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Oral Naturally Derived Agents as an Adjuvant Photoprotection after Dermatologic Surgery

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Abstract

To be effective in protecting against the harmful effects of ultraviolet radiation (UVR), many photoprotective strategies have been used. Inadequate physical protection, amount of topical application, and allergic reactions to topical agents are limitations associated with current photoprotective strategies. Systemic agents are an emerging alternative, providing promising protection against UVR. This chapter will thoroughly review photoprotective outcomes of oral naturally derived agents from randomized controlled trials using evidence-based method. From total 24 clinical trials with 850 participants, two categories of naturally derived agents were identified. Plant-derived agents include beta-carotene, green tea, golden serpent fern, tomato, cocoa bean, and vitamin E, whereas animal-derived products consist of nicotinamide and omega-3 polyunsaturated fatty acids. In conclusion, systemic plant and animal-derived photoprotective agents may be a promising alternative in addition to conventional photoprotection.

Keywords: oral photoprotection, sunscreen, natural products

1. Introduction

Ultraviolet radiation (UVR) can cause various adverse effects to the skin including pigmentary changes, epidermal hyperplasia, free radical formation, photoaging, immunosuppression, and photocarcinogenesis [1]. Physical and topical protective agents are the standard photoprotective strategies especially after dermatologic surgery. Sunscreen is the most widely used protective agent, providing protection only to the areas in which the agents are applied upon. However, the protection is only limited to the few hours subsequent to their applications. In addition, topical protective agents may cause allergic reactions on some individuals [2].

Systemic or oral protective agents in the form of supplementation, preventing free radicals formation and its harmful effects would be an alternative option for photoprotection. Several researches have studied the effects of oral agents to show the protective abilities against UV exposure. This chapter will demonstrate those extensive studies systematically.

All studies included only adult healthy participants aged 18 years and older. In vitro or animal studies were not included into the review. Minimal erythema dose (MED) or changes in UV-induced erythema (UIE) intensity was assessed in most of the studies providing measurement for clinical outcomes. Photoprotective effects of systemic products can be clinically observed through increased MED and decreased UIE intensity. In some studies, physical changes in skin, histopathology, and immunohistochemistry were identified as biomarker outcomes. Two main groups were categorized regarding to their natural sources (Tables 1 and 2).

	Dose/duration	Subjects	Comparison	Clinical outcomes	Histology/biomarker outcomes
Beta-carotene					
Heinrich et al. [3]	β -carotene 24 mg (from an algal source) daily vs. mixed carotenoids (β -carotene 8 mg, lutein 8 mg, and lycopene 8 mg) daily for 12 weeks	36	Placebo	Decreased UIE in both groups ($p < 0.001$)	N/A
Stahl et al. [4]	Total carotenoids 25 mg daily vs. carotenoids 25 mg with α -Toc 500 IU daily for 12 weeks	17	carotenoids	Decreased UIE in combination of carotenoids and α -Toc ($p < 0.01$) and in carotenoids alone ($p < 0.05$)	N/A
Mathews-Roth et al. [5]	β -Carotene 180 mg daily for 10 weeks	30	Placebo	Increased MED ($p < 0.05$), less pigmentary changes after sun exposure ($p < 0.05$)	N/A
<i>Camellia sinensis</i>					
Farrar et al. [6]	GTCs 540 mg with 50 mg vitamin C, twice daily for 12 weeks	50	Placebo	No significant changes in MED	No significant difference in leukocyte infiltration
Heinrich et al. [7]	Total catechins 1402 mg daily for 12 weeks	60	Placebo	Decreased UIE ($p < 0.05$)	Decreased skin elasticity ($p < 0.05$), TEWL ($p < 0.001$), roughness, scaling, wrinkles ($p < 0.05$). Increased hydration, cutaneous blood flow, and O ₂ saturation ($p < 0.05$).

