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# Role of ingestible carotenoids in skin protection: A review of clinical evidence

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## Summary

Carotenoids, a class of phytonutrients, have been well established to boost skin's innate resistance against ultraviolet (UV) B-induced erythema (sunburn). Many of the published clinical studies thus far have focused on the measurement of erythema as the primary clinical indicator of skin protection against UVB radiation. More recent studies have shown that carotenoid supplementation provides even more skin protection than previously shown as new clinical and molecular endpoints beyond UVB-induced erythema have been reported. These recent studies have demonstrated that carotenoids also provide photoprotection against UVA-induced pigmentation and inhibit molecular markers of oxidative stress such as intercellular adhesion molecule 1, heme oxygenase-1, and matrix metalloproteinases 1 and 9. This article provides a comprehensive review of the published clinical evidence on skin benefits of carotenoids in the last five decades and indicates new perspectives on the role of ingestible carotenoids in skin protection.

**KEYWORDS**

antioxidants, astaxanthin, carotenoids, lutein, MED, MPPD, multi-carotene, oxidative stress, pollution, skin protection, UV radiation, vitamin A, β-carotene

## 1 | INTRODUCTION

Skin, the largest organ of the human body, is exposed daily to environmental aggressors such as solar radiation and air pollution, resulting in many acute and chronic conditions.[1–3] The damaging effects of UV radiation on skin include erythema (sunburn), pigmentation (tanning), photocarcinogenesis, and photoaging.[4–7] Other exposomal factors such as air pollution,[8–11] tobacco smoke,[12] infrared radiations (IRs),[13,14] ozone,[15] and alcohol consumption[16] also have detrimental effects on skin health.[17] From a mechanistic point of view, all these environmental threats seem to involve oxidative stress as one common denominator. Interestingly, most of the skin's solar exposure throughout the lifetime is incidental, under normal conditions when no sunscreens are used.[18] Preventative strategies such as the use of sun protective clothing, avoiding sun exposure, and the use of sunscreens are ideal for photoprotection. In the Western world, where sunbathing and tanning are popular, combined with the global lack of consumer awareness for adequate or frequent use of sunscreens, these strategies are often rendered ineffective.

In the absence of any topical photoprotective intervention, skin's primary defense solely rests on endogenous protection. Intrinsically, the antioxidant capacity of the skin is one important defense mechanism against environmental damage. This inherent photoprotective function of skin can be compromised by

moderate UV exposure.[19] Thus, boosting skin's innate antioxidant potential (early response) through consumption of dietary phytonutrients found in fruits and vegetables, such as carotenoids, flavonoids, polyphenols, ascorbates, and tocopherols, could offer complementary protection against environmentally induced skin damage.

Among the most promising phytonutrients for skin protection are carotenoids, a class of over 600 fat soluble pigments that are responsible for many of the red, orange, and yellow colors seen in fruits and vegetables. These compounds play an important role in plants, working alongside chlorophylls to absorb and utilize light for photosynthesis, and providing photoprotection by quenching ROS and protecting the cells from oxidative stress.[20] Some of the commonly known carotenoids' structure are shown in Figure 1. Carotenoids have shown similar protective effects in humans, and epidemiological studies from the past 30 years demonstrate an association between higher levels of total plasma carotenoids and improved health outcomes.[20-24]

Carotenoids play several important roles within the human body. One of the most well-known mechanisms is the pro-vitamin A activity of β- and α-carotene, in which these carotenoids can be used as a precursor for endogenous production of essential vitamin A (retinol).[25] Lutein and zeaxanthin, in particular, are important for eye health as they protect the retina from phototoxic damage and have been associated with reduced risk of macular degeneration.[26] With the known antioxidative properties of carotenoids, the human health benefits are wide-reaching, and a large body of literature exists associating carotenoids with eye health, cognition, cardiovascular wellness, skin and mucosal membrane protection, and more.[20,22-32]

Humans are not able to synthesize carotenoids on their own and therefore need to consume them through the diet.[33] However, despite the numerous benefits, global dietary surveys repeatedly show inadequate intake of carotenoid-rich fruits and vegetables against the current recommendations.[25,34-38] For example, in reports on β-carotene in the United States and UK, the majority of individuals only consume in the range of 1-2 mg/d.[25] While regulatory agencies, such as the European Food Safety Authority (EFSA) and the US Food and Nutrition Board, have not established recommended intake levels, epidemiological evidence suggests a plasma level of 0.4 micromole/liter β-carotene supports preventative health benefits, which can be achieved with a 2-4 mg intake per day.[39-41] Other guidelines set by agencies such as the US National Cancer Institute and the US Department of Agriculture suggest a higher intake of 3-6 mg β-carotene for lowering risk of chronic disease.[42] Therefore, in addition to increasing fruit and vegetable intake, supplementation of key carotenoids may be beneficial for antioxidant protection.

Of note, there is growing evidence that dietary supplementation of β-carotene,[43,44] lycopene,[45-47] lutein,[47,48] astaxanthin,[49] and mixed carotenoids[43,50,51] enhances skin's innate resistance against UVB-induced erythema (sunburn). Though conventional studies have focused on erythema measurement, more recent evidence suggests that protection offered by carotenoids could extend well beyond erythema protection into other clinical and molecular endpoints.[47,51,52] These recent studies have reported that carotenoids also provide photoprotection against UVA-induced pigmentation and reduce UVA-induced oxidative stress in human skin indicated by the expression of various molecular markers of oxidative stress such as intercellular adhesion molecule

