β-Carotene and other carotenoids in protection from sunlight[1–3]

Wilhelm Stahl and Helmut Sies

ABSTRACT

Protection against skin damage from sunlight by nutritional means has been examined. Likewise, there has been work on the topical application of phytochemicals to the skin. This review focuses on the nutritional aspect of phytochemicals in humans—ie, the provision of carotenoid micronutrients by dietary means to the skin and their role in protection. Human intervention studies have documented protective effects for β-carotene or for lycopene provided either by a carotenoid-rich diet or by supplementation. In exposed tissues, light induces primary and secondary photooxidative processes. Scavenging of reactive oxygen species is considered to be a mechanism of action underlying the protective activity of carotenoids. However, food comprises a complex mixture of numerous constituents, so that other components may also contribute to the observed activity. Molecules with suitable structures absorb UV light and prevent direct damage of cellular targets. Phytoene and phytofluene are precursor molecules of higher unsaturated carotenoids and occur in various fruit and vegetables. Their absorption spectra cover the UVB and UVA range, respectively, thus potentially contributing to photoprotective effects of carotenoid-rich food. Because of the physiologic turnover time of skin, several weeks are required for protective effects to appear. Photoprotection through individual dietary components such as β-carotene or lycopene in terms of sun protection factor is considerably lower than that achieved by using topical sunscreens. However, an optimal supply of antioxidant micronutrients in the skin increases basal dermal defense against UV irradiation, supports longer-term protection, and contributes to maintenance of skin health and appearance. *Am J Clin Nutr* 2012;96(suppl):1179S–84S.

INTRODUCTION

Protection against skin damage from sunlight by nutritional means has recently been examined by various groups (1–5). Likewise, there has been work on the topical application of phytochemicals to the skin (6, 7). The focus of this review is on the nutritional aspect of phytochemicals in humans—that is, the provision of carotenoid micronutrients by dietary means to the skin and their role in protection.

The capability of long-chain polyene structures to physically quench electronically excited molecules has attracted long-standing interest in chemistry. Likewise, carotenoids, the major class of polyene compounds in biology, which occur as important plant pigments, have been studied extensively. Because carotenoids are ingested by humans as part of the normal diet, interest has extended to nutrition and medicine.

Carotenoids are ingested with food components, notably fruit and vegetables, but also from animal sources. The transport of carotenoids from the gut occurs on uptake with chylomicrons into the lymph, followed by circulating in lipoprotein particles in the blood. The distribution into various tissues is nonuniform, with large interorgan differences. Some tissue concentrations of lycopene and β-carotene are presented in **Table 1** (with data from reference 8; our own data are shown in more detail in reference 9). A typical HPLC chromatogram of the carotenoid pattern of a human plasma sample is shown in **Figure 1**.

The biological properties of carotenoids are manifold; some are related to their function as provitamin A and others are related to the properties mentioned above, namely the quenching of electronically excited states (eg, under conditions of excess light exposure in the photosynthetic reaction center of plants) (10). The latter properties are particularly important for humans in light-exposed tissues such as the skin and eyes. Indeed, before the development of skin care products in recent centuries, humans depended entirely on biological protection of skin from sunlight, which derived from endogenously provided compounds. A major class of compounds consists of carotenoids in this context (*see* Table 1).

CHEMICAL BASIS

On exposure to UV light, suitable sensitizer compounds are electronically excited to the triplet state, which can undergo several subsequent reactions. In the presence of ground-state molecular oxygen, the excitation energy can be transferred to generate singlet molecular oxygen. This electronically excited oxygen species can undergo chemical reactions—eg, with DNA, proteins, and lipids—and thus contribute to oxidative stress. There is no known enzyme that is tailored directly to inactivate singlet molecular oxygen, but rather this task is fulfilled by small-molecule compounds, so-called singlet oxygen quenchers. Carotenoids are prominent in this function, which is called *physical quenching*. The excitation energy is transferred to the carotenoid, which, in turn, dissipates the excitation energy to the

[1] From the Institute of Biochemistry and Molecular Biology I, Faculty of Medicine (WS and HS) and the Leibniz Research Institute for Environmental Medicine (HS), Heinrich-Heine-University Düsseldorf, Düsseldorf, Germany, and the College of Science, King Saud University, Riyadh, Saudi Arabia (HS).

[2] Presented at the conference "New Developments in Carotenoids Research," held in Boston, MA, March 11–12, 2011.

