J Mol Med (1995) 73:7–17

REVIEW

F. Nachbar · H.C. Korting

The role of vitamin E in normal and damaged skin

Received: 4 May 1994 / Accepted: 1 June 1994

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

F. Nachbar (✉) · H.C. Korting
Dermatologische Klinik und Poliklinik,
Ludwig-Maximilians-Universität, Frauenlobstrasse 9–11,
D-80337 München, Germany

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-

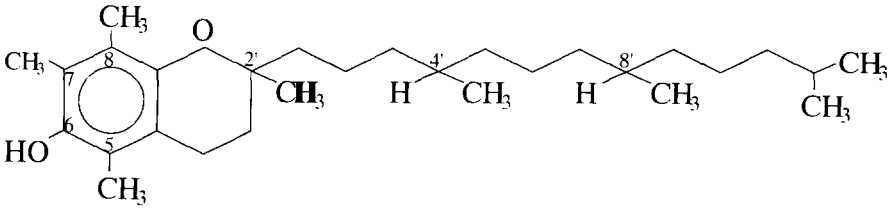

Fig. 1 Configuration of the natural RRR-α-tocopherol stereoisomer

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

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].

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

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

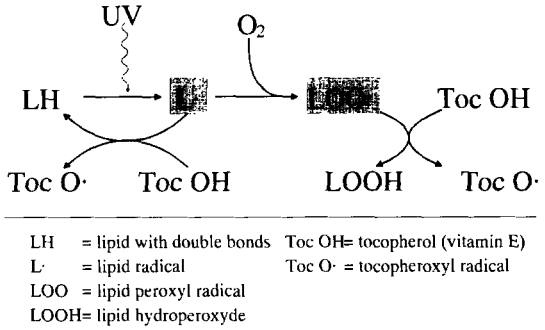

Fig. 2 Interruption of the lipid radical chain reaction by vitamin E. *LH*, Lipid with double bounds; *L*, lipid radical; *LOO*, lipid peroxyl radical; *LOOH*, lipid hydroperoxide; *Toc OH*, tocopherol; *Toc O·*, tocopheroxyl radical

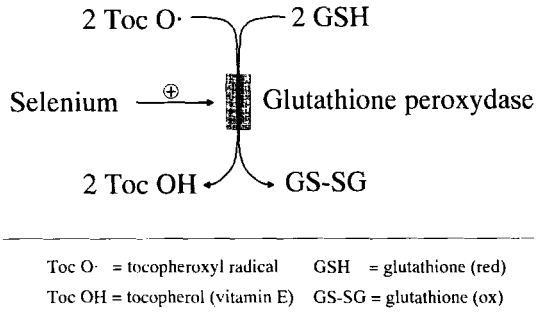

Fig. 3 Reoxygenation of α-tocopherol (*Toc OH*) in the presence of glutathione and selenium. *Toc O·*, Tocopheroxyl radical; *GSH*, glutathione, reduced; *GS-SG*, glutathione, oxidized

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.

References

1. Abdo KM, Rao G, Montgomery CA (1983) Thirteen-week toxicity study of *d*-alpha-tocopheryl acetate (vitamin E) in Fischer 344 rats. Int J Vitam Nutr Res 53:287–296
2. Anderson TW (1974) Vitamin E in angina pectoris. Can Med Assoc J 110:401–406
3. Anderson TW, Reid DB (1974) A double-blind trial of vitamin E in angina pectoris. Am J Clin Nutr 27:1174–1178
4. Anonymus (1981) Effect of vitamin E on prostanoid biosynthesis. Nutr Rev 39:317–320
5. Baker JL (1982) The effectiveness of alpha-tocopherol (vitamin E) in reducing the incidence of spherical contracture around breast implants. Plast Reconstr Surg 68:696–698
6. Beijersbergen van Henegouwen GMJ, de Vries H, van den Broeke LT, Junginger HE (1992) RRR-tocopherols and their acetates as a possible scavenger of free radicals produced in