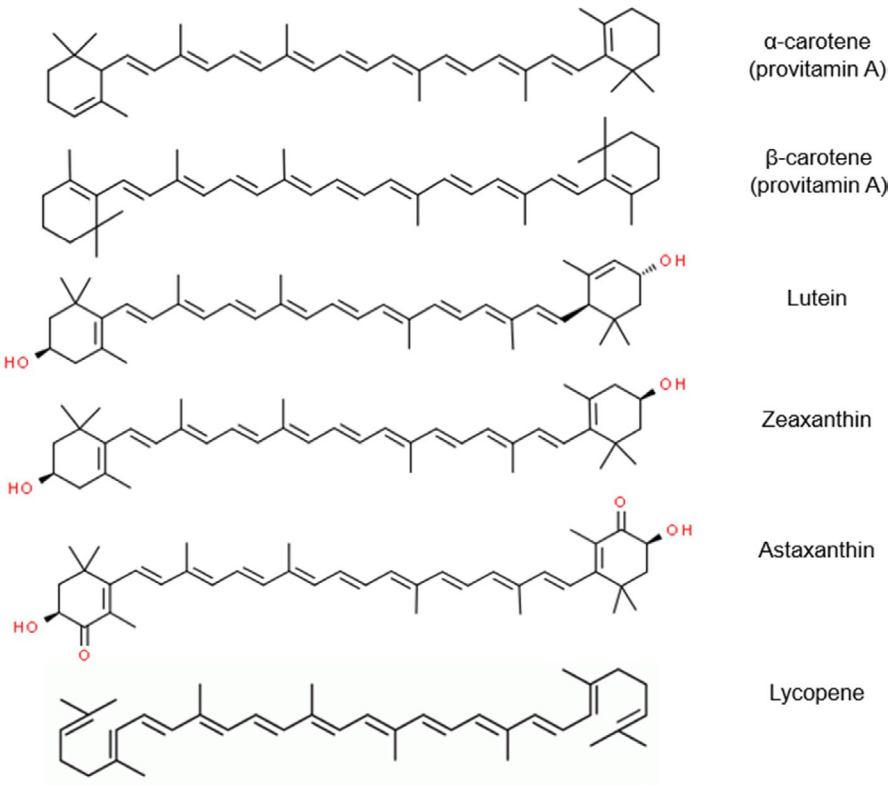


**FIGURE 1** Structure of commonly known carotenoids

**TABLE 1** Carotenoid intervention studies in the last 5 decades, which were focused on skin-oriented clinical and molecular outcomes

| Timeline | Number of studies | Total number of subjects | Reference |
|---|---|---|---|
| 1970-1979 | 3 | 86 | Mathews-Roth et al[54-56] |
| 1980-1989 | 1 | 23 | Wolf et al[63] |
| 1990-1999 | 3 | 48 | Garmyn et al,[57] Gollnick et al,[58] Stahl et al[94] |
| 2000-2009 | 8 | 217 | Stahl et al,[61,96] Lee et al,[59] Heinrich et al,[43] Cesarini et al,[110] McArdle et al,[60] Aust et al,[95] Palombo et al[73] |
| 2010-2019 | 7 | 486 | Cho et al,[83] Bouilly-Gauthier et al,[77] Rizwan et al,[64] Marini et al,[76] Grether-Beck et al,[47] Groten et al,[45] Ito et al[49] |
| Until December 2020 | 3 | 106 | Baswan et al[51,66] Zmitek et al,[111] Obana et al[112] |
| Total | 25 | 966 | |

1, heme oxygenase-1, interleukins, and matrix metalloproteinases. Thus, carotenoids may provide even more beneficial to skin than previously thought. This article provides a critical review of the published clinical evidence on skin benefits of carotenoids in the last five decades. We will also indicate new perspectives on the role of ingestible carotenoids in skin protection.

## 2 | METHOD

A PUBMED and Google Scholar search was conducted to identify human clinical trials investigating the ingestion of carotenoids in relation to skin-related clinical outcomes. Randomized, placebo-controlled trials (RCTs) were the primary focus. Studies that were not randomized or placebo-controlled were only included if the study was conducted on more than 10 subjects, and the duration was 4 weeks or longer.

## 3 | CLINICAL AND MOLECULAR EVIDENCE OF SKIN PROTECTION BY CAROTENOIDS

The photoprotective effects of carotenoid pigments were first reported on the bacterium *Rhodopseudomonas spheroides* in 1956 by Sistrom et al.[53] It was not until the 1970s that the notion of exploring photoprotective effects of carotenoids for humans was first clinically investigated by Mathews-Roth et al.[54-56] Since then, there has been a steady rise in the number of studies to fully understand the extent of photoprotection benefits offered by carotenoids. Table 1 provides a timeline overview of these studies over the last few decades. After a thorough review of hundreds of studies focused on ingestible carotenoids in the last 5 decades, a total of 25 human clinical intervention studies met our criteria of relevance and significance related to skin-oriented clinical outcomes. These studies are summarized in Table 2.

### 3.1 | Clinical photoprotection against UVB-induced erythema

In 1970, Mathews-Roth et al reported three case studies of β-carotene intervention for patients with erythropoietic protoporphyria (EPP), who suffer from extreme sensitivity to visible and long wavelength UV radiation, which might cause erythema, pruritus, pain, and potentially pigmentation disorders.[54] Though a small study, 2 out of 3 patients were reported to tolerate five to eight hours of sun without experiencing any photosensitivity, and the third patient reported less discomfort while tolerating sun exposure. A further study published in 1974 with a larger patient population provided more credibility to the notion that β-carotene supplementation helps improve the sunlight tolerance for patients with EPP.[56] While the aforementioned studies are focused on diseased skin conditions, Mathews-Roth et al also investigated and reported on the photoprotective effects of β-carotene in a healthy population.[55] A slight but statistically significant photoprotective effect of carotenoid supplementation against sunlight-induced erythema was reported.

Since the 1970s, more controlled and robust studies have been conducted to demonstrate the photoprotective effects of carotenoids against UVB-induced erythema. In 2008, based on a meta-analysis of 7 human clinical studies,[43,55,57-61] Kopcke and Krutmann concluded that the β-carotene supplementation is associated with enhanced protection against the development of UVB-induced sunburn reaction.[62] Since this last meta-analysis in 2008, most of the reported clinical studies strongly support the photoprotective benefits of carotenoids against UVB-induced erythema as listed in Table 2.