[3] Address correspondence to H Sies, Institute of Biochemistry and Molecular Biology I, University Street, Building 22.03, D-40225 Düsseldorf, Germany. E-mail: sies@uni-duesseldorf.de.

First published online October 10, 2012; doi: 10.3945/ajcn.112.034819.

TABLE 1
Lycopene and β-carotene tissue concentrations in humans[1]

Tissue	Stahl et al (9)	Kaplan et al (48)	Nierenberg and Nann (49)	Schmitz et al (50)
Lycopene (nmol/g wet weight)				
Liver	1.28	2.45	—	5.72
Kidney	0.15	0.39	—	0.62
Adrenal	1.90	21.60	—	—
Testis	4.34	21.36	—	—
Ovary	0.25	0.28	—	—
Adipose	0.20	1.30	—	—
Lung	—	—	0.22	0.57
Colon	—	—	0.31	—
Breast	—	—	0.78	—
Skin	—	—	0.42	—
β-Carotene (nmol/g wet weight)				
Liver	3.02	1.82	—	4.41
Kidney	0.55	0.31	—	0.55
Adrenal	5.60	9.39	—	—
Testis	2.68	4.36	—	—
Ovary	0.45	0.97	—	—
Adipose	0.38	0.38	—	—
Lung	—	—	0.12	0.35
Colon	—	—	0.17	—
Breast	—	—	0.71	—
Skin	—	—	0.27	—

[1] Adapted from reference 8.

solvent as heat and returns to the initial ground state. Thus, a catalytic cycle is generated, so that the carotenoid can undergo another round of singlet oxygen quenching. This is a quasi-enzymatic function in the sense that the catalyst comes out of the reaction unchanged. Because of the presence of carotenoids in the diet, there may not have been an evolutionary pressure to form an enzyme specialized for this task. The second-order reaction rate constants of carotenoids are very high, near diffusion control, with lycopene being the most efficient singlet molecular oxygen quencher (11).

Carotenoids can also undergo chemical reactions with singlet molecular oxygen and other reactive oxygen species (eg, peroxyl radicals). In these reactions, there are initial chemical adducts, which further lead to breakdown of the polyene structure and eventually the loss of the carotenoid to yield breakdown products (12). A general principle of photoprotection is the direct absorption of UV light using suitable compounds. Most carotenoids exhibit absorbance maxima at wavelengths in the visible range. However, phytoene and phytofluene, which contain only 3 and 5 conjugated double bonds, respectively, absorb at wavelengths covering the UVB and UVA range. Blue-light filtering by carotenoids is important for ocular protection and involves lutein and zeaxanthin (13, 14).

It should be made clear that, in addition to direct chemical interference with reactive oxygen species or light absorption, carotenoids can interfere with UV light–induced gene expression by multiple pathways (15). For example, carotenoids activate the antioxidant response element transcription system (16) and have antiproliferative properties (17, 18) as well as antiimmunosuppressive actions (19, 20). Furthermore, carotenoids upregulate gap junctional cell-cell communication by connexin gene expression, independent of provitamin A or antioxidant properties (21, 22). This means that not only do carotenoids have a molecular role in prevention but they also have a role in interception and repair (23).

HUMAN UV LIGHT EXPOSURE

The exposure to solar UV radiation has been estimated to be ~10% for outdoor-working adults and ~3% for indoor-working adults of the total available annual UV radiation (on a horizontal plane) (24). The UV doses that people are exposed to increase with increasing altitude and with decreasing latitude. Most indoor-working Europeans adults receive 10,000–20,000 J/m^2 per year, Americans receive 20,000–30,000 J/m^2 per year, and Australians receive 20,000–50,000 J/m^2 per year, excluding