	Dose/duration	Subjects	Comparison	Clinical outcomes	Histology/biomarker outcomes
Chow et al. [8]	EGCG 800 mg daily vs. EGCG 400 mg twice daily vs. EGCG as Polyphenon E 800 mg daily vs. EGCG as Polyphenon E 400 mg twice daily for 4 weeks	40	Placebo	No significant changes in MED	N/A
<i>Polypodium leucotomos</i>					
Nestor et al. [9]	PL extract 480 mg daily for 60 days	40	Placebo	Increased MED ($p = 0.01$), decreased UIE ($p < 0.01$)	Decreased sunburn cells ($p = 0.04$)
Villa et al. [10]	PL extract 480 mg before 2–3 MED exposure	10	Placebo	N/A	Decreased common deletion of mtDNA ($p = 0.06$). No significant difference in histology
Gonzalez et al. [11]	PL extract 1080 mg before UV exposure	23	Placebo	Increased MED ($p < 0.001$), IPD ($p < 0.01$)	Preservation of CD1a-expressing epidermal LCs
<i>Solanum lycopersicum</i>					
Sokoloski et al. [12]	Tomato paste (16 mg lycopene) vs. lycopene capsule (16 mg lycopene) daily for 10 weeks	20	Lycopene capsule	Decreased UIE in both groups ($p = 0.054$). No significant changes in MED in both groups.	N/A
Rizwan et al. [13]	Tomato paste 55 g (16 mg lycopene) in olive oil vs. olive oil alone daily for 12 weeks	20	Placebo	Increased MED ($p = 0.03$)	Reduced UV-induced MMP-1 ($p = 0.04$), increased in pCI deposition ($p = 0.05$), decreased mtDNA 3895-bp deletion ($p = 0.01$)
Aust et al. [14]	Tomato extract (9.8 mg lycopene) vs. drink containing solubilized tomato extract (8.2 mg lycopene) vs. synthetic lycopene (10.2 mg lycopene) daily for 12 weeks	36	Synthetic lycopene	Decreased UIE of both tomato extract ($p < 0.001$) and drink containing tomato extract ($p < 0.001$) but not in synthetic lycopene group	N/A
Stahl et al. [15]	Tomato paste 40 g (16 mg lycopene) in olive oil vs. olive oil alone daily for 10 weeks	19	Placebo	Decreased UIE ($p = 0.02$)	N/A

	Dose/duration	Subjects	Comparison	Clinical outcomes	Histology/biomarker outcomes
<i>Theobroma cacao</i>					
Mogollon et al. [16]	HFC 600 mg vs. LFC <30 mg daily for 12 weeks	74	LFC	Increased MED in both groups; however, no significant difference between HFC and LFC group	Increased skin elasticity and hydration in both groups
Williams et al. [17]	HFC 600 mg vs. LFC <30 mg daily for 12 weeks	30	LFC	Increased MED in HFC group ($p = 0.005$) but not in LFC. Significant difference between HFC and LFC group ($p \leq 0.05$).	N/A
Heinrich et al. [18]	HFC 329 mg vs. LFC 27 mg daily for 12 weeks	24	LFC	Decreased UIE ($p < 0.05$) in HFC group but not in LFC group. Significant difference between HFC and LFC group ($p < 0.05$)	Increased skin density, thickness and hydration, and decreased skin roughness, scaling and TEWL in HFC ($p < 0.05$). No different changes in LFC
Tocopherol					
McArdle et al. [19]	α -Toc 400 IU daily vs. β -carotene 15 mg daily for 8 weeks	16	β -Carotene	No significant changes in MED in both groups	Decreased skin malondialdehyde concentration in α -Toc ($p < 0.05$)
Mireles-Rocha et al. [20]	α -Toc 1200 IU daily vs. Asc 2 g daily vs. α -Toc 1200 IU with Asc 2 g daily for 1 week	45	Asc	Increased MED in α -Toc alone ($p = 0.002$) and in Asc with α -Toc ($p = 0.0001$). No significant changes in Asc alone group	N/A
Fuchs et al. [21]	α -Toc 2 g daily vs. Asc 3 g daily vs. α -Toc 2 g with Asc 3 g daily vs. placebo for 50 days	40	Placebo	Increased MED only in α -Toc with Asc group ($p < 0.005$)	N/A
Werninghaus et al. [22]	α -Toc 400 IU daily for 6 months	67	Placebo	No significant change in MED	No significant difference in sunburn cells