the skin upon UVA-exposure – an in vivo screening method. Fat Sci Technol 94:24–27
7. Bendich A, Machlin LJ (1988) Safety of oral intake of vitamin E. Am J Clin Nutr 48:612–619
8. Bendich A, D'Apolito P, Gabriel E, Machlin LJ (1984) Interaction of dietary vitamin C and vitamin E on guinea pig immune responses to mitogens. J Nutr 114:1588–1593
9. Bierenbaum ML, Noonan FJ, Machlin LJ (1985) The effect of supplemental vitamin E on serum parameters in diabetics, post coronary and normal subjects. Nutr Res Int 31:1171–1180
10. Bieri JG, Corash L, Hubbard VS (1983) Medical use of vitamin E. N Engl J Med 308:1063–1071
11. Bisset DL, Hillebrand GG, Hannon DP (1989) The hairless mouse as a model of skin photoaging: its use to evaluate photoprotective materials. Photodermatol Photoimmunol Photomed 6:228–233
12. Bisset DL, Chatterjee R, Hannon DP (1990) Photoprotective effect of superoxide-scavenging antioxidants against ultraviolet radiation-induced chronic skin damage in the hairless mouse. Photodermatol Photoimmunol Photomed 7:56–62
13. Bisset DL, Chatterjee R, Hannon DP (1992) Protective effect of a topical 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
14. Black HS (1974) Effects of dietary antioxidants on actinic tumor induction. Res Commun Chem Pathol Pharmacol 7:783–786
15. Black HS, Douglas DR (1985) Formation of a carcinogen of natural origin in the etiology of ultraviolet light induced carcinogenesis. Cancer Res 45:6254–6259
16. Black HS, Lenger W (1984) Inhibition of epidermal lipid peroxidation by dietarily-administered antioxidants (abstract). Proc Am Assoc Cancer Res 25:132
17. Black HS, Lenger W, MacCallum M, Gerguis J (1983) The influence of dietary lipid level on photocarcinogenesis. Photochem Photobiol 37:539–542
18. Black HS, Lenger WA, Gerguis J, Thornby JI (1985) Relation of antioxidants and level of dietary lipid to epidermal lipid peroxidation and ultraviolet carcinogenesis. Cancer Res 45:6254–6259
19. Blankenhorn G (1986) Klinische Wirksamkeit von Spondyvit (Vitamin E) bei aktivierten Arthrosen – eine multizentrische placebokontrollierte Doppelblindstudie. Z Orthop 124:340–343
20. Blum HF (1955) Sunburn. In: Hollaender A (ed) Radiation biology. McGraw-Hill, New York, pp 487–528
21. Burton GW, Ingoid KU (1989) Vitamin E as an in vitro and in vivo antioxidant. Ann NY Acad Sci 570:72–84
22. Burton GW, Ingold KU, Foster DO (1990) Application of deuterated α-tocopherols to the biokinetics and bioavailability of vitamin E. Free Rad Res Comm 11:99–107
23. Böhlau V (1984) Moderne Vitamintherapie für Senioren. Heilkunst 97:336–338
24. Cederbaum A (1989) Introduction: role of lipid peroxidation and oxidative stress in alcohol toxicity. Free Rad Biol Med 7:537–539
25. Chan JT, Black HS (1977) Antioxidant mediated reversal of ultraviolet light cytotoxicity. J Invest Dermatol 68:366–368
26. Chen LH, Chang HM (1979) Effects of high level of vitamin C on tissue antioxidant status of guinea pigs. J Int Vit Nutr Res 49:87–91
27. Chow CK (1975) Increased activity of pyruvate kinase in plasma of vitamin E-deficient rats. J Nutr 105:1221–1224
28. Chow CK (1990) Effect of dietary vitamin E and selenium on rats: pyruvate kinase, glutathione peroxidase and oxidative damage. Nutr Res 10:183–194
29. Chow CK (1991) Vitamin E and oxidative stress. Free Rad Biol Med 11:215–232
30. Cohen HM (1974) Fatigue caused by vitamin E? (letter). New Engl J Med 289:980
31. Comporti M (1989) Three models of free radical-induced cell injury. Chem Biol Interact 72:1–56