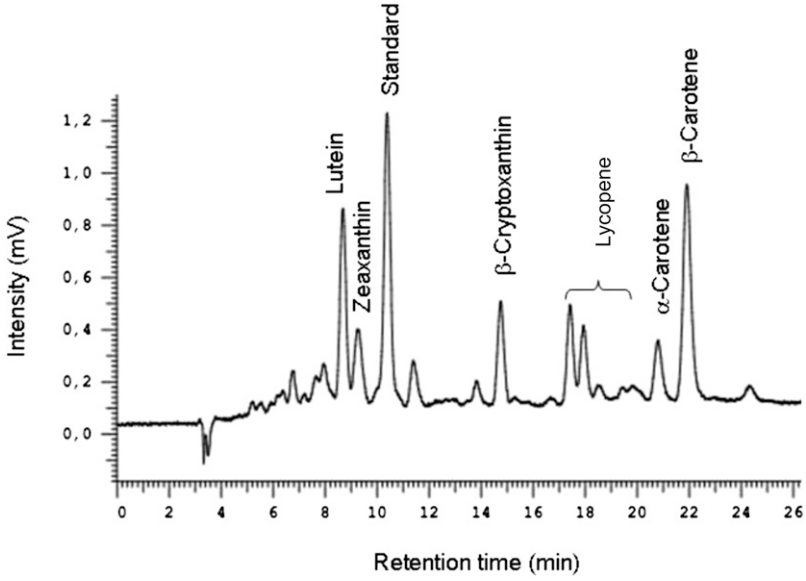

FIGURE 1. Typical carotenoid pattern of a human serum sample analyzed by means of HPLC according to the method described by Stahl et al (58).

during vacation, which can increase the dose by ≥30% (24). In view of the potential detrimental health effects such as sunburn, ocular damage, photoaging, immune suppression, DNA damage, and skin cancer, it is important to consider protective strategies.

Major factors that influence the UV dose other than avoidance (staying indoors) are shade from trees and shade or protection from buildings, awnings, umbrellas, and other direct personal sources (eg, clothing, hats, sunscreens). Controlled exposure of human volunteers to sunlight for 12 d (total UV dose of ~10,000 mJ/cm^2) led to significant decreases in skin and plasma β-carotene concentrations (25).

SYSTEMIC PHOTOPROTECTION

UV radiation impinging on the skin or eyes can be protected against by biological compounds in tissues, which are provided from nutritional sources via the bloodstream. Concentration of carotenoids and α-tocopherol in human skin are shown in **Table 2** and indicate that there are considerable differences in the patterns in different skin layers. Furthermore, there are large differences in different areas of the skin: high concentrations of carotenoids are found in the skin of the forehead, palm of the hand, and in dorsal skin. Lower concentrations occur in skin of the arm and the back of the hand (26).

The concept of endogenous photoprotection entails interaction of the protective compound at the site of impinging oxidative challenge—that is, the active compound must be present in sufficient amounts at the target site. Thus, structural features are important and influence pharmacokinetic variables such as absorption, distribution, and metabolism as well as transport of reaction products from the target site. Recently, carotenoid bioaccessibility in human skin was evaluated by using noninvasive resonance Raman spectroscopy on the palm and forehead skin (27). Clearly, carotenoids are not the only compounds that provide protection of skin against damage from sunlight. Other phytochemical compounds such as tocopherols, tocotrienols, ascorbate, polyphenols (flavonoids), selenium compounds, PUFAs, and others have been found to contribute (*see* references 1 and 5).

TABLE 2
Micronutrient concentrations in human skin[1]

Micronutrient and skin layer (reference)	Skin concentration
	nmol/g wet wt
α-Tocopherol	
Epidermis (51)	24.8 ± 9.6
Epidermis and dermis (52)	25.4 ± 0.2
Dermis (53)	16.2 ± 1.1
Epidermis (53)	31.0 ± 3.8
Stratum corneum (54)	33.0 ± 4.0
Carotenoids	
Epidermis and dermis (55)	
β-Carotene	0.05 ± 0.04
α-Carotene	0.02 ± 0.01
Lycopene	0.13 ± 0.10
Phytoene	0.12 ± 0.04
Phytofluene	0.03 ± 0.02
Epidermis and dermis (52)	
β-Carotene	0.11 ± 0.01
α-Carotene	0.01 ± 0.01
Lycopene	0.22 ± 0.01
Lutein	0.03 ± 0.01

[1] Values are means ± SD. Data from cited references were converted to nmol/g wet wt.

HUMAN INTERVENTION STUDIES

Dietary intervention

Intervention studies on the UV-protective effects of β-carotene are presented in **Table 3**. Most of these studies provided evidence that an elevated intake of carotenoids ameliorates UV-induced erythema (sunburn). Protection against UV-induced erythema was observed 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 (28) (Table 3). Ingestion of tomato paste (40 g/d, equivalent to 16 mg lycopene/d) over a period of 10 wk led to elevated serum concentrations of lycopene from ~0.4 μmol/L at baseline to 0.7 μmol/L after 10 wk of intervention; total carotenoids in skin also increased. No significant protection was found at week 4, but after 10 wk of treatment erythema formation was significantly lower in the group consuming the tomato paste than in control subjects. Erythema was induced with a solar light simulator at 1.25 minimal erythemal dose (MED), and reddening of the skin was evaluated before and 24 h after irradiation by a chromameter. Erythema intensity was significantly lower after treatment. This study (28) showed that UV-induced erythema can be ameliorated by dietary intervention.

