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NUTRITIONAL PROTECTION AGAINST SKIN DAMAGE FROM SUNLIGHT

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■ **Abstract** The concept of systemic photoprotection by dietary means is gaining momentum. Skin is continuously exposed to ultraviolet (UV) radiation, the major cause of skin disorders such as sunburn, photodamage, and nonmelanoma skin cancer. Most of the erythemal annual UV dose is encountered under nonvacation conditions, when no sunscreen is applied. In the absence of topically added compounds, skin protection depends solely on endogenous defense. Micronutrients can act as UV absorbers, as antioxidants, or can modulate signaling pathways elicited upon UV exposure. UV-induced erythema is a suitable parameter to assess photoprotection. Dietary protection is provided by carotenoids, tocopherols, ascorbate, flavonoids, or n-3 fatty acids, contributing to maintenance resistance as part of lifelong protection.

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INTRODUCTION

Exposure to ultraviolet (UV) radiation, the major cause for skin disorders such as sunburn, photodamage, and skin cancer, is an issue concerning the entire life span. Only recently it became clear that, interestingly, the predominant exposure to UV light occurs under everyday circumstances. The average erythemal UV dose in the United States is about 25,000 J/m^2 per year; 22,000 J/m^2 for females and 28,000 J/m^2 for males (65, 67). Additional exposure of about 7800 J/m^2 occurs with a conservative vacation. Thus, human skin is exposed to a large degree (about two thirds of the cumulative erythemal UV dose/year) inadvertently, when no topical protection is used, and especially fair-skinned individuals should be advised to protect themselves throughout their lives from excess UV radiation (66). Furthermore, contrary to previous assumptions, recent analysis of UV exposure data shows that Americans actually get less than 25% of their lifetime UV dose by the age of 18 (66). Three fourths of lifetime exposure is delivered during adulthood and older age. Photoprotection by endogenous compounds provided from components in the diet via endogenous delivery to the skin becomes a focus of lifelong major interest. Knowledge on systemic photoprotection is in its early stages (108), although pioneering studies stem from about 30 years ago (41, 54, 100). There is evidence from in vitro, animal, and human studies demonstrating actions of dietary constituents as endogenous photoprotectants (148). While protection through individual dietary components in terms of sun protection factor (SPF) may be considerably lower than that achieved using topical sunscreens, an increased lifelong overall protection via dietary supply may contribute significantly to skin health. This review addresses the concept of human dietary photoprotection.

DAMAGING EFFECTS OF SUNLIGHT

Molecular Mechanisms

Upon light exposure, a cascade of photo-induced chemical and biological reactions takes place in the target tissue (39, 64, 121, 124, 169). As a primary event, light interacts with a suitable chromophore. The chromophore may be damaged directly or may act as photosensitizer initiating subsequent chemical reactions. In the presence of oxygen, secondary reactive oxygen intermediates are generated. These reactive oxygen species (ROS) may damage molecules and cellular structures. The chemical reaction cascade leads to cellular biochemical responses including modified gene expression, impact on kinase-dependent signaling pathways, immune and inflammatory events, or induction of apoptosis.

An example of a direct modification of the chromophore is the formation of dimeric pyrimidine bases of DNA (124). Exogenous agents (70) and endogenously occurring compounds including porphyrins, flavins, DNA bases, or amino acids and their derivatives like urocanic acid are considered to act as photosensitizing molecules (78). According to the postexcitational chemistry of photooxidation,

the processes are assigned to either Type I or Type II photooxidation reactions (38, 56, 64, 124).

Photooxidative deterioration of cellular structures and biomolecules entails biochemical responses at different levels. UV radiation affects the immune system, and UVB-dependent immune suppression is thought to play a key role in photocarcinogenesis (11). Apoptotic keratinocytes (sunburn cells) are found in skin after UVB or high-dose UVA irradiation (33, 94). UV irradiation leads to the release of ceramides from specialized membrane domains known as rafts. Ceramides act as second messengers and are involved in cellular processes including proliferation, differentiation, senescence, and apoptosis (111). Cellular events and regulatory pathways are also directly triggered by specific reactive oxygen species (91, 169, 172). Singlet molecular oxygen is a mediator of UVA-induced signaling and affects, for example, the expression of heme oxygenase-1, ICAM-1, and matrix metalloproteinases (MMPs) (26, 73, 138). MMPs play a central role in the process of skin aging, cleaving collagen and other basement membrane components (169).

Skin Diseases

Sunburn is observed as a common reaction when skin is excessively exposed to sunlight. This injury is called UV-induced erythema, or *erythema solare* (36). Damage resulting from photochemical reactions leads to the stimulation of inflammatory pathways. UVB irradiation is considered the major cause of typical sunburn, which starts to develop within a few hours, culminating about 18–24 hours post irradiation.

The individual sensitivity toward erythematogenic UV exposure is characterized by the minimal erythemal dose (MED), which is defined as the lowest dose of UV radiation that will produce a detectable erythema 24 hours after exposure (114). MED values differ between individuals and depend on the actual endogenous protection by melanin (tanning) and on the skin type (3).

Basal cell carcinoma, squamous cell carcinoma, and malignant melanoma are the major types of skin cancer. Basal cell carcinoma is the most common and least dangerous skin cancer, whereas malignant melanoma is comparatively rare but among the most fatal of all kinds of cancer. There is increasing evidence that the incidence of the three main types of skin cancer is linked to sun exposure, individual sun sensitivity, and to some extent to the history of sunburn (5, 45, 106). Sunlight and especially the UVB part of the spectrum comprise a complete physical carcinogen (11, 121).

As does any other organ, skin ages in a chronological sense with impaired cellular and subcellar functions (169). However, skin may also age prematurely as a result of overexposure to exogenous environmetal factors such as UV radiation. This photoaging process is mainly related to increased exposure to UVA light, but UVB also initiates photoaging (26). Damage to components of the extracellular matrix such as collagen alters dermal structure. As a consequence, skin loses

rigidity, elasticity, and resilience, appearing rough, leathery, and wrinkled, with uneven pigmentation and brown spots (10).