32. Connor MJ, Wheeler LA (1987) Depletion of cutaneous glutathione by ultraviolet radiation. Photochem Photobiol 46: 239–245
33. Cook MG, McNamara P (1980) Effect of dietary vitamin E on dimethylhydrazine-induced colonic tumors in mice. Cancer Res 40:1329–1331
34. Corrigan JJ (1982) The effect of vitamin E on warfarin induced vitamin K deficiency. Ann NY Acad Sci 393:361–368
35. Cunnane SC (1988) Vitamin E intake affects serum thromboxane and tissue essential fatty acid composition in the rat. Ann Nutr Metab 32:90–96
36. Cunningham ML, Krinsky NI, Giovanazzi SM, Peak MJ (1985) Superoxide anion is generated from cellular metabolites by solar radiation and its components. J Free Rad Biol Med 1:382–385
37. Davies KJA, Quintanilha AT, Brooks GA, Packer L (1982) Free radicals and tissue damage produced by exercise. Biochem Biophys Res Comm 107:1198–1205
38. De Gruijl FR, van der Meer JB, van der Leun JC (1983) Dose time dependency of tumor formation by chronic UV exposure. Photochem Photobiol 37:53–62
39. Deutsche Gesellschaft für Ernährung (1985) Empfehlungen für die Nährstoffzufuhr, 4th edn. Umschau, Frankfurt
40. Dingemanse E, van Eck WF (1939) Wheat germ oil and tumor formation. Proc Soc Exp Biol Med 41:622–624
41. Diplock AT, Xu G, Yeow C, Okikiola M (1989) Relationship of tocopherol structure to biological activity, tissue uptake, and prostaglandin synthesis. In: Diplock AT, Machlin LJ, Packer L, Pryor WA (eds) Vitamin E: biochemistry and health implications. New York Academy of Sciences, New York, pp 72–84
42. Djerassi D, Machlin LJ, Nocka C (1986) Vitamin E: biochemical function and its role in cosmetics. Drug Cosmet 1:29–34
43. Douglas CH (1986) Vitamin E inhibits platelet phospholipase A_2. Biochim Biophys Acta 116:639–645
44. Dubouloz P, Dumas J, Vigne J (1950) Sur la présence de peroxydes lipidiques dans la peau après l'action de divers agents physiques. Comptes Rendus des Séances de la Société de Biologie et de ses Filiales (Paris) 144:1080–1081
45. Dubouloz P, Dumas J (1954) Sur le métabolisme des peroxydes lipidiques. IV. Présence de peroxydes lipidiques dans la peau au cours des processus inflammatoires. Bull Soc Chim Biol 36:983–991
46. Elmadfa I, Bosse W (eds) (1985) Vitamin E. Wissenschaftliche Verlagsgesellschaft, Stuttgart
47. Epstein JH (1977) The pathological effects of light on the skin. In: Prior W (ed) Free radicals in biology. Academic, New York, pp 219–249
48. Erlemann G, Merkle R (1991) Panthenol, Phytantriol, Vitamin E und Vitamin A in der Kosmetik. Seifen Öle Fette Wachse 117:379–384
49. Esterbauer H, Rotheneder M, Striegel G (1989) Vitamin E and other lipophilic antioxidants protect LDL against oxidation. Fat Sci Technol 91:316–324
50. Evans HM, Emerson GA (1939) Failure to produce abdominal neoplasms in rats receiving wheat germ oil extracted in various ways. Proc Soc Exp Biol Med 41:318–320
51. Finnen MJ, Lawrence CM, Shuster S (1984) Inhibition of dithranol inflammation by free radical scavengers. Lancet II: 1129–1130
52. Fischer L, Seuss J (1985) Antioxidans-Therapie rheumatischer Erkrankungen. Ergebnisse einer multizentrischen Pilotstudie mit Spondylonal (Vitamin E) bei 60 Patienten. Heilkunst 98:145–148
53. Foote CS, Clough RL, Yee BG (1978) Photooxidation of tocopherols. In: de Duve C, Hayashi O (eds) Tocopherol, oxygen and biomembranes. North Holland Biomedics/Elsevier, Amsterdam, pp 13–21
54. Fuchs J, Hufleit ME, Wilson LM (1988) Antioxidant potential of skin is decreased immediately after exposure to a large single fluence of ultraviolet light (>280 nm). International Symposium on Free Radicals in Medicine, Vienna, 8–12 November