In an intervention study with tomato extract and a drink containing solubilized tomato extract, photoprotective effects were compared with synthetic lycopene at a dose of 10 mg/d for ≤12 wk (29). The protective effect against erythema formation (Δ *a*-value) was more pronounced in the extract and drink groups than with synthetic lycopene. In the 2 former groups, phytoene and phytofluene may have contributed to the protection, because both compounds exhibit absorption maxima in the UV range, providing additional protection by direct absorption of damaging light. In the study groups in which tomato-based products were used, serum phytoene and phytofluene concentrations increased during intervention. Increases in phytofluene were more pronounced than in phytoene, and they exceeded lycopene concentrations at the end of the study (29). Both of these carotenoids are biosynthetic precursors of lycopene and β-carotene and are also present in carotenoid supplements that contain fruit or vegetable oleoresins.

In an intervention study in 20 healthy women conducted to examine whether tomato paste rich in lycopene protects against cutaneous photodamage (30), it was found that there was protection against acute and potentially longer-term aspects of photodamage. Biopsy samples were taken from unexposed and UV radiation–exposed (3 × MED 24 h earlier) buttock skin pre- and postsupplementation and analyzed immunohistochemically for procollagen, fibrillin-1, and matrix metalloproteinase (MMP) 1 and by quantitative polymerase chain reaction for mitochondrial DNA 3895-bp deletion (30). At presupplementation, UV radiation induced an increase in MMP-1 and a decrease in fibrillin-1. At postsupplementation, MMP-1 was lower in the

TABLE 3
Dietary intervention and supplementation studies on carotenoids that investigated UV protection with endpoints related to sunburn[1]

Dietary intervention or supplementation study (reference)	Duration	Result
	wk	
Dietary intervention studies		
40 g Tomato paste equivalent to 16 mg lycopene/d (28)	10	Erythema less pronounced.
Tomato extract (Lyc-o-Mato; LycoRed Ltd) vs lycopene, 10 mg/d (29)	12	Erythema less pronounced. Phytoene, phytofluene contribute?
55 g Tomato paste equivalent to 16 mg lycopene/d (30)	12	Erythema less pronounced, matrix metalloproteinase 1 lowered, mtDNA 3895-bp deletion lowered.
Supplementation studies		
β-Carotene plus canthaxanthin (35) 60 mg/d 90 mg/d	4	No protection.
β-Carotene		
180 mg/d (31)	10	MED increased.
90 mg/d (56)	3	No protection.
30 mg/d (57)	12	Erythema less pronounced.
24 mg/d (34)	12	Erythema less pronounced.
30–90 mg/d (32)	24	MED increased.
24 mg/d (33)	12	Erythema less pronounced.
Mixed carotenoids		
β-Carotene, lycopene, lutein (8 mg each); 24 mg/d (33)	12	Erythema less pronounced.
Lycopene 6 mg, β-carotene 6 mg, tocopherol 10 mg, Se 75 μg/d (39)	7	MED increased.

[1] MED, minimal erythemal dose; mtDNA, mitochondrial DNA.

tomato paste group compared with the control group, as was the 3965-bp deletion in mitochondrial DNA after UV radiation (30). Although erythemal $D_{(30)}$ was significantly higher after tomato paste, the MED was not altered.

Dietary supplementation

One of the first studies on the effects of β-carotene on the development of solar erythema was initiated by Mathews-Roth (31). Healthy volunteers received a supplement providing 180 mg β-carotene/d over a period of 10 wk. Threshold MED was significantly higher in the group supplemented with β-carotene. However, no significant difference in the degree of erythema between the supplemented group and the control group was found. In a placebo-controlled study, pretreatment with 30 mg β-carotene/dd for 10 wk diminished the intensity of erythema induced by sunlight (59). A modest protection against UVA- as well as UVB-induced erythema was also observed in a study in which increasing doses of β-carotene (30–90 mg/d) were applied for 24 wk; MED at the end of the study was 1.5-fold higher than MED before treatment (32).