It is also noteworthy to mention that there have been only a few contradictory studies, which have found little to no photoprotection with carotenoid supplementation.[57,60,63] These results could possibly be explained by the fact that the efficacy of systemic photoprotection by carotenoids is a function of the duration and dose of the treatment before the irradiation. Though many factors such as dose, formulation,

**TABLE 2** Human clinical intervention studies with carotenoid supplementation and skin-related outcomes

| Study | Design and duration | Subjects | Intervention | Main outcomes |
|---|---|---|---|---|
| Zmitek et al (2020)[111] | Randomized, double-blind, placebo-controlled study<br>Period: 12 wk | 30 healthy Caucasian females with Fitzpatrick skin phototypes (FT) II and III. | Group 1 (n = 15): lutein syrup (20 mg lutein daily)<br>Group 2 (n = 15): placebo syrup | • Group 1 showed a significant improvement (22%) in photoprotection against UV-induced erythema (MED) from baseline compared with group 2 after supplementation ($P < .001$).<br>• No significant differences in dermal density were found in either group by the end of the study. |
| Obana et al (2020)[112] | Prospective, single-arm, open-label study<br>Period: 16 wk | 16 healthy Japanese volunteers | All subjects took a supplement containing 20 mg/d of lutein and 4 mg/d of zeaxanthin, as well as other antioxidants (vitamin C, vitamin E, zinc, copper). | • Skin carotenoid levels increased significantly by week 4 and continued to increase until week 16 ($P <.0001$). |
| Baswan et al (2020)[51,66] | Randomized, double-blind, placebo-controlled study<br>Period: 12 wk | 60 healthy volunteers | Group 1 (n = 31): multi-carotene softgel capsules with daily dose of 12.75 mg β-carotene, 3.30 mg α-carotene, 3.36 mg lutein, and 0.16 mg zeaxanthin.<br>Group 2 (n = 29): placebo softgel capsules with non-functional excipients. | • Significant reduction in UVA-induced pigmentation by colorimetry.<br>• Significant reduction in UVB-induced erythema, both subjective and colorimetry assessments.<br>• Significant increase in the antioxidant levels in the skin.<br>• Safety: Study was well-tolerated by all the participants. Two subjects withdrew due to non-intervention-related reasons. |
| Groten et al (2019)[45] | Randomized, double-blind, placebo-controlled, multicenter study<br>Period: 12 wk. | 149 healthy volunteers (34 men and 115 women) | Group 1 (n = 75): daily dose of 15 mg lycopene, 5.8 mg phytoene and phytofluene, 0.8 mg β-carotene, 5.6 mg tocopherols from tomato extract, and 4 mg carnosic acid from rosemary extract.<br>Group 2 (n = 74): placebo containing medium-chain triglycerides. | • Protection against UVB-induced erythema by colorimetry assessment. Subjective evaluation did not show significant difference.<br>• Significant molecular protection against UVB-induced upregulation of proinflammatory cytokines (IL-6 and TNF-α) compared with placebo.<br>• Safety: The intervention was reported to be well-tolerated. |
| Ito et al (2018)[49] | Randomized, double-blind, placebo-controlled study<br>Period : 10 wk (1 wk baseline, 9 wk supplementation) | 23 healthy Japanese volunteers (21 female, 2 male) | Group 1 (n = 12): 4 mg astaxanthin/d<br>Group 2 (n = 11): placebo containing a filling agent per day | • Group 1 showed a significant improvement in protection against UV-induced erythema (MED) from baseline compared with group 2 after supplementation.<br>• Decrease in moisture in the irradiated area was significantly attenuated in group 1 vs. group 2 after 7 d of UV irradiation.<br>• No significant differences in transepidermal water loss (TWEL) were observed between groups.<br>• Significant improvement was seen in skin texture in non-irradiated areas of skin in group 1 vs. group 2.<br>• Safety: No adverse events or severe changes in hematological tests were observed. |

(Continues)

**TABLE 2** (Continued)

| Study | Design and duration | Subjects | Intervention | Main outcomes |
|---|---|---|---|---|
| Grether-Beck et. al. (2017)[47] | Randomized, double-blind, placebo-controlled, crossover study<br>Period: 2, 12-wk period, separated by 2 wk of washout period. | 65 healthy volunteers (52 men and 13 women) | Group 1 (n = 15): lycopene-rich softgel capsules containing 20 mg lycopene, other tomato phytonutrients, such as phytoene and phytofluene, tocopherols, and phytosterols, per day.<br>Group 2 (n = 14): lutein softgel capsules containing 20 mg free lutein stabilized by 10% carnosic acid, per day.<br>Group 3 (n = 14): placebo softgel capsules contained soybean oil (lycopene arm).<br>Group 4 (n = 14): placebo softgel capsules contained soybean oil (lutein arm). | • Inhibition of UVA1 and UVA/B-induced expression of HO-1 (heme oxygenase-1), ICAM-1 (intercellular adhesion molecule 1), and MMP-1 (matrix metalloprotinases 1) genes, which are indicators of oxidative stress.<br>• Safety: One adverse event (diarrhea) was reported in lycopene arm. Cause was identified as viral infection of upper intestine. Subject continued study after few days. |
| Marini et al (2014)[76] | Randomized, placebo-controlled, double-blind study<br>Period: 12 wk | 60 PLE (polymorphic light eruption) patients<br>(17 males, 43 females) | Group 1 (n = 30): capsule with 2.5 mg lycopene, 4.7 mg of β-carotene, and 5.108 cfu of the probiotic *L johnsonii*<br>Group 2 (n = 30): placebo capsule with microcrystalline cellulose | • Significant reduction in the PLE score after one exposure as compared with placebo ($P < .001$).<br>• Significant reduction in ICAM-1 mRNA expression ($P = .022$), which are associated with the development of skin lesions at the molecular levels.<br>• Safety: No adverse effects reported. |
| Rizwan et al (2011)[64] | Randomized, single-blinded, placebo-controlled study<br>Period: 12 wk | 20 healthy female volunteers | Group 1 (n = 10): 55 g tomato paste (16 mg lycopene) in olive oil per day.<br>Group 2 (n = 10): olive oil as placebo. | • Significant reduction in UVB-induced erythema by colorimetry, but not visual assessment, compared with the placebo group.<br>• Reduction in UVR-induced MMP-1, increase in procollagen I (pCI) deposition.<br>• UVR-induced reduction in fibrillin-1 was abrogated in both groups.<br>• Safety: Three subjects dropped out due to personal reasons, not associated with the study. |
| Cho et al (2010)[83] | Randomized study<br>Period: 90 d | 30 healthy female volunteers over the age of 50 | Group 1 (n = 15): 30 mg/d beta-carotene in capsule format.<br>Group 2 (n = 14): 90 mg/d beta-carotene in capsule format. | • Facial wrinkles and elasticity improved significantly in the low-dose group (compared with baseline).<br>• MED decreased significantly in the high-dose group (compared with baseline).<br>• Low-dose beta-carotene significantly increased gene expression of type I procollagen<br>• Low-dose beta-carotene demonstrated a beneficial effect on cutaneous photoaging, but the higher dose showed a deleterious effect. |
| Bouilly-Gauthier et al (2010)[77] | Randomized, double-blind, placebo-controlled study<br>Period: 10 wk | 139 healthy female volunteers | Intervention group: daily dose of 7.2 mg carotenoids and $5 \times 10^8$ colony-forming units of Lactobacillus johnsonii (La1)<br>Placebo group: maltodextrin | • Prevention of UV-induced decrease in Langerhans cell density and increase in factor XIIIa + type I dermal dendrocytes<br>• Reduction in dermal inflammatory cells.<br>• Increase in instrumental and clinical MED values by 19% and 20%, respectively.<br>• Safety: No adverse events reported. |