Abbreviation: Asc = ascorbic acid, EGCG = epigallocatechin gallate, GTCs = green tea catechins, HFC = high-flavanol chocolate, IPD = immediate pigment darkening, LCs = Langerhans cells, LFC = low-flavanol chocolate, MED = minimal erythema doses, MMP-1 = matrix metalloproteinase-1, mtDNA = mitochondrial DNA, PL = *Polypodium leucotomos*, SPT = skin phototype, TEWL = transepidermal water loss, UIE = UV-induced erythema, and α -Toc = D- α -tocopherol.

Table 1. Plant-derived photoprotective agents.

	Dose/duration	Subjects	Comparison	Clinical outcomes	Histology/biomarker outcomes
Nicotinamide					
Thanos et al. [23]	Nicotinamide 500 mg twice daily for 1 week	30	Crossover study	Reduced MIE (p < 0.0001)	Reduced Mantoux diameter (p < 0.0001)
Yiasemides et al. [24]	Nicotinamide 500 mg three times daily (high dose) vs. once daily (low dose) vs. placebo for 1 week	61	Crossover study	No significant changes in MED	Reduced Mantoux diameter (p < 0.001) in both groups
ω-3 polyunsaturated fatty acids					
Rhodes et al. [25]	95% EPA 4 g vs. 95% oleic acid 4 g daily for 12 weeks	42	Oleic acid	Increased MED (p < 0.01) in EPA but not in OA.	Reduced UV-induced p53 expression (p < 0.01) in EPA but not in OA. No statistical difference in CPDs changes. Decreased in tail moment by comet assay (p < 0.05) in EPA but not in OA.
Orengo et al. [26]	Fish oil (2.8 g EPA + 1.2 g DCHA) daily for 4 weeks	20	Placebo	Increased MED (p < 0.02)	No significant changes in PGE2

CPDs = cyclobutane pyrimidine dimers, DCHA = docosahexaenoic acid, EPA = eicosapentaenoic acid, MED = minimal erythema doses, MIE = Mantoux induced erythema, OA = oleic acid, PGE2 = prostaglandin E2, and SPT = skin phototype.

Table 2. Animal-derived photoprotective agents.

2. Plant-derived photoprotective agents

2.1. Beta-carotene

Previous study reported an increase in the ability to tolerate sunlight among photosensitive subjects, especially in erythropoietic porphyria after high-dose administration of beta-carotene [27]. However, only three RCTs of beta-carotene reported significant decrease in UIE intensity and increased MED after 10–12 weeks of supplementation in healthy subjects [3–5]. The major source of beta-carotene in two studies was from *Dunaliella salina*, a unicellular biflagellate green alga [3, 4]. Heinrich et al. [3] compared the administration of 24 mg of beta-carotene daily versus mixed carotenoids (beta-carotene 8 mg, lutein 8 mg, and lycopene 8 mg) for 12 weeks. The results showed the statistically significant decrease in UIE intensity in both groups. In another study conducted

by Stahl et al. [4], a 25-mg-carotenoid supplement was given daily comparing to the supplementation of the combination of 25-mg-carotenoid and 500-IU- α -tocopherol during 12-week period. Both groups demonstrated significant decrease in UIE intensity at the end of the study. However, it seemed that in combination with vitamin E revealed more significant changes than with the carotenoid supplementation alone. Also, the study by Mathews-Roth et al. [5] suggested that high dose supplementation of a 180-mg-beta-carotene daily for 10 weeks could significantly reduce in MED and showed less pigmentary changes after sun exposure.

