *dl*-α tocopherol on the minimal erythema dose in rabbits using a sunlight-mimicking UV source. Topical application of tocopherol 1 h before irradiation increased the minimal erythema dose by 40%. Application immediately after irradiation was even more effective, showing an increase in minimal erythema dose (MED) by 1.7-fold compared with the base.

Beijersbergen van Henegouwen et al. [6] investigated free radical production in the skin of shaved rats upon UVA exposure after application of photosensitizing agents (8-methoxypsoralen). Considering irreversible binding of reactive intermediates of photosensitizing agents in the epidermis, a significant decrease in reactive tritium-labeled 8-methoxypsoralen intermediates was observed when α-tocopherol was applied to the skin prior to 8-methoxypsoralen and UVA irradiation, as compared with the control group.

In contrast, Kagan and his group [72] have suggested a photosensitizing effect of vitamin E in the skin. They found that α-tocopheroxyl radicals are generated directly by solar UV light, subsequently decreasing the pool of other antioxidants such as ascorbic acid which are required for the recycling of tocopherol. The depletion of these antioxidants was thought to enhance skin susceptibility to free radical attack and, secondarily, to facilitate skin tumor development. Viewing most other experimental data, it appears unlikely that vitamin E is actually transformed to a radical by UV light on a large scale without previously reducing reactive oxygen-induced radicals. However, the experiments of Kagan et al. document the complex and possibly antagonistic effects of vitamin E in the skin, which are as yet not understood in detail.

Photoprotective effects of vitamin on human skin

As early as in 1980 Potapenko and colleagues [119] suggested the potential photoprotective properties of vitamin E on human skin. Psoriasis patients who had been treated by the psoralen UVA method showed a later onset of erythema on their skin lesions when they were pretreated with α-tocopherol.

Meyer and Salka tested a 5% RRR-α-tocopherol oil-in-water cream applied in the outer eye areas of volunteers for 4 weeks and subsequently assessed the skin surface by profilometry via three-dimensional topographic images [95]. Compared with the placebo the α-tocopherol containing cream decreased skin roughness, length of facial lines, and depth of wrinkles. In a further study, skin roughness in 20 women was determined after a 10-day treatment with an indifferent water-in-oil cream (placebo) and an 8% tocopherol-containing water-in-oil cream followed by three UV irradiations at a suberythemogenous dose. Enhanced skin smoothness was observed in the topically vitamin E treated persons both before and after irradiation [95]. However, although the investigators describe their profilometry assessment as highly sensitive, results should be reconsidered in further

studies since the method is not ubiquitously established so far.

Möller et al. [101] reported that purified *d*-α-tocopherol preparations, 5% and 20% in ethanol, significantly improve light protection by the 1.34- and 2.03-fold, respectively, compared with untreated skin. In addition, a 5% *d*-α-tocopherol emulsion also showed a good protection (2.03-fold increase of light protection). Free tocopherol turned out to be far more effective than tocopherol acetate [102]. The inhibition of UV-induced edema and erythema by α-tocopherol which has been claimed in animal studies has not been shown on human skin so far; however, reexamination of this issue has been suggested [102].

Much debate has focused on the question of whether the photoprotective property of vitamin E is due mainly to its antioxidative efficacy or to its sunlight absorption. The UV absorption maximum of natural vitamin E is at approximately 295 nm whereas the most hazardous UV wavelength to skin is believed to be at 310 nm [95]. This and the experimental data mentioned above favor the hypothesis that the reduction in UV damage is mediated mainly – if not exclusively – by the antioxidative and not the absorptive qualities of vitamin E [18, 95, 150].

Photoprotective properties of vitamin E: in vitro models

Free radical aggression can be investigated in vitro in human skin cell cultures, particularly fibroblasts and keratinocytes by exposing them to physically or chemically generated free radicals (UV light, enzymatic systems such as the hypoxanthine-xanthine oxidase system, and others) [74, 93, 94, 104, 110]. In cell culture models cell growth and survival can be quantified by simple and rapid colorimetric assays (manual muscle test, neutral red absorption test). Involving the use of UV irradiation of cell cultures, the protective effect and mode of action of possible photoprotective agents can be evaluated by measuring the free radical production under the different conditions: (a) without radiation, (b) with radiation, and (c) with radiation in the presence of antioxidants.