(Continues)

**TABLE 2** (Continued)

| Study | Design and duration | Subjects | Intervention | Main outcomes |
|---|---|---|---|---|
| Palombo et al (2007)[73] | Randomized, double-blind, placebo-controlled, multicenter study<br>Period: 12 wk | 40 healthy female volunteers | All treatments were administered 2× per day.<br>Group 1: oral placebo + topical placebo<br>Group 2: oral placebo + topical active (lutein 50 ppm/zeaxanthin 3 ppm)<br>Group 3: oral active (lutein 5 mg/zeaxanthin 0.3 mg) + topical placebo<br>Group 4: oral active (lutein 5 mg/zeaxanthin 0.3 mg) + topical active (lutein 50 ppm/zeaxanthin 3 ppm) | • All lutein/zeaxanthin treatments but not the placebo provide protection from UV radiation-induced damage, regardless of route of administration.<br>• Oral, topical, and combination administration of lutein and zeaxanthin showed a significant improvement in skin lipid peroxidation as compared to placebo ($P < .05$). The greatest decrease was found for the combination treatment.<br>• Oral, topical, and combination administration of lutein and zeaxanthin showed a significant improvement in free radical-related photoprotective activity as compared to placebo ($P < .05$). By week 2, the topical treatment provided a twofold increase in activity, the oral treatment provided over a fourfold increase, and the combination of both provided a sixfold increase, demonstrating the compounding benefits of mixed treatments.<br>• Safety: All subjects completed the study. No adverse events reported. |
| Aust et al (2005)[95] | Randomized, parallel group intervention study<br>Period: 12 wk | 36 healthy adult volunteers | Group 1 (n = 12): daily dose of 10.2 mg synthetic lycopene capsules.<br>Group 2 (n = 12): daily dose (capsules) with 9.8 mg lycopene, 0.8 mg phytofluene, 1.0 mg phytoene, and 0.4 mg β-carotene.<br>Group 3 (n = 12): solubilized tomato extract (drink format) - 8.2 mg lycopene, 3.2 mg phytofluene, 4.6 mg phytoene, and 0.4 mg β-carotene. | • Significant increases in lycopene serum levels and total skin carotenoids were observed in all groups.<br>• Significant increases in the serum levels of phytofluene and phytoene in the groups 2 and 3.<br>• A decrease in the Δ a-value from week 0 to week 12, indicating prevention of erythema formation, was observed in all groups.<br>• The protective effect was more pronounced in the groups 2 and 3.<br>• Safety: No adverse events reported. |
| McArdle et al (2004)[60] | Randomized, intervention study<br>Period: 8 wk | 16 healthy subjects (8 men and 8 women) | Group 1 (n = 8): α-tocopherol (vitamin E; 400 IU/d)<br>Group 2 (n = 8): β-carotene (15 mg/d) | • Increase in plasma and skin levels of vitamin E.<br>• Increase in plasma levels of β-carotene, but not detectable in skin.<br>• No significant effect of vitamin E or β-carotene on indicators of oxidative damage, before or after UVR exposure.<br>• Safety: No adverse event reported. |
| Ce´sarini et al (2003)[110] | Randomized intervention study<br>Period: 7 wk | 25 healthy volunteers (5 men and 20 women) | Daily dose of 6 mg of α- and β-carotene, 6 mg of lycopene, 10 mg of α-tocopherol, and 75 μg of selenium, incorporated in Saccharomyces cerevisiae in dry form. | • Increase in actinic erythema threshold by 20%<br>• Reduction in expression of UV-induced p53, sunburn cells, and lipid peroxide levels.<br>• Safety: No adverse event reported. Tolerance and compliance by subjects were excellent. |

(Continues)