The efficacy of β-carotene in systemic photoprotection depends on the duration of treatment before exposure and on the dose (Table 3). In studies that documented protection against UV-induced erythema, supplementation with carotenoids lasted for $\geq$7 wk, and the dose was a total of $\geq$12 mg carotenoids/d (31–34). In studies that reported no protective effects, the treatment period was only 3–4 wk (35). No significant change in light sensitivity was found when a mixture of antioxidants containing $\sim$5 mg β-carotene/d and some additional lycopene was ingested (36). However, a decrease in UV-dependent expression of MMP-1 and MMP-9 was measured.

Concerns about the safety of β-carotene when applied at high doses raised a discussion on suitable dose amounts for photoprotection. In 2 long-term intervention trials in individuals at high risk of cancer, an increased incidence of lung cancer of $\sim$20% was found in the groups who received β-carotene supplements. In these studies, β-carotene was applied for several years at doses of 20 and 30 mg/d alone or in combination with α-tocopherol or retinol (37). Although the potential mechanisms underlying adverse effects of carotenoids have not yet been fully elucidated, it was recently observed that eccentric cleavage products of β-carotene can interfere with the retinoic acid receptor–mediated signaling pathway (38); these products likely are formed at higher doses, and they can modulate cancer risk.

To lower the dose of β-carotene, it was investigated whether the compound can be partially substituted by other carotenoids for sun protection (33). The photoprotective effect of β-carotene (24 mg/d) was compared with that of a carotenoid mixture consisting of β-carotene, lutein, and lycopene (8 mg/d for each). Supplementation was performed for 12 wk, and carotenoid concentrations 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 wk of treatment. The intensity of erythema 24 h after irradiation was diminished to a similar extent in both groups receiving carotenoids. Hence, supplementation for 12 wk with 24 mg of a carotenoid mixture supplying 8 mg each of β-carotene, lutein, and lycopene ameliorates UV-induced erythema in humans (33).

By using an antioxidant mixture that provided 6 mg β-carotene and 6 mg lycopene/d (with an additional 10 mg RRR-α-tocopherol and 75 μg selenium), protection against UV-induced skin damage was achieved in humans (39). Intervention for a period of 7 wk resulted in the elevation of the actinic erythema

threshold and diminished UV-induced erythema. In addition, pigmentation was increased, lipid peroxidation diminished, and the numbers of apoptotic keratinocytes ("sunburn cells") were found to be lower.

The issue of *optimum dose* remains elusive. Among the many factors that determine the content at the target site, which include biokinetics, metabolism, transport, and elimination, the optimum concentration at the target site itself is of interest. In a model system that used skin fibroblasts and standardized UV exposure, we found that there is an optimum dose for carotenoids in protecting against lipid peroxidation (40). β-Carotene, lycopene, and lutein each exhibited protection at lower concentrations when incorporated into the membranes. With increasing concentrations of carotenoids, even prooxidative effects were detected (40). Studies in individuals to identify optimum skin concentrations of carotenoids for protection are missing. Recent developments in noninvasive assessment of carotenoid concentrations in skin and macular tissues are promising (41–44).

A recent study on vitamins and photoaging posed the question, "Do scientific data support their use?" (45). With regard to carotenoids, the conclusion was as follows: "Although the evidence available at this time is not strong enough to offer definitive support for the use of dietary carotenoids for photoprotection in healthy patients, it is sufficient to propose that a role for carotenoids as adjuvant photoprotective agents should not yet be discounted" (45).

BEYOND PHOTOPROTECTION

Micronutrients are of additional benefit for skin, influencing moisture and texture as well as elasticity and structure. 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, although providing endogenous nutrients for optimum skin health and care is an interesting new idea. Such a concept, unfortunately, lacks suitable data from nutrition research to provide a mechanistic base. Appropriate biokinetic, biochemical, and histologic data are required before such an approach can be considered sound. Because the wider public is concerned, caution is recommended at this stage. This also applies to the efforts to develop food items enriched with micronutrients (functional food).

DIETARY COMPARED WITH TOPICAL PROTECTION?

It is important to note that the nutritional aspect focused on in this review is complementary to topical photoprotection, and these 2 concepts of prevention should certainly not be considered mutually exclusive. One major aspect with regard to dietary photoprotection is the time frame: as noted in all studies so far carried out, there is a time of ~7–10 wk until protection against erythema formation becomes significant (Table 3). Skin turnover and skin biochemistry, therefore, require this timeframe, whereas protection by topical sunscreen is practically instantaneous.