Noel-Hudson and coworkers [110] reported that α-tocopherol is an active radical scavanger only when the radicals are generated intracellularly by UV irradiation, and that no protection is provided when the radical formation occurs in the extracellular space initiated by the hypoxanthine-xanthine oxidase system. Tocopherol yielded a significant decrease in cell injury when applied before or after (but not during) UV exposure. The cell damage by extracellularly generated radicals was not biased.

Wernighaus and colleagues [155] reported a protective effect of α-tocopherol in carrier liposomes on UV light mediated epidermal cell damage in vitro using a human squamous cell carcinoma line or human newborn keratinocytes. Compared with carrier liposomes alone, α-tocopherol (1 μg/ml) containing liposomes exhibited a 25–29% increased cell viability in UV-predamaged cultures. Interestingly, cell protection was not found at a statistically significant level when α-tocopherol was added without encapsulation into liposomes, indicating that carrier systems may contribute to the intracellular availability of α-tocopherol.

Niki et al. [108] quantified the antioxidative properties of vitamin E by the direct measurement of oxygen consumption and oxidation products. They reported a markedly suppressed oxygen uptake when vitamin E was added in the oxidation of phosphatidylcholine, as well as a rapid progression of oxygen decrease after vitamin E was consumed. In the presence of both vitamins C and E, vitamin C was first consumed while vitamin E remained constant until no more vitamin C was present, affirming the synergistic effect of vitamins C and E in animal studies [8, 162].

Kralli and Ross [84] demonstrated that cultured fibroblasts of patients with actinic reticuloid are significantly photoprotected by the tocopherol-derivative trolox-C. Measuring peroxide contents in various kinds of fat by a iodometric method Masinova and Yanisklieva [91] claimed an α-tocopherol induced inhibition of peroxidation, however, without presenting exact data.

Analysis of dermal collagen with respect to its glycosylation, fragmentation and cross-linking [74, 78, 144, 159], and measurement of the release of key mediators of the eicosanoid system and interleukin-1α may also reliably predict skin damage or protection, respectively, under the influence of oxidative stress and antioxidants [104]. However, there are no studies so far examining the effect of α-tocopherol with these methods disclosing a broad field of in vitro investigations for the future.

Cosmetic and dermatological use of vitamin E

The benefit of vitamin E in dermatological practice is reflected in its cosmetic application and the treatment of cutaneous diseases. For both objectives, α-tocopherol is used in topical preparations. It has been suggested for the following purposes:

- To protect skin from sunburn and from acute and chronic dermatitis (pain, erythema, edema) [75, 101].
- To protect skin from UV light induced long-term damages (photoaging) including skin roughness, skin dehydration, elastosis, wrinkling, facial lines, and senile lentigines [23, 42, 59, 67, 95, 109, 125].
- To reduce sebum production in the skin of seborrheics [98, 101].
- To promote hair growth possibly due to the induction of increased microcirculation [59].
- To accelerate wound healing and to protect from hypertrophic scar formation [5, 89, 152].
- To decrease pruritus, for example, in dialysis patients [102].

Whereas the anti-inflammatory and antiphotoaging benefits of vitamin E due to its antioxidative properties

have been well documented in recent decades, its efficacy in the other indications mentioned (acceleration of hair growth, reepithelization, sebum reduction) is uncertain since long-term and double-blind studies are lacking, and the mode of action is not known.

As an antioxidative photoprotective agent the stable α-tocopheryl acetate is used topically at concentrations ranging from 0.02% to 0.5% [48, 59]. For other purposes such as anti-inflammation or promotion of hair growth, higher concentrations up to 2% may be required [59]. To treat sunburn and sunburn-associated edema and pruritus as well as to accelerate wound healing preparations containing vitamin E in a range of 5–20% have been proposed [101, 102, 146]. However, the benefit of vitamin E in these indications has not yet been confirmed, and study results concerning this are inconsistent and partially contradictory.