**TABLE 2** (Continued)

| Study | Design and duration | Subjects | Intervention | Main outcomes |
|---|---|---|---|---|
| Heinrich et al (2003)[43] | Randomized, placebo-controlled, parallel study<br>Period: 12 wk | 36 healthy adults (12 men and 24 women) | Group 1 (n = 12): β-carotene, 24 mg/d from an algal source.<br>Group 2 (n = 12): multi-carotene, 24 mg/d, consisting of the three main dietary carotenoids, β-carotene, lutein, and lycopene (8 mg/d each)<br>Group 3 (n = 12): placebo (soybean oil only | • Serum beta-carotene concentration increased three- to fourfold ($P < .001$) in the beta-carotene group, whereas in the mixed carotenoid group, the serum concentration of each of the three carotenoids increased one- to threefold ($P < .001$). No changes occurred in the control group.<br>• Increase in total carotenoids in skin over 12-wk period in groups 1 and 2. No changes in total carotenoids in skin occurred in the control group.<br>• The intensity of erythema 24 h after irradiation was lower in both groups 1 and 2 and was significantly lower than baseline after 12 wk of supplementation.<br>• 12-wk supplementation with 24 mg/d of beta-carotene alone and similar amounts of multi-carotene (beta-carotene, lutein, and lycopene) reduced UV-induced erythema in humans.<br>• Safety: No adverse events reported. |
| Stahl et al (2001)[96] | Randomized, placebo-controlled study<br>Period: 10 wk | 22 healthy volunteers, 19 completed the study. | Group 1 (n = 9): 40 g tomato paste equivalent to 16 mg/d of lycopene, 0.5 mg β-carotene, and 0.1 mg lutein with 10 g olive oil.<br>Group 2 (n = 10): placebo – 10 g olive oil only. | • Serum levels of lycopene increased significantly in the intervention group as compared to placebo by week 4; other serum carotenoid levels did not change significantly.<br>• Skin erythema measures were significantly lower in the treatment group at week 10 as compared to placebo.<br>• Safety: No adverse effects related to the treatment were reported. One subject dropped from the study due to skin sensitivity from UV exposure, and two other subjects did not complete the study for personal reasons not related to the treatment. |
| Stahl et al (2000)[61] | Randomized intervention study<br>Period: 12 wk | 20 healthy subjects (6 men and 14 women) | Group 1 (n = 10): 25 mg total carotenoids per day<br>Group 2 (n = 10): combination of the carotenoid supplement (25 mg total carotenoids per day) and vitamin E [335 mg (500 IU) RRR-alpha-tocopherol per day] | • Serum levels of β-carotene and α-tocopherol increased with supplementation.<br>• Significant decrease in erythema after week 8.<br>• Erythema suppression was greater with the combination of carotenoids and vitamin E than with carotenoids alone.<br>• Safety: No adverse effects were reported. A slight yellowing of skin was observed in both groups, and the palms of hands and facial skin were specially affected. |

(Continues)

**TABLE 2** (Continued)

| Study | Design and duration | Subjects | Intervention | Main outcomes |
|---|---|---|---|---|
| Lee et al (2000)[59] | Intervention study<br>Period: 24 wk | 22 subjects (11 men and 11 women) | For the first 8 wk, daily dose of 30 mg of natural carotenoids (29.4 mg of beta-carotene, 0.36 mg of alpha-carotene, and traces of other carotenoids) in vegetable oil. The daily dose of natural carotenoid was progressively raised by 30 mg increments, at every 8 wk, from 30 mg to 90 mg. | • Significant increase in the MED during the natural carotenoid supplementation period.<br>• After 24 wk of supplementation, significant increase in serum β-carotene and α-carotene levels.<br>• Significant, dose-dependent inhibition of serum lipid peroxidation during the supplementation.<br>• Safety: No adverse events reported. |
| Stahl et al (1998)[94] | Intervention study<br>Period: 12 wk | 12 healthy adult women | Daily dose of 24 mg of β-carotene. | • Increase in serum and skin carotenoid levels.<br>• Safety: No adverse events reported. |
| Gollnick et al (1996)[58] | Randomized, double-blind, placebo-controlled study<br>Period: 10 wk | 20 healthy young females | Daily dose of 30 mg β-carotene for 10 wk followed by 13 d of time and intensity-controlled sun exposure, with and without the use of topical UVA/B sunscreens. | • In the intervention group, the erythema development was lower in the selected skin areas exposed to natural sunlight.<br>• Body areas that were protected with sunscreen (plus supplementation) showed lower median degree of erythema.<br>• Serum levels of β-carotene did not fall during sun exposure in the intervention group, whereas it decreased significantly below sub-physiological levels in placebo group.<br>• After 10 wk, a significant increase in Langerhans cells (LHC) density ($P < .01$) in intervention group. After sun exposure, LHC density decreased in both groups, but more significant for placebo group compared with the baseline.<br>• Safety: No adverse events reported. No visible carotenodermia was reported. |
| Garmyn et al (1995) [57] | Double-blind, placebo-controlled study<br>Period: 23 d | 16 healthy women | Group 1 (n = 8): single dose of β-carotene 120 mg to dietary-restricted subjects. Same subjects were then on β-carotene 90 mg supplement with standard diets<br>Group 2 (n = 8): placebo | • Increased β-carotene plasma and skin levels compared with pretreatment levels and placebo-treated controls.<br>• No clinically or histologically detectable protection was observed against a 3 MED sunburn reaction.<br>• Safety: No adverse events were reported. |
| Wolf et al (1988)[63] | Intervention study<br>Period: 4 wk | 23 health volunteers | Daily dose of 150 mg of carotenoids (β-carotene 60 mg + canthaxanthin 90 mg) | • No significant protection against UVA, UVB, and psoralen UVA-induced erythema.<br>• Safety: No adverse effects were reported. |
| Mathews-Roth et al (1974)[56] | Intervention study<br>Period: 5-24 mo | 53 patients with EPP (erythropoietic protoporphyria) | Dose ranging from 15 to 180 mg/d, increased dosage with time. | • Improved tolerance to sunlight for patients with EPP.<br>• Safety: No side effects were observed. |
| Mathews-Roth et al (1972)[55] | Randomized, placebo-controlled study<br>Period: 10 wk | 30 healthy male subjects | Group 1 (n = 18): β-carotene (180 mg/d)<br>Group 2 (n = 12): placebo | • Slight but statistically significant protective effect against sunlight-induced erythema.<br>• Safety: No adverse events were reported. |

and diet could determine the efficacy of carotenoid intervention, the clinical data thus far indicate that achievement of significant protection requires at least 10 weeks of supplementation with carotenoid intervention. The studies that have reported no photoprotective effects were conducted for a period of 3-8 weeks.[57,60,63] In a few other studies, though photoprotection was observed by objective methods such as colorimetry/spectroscopy, subjective assessments by clinical graders did not yield a statistically significant difference.[45,64] This brings into question the reliability and reproducibility of subjective assessments of UVB-induced erythema as an endpoint for observing clinical benefits of carotenoid supplementation.[21,65]