PHOTOPROTECTION: BIOLOGICAL STRATEGIES

Topical Photoprotection

There are different strategies for protection of skin against UV-dependent damage (174). Most simple are avoidance of sun exposure and wearing protective clothing as well as topical application of sunscreens, generally recommended during times of intense exposure, e.g., during holidays or stays at high altitude. It has been speculated that an increased topical protection against UV light might affect endogenous vitamin D synthesis in the skin and may cause disorders related to vitamin D deficiency, e.g., reduced bone strength (81, 107). However, at present the intake of a vitamin D supplement during use of a sunscreen is discussed controversially (61, 107).

Human skin is protected against UV radiation by melanins, endogenous pigments that scatter and absorb UV light (115). Upon sun exposure, pigmentation is enhanced by stimulated synthesis of melanin in the epidermal melanocytes (suntan). The risk for UV-related skin disorders is correlated with pigmentation; the darker the skin, the lower the risk (176). Application of L-tyrosine as a key component of melanin biosynthesis was investigated in animals and humans. However, only minor effects were observed (28). Improved pigmentation was achieved with L-DOPA in animals. Topically applied, synthetic tanning compounds like dihydroxyacetone do not stimulate melanin production. Increased pigmentation results from chemical modifications of stratum corneum–associated proteins (93, 109).

The use of sunscreens for topical protection is promoted as an integral part of skin cancer prevention programs (107). In most of the sunscreens, UV-absorbing compounds and inorganic pigments like titanium dioxide or zinc oxide are combined. Thus, absorption, reflection, and light scattering are the chemical and physical principles of protection.

The effectiveness of sunscreens to protect against UVB is denoted by the SPF, which is determined following standardized methods (75). SPF is calculated as the ratio of the MED measured on protected skin over the MED of unprotected skin. In the assay 2 mg of sunscreen are applied per cm^2 of skin (53, 75). In practical use, sunscreens are employed under nonstandardized conditions, and often topical application may be inadequate to obtain optimal protection expected from SPF (9, 93, 126).

Endogenous Photoprotection

Systemic photoprotection through endogenous supply of components provides an important contribution to the defense against UV effects. In addition to some drugs like psoralens or antimalarial agents, dietary constituents have been investigated. Structural requirements for suitable systemic photoprotection depend on

the supposed underlying mechanism of action (19):

- increasing the barrier for UV light; e.g., UV-absorbing compounds
- protecting target molecules while acting as scavengers; e.g., antioxidants
- repairing UV-induced damage by induction of repair systems
- suppressing cellular responses; e.g., anti-inflammatory agents

Dietary micronutrients include efficient antioxidants capable of directly scavenging lipophilic and hydrophilic prooxidants or serving as constituents of antioxidant enzymes. Carotenoids, tocopherols, flavonoids and other polyphenols as well as vitamin C (for chemical structures see Figure 1) contribute to antioxidant defense and may also contribute to endogenous photoprotection.

The levels of antioxidant vitamins and micronutrients in skin vary with respect to skin area and skin layer (144, 155, 157) (see Table 1). High levels of carotenoids are found in skin of the forehead, palm of the hand, and in dorsal skin; lower levels are found in skin of the arm and the back of the hand. Vitamins E and C are lower in the dermis than in the epidermis. The stratum corneum contains amounts of tocopherol similar to that in the epidermis with increasing levels at inner layers (158). Polyunsaturated fatty acids and retinoids play a role during inflammatory reactions and cellular signaling and might thus serve in systemic photoprotection.

Mitochondrial mutations of DNA accumulate during aging and can be detected at elevated levels in prematurely aged skin following chronic exposure to UV light. In vitro data provide evidence that dietary micronutrients like β-carotene interact with UVA in the cell and prevent the induction of photoaging-associated mtDNA mutations (48). UV-induced signal transduction pathways provide targets for compounds that activate enzymes (49), and polyphenols have been shown to inhibit UV-dependent activation of mitogen-activated protein kinases (MAPK) and AP-1 (110).

The concept of endogenous photoprotection implies that the active compound is available in sufficient amounts at the target site (151). Thus, structural features are important, and influence pharmacokinetic parameters like absorption, distribution, and metabolism, and may affect the level of the compound in skin (160, 175).

CAROTENOIDS AND RETINOIDS

Carotenoids as plant pigments function in the protection of the plant against excess light (42). A system of conjugated double bonds comprises the backbone of these molecules, which carry acyclic or cyclic substituents and, in the case of xanthophylls, contain functional oxygen groups (112). Major carotenoids in the human organism are β-carotene, α-carotene, lycopene, phytoene, and phytofluene, as well as the xanthophylls lutein, zeaxanthin, and α- and β-cryptoxanthin (89, 150). A number of other dietary carotenoids such as violaxanthin or capsorubin are rarely found in human blood, due to poor absorption or direct metabolism (120). The extended system of conjugated double bonds is crucial for the antioxidant