55. Fuchs J, Huflejt ME, Rothfuss LM (1989) Acute effects of near ultraviolet and visible light on the cutaneous antioxidant defense system. Photochem Photobiol 50:739–744
56. Fuchs J, Hufleit ME, Rothfuss LM (1989) Impairment of enzymatic and nonenzymatic antioxidants in skin by UVB irradiation. J Invest Dermatol 93:769–773
57. Fuchs J, Mehlhorn RJ, Packer L (1989) Free radical reduction mechanisms in mouse epidermis skin homogenates. J Invest Dermatol 93:633–640
58. Fuchs J, Milbradt R (1990) Vitamin E als Therapeutikum in der klinischen Dermatologie. In: Hornstein OP, Hundeiker M, Schönfeld J (eds) Neue Entwicklungen in der Dermatologie. Springer, Berlin Heidelberg New York, pp 112–130
59. Furuse K (1987) Vitamin E: biological and clinical aspects of topical treatment. Cosmetics Toiletries 102:99–116
60. Gensler HL, Maydaleno M (1991) Topical vitamin E inhibition of immunosuppression and tumorgenesis induced by ultraviolet irradiation. Nutr Cancer 15:97–106
61. Gisinger C, Jeremy J (1988) Effect of vitamin E supplementation on platelet thromboxane A_2 production in type I diabetic patients. Double-blind crossover trial. Diabetes 37:1260–1264
62. Goldstein RK, Zillikens D, Miller K (1991) Lokalbehandlung des disseminierten Granuloma annulare mit einer Vitamin-E-Emulsion. Hautarzt 42:176–178
63. Gunstone FD (1984) Reaction of oxygen and unsaturated fatty acids. J Am Organic Chem 61:441–447
64. Haeger K (1982) Long-term study of alpha-tocopherol in intermittent claudication. Ann NY Acad Sci 393:369–374
65. Hemler ME, Cook HW, Lands WEM (1979) Prostaglandin biosynthesis can be triggered by lipid peroxides. Arch Biochem Biophys 193:340–345
66. Hong CB, Chow CK (1988) Induction of eosinophilic enteritis and eosinophils in rats by vitamin E and selenium deficiency. Exp Mol Pathol 48:182–192
67. Horio T, Okamoto H (1987) Oxygen intermediates are involved in ultraviolet radiation induced damage of Langerhans cells. J Invest Dermatol 88:699–702
68. Horvath PM, Ip C (1983) Synergistic effect of vitamin E and selenium in the chemoprevention of mammary carcinogenesis in rats. Cancer Res 43:5335–5341
69. Howard LJ (1990) The neurologic syndrome of vitamin E deficiency: laboratory and electrophysiologic assessment. Nutr Rev 48:169–177
70. Huang N, Lineberger B, Steiner M (1988) Alpha-tocopherol, a potent modulator of endothelial cell function. Thromb Res 50:547–557
71. Kagan V, Serbinova E, Packer L (1990) Antioxidant effects of ubiquinones in microsomes and mitochondria are mediated by tocopherol recycling. Biochem Biophys Res Commun 169:851–857
72. Kagan V, Witt E, Goldman R (1992) Ultraviolet light-induced generation of vitamin E radicals and their recycling. A possible photosensitizing effect of vitamin E in skin. Free Rad Res Comm 16:51–64
73. Kappus H, Diplock AT (1992) Tolerance and safety of vitamin E: a toxicological position report. Free Rad Biol Med 13:55–74
74. Kang SJ, Hong SD, Cho WG, Chae Q (1992) The role of reactive oxygen species on UVA-induced aging of dermal collagen. IFSCC International Congress Yokohama, book of abstracts. October 13–16:1027–1040 (A 303)
75. Kamimura M (1972) Anti-inflammatory activity of vitamin E. J Vitaminol 18:204–209
76. Kayden HJ, Traber MG (1993) Absorption, lipoprotein transport, and regulation of plasma concentrations of vitamin E in humans. J Lipid Res 34:343–358
77. Kelleher J, Losowsky MS (1970) The absorption of alpha-tocopherol in man. Br J Nutr 24:1033–1047
78. Kent MJC, Light ND, Bailey AJ (1985) Evidence for glucose-mediated covalent cross-linking of collagen after glycosylation in vitro. Biochem J 225:745–752