All of the studies reviewed in this paragraph have assessed the reduction in erythema by carotenoids. The reason is mainly of regulatory nature, because the European Food Safety Authority (EFSA) requests that nutritional supplements, which claim photoprotective efficacy, must show a reduction in erythema. This has likely lead to an underestimation of carotenoids in photoprotection. Accordingly, carotenoids mainly act as antioxidants. UVB-induced erythema, however, primarily results from the direct induction of DNA damage (only a small part is due to oxidative stress), that is, a photochemical reaction, which cannot be well targeted by antioxidants. In this regard, recent studies, which we will review in the following paragraphs, are important, which indicate that oral supplementation with carotenoids is effective in reducing skin damage caused by longer UV wavelengths such as UVA2 and, in particular, UVA1 (340 - 400 nm).

## 3.2 | Clinical photoprotection against UVA-induced pigmentation

The only clinical study supporting the notion that photoprotective effects of carotenoids supplementation can be extended against UVA-induced pigmentation was published recently by Baswan et al.[51,66] In a 12-week placebo-controlled intervention study, a significant reduction in UVA-induced pigmentation was observed by colorimetry in the intervention group relative to the placebo control group. No significant difference was observed by subjective clinical assessment. As this is a new finding, more clinical studies are needed to conclude the photoprotective effects against UVA-induced pigmentation.

## 3.3 | Protection of cellular and molecular targets

The underlying mechanism of action for systemic photoprotection potentially involves one or more of the following aspects: (a) enhancement in barrier function against UV light (eg, UV-absorbing molecules offering protection against photooxidation); (b) protection of target molecules by scavenging photo-induced free radicals (eg, antioxidants); (c) suppression of cellular inflammatory responses; and (d) repairing UV-induced damage. It is currently not known whether the photoprotective effects of carotenoids are due to primary protection against photooxidation (singlet oxygen quenching), antioxidant response against secondary reactive oxygen species, or by suppression of cellular inflammatory signaling pathways. Most of the carotenoids with 9 or more conjugated double bounds are efficient quenchers of singlet oxygen and are usually associated with the prevention of photooxidative damage in plants.[25,67] Carotenoids, as an antioxidant, enhance the ability of the endogenous antioxidant system to neutralize ROS such as lipid peroxides, superoxide anions, and hydroxyl radicals, which are usually formed in skin after UV and visible light exposure.[68] Some of the molecular markers, which are induced by UV exposure, are cyclobutane pyrimidine dimers (CPDs), cyclooxygenase-2, cyclin D1, COX-2, Ki67, protein carbonylation, etc.[69-72] A growing level of evidence suggests that carotenoids are effective against suppressing various biomarkers induced by oxidative stress.

### 3.3.1 | Prevention of lipid peroxidation and inhibition of reactive oxygen species

In a clinical study by Palombo et al, oral, topical, and combined administration of lutein and zeaxanthin showed a significant improvement in the prevention of skin lipid peroxidation and improvement in free radical-related photoprotective activity compared with placebo group.[73] Due to the hydrophobic nature of carotenoids, it is likely to be incorporated into the cell membranes resulting in the prevention of lipid oxidation,[63,74] and its antioxidant activity is responsible for the ROS inhibition activity. Dietary lutein intervention in a mouse model has also been shown to decrease ROS levels in the skin.[48]

### 3.3.2 | Inhibition of matrix metalloproteinases

Matrix metalloproteinase (MMP) enzymes are responsible for degradation of the extracellular matrix (ECM) and can be induced by UV exposure resulting in the degradation of ECM proteins. Rizwan et al demonstrated that a lycopene-rich tomato paste provided protection against UVR-induced molecular markers by upregulating deposition of procollagen I and inhibiting the expression of UV-induced MMP-1.[64] Grether-Beck et al also demonstrated that a lycopene-rich tomato nutrient complex (TNC) supplementation resulted in reduced expression of MMP-1 genes.[47] Gruel et al reported that a 16-week supplementation with a mixture of carotenoids (beta-carotene and lycopene), vitamins C and E, selenium, and proanthocyanidins resulted in a decrease in UV-dependent expression of MMP-1 and MMP-9.[75]

### 3.3.3 | Other markers of oxidative stress and inflammatory pathways

Marini et al reported that an intervention of multi-carotenoid plus probiotic supplementation in a polymorphic light eruption (PLE)

patient population resulted in significant reduction in intercellular adhesion molecule 1 (ICAM-1) mRNA expression, which is usually associated with the development of skin lesions at the molecular levels.[76] Grether-Beck et al reported that a 12-week supplementation of lycopene-rich tomato nutrient complex (TNC) completely inhibited UVA1- and UVA/B-induced gene expression of intercellular adhesion molecule 1, heme oxygenase-1, and matrix metalloproteinases 1, which are regarded as the indicators of oxidative stress, regardless of the sequence of the crossover study. In the same study, lutein provided complete protection when taken during the first period and the effects were less pronounced in the second period relative to TNC.[47] Groten et al also reported that supplementation with carotenoid-rich tomato complex resulted in significant molecular protection against UVB-induced upregulation of proinflammatory cytokines (IL-6 and TNF-α) compared with placebo.[45] Gollnick et al observed a significant increase in Langerhans cell (LHC) density in the group treated with β-carotene for 10 weeks.[58] Similarly, in a combination study of carotenoids with a probiotic *Lactobacillus johnsonii*, a decrease in dermal inflammatory cells, improvement in LHC density, and increase in factor XIIIa+ type I dermal dendrocytes were reported by Bouilly et al.[77]