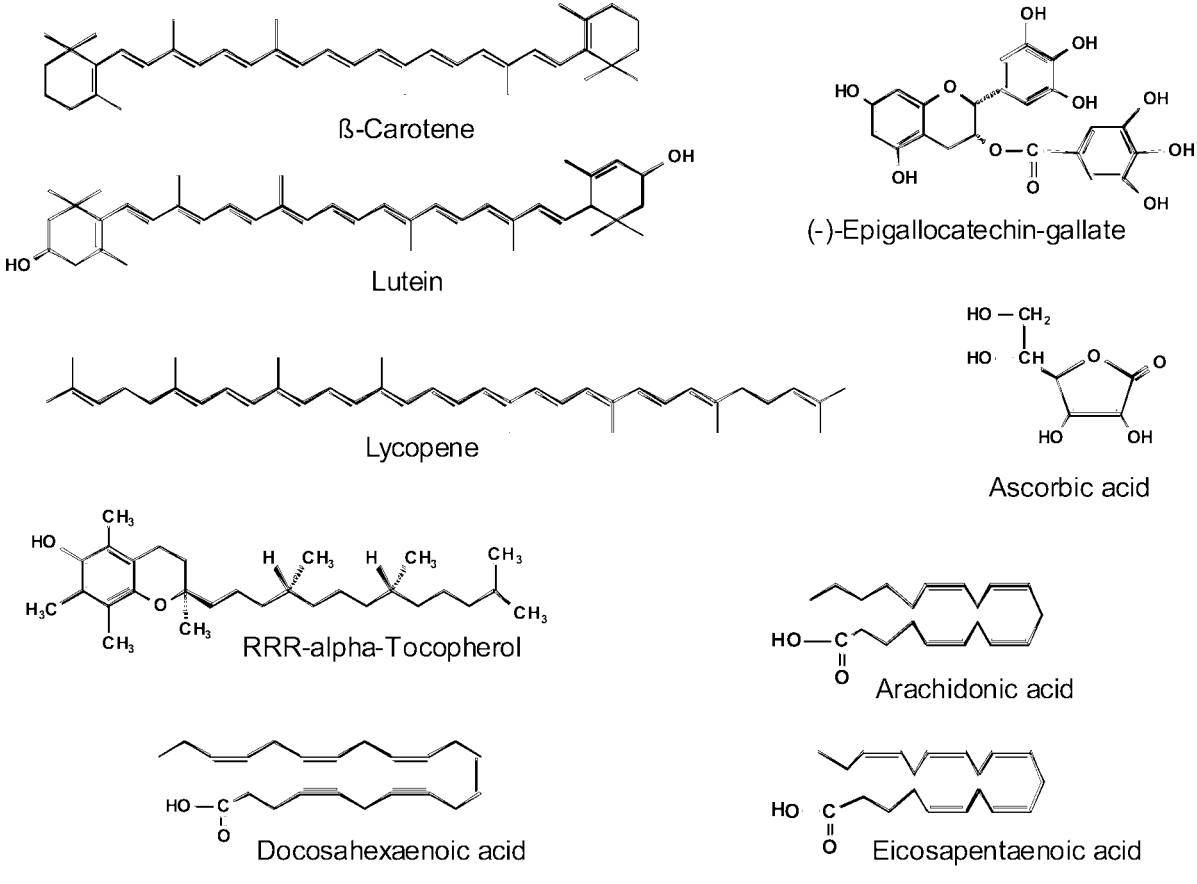

Figure 1 Chemical structures of selected dietary compounds used in photoprotection.

TABLE 1 Micronutrient levels in human skin

Micronutrient (skin layer)	Skin level (pmol/mg wet wt)[a]	Reference
α-Tocopherol		
Epidermis	24.8 ± 9.6	(60)
Epidermis and dermis	25.4 ± 0.2	(118)
Dermis	16.2 ± 1.1	(140)
Epidermis	31.0 ± 3.8	(140)
Stratum corneum	33.0 ± 4.0	(158)
Carotenoids (Epidermis and dermis)		
β-Carotene	0.05 ± 0.04	(79)
α-Carotene	0.02 ± 0.01	
Lycopene	0.13 ± 0.10	
Phytoene	0.12 ± 0.04	
Phytofluene	0.03 ± 0.02	
β-Carotene	0.11 ± 0.01	(118)
α-Carotene	0.01 ± 0.01	
Lycopene	0.22 ± 0.01	
Lutein	0.03 ± 0.01	

[a]Data from cited references, converted to pmol/mg wet wt.

properties of carotenoids (99, 149). Carotenoids are among the most efficient natural scavengers of singlet molecular oxygen (147). At low oxygen tension carotenoids are also able to scavenge peroxyl radicals (32).

Carotenoids are found in the all-trans configuration in most plants, whereas several *cis*-isomers have been identified in human blood and skin. Such *cis*-isomers exhibit an additional absorption maximum in the UV range, depending on the position of the cis double bond in the molecule (27). Phytoene and phytofluene are noncolored carotenoids with only three and five double bonds in conjugation, respectively, with high UV absorption maxima.

Carotenoids are present at the target sites of light-induced damage, the skin and the eye (24, 171). The dermal pattern of carotenoids resembles that of plasma (119, 171), and the absolute levels vary between different skin areas (144). Small amounts of fatty acid esters of lutein, zeaxanthin, 2′,3′-anhydrolutein, α-cryptoxanthin, and β-cryptoxanthin are also found in human skin (171). Carotenoids contribute significantly to normal human skin color, in particular the appearance of yellowness (1). Noninvasive methods have been developed, using reflectance spectroscopy or Raman spectroscopy to determine carotenoid levels in skin (79, 144). Consuming high amounts of carotenoids may result in discoloration to orange or yellow (carotenodermia) (29, 105).

Dietary Intervention

Intervention studies on UV-protective effects of carotenoids are presented in Table 2. In one study (145), protection against UV-induced erythema was observed

TABLE 2 Dietary intervention and supplementation studies with micronutrients investigating UV protection with endpoints related to sunburn

	Duration (wk)	Result	Reference
Dietary intervention: 40 g tomato paste equivalent to 16 mg lycopene/d	10	Erythema less pronounced	(145)
Supplementation: β-Carotene 60 mg/d Plus canthaxanthin 90 mg/d	4	No protection	(173)
β-Carotene 180 mg/d	10	MED[a] increased	(102)
90 mg/d	3	No protection	(62)
30 mg/d	12	Erythema less pronounced	(68)
24 mg/d	12	Erythema less pronounced	(143)
30–90 mg/d	24	MED increased	(96)
24 mg/d	12	Erythema less pronounced	(80)
Mixed carotenoids 24 mg/d (β-carotene, lycopene, lutein; 8 mg each)	12	Erythema less pronounced	(80)
Lycopene 6 mg, β-carotene 6 mg, tocopherol 10 mg, Se 75 μg/d	7	MED increased	(34)
RRR-α-tocopheryl-acetate 400 IU/d	26	No protection	(170)
RRR-α-tocopherol 3000 IU/d	7	No protection	(59)
RRR-α-tocopherol 1000 IU/d Plus ascorbate 2000 mg/d	1	MED increased	(46)
RRR-α-tocopherol 3000 IU/d Plus ascorbate 3000 mg/d	7	MED increased	(59)
Ascorbate 3000 mg/d	7	No protection	(59)
500 mg/d	8	No protection	(103)