79. Kitagawa M, Mino M (1989) Effects of elevated *d*-alpha-(RRR)-tocopherol dosage in man. J Nutr Sci Vitaminol 35:133–142
80. Klein KG, Blankenhorn G (1987) Vergleich der klinischen Wirksamkeit von Vitamin E und Diclofenac-Natrium bei Spondylitis ankylosans (Morbus Bechterew). Vitam Miner Spur 2:137–142
81. Kligman LH (1989) Skin changes in photoaging: characteristics, prevention, and repair. In: Balin AK, Kligman AM (eds) Aging and the skin. Raven, New York, pp 331–346
82. Kligman LH (1991) Yearly review. The hairless mouse and photoaging. Photochem Photobiol 54:1109–1118
83. Knekt P (1991) Role of vitamin E in the prophylaxis of cancer. Ann Med 23:3–12
84. Kralli A, Moss SH (1987) The sensitivity of an actinic reticuloid cell strain to near ultraviolet radiation and its modification by trolox-C, a vitamin E analogue. Br J Dermatol 116: 761–772
85. Lands WEM (1985) Interaction of lipid hydroperoxides with eicosanoid biosynthesis. J Free Rad Biol Med 1:97–101
86. Lawrence CM, Shuster S (1987) Effects of arachidonic acid on anthralin inflammation. Br J Clin Pharmacol 24:125–131
87. Lieber CS (1990) Mechanism of ethanol induced hepatic injury. Pharmacol Ther 46:1–46
88. Livingstone PD, Jones C (1958) Treatment of intermittent claudication with vitamin E. Lancet 2:602
89. Lovas RM (1984) Erfahrungen mit Vitamin E-Langzeitapplikation in der ästhetisch-plastischen Chirurgie. In: Böhlau V (ed) Vitamin E in der Rehabilitation und ärztlichen Praxis. Notamed, Melsungen, pp 154–158
90. Machlin LJ (1984) Vitamin E. In: Machlin LJ (ed) Handbook of vitamins, nutritional, biochemical and clinical aspects. Marcel Dekker, New York, pp 99–106
91. Marinova EM, Yanishlieva NV (1992) Inhibited oxidation of lipids. III. On the activity of ascorbyl palmitate during the autoxidation of two types of lipid systems in the presence of alpha-tocopherol. Fat Sci Technol 94:448–452
92. Martin MM, Hurley LS (1977) Effect of large amounts of vitamin E during pregnancy and lactation. Am J Clin Nutr 30:1629–1637
93. Masaki H, Sekihara K, Sakaki S (1992) Development of antiaging component as a cosmetic ingredient – effect of hammamelitannin as the active oxygen scavenger. IFSCC International Congress Yokohama, book of abstracts. October 13–16:437–449 (A 201)
94. Masini V, Noel-Hudson MS, Wepierre J (1992) Biological activity of two human plasmatic fractions on cultured human skin fibroblasts during free radical aggressions. IFSCC International Congress Yokohama, book of abstracts. October 13–16:490–503 (P 59)
95. Mayer P (1993) The effects of vitamin E on the skin. Cosmetics Toiletries 108:99–109
96. McCay PB, Fong KL, Lai EK, King M (1978) Possible role of vitamin E as a free radical scavenger and singlet oxygen quencher in biological system which initiate radical mediated reactions. In: de Duve C, Hayashi O (eds) Tocopherol, oxygen and biomembranes. North Holland Biomedics/Elsevier, Amsterdam pp 41–57
97. Meyskens FL, Prasad KN (1986) Vitamins and cancer; human cancer prevention by vitamins and micronutrients. Humana, Clifton, pp 1–24
98. Michaelsson G, Edqvist LE (1984) Erythrocyte glutathione peroxidase activity in acne vulgaris and effect of selenium and vitamin E treatment. Acta Dermatol Venerol 64:9–14
99. Miyachi Y, Horio T, Imamura S (1983) Sunburn cell formation is prevented by scavenging oxygen intermediates. Clin Exp Dermatol 8:305–310
100. Miyachi Y, Imammura S, Niwa Y (1987) Decreased skin superoxide dismutase activity by a single exposure of ultraviolet radiation is reduced by liposomal superoxide dismutase pretreatment. J Invest Dermatol 89:111–112