### 3.3.4 | Effects on visual appearance and biophysical properties of skin

Studies performed at the molecular level have found that specific genes, which play a role in skin aging, might reflect on skin appearance.[78] Thus, cellular and molecular protection offered by carotenoids has a potential to maintain healthy skin resulting in improved appearance compared with what would be expected at one's chronological age. Darvin et al reported a significant correlation between the cutaneous concentration of lycopene and the roughness of the skin and proposed a hypothesis that high levels of antioxidant substances may be correlated with lower levels of skin roughness.[79] Similarly, other studies have demonstrated the beneficial effect of ingestible carotenoids on skin hydration, wrinkle count, skin texture, elasticity, and other parameters.[49,80-84] A few studies have also reported that a combined intervention of oral and topical products results in superior benefits of skin hydration, improvement in skin roughness, wrinkle count severity, etc, than the single mode of administration.[73,85]

## 4 | CAROTENOID DISTRIBUTION IN SKIN

The most prevalent carotenoids in the human body are α-carotene, β-carotene, and lycopene, and it also contains xanthophylls such as lutein, zeaxanthin, and α- and β-cryptoxanthin.[86,87] The distribution of carotenoids through the various layers of skin (stratum corneum, epidermis, dermis, and hypodermis) is not uniform. The highest levels are usually found in the stratum corneum closest to the skin surface.[79] Skin deposition of dietary carotenoids, whether obtained through fruit and vegetables or dietary supplements, ultimately depends on absorption and bioavailability. After ingestion, the small intestine is responsible for absorbing carotenoids, so they can be subsequently delivered through the blood stream to the skin and other peripheral tissues. During digestion in the upper intestine, carotenoids are incorporated into mixed micelles composed of phospholipids, lipids, cholesterol, and bile salts and absorbed into the enterocyte through passive and facilitated diffusion.[88-90] For this reason, absorption and ultimate skin deposition of dietary carotenoids are improved if consumed at the same time as a dietary lipid source. After absorption through the enterocyte, carotenoids are packaged into plasma and secreted into the lymph system for transport to the bloodstream, where they can be metabolized and deposited into the skin and other target tissue.

There appear to be two main pathways in which carotenoids are delivered and distributed into the skin layers. Through the first pathway, carotenoids are transported from the blood, hypodermis, and dermis to the epidermis through sweat gland secretions onto the skin surface, where the carotenoids are then able to penetrate back into the stratum corneum.[91,92] This mechanism may explain why the highest levels of skin carotenoids are found in skin locations with the highest density of sweat glands.[93] The second pathway is through diffusion from the adipose tissue, blood, and lymph into skin cells themselves. The carotenoids are deposited for storage within the subcutaneous fatty tissue, and from here, they can be loaded into the continuously forming keratinocytes at the basal layer of the epidermis. As these cells transform to corneocytes and migrate to the surface of the epidermis, they bring with them the carotenoids to the stratum corneum. The stratum corneum renewal process, the process by which skin cells transform from keratinocytes to corneocytes, traveling from basal layer to skin surface, may explain the length of time for skin photoprotection to be detected with carotenoid supplementation.[50]

After ingestible carotenoid intervention for 3-24 weeks, an increase in plasma levels of β-carotene[57,60]; serum levels of β-carotene,[43,59,94] α-carotene,[59] lutein,[43] lycopene,[43,95,96] phytofluene,[95] and phytoene[95]; and skin levels of β-carotene[57] and total carotenoids[51,57,94] have been reported. The levels of β-carotene and lycopene in the skin have been reported to decrease after UV radiation exposure, though lycopene's degradation is preferentially more rapid than that of β-carotene.[97] This decrease in carotenoid levels could potentially be attributed to reactive oxygen species (ROS), which usually deplete the body's stores of carotenoids resulting from the exposure to stressors such as pollution, UV light, and ozone.

Though the levels of carotenoids in skin range from 0.01 to 0.22 pmol/mg wet tissue weight as described in Table 3, the individual carotenoid levels in the skin vary among different skin sites and layers.[18,98,99] Interestingly, even with site-to-site variability in skin carotenoid levels, correlation has been reported between the serum levels of β-carotene and total skin carotenoid levels measured non-invasively from the palm of hand ($R^2 = 0.94$) and forehead ($R^2 = 0.89$).[94] This is the rationale behind the thenar eminence of the

**TABLE 3** Concentration of carotenoids in human skin

| Carotenoids | Skin (epidermis + dermis) levels (pmol/mg wet weight)[a] | Reference |
|---|---|---|
| β-Carotene | 0.05 ± 0.04 | 98 |
| | 0.11 ± 0.01 | 99 |
| α-Carotene | 0.02 ± 0.01 | 98 |
| | 0.01 ± 0.01 | 99 |
| Lycopene | 0.13 ± 0.10 | 98 |
| | 0.22 ± 0.01 | 99 |
| Phytoene | 0.12 ± 0.04 | 98 |
| Phytofluene | 0.03 ± 0.02 | 98 |
| Lutein | 0.03 ± 0.01 | 99 |

[a]Data converted to pmol/mg wet weight as described by Sies et al.[18]

palm of the hand being the site of measurement for non-invasive carotenoid measurement in the human body.[100-102]

## 5 | NEW PERSPECTIVES

### 5.1 | Skin benefits of carotenoids extends beyond erythemal protection

The photoprotection offered by carotenoids against UVB-induced erythema has been supported by numerous studies as listed in Table 2. We believe that this end point is not ideal to assess their efficacy. Accordingly, UVB-induced erythema mainly results from the direct induction of DNA damage, which is difficult to be targeted by oral carotenoids. In contrast, biological effects induced by UVA radiation mainly result from oxidative stress, and in this regard, the clinical significance of orally ingested carotenoids, which are potent antioxidants—might be more relevant. Accordingly, recent studies have demonstrated the photoprotective effects of carotenoids against UVA-induced pigmentation, and other cellular and molecular markers of oxidative stress as described in section 3.3. Carotenoids may play an even more important role in skin health than previously thought as recent research is indicative of more reliable clinical and molecular endpoints than erythema.[21,65] In a non-carotenoid photoprotection intervention study by Kohli et al,[69] molecular effects were observed for all 22 subjects, whereas an increase in the UVB MED was observed only in 17 of 22 subjects. This supports the notion that the use of erythema as an endpoint may not be a robust indicator of photoprotection, and other endpoints such as MPPD and gene expression should also be monitored for photoprotection clinical studies.