[a]MED, minimal erythemal dose.

after dietary intervention, as opposed to supplementation with isolated compounds (see below). Tomato paste contains high amounts of the tomato-specific carotenoid lycopene and was selected as a natural dietary source providing carotenoids to protect against UV-induced erythema in humans (145) (Table 2). Ingestion of tomato paste (40 g/day, equivalent to 16 mg lycopene/day) over a period of 10 weeks led to elevated serum levels of lycopene from about 0.4 μmol/L at basal to 0.7 μmol/L after 10 weeks of intervention; total carotenoids in skin also increased. No significant protection was found at week 4, but after 10 weeks of treatment, erythema formation was significantly lower in the group consuming the tomato paste than in the controls. Erythema was induced with a solar light simulator at 1.25 MED, and reddening of the skin was evaluated before and 24 hours after irradiation by chromametry. Erythema intensity was lower after treatment. This

study (145) demonstrates that UV-induced erythema can be ameliorated by dietary intervention.

Dietary Supplements

One of the first studies regarding effects of β-carotene on the development of *erythema solare* was initiated by Mathews-Roth (102). Healthy volunteers received a supplement providing 180 mg of β-carotene per day over a period of 10 weeks. Threshold MED was significantly higher in the group supplemented with β-carotene. However, no signifcant difference between the supplemented group and the control was found in the degree of erythema. In a placebo-controlled study, pretreatment with 30 mg of β-carotene per day for 10 weeks diminished the intensity of erythema induced by sunlight (68). A modest protection against UVA- as well as UVB-induced erythema was also observed in a study where increasing doses of β-carotene (30–90 mg/d) were applied for 24 weeks; MED at the end of the study was 1.5-fold higher than the MED before treatment (96).

The efficacy of β-carotene in systemic photoprotection depends on the duration of treatment before exposure and on the dose (Table 2). In studies documenting protection against UV-induced erythema, supplementation with carotenoids lasted for at least seven weeks, and the dose was at least a total of 12 mg of carotenoids per day (68, 80, 96, 102, 143). In studies reporting no protective effects the treatment period was only three to four weeks (62, 173). No statistically significant change in the light sensitivity was found when a mixture of antioxidants with about 5 mg β-carotene per day and some additional lycopene was ingested (74). However, a decrease in UV-dependent expression of MMP-1 and MMP-9 was measured.

Concerns about the safety of β-carotene when applied in high doses raised a discussion on suitable dose levels for photoprotection (14). In two long-term intervention trials with individuals at high risk for cancer, an increased incidence for lung cancer of about 20% was found in the groups that received β-carotene supplements. In these studies, β-carotene was applied for several years at doses of 20 and 30 mg per day alone or in combination with α-tocopherol or retinol (2, 113).

In order to lower the dose of β-carotene, it was investigated whether the compound can be partially substituted by other carotenoids for sun protection (80). The photoprotective effect of β-carotene (24 mg/d) was compared to that of a carotenoid mixture consisting of β-carotene, lutein, and lycopene (8 mg each/d). Supplementation was performed for 12 weeks, and carotenoid levels in serum and skin, as well as erythema intensity after irradiation with a solar light simulator were determined at baseline and after 6 and 12 weeks of treatment. The intensity of erythema 24 hours after irradiation was diminished to a similar extent in both groups receiving carotenoid. Hence, supplementation for 12 weeks with 24 mg of a carotenoid mixture supplying 8 mg each of β-carotene, lutein, and lycopene ameliorates UV-induced erythema in humans (80).

Protective effects of lutein in combination with zeaxanthin (ratio 20:1) have also been demonstrated in an animal experiment with hairless mice (69). Upon supplementation with a mixture of both carotenoids, epidermal hyperproliferation and inflammatory response following UVB irradiation were diminished. Using an antioxidant mixture providing 6 mg of β-carotene and 6 mg of lycopene per day (with an additional 10 mg RRR-α-tocopherol and 75 μg selenium), protection against UV-induced skin damage was achieved in humans (34). Intervention for a period of seven weeks resulted in elevation of the actinic erythema threshold and diminished UV-induced erythema. Additionally, pigmentation was increased, lipid peroxidation diminished and the number of sunburn cells were found to be lower.

Skin Cancer

In animal studies, carotenoids proved to be useful agents to prevent skin cancer, and the incidence of nonmelanoma skin cancers was inversely related to β-carotene serum levels (95). However, at present there is no clear evidence from epidemiological or interventional studies that β-carotene or other carotenoids contribute to the prevention of any type of skin cancer in humans (4, 7). In two intervention trials with β-carotene at 50 or 30 mg/d, no significant effect on the incidence for nonmelanoma skin cancers was found (71, 72). Also, no effect of β-carotene (30 mg/d) on the incidence of solar keratosis was observed in a randomized controlled study with more than 1600 participants (37). However, protection was associated with the use of sunscreen with or without additional β-carotene supplement.

Erythropoietic Protoporphyria

β-Carotene and, to a lesser extent, lycopene and other antioxidants are successfully applied to ameliorate secondary effects of erythropoietic protoporphyria (EPP) (101). High levels of porphyrins trigger photooxidative reactions leading to skin damage. Upon light exposure, the patients experience a burning sensation followed by erythema formation. Singlet molecular oxygen and electronically excited triplet states of suitable sensitizers are involved in the pathogenesis of EPP. Some patients respond positively to treatment with high doses of carotenoids (up to 180 mg β-carotene/d for several months); the symptoms following photosensitization are ameliorated (57, 164).

Retinoids

Retinoids, retinoic acid or natural and synthetic derivatives, are widely applied in the treatment of skin disorders including acne, psoriasis, ichthyosis, and keratodermatosis (25). Clinical trials using retinoids in the treatment of skin cancers led to conflicting results (82). Although retinoic acid triggers pathways of cell growth and differentiation, its use as a preventive agent is limited due to toxicological

concerns (25). The major retinoid present in human blood and tissues is retinol (vitamin A) and its fatty acid esters. In a small case-control study, the level of serum retinol was found to be inversely correlated with the occurrence of nonmelanoma skin cancer (95).