101. Möller H, Potokar M, Wallat S (1987) Vitamin E als kosmetischer Wirkstoff. Parfüm Kosmet 68:688–694
102. Möller H, Ansmann A, Wallat S (1989) Wirkungen von Vitamin E auf die Haut bei topischer Anwendung. Fat Sci Technol 91:295–305
103. Moysan A, Marquis I, Gaboriau F (1993) Ultraviolet A-induced lipid peroxidation and antioxidant defense systems in cultured human skin fibroblasts. J Invest Dermatol 100: 692–698
104. Müller-Decker K, Fürstenberger G, Marks F (1992) Development of an in vitro alternative assay to the Draize skin irritancy test using human keratinocyte-derived proinflammatory key mediators and cell viability as test parameters. In Vitro Toxicol 5:191–209
105. Natta CL, Machlin LJ, Brin M (1980) A decrease in irreversibly sickled erythrocytes in sickled cell anemia patients given vitamin E. Am J Clin Nutr 33:968–971
106. Niki E (1987) Antioxidants in relation to lipid peroxidation. Chem Phys Lipids 44:227–253
107. Niki E, Tsuchiya J, Tanimura R, Kamiya Y (1982) Regeneration of vitamin E from alpha-chromanoxy radical by glutathione and vitamin C. Chem Lett:789–792
108. Niki E, Kawakami A, Yamamoto Y, Kamiya Y (1985) Oxidation of lipids. VIII. Synergistic inhibition of oxidation of phosphatidylcholine liposome in aqueous dispersion by vitamin E and vitamin C. Bull Chem Soc Jpn 58:1971–1975
109. Nikolowski W (1985) Vitamin E in der Dermatologie. Apotheker J 7:53–56
110. Noel-Hudson MS, Cornelis M, Lindenbaum A, Wepierre J (1990) Screening tests for free radical scavengers on cutaneous cultured cells. Int J Cosm Sci 12:105–114
111. Norins AL (1962) Free radical formation in the skin following exposure to ultraviolet light. J Invest Dermatol 5:445–447
112. Ohzawa S, Arai M, Takeda Y (1984) Vitamin E in topical preparations. Nippon Kosh Kaka (BJJAEV) 8:18–27
113. Packer L (1984) Vitamin E, physical exercise and tissue damage in animals. Med Biol 62:105–109
114. Panganamala RV, Cornwell DG (1982) The effects of vitamin E on arachidonic acid metabolism. Ann NY Acad Sci 393:376–390
115. Pathak MA, Stratton K (1968) Free radicals in human skin before and after exposure to light. Arch Biochem Biophys 123: 468–476
116. Perchellet JP, Abney NL, Thomas RM (1987) Effects of combined treatments with selenium, glutathione and vitamin E on glutathione peroxidase activity, ornithine decarboxylase induction and complete and multistage carcinogenesis in mouse skin. Cancer Res 47:477–485
117. Plack PA, Bieri JG (1964) Metabolic products of α-tocopherol in the livers of rats given intraperitoneal injections of C^{14}-alpha-tocopherol. Biochim Biophys Acta 84:729–738
118. Posin CJ, Clark KW, Jones MP (1979) Human biochemical response to ozone and vitamin E. J Toxicol Environ Health 5:1049–1057
119. Potapenko AY, Abier GA, Pliquett F (1980) Inhibition of erythema of the skin of mice photosensitized with 8-methoxypsoralen by alpha-tocopherol. Bull Exp Biol Med 89: 611–615
120. Potokar M, Holtmann W, Werner-Busse A (1990) Effectiveness of vitamin E protecting against UV light. Comparative testing of natural tocopherols on the skin of hairless mice. Fat Sci Technol 92:406–410
121. Prasad KN (1988) Mechanisms of action of vitamin E on mammalian tumor cells in culture. Prog Clin Biol Res 259:363–375
122. Prasad KN, Edwards-Prasad J (1982) Effects of tocopherol (vitamin E) acid succinate on morphological alterations and growth inhibition in melanoma cells in culture. Cancer Res 42:550–555
123. Prensky AL (1984) Vitamin E and the nervous system. Develop Med Child Neurol 26:669–676