Whereas the profile of micronutrients in blood or plasma can be assessed readily (46), noninvasive monitoring of skin depends on specialized equipment, such as reflectance spectrophotometry or Raman spectroscopy. Because there are responders and nonresponders to carotenoid supplementation, monitoring in the target organ becomes important. Likewise, the success of 5-a-Day campaigns, which provide fruit and vegetables, needs to be monitored (47).

The authors' responsibilities were as follows—WS and HS: contributed equally to the research and the writing of this manuscript. HS receives support from the National Foundation for Cancer Research, Bethesda, MD. Neither of the authors declared a conflict of interest.

REFERENCES

1. Dinkova-Kostova AT. Phytochemicals as protectors against ultraviolet radiation: versatility of effects and mechanisms. Planta Med 2008;74:1548–59.
2. Köpcke W, Krutmann J. Protection from sunburn with beta-carotene–a meta-analysis. Photochem Photobiol 2008;84:284–8.
3. Stahl W, Sies H. Photoprotection by dietary carotenoids: concept, mechanisms, evidence and future development. Mol Nutr Food Res 2012;56:287–95.
4. Shapira N. Nutritional approach to sun protection: a suggested complement to external strategies. Nutr Rev 2010;68:75–86.
5. Sies H, Stahl W. Nutritional protection against skin damage from sunlight. Annu Rev Nutr 2004;24:173–200.
6. Afaq F, Adhami VM, Ahmad N, Mukhtar H. Botanical antioxidants for chemoprevention of photocarcinogenesis. Front Biosci 2002;7:d784–92.
7. Gupta S, Mukhtar H. Chemoprevention of skin cancer through natural agents. Skin Pharmacol Appl Skin Physiol 2001;14:373–85.
8. Stahl W, Sies H. Lycopene: a biologically important carotenoid for humans? Arch Biochem Biophys 1996;336:1–9.
9. Stahl W, Schwarz W, Sundquist AR, Sies H. cis-trans isomers of lycopene and beta-carotene in human serum and tissues. Arch Biochem Biophys 1992;294:173–7.
10. Demmig-Adams B, Gilmore AM, Adams WW III. Carotenoids 3: in vivo function of carotenoids in higher plants. FASEB J 1996;10:403–12.
11. Di Mascio P, Kaiser S, Sies H. Lycopene as the most efficient biological carotenoid singlet oxygen quencher. Arch Biochem Biophys 1989;274:532–8.
12. Burton GW, Ingold KU. beta-Carotene: an unusual type of lipid antioxidant. Science 1984;224:569–73.
13. Junghans A, Sies H, Stahl W. Macular pigments lutein and zeaxanthin as blue light filters studied in liposomes. Arch Biochem Biophys 2001;391:160–4.
14. Krinsky NI, Landrum JT, Bone RA. Biologic mechanisms of the protective role of lutein and zeaxanthin in the eye. Annu Rev Nutr 2003;23:171–201.
15. Wertz K, Hunziker PB, Seifert N, Riss G, Neeb M, Steiner G, Hunziker W, Goralczyk R. beta-Carotene interferes with ultraviolet light A-induced gene expression by multiple pathways. J Invest Dermatol 2005;124:428–34.
16. Ben-Dor A, Steiner M, Gheber L, Danilenko M, Dubi N, Linnewiel K, Zick A, Sharoni Y, Levy J. Carotenoids activate the antioxidant response element transcription system. Mol Cancer Ther 2005;4:177–86.
17. Gerster H. Anticarcinogenic effect of common carotenoids. Int J Vitam Nutr Res 1993;63:93–121.
18. Kelkel M, Schumacher M, Dicato M, Diederich M. Antioxidant and antiproliferative properties of lycopene. Free Radic Res 2011;45:925–40.
19. Fuller CJ, Faulkner H, Bendich A, Parker RS, Roe DA. Effect of beta-carotene supplementation on photosuppression of delayed-type hypersensitivity in normal young men. Am J Clin Nutr 1992;56:684–90.
20. Herraiz LA, Hsieh WC, Parker RS, Swanson JE, Bendich A, Roe DA. Effect of UV exposure and beta-carotene supplementation on delayed-type hypersensitivity response in healthy older men. J Am Coll Nutr 1998;17:617–24.
21. Zhang LX, Cooney RV, Bertram JS. Carotenoids up-regulate connexin43 gene expression independent of their provitamin A or antioxidant properties. Cancer Res 1992;52:5707–12.
22. Stahl W, Nicolai S, Briviba K, Hanusch M, Broszeit G, Peters M, Martin HD, Sies H. Biological activities of natural and synthetic carotenoids: induction of gap junctional communication and singlet oxygen quenching. Carcinogenesis 1997;18:89–92.