Vitamin A absorbs in the UVB range, but may be a direct target of both UVB and UVA, and it participates in an adaptive response to UV exposure. The physiological role of this adaptive response to acute and chronic sun exposure is not yet understood (137).

TOCOPHEROL AND ASCORBATE

Vitamin E (a term comprising several tocopherols and tocotrienols) and vitamin C are present in human skin (116). Protection against UV-induced damage is thought to be due to their antioxidant properties; in particular, the interaction between tocopherol and ascorbate is important in protection against photooxidative damage (Table 2). Lipophilic tocopherols and the hydrophilic ascorbate scavenge reactive intermediates in cellular compartments of different lipophilicity (142). In vitro studies suggest that vitamin C regenerates tocopherol from the tocopheroxyl radical and transfers the radical load to the aqueous compartment where it is finally eliminated by antioxidant enzymes (168).

In a study on the cooperative activity of both vitamins against UV-induced erythema over a period of 50 days, four treatment groups were investigated: RRR-α-tocopherol (2 g/d) and ascorbate (3 g/d) as single components, a combination of α-tocopherol and ascorbate (2 and 3 g/d, respectively), and controls without treatment (59). Upon treatment with the combination the sunburn threshold was significantly increased; MED was about 100 mJ/cm^2 before and about 180 mJ/m^2 after supplementation. The single compounds provided moderate but statistically not significant protection.

Short-time intervention with high doses of both vitamin E and C also affords some protection. When vitamins were ingested at doses of 1000 IU D-α-tocopherol together with 2 g ascorbic acid/d over a period of eight days, there was a minor increase in MED (46). RRR-α-tocopherol has also been tested in combination with carotenoids as an oral sun protectant. Coapplication of vitamin E and β-carotene tended to be superior to β-carotene treatment alone, but the difference was statistically not significant (143). Vitamin E alone, in the form of α-tocopheryl acetate, was administered orally at 400 IU/d over a period of six months, but no significant protection was achieved (170). Parameters determining the bioavailability of tocopherol in human skin are not yet known. MED is not correlated with the epidermal content of vitamin E (60). In addition to the supply via epidermal blood vessels, alpha- and gamma-tocopherol are continuously secreted with the human sebum (159). Thus, vitamin E is also a constituent of the antioxidant network of the *stratum corneum*, the first line of defense against exogenous oxidants such as ozone (156, 157).

In a study including 12 volunteers, vitamin C was applied at 500 mg/d over eight weeks, and UV-induced erythemal response was determined (103). Supplementation had no effect on MED.

Human and animal studies have shown that vitamin E, and to a lesser extent vitamin C, provide UV protection when applied topically (44, 97). Various endpoints indicating phototoxic damage, such as UV-dependent erythema, formation of sunburn cells, skin wrinkling, lipid peroxidation, and DNA damage, can be modulated (58, 104, 155). Using a combination of the vitamins is more efficient than the use of single compounds as ingredients of a topically applicable sunscreen (52, 97).

POLYPHENOLS

Phenolic compounds as secondary plant metabolites are major constituents of the diet, comprising a large variety of structurally different molecules such as cinnamic acids, benzoic acids, proanthocyanidins, stilbenes, coumarins, or flavonoids (135). Polyphenols are efficient antioxidants in vitro, and the antioxidant activity of a number of regularly consumed fruits and vegetables can be attributed largely to their phenolic constituents (122, 131). Considerable amounts of polyphenols are also found in cocoa, tea, and red wine (63, 77). The antioxidant properties are due to the presence of hydroxyl groups, and structure-activity relationships have been elaborated (130, 136). Due to their amphiphilic properties, polyphenols may serve as lipophilic or hydrophilic scavengers operative in different compartments (139). Beyond antioxidant activity, polyphenols (especially flavonoids and isoflavones) exhibit other biochemical properties, acting as enzyme inhibitors or enzyme inducers influencing anti-inflammatory pathways and affecting cell division.

Flavonoid consumption with the diet has been associated with lowered risks for cardiovascular disease and cancer. However, human studies on the importance of flavonoids in health have been inconclusive (133, 135, 163).

In plants, flavonoids are present as glycosides and are cleaved before absorption in the human gastrointestinal tract. Data on metabolism of flavonoids indicate a pronounced first-pass effect, which means that they are efficiently conjugated by phase II enzymes yielding glucuronide and sulfate conjugates (151). Thus, bioavailability of free flavonoids with functional hydroxyl groups is thought to be low. However, human feeding studies provide evidence that absorption and bioavailability of specific flavonoids is higher than anticipated (135).

The so-called green tea polyphenols gained attention as protective agents against UV-induced damage. The most prominent phenolic compounds in green tea are the flavanols (−)-epigallocatechin, (−)-epigallocatechin-3-gallate, (−)-epicatechin, (−)-epicatechin gallate, (+)-gallocatechin, and (+)-catechin. Animal studies provide evidence that tea polyphenols, when applied orally or topically, ameliorate adverse skin reactions following UV exposure, including skin damage, erythema, and lipid peroxidation (90). Topical application of green tea polyphenols prior to exposure protects against UVB-induced local as well as systemic immune

suppression; the effects were associated with inhibition of UVB-induced infiltration of inflammatory leukocytes (85).

(−)-Epigallocatechin-3-gallate inhibits UV-dependent activation of AP-1 in cell culture (8, 110). Activation of AP-1 is an important step in tumor promotion, so that this inhibitory effect of green tea polyphenols could be a mechanism of protection. In hairless mice (SKH-1), feeding of green tea polyphenols significantly lowered the yield of UVB-induced skin tumors (167). In a similar model, topical application of green tea polyphenols or its major constituent (−)-epigallocatechin-3-gallate lowered UVB-dependent oxidation of lipids and proteins, depletion of antioxidant enzymes, and phosphorylation of proteins of the MAPK family such as ERK1/2, JNK, and p38 (162).