Emulsions, lotions, hydrophilic creams or hydrophilic ointments usually serve as vehicles for vitamin E since the penetration and cutaneous absorption of the fat-soluble ingredient is significantly improved by applying it in hydrophilic vehicles [59, 101, 150].

In recent reviews Fuchs and Milbradt [57] and Furuse [59] have grouped dermatoses in which a treatment – either systemic or topical – with vitamin E has been carried out. The exclusively systemic treatments address:

- Acrodermatitis chronica atrophicans
- Epidermolysis dystrophicans
- Epidermolysis bullosa simplex
- Gingivitis
- Induratio penis plastica
- Lichen ruber
- Lichen sclerosus et atrophicus
- Male subfertility
- Necrobiosis lipoidica
- Pigmented contact dermatitis
- Porphyria cutanea tarda
- Pseudoxanthoma elasticum
- Purpura
- Scleroderma (localized, systemic)
- Ulcus cruris
- Yellow nail syndrome

The list of exclusively topically treated dermatoses is as follows:

- Alopecia areata
- Atopic dermatitis
- Axillar bromidrosis
- Chloasma
- Darier's disease
- Dry eczema
- Eczema ani
- Fox-Fordyce disease
- Ichthyosis
- Keloids
- Keratoderma tylodes palmaris progressiva
- Keratotic rhagadiform eczema of palms and plants
- Mycosis of the nails
- Pompholyx
- Pustulosis palmoplantaris

In addition, the following dermatoses have been treated both systemically and topically:

- Acne vulgaris (inflammatory type, in combination with vitamin A)
- Chilblain lupus
- Cutaneous lupus erythematosus
- Granuloma annulare
- Lichen pilaris
- Psoriasis vulgaris
- Radiodermatitis

The data suggest that vitamin E is beneficial in several skin diseases in which free radical generation and inflammation may play a decisive pathogenic role. However, double-blind controlled studies are lacking for most of the described disorders, and for this reason occasional reports on the therapeutic efficacy of vitamin E must be considered with caution. Accordingly, vitamin E is currently not approved in the treatment of dermatoses in North America or Europe. On the other hand, there is growing evidence that vitamin E decreases the risk of cancer and degenerative processes, particularly atherosclerosis, via its antioxidative, radical-scavenging properties [76, 83, 128, 140]. These conclusions drawn from studies in nondermatological specialities warrant further clinical examinations on vitamin E in dermatoses. Clinical investigations on its efficacy should focus particularly upon disorders for which no definite successful treatment is available so far, such as granuloma annulare, alopecia areata, lichen ruber, and ichthyosis [57, 59, 69].

Pharmacological and toxicological aspects of vitamin E treatment

Vitamin E is either administered systemically (orally, i.m., i.v.), or topically. When applied orally, the average enteral intake has been estimated to be about 30 mg daily in low-fat diets and up to 400 mg in high-fat diets [46, 57]. The World Health Organization has recommended a minimum daily uptake of 0.15 mg/kg body weight and a maximum of 2 mg/kg α-tocopherol [157]. According to the German Society of Nutrition, a daily intake of 12 mg *d*-α-tocopherol is sufficient for healthy adults [39]. The intestinal absorption rate of vitamin E is suggested to be 50–70%, but significantly lower when high doses are fed [46, 77].

The recommended daily therapeutic dose for the treatment of the above-mentioned dermatoses is inconsistent, and ranges from 100 to 10 000 mg *d*-α-tocopherol equivalent [11, 57, 73]. Summarizing the data, the therapeutically effective dose appears to be by far higher (several hundred milligrams) than that required for a vitamin E supplementation in deficiency syndromes.