23. Stahl W, Sies H. Bioactivity and protective effects of natural carotenoids. Biochim Biophys Acta 2005;1740:101–7.
24. Godar DE. UV doses worldwide. Photochem Photobiol 2005;81: 736–49.
25. Biesalski HK, Hemmes C, Hopfenmuller W, Schmid C, Gollnick HP. Effects of controlled exposure of sunlight on plasma and skin levels of beta-carotene. Free Radic Res 1996;24:215–24.
26. Darvin ME, Fluhr JW, Caspers P, van der Pool A, Richter H, Patzelt A, Sterry W, Lademann J. In vivo distribution of carotenoids in different anatomical locations of human skin: comparative assessment with two different Raman spectroscopy methods. Exp Dermatol 2009;18: 1060–3.
27. Meinke MC, Darvin ME, Vollert H, Lademann J. Bioavailability of natural carotenoids in human skin compared to blood. Eur J Pharm Biopharm 2010;76:269–74.
28. Stahl W, Heinrich U, Wiseman S, Eichler O, Sies H, Tronnier H. Dietary tomato paste protects against ultraviolet light-induced erythema in humans. J Nutr 2001;131:1449–51.
29. Aust O, Stahl W, Sies H, Tronnier H, Heinrich U. Supplementation with tomato-based products increases lycopene, phytofluene, and phytoene levels in human serum and protects against UV-light-induced erythema. Int J Vitam Nutr Res 2005;75:54–60.
30. Rizwan M, Rodriguez-Blanco I, Harbottle A, Birch-Machin MA, Watson RE, Rhodes LE. Tomato paste rich in lycopene protects against cutaneous photodamage in humans in vivo: a randomized controlled trial. Br J Dermatol 2011;164:154–62.
31. Mathews-Roth MM, Pathak MA, Parrish J, Fitzpatrick TB, Kass EH, Toda K, Clemens W. A clinical trial of the effects of oral beta-carotene on the responses of human skin to solar radiation. J Invest Dermatol 1972;59:349–53.
32. Lee J, Jiang S, Levine N, Watson RR. Carotenoid supplementation reduces erythema in human skin after simulated solar radiation exposure. Proc Soc Exp Biol Med 2000;223:170–4.
33. Heinrich U, Gartner C, Wiebusch M, Eichler O, Sies H, Tronnier H, Stahl W. Supplementation with beta-carotene or a similar amount of mixed carotenoids protects humans from UV-induced erythema. J Nutr 2003;133:98–101.
34. Stahl W, Heinrich U, Jungmann H, Sies H, Tronnier H. Carotenoids and carotenoids plus vitamin E protect against ultraviolet light-induced erythema in humans. Am J Clin Nutr 2000;71:795–8.
35. Wolf C, Steiner A, Honigsmann H. Do oral carotenoids protect human skin against ultraviolet erythema, psoralen phototoxicity, and ultraviolet-induced DNA damage? J Invest Dermatol 1988;90:55–7.
36. Greul AK, Grundmann JU, Heinrich F, Pfitzner I, Bernhardt J, Ambach A, Biesalski HK, Gollnick H. Photoprotection of UV-irradiated human skin: an antioxidative combination of vitamins E and C, carotenoids, selenium and proanthocyanidins. Skin Pharmacol Appl Skin Physiol 2002;15:307–15.
37. Pryor WA, Stahl W, Rock CL. Beta carotene: from biochemistry to clinical trials. Nutr Rev 2000;58:39–53.
38. Eroglu A, Hruszkewycz DP, Dela Sena C, Narayanasamy S, Riedl KM, Kopec RE, Schwartz SJ, Curley RW Jr, Harrison EH. Naturally occurring eccentric cleavage products of provitamin A β-carotene function as antagonists of retinoic acid receptors. J Biol Chem 2012; 287:15886–95.
39. Cesarini JP, Michel L, Maurette JM, Adhoute H, Bejot M. Immediate effects of UV radiation on the skin: modification by an antioxidant complex containing carotenoids. Photodermal Photoimmun Photomed 2003;19:182–9.
40. Eichler O, Sies H, Stahl W. Divergent optimum levels of lycopene, beta-carotene and lutein protecting against UVB irradiation in human fibroblaststst. Photochem Photobiol 2002;75:503–6.