Beta-carotene alone, mixed of carotenoids, and in combination with α -tocopherol were effective. Nevertheless, there was no study evaluating histological changes. In animal study, *Dunaliella salina* exhibited potent protection from UV-induced oxidative damage due to the increase of antioxidative activities and the inhibition of lipid peroxidation [28].

2.2. *Camellia sinensis*

Camellia sinensis leaves that have not undergone the withering and oxidation process are commonly known as green tea. Four major polyphenols in green tea include epicatechin, epicatechin-3-gallate, epigallocatechin, and epigallocatechin-3-gallate (EGCG), the most potent antioxidant. In animal models, green tea polyphenols and EGCG demonstrated the protection against the UV-induced sunburn and photoaging of the skin [29].

A 540 mg of green tea catechins (GTCs) in combination with a 50 mg of vitamin C supplement was administered twice daily comparing to placebo group for 12 weeks [6]. There were no significant differences both in clinical outcomes of MED changes and in histological outcomes of leukocytic infiltration or the cutaneous production of proinflammatory metabolites. Similarly, supplementation of epigallocatechin gallate (EGCG) or Polyphenon E (decaffeinated green tea polyphenol mixture) at a dose of 800 mg was administered daily in comparison with placebo for 4 weeks [8]. There were no significant changes in MED after the supplementation. Therefore, these may conclude that there was no statistical effect on both clinical and histological changes of the skin basal inflammatory status or the response to acute proinflammatory UVR challenge based on histologic sunburn cells and proinflammatory mediators. However, one double-blinded RCT exhibited a significant reduction of UIE intensity following daily administration of total catechins 1402 mg for 3 months [7]. Skin elasticity, roughness, wrinkles, hydration, and cutaneous blood flow were also improved.

Green tea, a notable antioxidant product, has an extensive in vitro studies of its properties, including systemic antioxidant, anti-inflammatory activities, prevention of DNA damage [30], immunoregulation, and antiphotaging properties. However, only one randomized, double-blind, placebo-controlled trial indicates an increase in photosensitivity threshold and improves skin physiology following a daily intake. Therefore, further clinical studies should be conducted to evaluate the exact efficacy of green tea for its photoprotective property.

2.3. *Polypodium leucotomos*

Polypodium leucotomos (PL), commonly known as golden serpent fern, is a tropical fern plant found in Central America. Its active ingredients are polyphenols including phenolic acids p-coumaric, ferulic, fumaric, vanillic, quinic, caffeic, chlorogenic, 3,4-dihydroxybenzoic, and 4-hydroxybenzoic, along with five phenolic chlorogenic acid isomers. The photoprotective properties of PL may link to its antioxidant activities, scavenging reactive oxygen species (ROS), and possessing anti-inflammatory properties.

There were three studies with a daily intake ranging from 480 to 1080 mg of PL for 1–60 days [9–11]. Two studies [9, 11] showed a statistically significant increase in MED and lower erythema intensity after UV exposure. The result was confirmed by the reduction of sunburn cells [9] and preservation of CD1a-expressing epidermal Langerhans cells [11]. For the ingestion just prior to UV exposure, a standard dose of 480 mg PL supplements did not demonstrate significant photoprotection in both clinical and histological outcomes [10].

Polyphenols are a large group of plant products occurring naturally. It prevents damages affecting cellular lipids, protein, DNA, and premature aging of the skin from photooxidative damage. Based on chemical structures, polyphenols can be classified into flavonoids, stilbenes, lignans, and phenolic acids [31]. Golden serpent fern, green tea, and cocoa bean have polyphenol structures, and they exhibited the same mechanisms of action in ROS suppression and anti-inflammation [31]. Though PL extract is one of the most well-known systemic photoprotective agents, there were only three RCTs comparing PL and placebo in healthy subjects. Daily supplements of PL at 480 mg exhibited photoprotection [9]. However, only high dose of PL at 1080 mg could prevent acute sunburn [11]. Immunomodulating effect of PL was found by the preservation of CD1a-expressing epidermal LCs in human skin [11].