124. Pryor WA, Prier DG, Church DF (1983) Electron-spin resonance study of the mainstream and sidestream cigarette smoke: nature of the free radicals in gas-phase and in cigarette tar. Environ Health Perspect 47:345–355
125. Pugliese T (1987) Concepts in aging and skin. Cosmetics Toiletries 102:19–44
126. Raab W (1980) Die Wirkung von langwelligem Ultravioletttlicht (UV-A) und von mittelwelliger Ultravioletttstrahlung (UV-B) auf die menschliche Haut. Ein kritischer Vergleich. Z Hautkr 55:497–513
127. Record IR, Dreosti IE, Konstantinopoulos M, Buckley RA (1991) The influence of topical and systemic vitamin E on ultraviolet light-induced skin damage in hairless mice. Nutr Cancer 16:219–225
128. Rimm EB, Stampfer MJ, Ascherio A (1993) Vitamin E consumption and the risk of coronary heart disease in men. N Engl J Med 328:1450–1456
129. Roberts HJ (1981) Perspective of vitamin E as therapy. JAMA 246:129–131
130. Roshchupkin DI, Pistsov MY, Potapenko AY (1979) Inhibition of ultraviolet light-induced erythema by antioxidants. Arch Dermatol Res 266:91–94
131. Sahu SN, Edwards-Prasad J, Prasad KN (1987) Alpha-tocopheryl succinate inhibits melanocyte-stimulating hormone (MSH)-sensitive adenylate cyclase activity in melanoma cells. J Cell Physiol 133:585–589
132. Salkeld RM (1979) Safety and tolerance of high-dose vitamin E administration in man: A review of the literature. Draft of unpublished data is included in OTC Vol. 150121. Cited in: Fed. Register 44:16169–16173
133. Scarpa M, Rigo A, Mairino M (1984) Formation of alpha-tocopherol radical and recycling of α-tocopherol by ascorbate during peroxidation of phosphatidylcholine liposome. An electron paramagnetic resonance study. Biochim Biophys Acta 114:1588–1593
134. Schmidt K, Bayer W, Blankenhorn G (1990) Vitamin E – aktueller wissenschaftlicher Erkenntnisstand. Vitam Miner Spur 5:3–18
135. Sies H, Murphy ME (1991) Role of tocopherols in the protection of biological systems against oxidative damage. J Photochem Photobiol B: Biol 8:211–218
136. Simon-Schnass I, Pabst H (1988) Influence of vitamin E on physical performance. Int J Vitam Nutr Res 58:49–54
137. Slaga TJ, Bracken WM (1977) The effects of antioxidants on skin tumor initiation and aryl hydrocarbon hydroxylase. Cancer Res 37:1631–1635
138. Smith CV (1992) Free radical mechanisms of tissue injury. In: Moslen MT, Smith CV (eds) Free radical mechanisms of tissue injury. CRC, Boca Raton, pp 1–22
139. Sokol RJ (1989) Vitamin E in human health. Vitamin information; status paper. Hoffmann-La Roche, Basel
140. Stampfer MJ, Hennekens CH, Manson JE (1993) Vitamin E consumption and the risk of coronary disease in women. N Engl J Med 328:1444–1449
141. Strickland PT (1986) Photocarcinogenesis by near ultraviolet (UVA) radiation in sencar mice. J Invest Dermatol 87: 272–275
142. Sugai M, Tappel AL (1978) Effect of vitamin E on carbon tetrachloride-induced lipid peroxidation as demonstrated by in vivo pentane production. Toxicol Lett 2:149–155
143. Trevithick JR, Xiong H, Lee S (1992) Topical tocopherol acetate reduces post-UVB, sunburn-associated erythema, edema, and skin sensitivity in hairless mice. Arch Biochem Biophys 296:575–582
144. Trueb B, Fluckiger R, Winterhalten KH (1984) Nonenzymatic glycosylation of basement membrane caused by diabetes mellitus. Collagen Rel Res 4:239–251
145. Tsai AC, Kelley JJ, Peng B, Cook N (1978) Study on the effect of megavitamin E supplementation in man. Am J Clin Nutr 31:831–837
146. Tucker SB, Flannigan SA (1983) Cutaneous effects from occupational exposure to fenvalerate. Arch Toxicol 54:195–202