Topical application of green tea polyphenols to human skin inhibited the UVB-induced erythema response and decreased the formation of cyclobutane pyrimidine dimers in skin, found both in epidermis and dermis (88). In order to identify active components, the skin of healthy volunteers was treated with either an extract of green tea or one of its constituents (50). (−)-Epigallocatechin-3-gallate and (−)-epicatechin-3-gallate polyphenolic fractions were most efficient in inhibiting erythema. Skin treated with green tea extracts showed a lower number of sunburn cells; treatment protected epidermal dendritic cells from UV damage. Green tea extracts also lowered the DNA damage formed after UV radiation.

Topical application of (−)-epigallocatechin-3-gallate at about 1 mg/cm^2 was found to protect human skin against UV-induced oxidative stress (86). Pretreatment with the polyphenol prior to exposure to four times the MED led to a decrease in the formation of hydrogen peroxide and nitric oxide, and inhibited lipid peroxidation and UV-induced infiltration of inflammatory leukocytes into the skin. Taken together, polyphenolic extracts of green tea and their major constituents can provide some dietary contribution to photoprotection. Topical epigallocatechin-3-gallate was tested for the prevention of nonmelanoma skin cancer in a randomized, double blind, placebo-controlled phase II clinical trial (98). A total of 51 subjects with actinic keratosis, a readily identifiable precursor of nonmelanoma skin cancer, were treated for 12 weeks; no significant effects were found.

Other polyphenols and flavonoids have been investigated in vitro and in animal models for photoprotection. In a mouse model, topically applied silymarin provided prevention against UV-induced skin tumors (87). Additionally, silymarin lowered UVB-caused sunburn and apoptosis, skin edema, depletion of catalase activity, and induction of cyclooxygenase and ornithine decarboxylase activities as well as ornithine decarboxylase mRNA expression (87). Similar effects were reported for the flavonoid apigenin (15).

SELENIUM

The trace element selenium plays a major role in antioxidant defense (92). In the form of selenocysteine, it occurs in selenoproteins such as glutathione peroxidase, thioredoxin reductase, and selenoprotein P. Selenomethionine is found

in low amounts in proteins in place of methionine. There is evidence from animal studies that topical application of selenomethione provides some protection against UV-induced skin cancer (30, 31). In an in vitro study (123), the selenoprotein profile of cultured human skin cells was examined. Labeling studies using [^{75}Se] selenite showed qualitative and quantitative differences in selenoprotein expression by human fibroblasts, keratinocytes, and melanocytes. This was most noticeable for thioredoxin reductase (60 kDa) and phospholipid hydroperoxide glutathione peroxidase (21 kDa). A 24-hour preincubation with sodium selenite or selenomethionine protected both cultured human keratinocytes and melanocytes from UVB-induced cell death. With primary keratinocytes, the greatest protection from cell death was found with 10 nM sodium selenite and with 50 nM selenomethionine. Protection was obtained with concentrations as low as 1 nM with sodium selenite and 10 nM with selenomethionine. When selenium was added after UVB radiation, little protection was achieved. In all experiments sodium selenite was more potent than selenomethionine.

In an interesting twist in selenium research, a candidate selenoprotein homologous to glutathione peroxidase was deduced from the sequence of molluscum contagiosum, a poxvirus that causes persistent skin neoplasms in children and in AIDS patients (141). Selenium was incorporated into this protein during biosynthesis. The selenoprotein protected human keratinocytes against cytotoxic effects of UV irradiation and hydrogen peroxide, providing a mechanism for a virus to defend itself against environmental stress.

However, no skin protection by selenium was observed in a human intervention study. In a randomized controlled trial, selenium supplementation did not protect against development of basal or squamous cell carcinoma of the skin (35).

LIPIDS: LOW-FAT DIET, OMEGA-3-FATTY ACIDS

Based on a series of animal experiments it has been suggested that high fat intake may increase the sensitivity of skin toward UV-induced carcinogenesis. In a mouse model, high levels of dietary fat led to enhanced photocarcinogenesis (18). Consequently, a low-fat diet may contribute to the prevention of UV-induced skin cancer. In a two-year clinical trial, patients suffering from nonmelanoma skin cancers (NMSCs) were assigned either to a group receiving a low-fat diet (caloric intake from fat limited to 20%) or a control group (16, 17). The cumulative number of newly developed actinic keratosis (as a premalignant skin lesion) was compared between groups. In the control group the number of new actinic keratoses per patient was about three- to fourfold higher than in the dietary intervention group, indicating a preventive effect of a low-fat diet on the incidence of actinic keratosis. As to the number of new NMSCs within eight-month periods during the two years of intervention, the control group's skin-cancer occurrence revealed no significant changes, whereas in the dietary intervention group the occurrence of new NMSCs declined after the first eight-month period and reached statistical significance by

the third eight-month period (16, 21). As a general advice derived from these studies, it is suggested to lower the intake of calories from fat and increase the consumption of grains, fruits, and vegetables in order to prevent actinic keratosis and NMSC (83).

The correlation between dietary habit and basal cell carcinoma of the skin was investigated in a prospective cohort of men (161). In 1986, diet was assessed by a food-frequency questionnaire in 43,217 male participants of the Health Professionals Follow-up Study. During eight years of follow-up, 3190 cases with basal cell carcinoma (BCC) were newly diagnosed. Evaluation of dietary intake did not support the idea that a lower intake of fat is associated with a diminished risk for BCC. However, a higher intake of monounsaturated fatty acids was associated with a slight decrease in cancer risk. The correlation between dietary factors and the incidence of BCC was also investigated in a nested case-control study drawn from the EPIC-Norfolk cohort (40). Based on the evaluation of 109 cases, no association between the intake of dietary fat and the incidence of BCC was found. The number of cases was too low to evaluate the risk for squamous cell carcinoma (SCC). Among ten other components of the diet including protein, carbohydrate, carotenoids, and vitamins A, C, D, and E, a substantial protective effect was only found for vitamin E. The problem of high fat intake, dietary intervention with lipid restriction, and the risk for NMSC is apparently more complex and might involve the action of lipid antioxidants and the composition of dietary fat. Different classes of dietary fatty acids have an impact on carcinogenesis. In a case-control study on fat consumption and the risk of squamous cell carcinoma of the skin, the association between dietary n-3 and n-6 fatty acid intake and cancer risk was investigated (76). There was a consistent tendency for a lower risk of SCC with higher intakes of n-3 fatty acids. An increased intake of diets with a high ratio of n-3 to n-6 fatty acids was also associated with a tendency toward a decreased risk of SCC. N-3 and n-6 fatty acids differently affect skin tumor formation (20). Hairless mice received isocaloric diets either rich in n-6 or n-3 fatty acids and were irradiated with UV light to induce photocarcinogenesis. Analysis of tumor incidence and tumor multiplicity provided evidence that a diet rich in n-6 fatty acids significantly enhanced carcinogenesis, whereas an n-3 fatty acid source was protective.