2.4. *Solanum lycopersicum*

Lycopene, one of the powerful carotenoids antioxidants, is found abundantly in tomatoes, *Solanum lycopersicum*. Depending on the type of tomato and its state of ripening, lycopene contents vary significantly. Lycopene levels can reach as high as 50 mg/kg in the reddest strains of tomatoes and reach as low as 5 mg/kg in the yellow strains. Through thermal processing and dietary lipids coingestion, the bioavailability of lycopene from dietary sources increases substantially. As the bioavailability of carotenoids rises through cooking and food-processing process, an ingestion of tomato paste (processed tomatoes) yields a higher lycopene uptake than an ingestion of fresh tomatoes [32].

Four RCTs of lycopene from tomato paste or tomato extract showed similar trends of photoprotection. After 10–12 weeks of tomato paste ingestion at a dose ranging between 8.2 and 16 mg of lycopene daily, a significant decrease in UIE intensity or an increase in MED in lycopene group was noticed [12–15]. Significant decrease in MMP1 and the 3895-bp deletion in mitochondrial DNA following UV exposure were also found in histology [13]. It

suggested that tomato paste may play a role in photoprotection through decreasing DNA mutagenesis.

Carotenoids, naturally fat-soluble pigments, are synthesized by plants and algae. Most of the carotenoids are from food with yellow to orange hues such as carrots, plums, and apricots. Carotenoids are usually classified into two broad classes: carotenes (lycopene, α -carotene, and β -carotene) and xanthophylls (β -cryptoxanthin, lutein, and zeaxanthin). Major biological effects of carotenoids include provitamin A activity, cellular signaling, and antioxidation [33]. Since tomato paste administration could reduce mitochondrial DNA deletion, this might also represent its role in mutagenic suppression [13].

2.5. *Theobroma cacao*

Freshly harvested cocoa beans are abundant in polyphenols. Flavonoids are the main phenolic phytochemical structure. However, during the production process of conventional chocolate, much of the antioxidant capacity of fresh cocoa beans is greatly diminished [34].

In three randomized controlled studies, daily intake of high flavanol cocoa (HFC, more than 329 mg) and low flavanol cocoa (LFC, less than 30 mg) for 3 months were compared. All studies revealed an increase in MED or a decrease in UVE intensity following HFC ingestion [16–18]. Only one research reported increasing MED in LFC administration [16]. Moreover, skin elasticity and hydration were improved after HFC administration [16, 18].

All three RCTs in cocoa bean demonstrated similar trends. Daily ingestion of chocolate with high flavanol cocoa for 3 months exhibited higher photosensitivity threshold [16–18]. Correspondingly, several in vitro studies showed antioxidative activities and anti-inflammatory properties of cocoa beans [35, 36]. These effects may be associated with the mechanisms of photoprotection of cocoa.

2.6. Tocopherol

Vitamin E is a group of compounds including tocopherols and tocotrienols. γ -tocopherol is considered to be the common form of vitamin E widely found in soybean oil, corn oil, margarine, and dressings. α -tocopherol, another form of vitamin E, can be found most abundantly in wheat germ oil, sunflower, and safflower oils. It affects oxidative stress by interrupting the free radical formation.

Four RCTs with daily supplement of α -tocopherol, at dosage between 400 and 1200 IU, alone or in combination with ascorbic acid were revealed [19–22]. The results were controversial. Two studies with daily intake of 400 IU of α -tocopherol showed no significant change in MED following the supplementation for 2 or 6 months [19, 22]. In contrast, a daily ingestion of 1200 IU or 2 g of α -tocopherol together with ascorbic acid administration could increase MED significantly [20, 21]. As a result for daily supplement of vitamin E, only high dosage could exhibit an increase of photoprotection. The mechanism of photoprotective activities may involve lipid peroxidation through the reduction of cutaneous malondialdehyde concentration after UV exposure [19].