Vitamin E intake up to 300 mg *d*-α tocopherol daily can be considered as harmless and not causing toxic events [46]. From a toxicological point of view, even long-term intake of large doses of vitamin E (more than 3000 mg/d *d*-α tocopherol or 3 200 USP U/day) appears to be relatively safe [7, 73]. In a recent review Kappus and Diplock [73] reported studies on the acute and chronic toxicity of vitamin E and on possible adverse effects. Summarizing data of numerous animal experiments, they found no abnormalities in animals fed diets of up to 500 USP U vitamin E daily for 3 months. In vitamin E toxicity studies by Abdo et al. [1] only a dose of 2000 mg/kg body weight *d*-α-tocopheryl acetate (equivalent to 2000 USP U) caused an increase in relative liver weights, prolonged prothrombin and thromboplastin times, and other disturbances in the test rats whereas lower doses led to no objective adverse effects. Similarily, Young et al. [161] observed no severe side effects in rats which received 25–25 000 USP U vitamin E/kg body weight over a period of 8–16 months, except for depressed body weights, elevated levels of alkaline phosphatase, and increased heart and spleen weights at the highest doses. Animal experiments on the mutagenicity, carcinogenicity, and teratogenicity disclosed no dangerous effects of vitamin E even when administered at extraordinarily large doses for a long time [40, 50, 73, 92, 156].

In contrast, several authors have seriously criticized high-dosage vitamin E intake [2, 129]. From single observations or uncontrolled studies, they concluded that numerous pathological events such as thrombophlebitis, hypertension, thyroid disturbances, hyperlipidemia, and nonspecific symptoms including headache, muscle weakness, and intestinal disturbances can be attributed to the uptake of vitamin E in large doses [2, 30, 73, 129]. A series of placebo-controlled clinical studies was not able to confirm any of these suspected side effects [73]. In particular, nonspecific side effects such as generally not being well, headache, muscle weakness, and fatigue were not reproducible [3, 146]. Serum lipids may be increased by doses of more than 3 000 mg vitamin E given over several months but are not affected by lower doses [3, 9, 34, 79, 145]. Thyroid and liver function are not affected during the intake of large amounts (up to 1 000 IU/day) of vitamin E [79]. The level of thyroid hormones, however, may be reduced when doses up to 3 000 mg are administered daily, although other studies did not substantiate these results [3, 9, 145]. Blood coagulation disturbances as well as changes in the amount of red and white blood cells and platelets certainly do not occur when medium-dose vitamin E (900 IU/day) is given over several months [79]. However, vitamin E may contribute to the anticoagulant effect of vitamin K antagonists by competitively inhibiting the intestinal absorption of vitamin K [34]. Similarily, vitamin E enhances vitamin K deficiency in fat malabsorption syndromes [73]. Thus vitamin E therapy is contraindicated in orally anticoagulant-treated and vitamin K deficient patients. Thrombophlebitis has not been observed in various studies with patients receiving up to 2 000 IU vitamin E for up to 6 weeks [9]. Mild symptoms concerning gastrointestinal complaints and emotional disturbances may occur when high-dose vitamin E (3 200 IU/day for months) is administered, but these disorders are infrequent [3, 132].

Kappus and Diplock [73] concluded from these studies that daily vitamin E doses of up to 400 mg can be considered absolutely safe. Doses between 400 and 2 000 mg are not likely to cause side effects. Only at higher doses (more than 3 000 IU/day over a long period) increasing dose-dependent side effects can be expected [73]. Among the latter, exacerbation of blood coagulation defects in vitamin K deficiency subjects are the most dangerous [73]. It is noteworthy that therapeutic usage of vitamin E at doses up to 4 000 IU did not cause relevant adverse effects in hundreds of patients treated for arthrosis, Bechterew's disease, joint injuries, extra-articular rheumatic disease, and others [19, 52, 80].

Conclusions

Vitamin E is a potent antioxidative agent. It is likely to be involved in numerous physiological processes, thereby protecting cells from oxidative damage. In the skin vitamin E acts as an important inhibitor of lipid peroxydation and anti-inflammatory agent. Since UV light is the main source of oxidative stress in skin tissue, vitamin E may prevent skin from the harmful short- and long-term adverse effects of UV irradiation such as photoaging and tumorigenesis. Moreover, vitamin E has proven beneficial in numerous disorders of various tissues including atherosclerosis [128, 140]. However, there is still a lack of knowledge about its possible prophylactic or therapeutic use in dermatological diseases. Viewing the low toxicity and low frequency of adverse effects, clinical trials with vitamin E as a therapeutic agent are required at least in dermatoses for which no efficacious or safe therapeutic management has yet been established. Moreover, further clinical studies should be performed to examine its benefit in the prevention and therapy of actinic damages and to develop appropriate oral and topical preparations.

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