### 5.2 | Trend toward the use of a combination of carotenoids and other antioxidants

In the United States, there are no proposed daily intake levels for carotenoids, rather public health communication initiatives are put in place to support consumption of carotenoid-rich fruits and vegetables as part of a healthy diet. To aid in this communication, the US Department of Agriculture (USDA) has established data on carotenoid level of more than 3000 foods.[103] Though carotenoids have great health benefits and have been shown to be well tolerated across different population segments, some concerns have been raised on the prolonged supplementation of β-carotene over a period of years at non-physiological levels. Based on the adverse effect on the incidence of lung cancer during the β-carotene and retinol efficacy trial, a warning to heavy smokers may be applicable.[27,104] Further, the EFSA has published a statement on the safety of β-carotene use in heavy smokers and workers with occupational exposure to asbestos. The EFSA Panel states that although there are insufficient data to set a precise tolerable upper intake level (UL), exposure of β-carotene supplements at a level below 15 mg/day would not give rise to adverse health or safety concerns including heavy smokers.[105]

Occasionally, excessive carotenoid intake causes noticeable orange pigmentation to the skin, known as carotenemia. This harmless condition is a documented biological effect of high carotenoid intake beginning with yellow pigmentation of the skin. There is a coloration of the skin (yellow to orange) when high levels of carotenoids in food and supplements are consumed. It is believed that carotenemia occurs when serum levels are in the range of 2.5 mg/L.[106]

Due to the safety concerns raised with the prolonged supplementation of β-carotene alone, there is a trend toward the use of low-dose, multi-carotenoids, combined with other antioxidants for safe and even more efficacious benefits. Table 2 lists a comprehensive set of studies, which reports benefits of multi-carotenoids at lower doses, with some studies even reporting comparable or better benefits than stand-alone supplementation with a single carotenoid. In particular, Heinrich et al reported that photoprotection efficacy achieved by a daily dose of multi-carotenoids (8 mg each of β-carotene, lycopene, and lutein) is similar to that provided by 24 mg dose of β-carotene.[43] Also, Aust et al showed that a combination of tomato phytonutrients from tomato-based supplements was significantly better in offering photoprotection versus a stand-alone lycopene treatment.[95] Thus, ingestion of multi-carotenoids even in lower quantities, whether from diet or supplementation, could result in better health benefits.

### 5.3 | Can ingestible carotenoids replace the use of sunscreens?

The extent of protection provided by ingestible carotenoids is variable and is not comparable to the use of a high sun protection factor (SPF) sunscreen in terms of clinical efficacy. We would like to emphasize that ingesting carotenoids alone does not provide absolute photoprotection and should not replace the use of sunscreens, which should be practiced for prolonged sun exposure scenarios. Carotenoid supplementation alone is not enough to guarantee protection against serious conditions, such as keratinocyte cancers and

solar keratosis, as reported by Green et al[107] and Darlington et al,[108] respectively.

However, the reviewed studies do suggest that the basal skin protection can be boosted systemically to build skin's resilience against UV-mediated skin damage. According to Kopcke and Krutmann, oral supplementation of β-carotene could at the best yield a SPF of 4.[44] Unlike topically applied sunscreens, once systemic photoprotection is achieved after a minimum of 8 weeks of carotenoid supplementation, it is inherently present in the skin and protects the body across the full surface area of skin. Thus, systemic photoprotection by carotenoids and topical photoprotection by sunscreens are not competing but rather complementary strategies of photoprotection. This notion is further bolstered by Palombo et al's study, which demonstrated that the combined topical and oral administration of lutein and zeaxanthin provided the highest degree of photoprotection relative to topical or oral administration alone (which are impart antioxidant protection). Much of the UV photodamage over a lifetime happens when the skin is not protected; thus, innate photoprotection by means of dietary interventions such as carotenoids can provide substantial protection against incidental exposure to UV rays across the full surface area of the human body and may also significantly contribute to skin health. Along these lines, a group of internationally renowned dermatologists has recently defined oral photoprotection as an essential and integral part of effective photoprotection of human skin.[109] The authors believe that future clinical research is needed to further address whether and to what extend the benefits of nutritional supplementation with carotenoids can mitigate or prevent clinical consequences of UV radiation such as photoaging and photocarcinogenesis, beyond UVB-induced erythema and UVA-induced pigmentation.

## 6 | CONCLUSION

Increasing evidence now suggests that carotenoids more effectively support skin photoprotection than previously thought, as other, more reliable endpoints such as pigmentation and molecular gene expression, than MED, have been established as indicator of photoprotection for skin. Oral supplementation with multi-carotene supplements may provide incidental photoprotection with a more uniform coverage over the total body surface area and could potentially help maintain a healthy-looking skin. Given their potential to act as antioxidants, future areas of research on carotenoids might include their use in protection of human skin against non-UV wavelengths such as near infrared radiation and visible light, as well as other environmental threats such as air pollutants, all of which are known to be an important part of the skin aging exposome.[109]

### CONFLICT OF INTEREST

SMB, AK, CW, DSV, KG, and JL are employees of Amway Corporation, which has commercial offerings in the health, wellness, and beauty space. Dr Krutmann is a consultant for Amway Corporation.

### DATA AVAILABILITY STATEMENT

Data sharing not applicable - no new data generated.

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