41. Scarmo S, Cartmel B, Lin H, Leffell DJ, Welch E, Bhosale P, Bernstein PS, Mayne ST. Significant correlations of dermal total carotenoids and dermal lycopene with their respective plasma levels in healthy adults. Arch Biochem Biophys 2010;504:34–9.
42. Mayne ST, Cartmel B, Scarmo S, Lin H, Leffell DJ, Welch E, Ermakov I, Bhosale P, Bernstein PS, Gellermann W. Noninvasive assessment of dermal carotenoids as a biomarker of fruit and vegetable intake. Am J Clin Nutr 2010;92:794–800.
43. Ermakov IV, Gellermann W. Validation model for Raman based skin carotenoid detection. Arch Biochem Biophys 2010;504:40–9.
44. Bone RA, Landrum JT. Dose-dependent response of serum lutein and macular pigment optical density to supplementation with lutein esters. Arch Biochem Biophys 2010;504:50–5.
45. Zussman J, Ahdout J, Kim J. Vitamins and photoaging: do scientific data support their use? J Am Acad Dermatol 2010;63:507–25.
46. Polidori MC, Stahl W, Eichler O, Niestroj I, Sies H. Profiles of antioxidants in human plasma. Free Radic Biol Med 2001;30:456–62.
47. Polidori MC, Pratico D, Mangialasche F, Mariani E, Aust O, Anlasik T, Mang N, Pientka L, Stahl W, Sies H, et al. High fruit and vegetable intake is positively correlated with antioxidant status and cognitive performance in healthy subjects. J Alzheimers Dis 2009;17:921–7.
48. Kaplan LA, Lau JM, Stein EA. Carotenoid composition, concentrations, and relationships in various human organs. Clin Physiol Biochem 1990;8:1–10.
49. Nierenberg DW, Nann SL. A method for determining concentrations of retinol, tocopherol, and five carotenoids in human plasma and tissue samples. Am J Clin Nutr 1992;56:417–26.
50. Schmitz HH, Poor CL, Wellman RB, Erdman JW Jr. Concentrations of selected carotenoids and vitamin A in human liver, kidney and lung tissue. J Nutr 1991;121:1613–21.
51. Fuchs J, Weber S, Podda M, Groth N, Herrling T, Packer L, Kaufmann R. HPLC analysis of vitamin E isoforms in human epidermis: correlation with minimal erythema dose and free radical scavenging activity. Free Radic Biol Med 2003;34:330–6.
52. Peng YM, Peng YS, Lin Y. A nonsaponification method for the determination of carotenoids, retinoids, and tocopherols in solid human tissues. Cancer Epidemiol Biomarkers Prev 1993;2:139–44.
53. Shindo Y, Witt E, Han D, Epstein W, Packer L. Enzymic and nonenzymic antioxidants in epidermis and dermis of human skin. J Invest Dermatol 1994;102:122–4.
54. Thiele JJ, Traber MG, Packer L. Depletion of human stratum corneum vitamin E: an early and sensitive in vivo marker of UV induced photooxidation. J Invest Dermatol 1998;110:756–61.
55. Hata TR, Scholz TA, Ermakov IV, McClane RW, Khachik F, Gellermann W, Pershing LK. Non-invasive raman spectroscopic detection of carotenoids in human skin. J Invest Dermatol 2000;115:441–8.
56. Garmyn M, Ribaya-Mercado JD, Russel RM, Bhawan J, Gilchrest BA. Effect of beta-carotene supplementation on the human sunburn reaction. Exp Dermatol 1995;4:104–11.
57. Gollnick H, Hopfenmuller W, Hemmes C, Chun SC, Schmid C, Sundermeier K, Biesalski HK. Systemic beta carotene plus topical UV-sunscreen are an optimal protection against harmful effects of natural UV-sunlight: Results of the Berlin-Eilath study. Eur J Dermatol 1996;6:200–5.
58. Stahl W, Sundquist AR, Hanusch M, Schwarz W, Sies H. Separation of beta-carotene and lycopene geometrical isomers in biological samples. Clin Chem 1993;39:810–4.