In a study with 42 healthy human volunteers, the effects of eicosapentaenoic acid (n-3) or oleic acid on skin responses and early genotoxic markers after UV radiation were investigated (129). Four g of fatty acids were ingested daily for three months. In the group supplemented with eicosapentaenoic acid (EPA), UV-induced p53 expression in skin and DNA strand breaks in peripheral blood lymphocytes were lowered, indicating protection by dietary EPA against acute UV-dependent genotoxicity. As the most prominent result, sunburn sensitivity was diminished by ingestion of eicosapentaenoic acid. In comparison to baseline, the UV-induced erythemal threshold was increased about 1.4-fold at the end of the study. None of these parameters was significantly changed in the group that received oleic acid. These results confirm earlier studies on the protective effects of dietary fish oil

rich in omega-3 fatty acids toward the susceptibility to UVB-induced erythema and epidermal lipid peroxidation (128). After six months of supplementation with about 10 g of fish oil per day, the MED was increased about 2.1-fold. Photoprotective effects of fish oil were also determined in light-sensitive patients with polymorphic light eruption accompanied by diminished basal and UVB-dependent PGE_2 levels (127). Prostaglandin E_2 and nitric oxide in combination play a role in UVB-induced erythema formation (125). Thus, the amelioration of the UV-induced inflammatory response may be due to lowered prostaglandin E_2 levels (84).

CONCLUSION AND OUTLOOK

Nutritional contribution to systemic photoprotection is emerging as a topic of interest in public health and preventive medicine. Based on in vitro experiments in cell culture and on various types of animal studies, in vivo studies on healthy volunteers provided the proof of principle, using a suitable biomarker, erythema formation. The dietary components, carotenoids [notably β-carotene, lutein or lycopene (108)] are those that plants and other organisms use for their protection against excess light (42).

The concept of endogenous skin protection is to provide a maintenance level at sensitive dermal target sites, beyond those reached by topical, and temporary, coverage through the use of sunscreen. While endogenous protection in terms of sun protection factor may be low or even marginal, the cumulative effect receives increasing attention. Lifelong inadvertent sunlight exposure is important (66).

WHAT ARE THE STRATEGIES? Depending on the chemical structure and physicochemical properties, micronutrients may directly absorb or scatter light and thus contribute to UV defense. The obvious strategy for a dietary antioxidant delivered to the target site is the direct interception of reactive species, as is perceived in the case of carotenoids and other direct antioxidants such as tocopherols and ascorbate. These compounds have also been identified analytically to be present as such within dermal cell layers. However, at present it is not known whether indeed the observed action is due to a direct antioxidant function of these micronutrients. A growing body of evidence demonstrates that these compounds can serve important functions independent of direct antioxidant chemistry, by modulating enzyme activity and gene expression. Changing levels of protein kinase C or of DNA repair enzymes, for example, could impact resistance to photooxidative stress. Thus, modification of signaling cascades by nutrients is a developing area of research (52). Consequently, it may not be a prerequisite for a systemically photoprotective agent to be present at or near a sensitive target site. Remote control through genomic and proteomic reset patterns is a further strategy. Examples in this sense are not yet available at the level of the human, but the improvement of cell-to-cell communication by carotenoids could well be a suitable candidate area of research. Major dietary carotenoids, including β-carotene, lycopene, and several xanthophylls can

increase connexin expression and, consequently, cell-to-cell communication (12, 146, 152, 154). There is evidence that not the parent carotenoids but metabolites or oxidation products such as retinoids or apocarotenals are the ultimate active agents (6, 13, 152, 154). Various connexins are found in skin and are of importance for normal development and differentiation of human epidermis (132).

Other strategies may rely on the specific biochemistry and physiology of skin. For example, the content of nitrite in sweat, covering skin, could provide benefit, because there is generation of NO from nitrite under UVA radiation (153). NO is a signaling molecule involved in UVB-induced melanogenesis (134). However, to date it is unknown whether nutrition may influence the availability of the NO synthase substrate, L-arginine, in the skin or nitrate levels in sweat.

Another approach is focused on alternative pathways of transport. Protective agents may be delivered via sebaceous gland secretion, as has been shown for the delivery of vitamin E to upper layers of facial skin (159).

WHAT ARE THE MOLECULES? The above-mentioned molecules occur as dietary micronutrients (Figure 1), and they are detected in skin. However, skin as a metabolically active organ is capable of modifying compounds by various routes of metabolism, and it is possible that the compounds reaching skin are already metabolized, predominantly by so-called Phase II reactions. This may apply to flavonoids and polyphenols, an important class of compounds shown to act topically in terms of photoprotection (108), but there is no analytical proof to date for the existence of polyphenols in skin.

It is quite likely that, as in other organs, a network of active compounds is of prime importance. Thus, building blocks for antioxidant defense enzymes, including trace metals such as copper, zinc, cysteine, and selenocysteine, are included in the scope of this topic.

WHAT ARE THE PROCESSES ADDRESSED, AND WHAT ARE THE MOLECULAR BIOMARKERS? Sunburn is one phenomenon related to exposure to UV radiation. Erythema formation can be readily quantified and is being used successfully as a noninvasive parameter for the assessment of the biological response to UV exposure. Whether erythema formation is the most suitable surrogate endpoint for long-term degenerative diseases such as skin cancer (of the various types), photodermatoses, or photoaging needs to be scrutinized in further work. Protection against UV-induced erythema, or sunburn, does not necessarily mean protection against skin cancer. Other biomarkers suitable in relation to skin cancer may be modified DNA bases (124). Increasing numbers of sunburn cells have been taken as a measure for UV-induced damage indicating apoptotic responses (33).