3. Animal-derived photoprotective agents

3.1. Nicotinamide

Nicotinamide, an amide form of vitamin B3, is the precursor of nicotinamide adenine dinucleotide (NAD), an essential coenzyme for ATP production. Therefore, nicotinamide supplementation can accelerate cellular energy and elevate DNA repair, an energy-dependent cellular processes. Vitamin B3, an essential water-soluble vitamin, is generally not stored in the body. It is usually excreted in the urine on a daily basis. Maintenance is only possible through dietary consumption of vitamin B3 and tryptophan, an essential amino acid which is frequently reported in most variations of protein and makes up approximately 1% of total dietary protein. Nicotinamide are found mainly in meats, nuts, grain products, yeast extracts, eggs, and legumes. In animal studies, nicotinamide has photoprotective, anticarcinogenic, and immunosuppressive effects [37].

Using a Mantoux delayed-type hypersensitivity model, oral nicotinamide at dosage ranging from 500 to 1500 mg daily was administered in healthy subjects [23, 24]. The studies revealed the reduction of Mantoux diameter following the supplementation for a week. This might demonstrate the ability of UV-induced immunosuppression of the skin. Nevertheless, there were no significant changes in MED [24].

It has been demonstrated that nicotinamide prevents UV-induced ATP depletion, enhances UV-induced DNA repair, regulates inflammatory cytokines and mediators in human keratinocytes [38], and prevents photocarcinogenesis in animal studies [39]. In human studies, topical and oral nicotinamide administration could reduce the number of actinic keratoses [40, 41]. However, only two controlled studies could demonstrate the reduction of Mantoux-induced erythema and diameter at irradiated sites, indicating its immunosuppressive effect [23, 24].

3.2. Omega-3 polyunsaturated fatty acids

Dietary omega-3 polyunsaturated fatty acids (ω -3 PUFAs) are extracted mostly from oily fish such as mackerels, sardines, and salmons. Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DCHA) are major components.

Rhodes et al. [25] reported daily intake of 4 g of purified ω -3 PUFAs comparing to a supplement of 4 g oleic acid. This trial demonstrated the significant increase in MED and UIE threshold following the supplementation of ω -3 PUFAs for 3 months. In immunohistochemical study, UV-induced p53 expression was also suppressed. Moreover, Orengo et al. [26] exhibited that daily supplements of fish oil composing of 2.8 g EPA for 1 month could significantly increase MED. Nevertheless, there was no significant change in PGE2 from immunohistological outcomes.

ω -3 PUFAs modulate NF- κ B and AP-1, which control genes associated with inflammation and lipid metabolism. Dietary ω -3 PUFAs have been previously reported to reduce UVR-induced prostaglandin E₂, a mediator of UV immunosuppression, in both animals and human skins [42]. Clinical studies also indicated an increase in UIE threshold [25, 26]. Reduction in

UV-induced p53 expression indicating its effect on skin cancer reduction or DNA repair was observed in histology [25].

4. Conclusion

Conventionally, topical sunscreens, physical protection, and sun avoidance are recommended as standard photoprotection following most of the dermatologic surgery. However, several limitations including inadequate amount, reapplication needs, and photoallergic reactions limit their use in clinical practice. Regarding to the evidences of available natural product based, oral naturally derived agents are promising as an addition for photoprotection. Although, there are numerous in vitro and animal studies of the agents, the numbers of clinical studies are limited with small sample size of the subjects. Further high-quality controlled trials with higher number of participants are needed in order to get better understanding of the efficacy, mechanism of actions, and role of a natural product for photoprotection.

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