147. United States Pharmacopeial Convention (1984) United States Pharmacopeia, 21st edn. Rockville, pp 1118–1120
148. Van Welden H, de Gruijl FR, van der Putte SCJ (1988) The carcinogenetic risks of modern tanning equipment: is UV-A safer than UV-B? Arch Dermatol Res 280:300–307
149. Varga M (1992) Understanding the role of oxyradicals in general and in toxic hepatic damage can help safer drug design. Med Hypoth 39:133–136
150. Veris (1992) Vitamin E: Biologische Wirkungen auf die Haut. Vitamin E Übersichtsartikel 2:1–8
151. Wefers H, Sies H (1988) The protection by ascorbate and glutathione against microsomal lipid peroxidation is dependent on vitamin E. Eur J Biochem 174:353–357
152. Weiser H, Erlemann GA (1982) Beschleunigte Heilung oberflächlicher Wunden durch Panthenol und Zinkoxid. Parfüm Kosmet 58:425–428
153. Weiser H, Vecchi M (1982) Stereoisomers of alpha-tocopheryl-acetate. II. Biopotencies of all eight stereoisomers, individually or in mixtures, as determined by rat resorption-gestation test. Int J Vitam Nutr Res 52:351–370
154. Weiss JF, Kumar KS (1988) Antioxidant mechanisms in radiation injury and radioprotection. In: Chow CK (ed) Cellular antioxidant defense mechanisms, vol II. CRC, Boca Raton, pp 163–189
155. Werninghaus K, Handjani RM, Gilchrest BA (1991) Protective effect of alpha-tocopherol in carrier liposomes on ultraviolet-mediated human epidermal cell damage in vitro. Photodermatol Photoimmunol Photomed 8:236–242
156. Wheldon GH, Bhatt A, Keller P, Hummler H (1983) *dl*-Alpha-tocopheryl acetate (vitamin E): a long term toxicity and carcinogenicity study in rats. Int J Vitam Nutr Res 53: 287–296
157. WHO Food Additives Series (1987) 21st. Toxicological evaluation of certain food additives and contaminants. Prepared by the 30th Meeting of Joint FAO/WHO Expert Committee on Food Additives. June 2–11,1986. Cambridge University Press, Cambridge, pp 55–69
158. Winkelmann RK, Blades EJ, Zollmann PE (1960) Squamous cell tumors induced in hairless mice with ultraviolet light. J Invest Dermatol 34:131–138
159. Wolff SP, Bascal ZA, Hunt JV (1989) Autoxidative glycosylation: free radicals and glycation theory. In: Baynes W, Monnier VM (eds) The Maillard reaction in aging, diabetes, and nutrition. Liss, New York, pp 259–275
160. Yagi K, Yamada H, Nishikimi M (1978) Oxidation of alpha-tocopherol with O_2. In: de Duve C, Hayashi O (eds) North Holland Biomedics/Elsevier, Amsterdam, pp 1–11
161. Yang NY, Desai ID (1977) Effect of high levels of dietary vitamin E on hematological indices and biochemical parameters in rats. J Nutr 107:1410–1417
162. Yen JT, Ku PK, Pond WG, Miller ER (1985) Response to dietary supplementation of vitamin C and vitamin E in weanling pigs fed low vitamin E-selenium diets. Nutr Rep Int 31:877–885