WHAT ARE THE RISKS? Lipophilic micronutrients are embedded at low levels in lipid phases, e.g., cellular membranes, or lipoproteins. There is heterogeneity of membrane domains, and it is obvious (but not yet analytically proven) that there should be local areas of high and low concentration. The mechanisms that lead

to the incorporation of micronutrients such as carotenoids into their final site of residence are not yet known. Clearly, there are large disparities between skin areas in terms of embedded micronutrient, as shown for instance in the high levels of β-carotene in the palm of the hand as compared to other skin areas (144). Could there be a risk with levels too high? To date, there are no studies related to skin regarding any of the micronutrients addressed. The use of vitamins E and C has been examined at the level of the intact organism, and recommended daily intake as well as upper levels of intake have been identified (43, 55). As for carotenoids, there are no recommendations yet, and concern was raised that they are prooxidant (99, 117). Such prooxidant activities may lead to formation of oxidation products that are not generated at physiological levels of micronutrients. The increased risk for lung cancer under supplementation with high amounts of β-carotene to a population at risk was ascribed to the generation of oxidative metabolites with impact on retinoic acid signaling (14, 165, 166). Apparently, there are optimum levels of micronutrients for antioxidant defense, as illustrated in Figure 2. With increasing levels of different carotenoids in cell culture, an increased antioxidant effect was determined (47). However, further increases of carotenoids lead to a rise of malondialdehyde indicative of prooxidant activity. Thus, optimum levels have to be achieved for optimal function at the target site. As already noted, antioxidants interact synergistically. One of the major tasks in micronutrient research will be the development of tools that allow estimation of optimum levels.

BEYOND PHOTOPROTECTION Micronutrients are of additional benefit for skin, influencing moisture and texture as well as elasticity and structure (22, 23). For example, ascorbate is essential as a cofactor in collagen biosynthesis.

Claims on cosmetic effects of micronutrients have been made, and an array of natural compounds is used in topically applied cosmetic products. However, the field of cosmeceuticals is only in its developing stages (51). Providing endogenous nutrients for optimum skin health and care is an interesting new aspect. Such a concept, unfortunately, lacks suitable data from nutrition research in order to provide a mechanistic base. Appropriate biokinetic, biochemical, and histological data are required before such an approach can be considered sound. Because the wider public is concerned here, caution is to be recommended at this stage. This applies also to the efforts to develop food items enriched with micronutrients (functional food).

DIETARY VERSUS TOPICAL? It is important to note that the nutritional aspect focused on in this review is complementary to topical photoprotection, and these two concepts of prevention should certainly not be considered mutually exclusive. One major aspect regarding dietary photoprotection is the time frame: As noted in all studies so far carried out, there is a time of approximately eight to ten weeks until protection against erythema formation becomes significant (Table 2). Skin turnover and skin biochemistry therefore require this time frame, whereas protection by topical sunscreen is practically instantaneous.

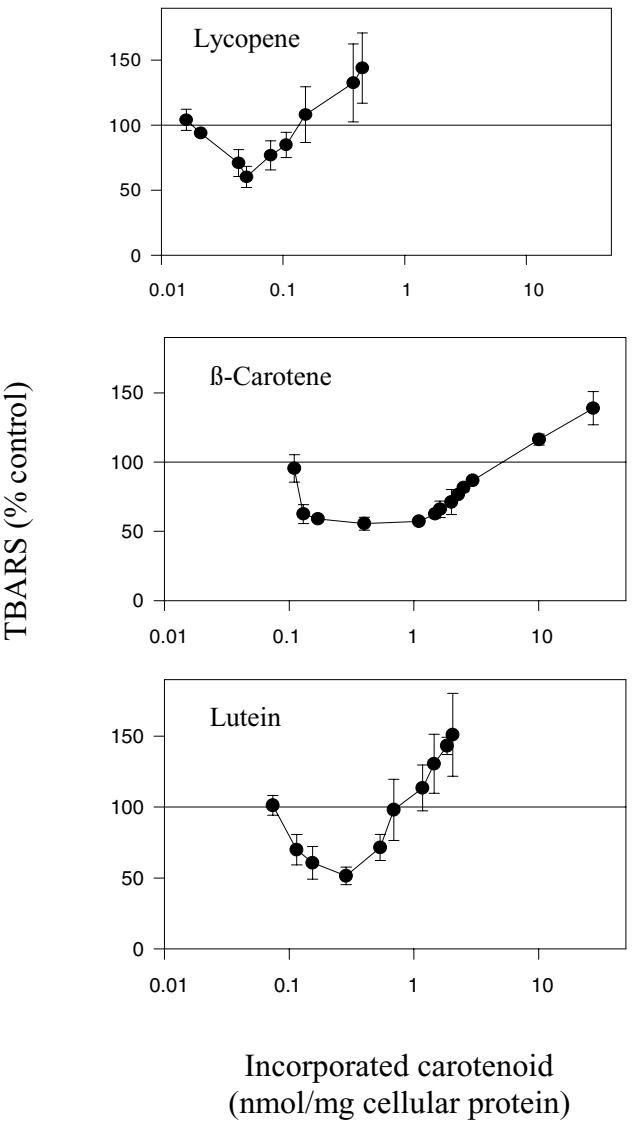

Figure 2 Optimum levels of protection against UV-induced lipid peroxidation in cell culture achieved with different carotenoids. Thiobarbituric acid-reactive substances (TBARS) formation in human skin fibroblasts was induced by irradiation with UVB; prooxidant and antioxidant effects of lycopene (*top*), β-carotene (*center*), and lutein (*bottom*). (—): controls without carotenoids (100%); numbers below 100% indicate antioxidant activity, numbers above 100% indicate prooxidant activity. Modified from Reference 47.

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