What's New in Natural Compounds for Photoprotection?

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We have reviewed the newest properties of natural compounds for photoprotection. Photoprotection by dietary means has garnered much interest in both the public and research communities. Plant constituents, such as carotenoids, flavonoids, β-carotene, and lycopene, and other natural compounds, such as caffeine, are involved in protection against oxidative damage in plants that is induced by excess light and can contribute to the prevention of UV radiation damage in humans. These micronutrients, when ingested, are distributed to light-exposed tissues, such as the skin, where they provide systemic photoprotection. Systemic endogenous compounds have been demonstrated to be important adjunctive tools against UV effects. In vitro and in vivo animal and human studies suggest that many natural compounds are photoprotective in nature and may be valuable pharmacologic agents in the prevention of solar UVB light–induced skin disorders, including photoaging and melanoma and nonmelanoma skin cancers. More clinical trials in humans are needed to determine the safety and efficacy of these promising compounds.

We have reviewed the newest properties of natural compounds for photoprotection. Photoprotection by dietary means has attracted much interest in both the public and research communities. Plant constituents, such as carotenoids, flavonoids, β-carotene, and lycopene, and other natural compounds, such as caffeine, are involved in protection against oxidative damage in plants that is induced by excess light and can contribute to the prevention of UV radiation (UVR) damage in humans.[1] These micronutrients, when ingested, are distributed to light-exposed tissues, such as the skin or the eye, where they provide systemic photoprotection. Current recommendations in sun protection include avoiding outdoor activities when UV rays are strongest, particularly between 10:00 AM and 2:00 PM; seeking shade whenever possible; and applying a broad-spectrum sunscreen with a sun protection factor (SPF) of at least 15 and reapplying it every 2 hours. Educational awareness programs have been only partially effective, mostly because of their impracticality, especially for young people.

UVR represents a major source of environmental stress, exerting hazardous effects on health (eg, precancerous and cancerous skin lesions and cutaneous photoaging).[2] Photoaging is the superposition of chronic UV-induced damage on intrinsic aging and accounts for most age-related changes in skin appearance. It is triggered by receptor-initiated signaling, mitochondrial damage, protein oxidation, and telomere-based DNA damage responses.[2] UV carcinogenic properties are mediated by the ability of UVR to generate

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DNA damage. Cellular responses to UV-induced DNA damage, which are wavelength dependent, profoundly modulate the carcinogenic effects of UVR. However, the exact contributions of different wavelengths of UVR to DNA damage, cellular damage responses, mutation, and skin carcinogenesis are incompletely understood.

UVR directly interacts with DNA, causing DNA damage (eg, thymine dimer formation).[3] UVR induces high levels of the p53 tumor suppressor protein, mainly through posttranslational stabilization of the protein.[4] In turn, p53 activates the transcription of downstream genes responsible for cell cycle arrest, which allows for the repair of DNA damage.[5] However, p53 can also cause apoptosis of cells with excessive unrepaired DNA damage.[6] UVR also increases nitric oxide (NO) production, which may contribute to UVR-induced DNA damage and inhibition of DNA repair.[5,7] In human cells treated with cytokines, lipopolysaccharide and 1,25-dihydroxyvitamin D_3 ($1,25[OH]_2D_3$) have been reported to reduce apoptosis through a decrease in NO products.[8,9] Systemic endogenous photoprotection compounds are important adjunctive tools against UV effects; however, these supplements provide an SPF lower than that achieved by topical sunscreens and should be considered as complementary measures to traditional topical photoprotection, mostly for the long-term prevention of UVR-induced skin damage.[10]

PHYTOCHEMICALS

Phytochemicals and dietary supplements are bioactive plant compounds that are found in fruits, vegetables, grains, and other plants and are associated with health improvement and risk reduction of some chronic diseases.[11-13] These plant foods, also known as *functional foods* and *nutraceuticals,* contain supplements that have the same treatment objectives as available drugs. Examples of these supplements include foods containing omega-3 fatty acids, which, similar to the fibrates, aim to lower triglycerides, and foods enriched with phytosterol/stanol esters, which, similar to statins and ezetimibe, aim to decrease low-density lipoprotein cholesterol.[12] Studies have demonstrated a strong association between a diet rich in fruits, vegetables, and whole grains and a reduced risk of developing certain conditions, particularly chronic diseases such as cancer and cardiovascular disease.[14,15] Acute and chronic skin conditions that can benefit from these compounds include sunburn, photosensitivity disorders, photoaging, and skin cancers.[16-28] Most functional foods have the potential of being photoprotectants in humans; as antioxidants, they decrease the production of reactive oxygen species (ROS) and free radicals that may lead to DNA damage as well as modulate inflammatory and immune reactions, all of which are induced by UVR.[16] Other actions include inducing gene suppression and detoxifying carcinogens.[29] Carotenoids, tocopherol, and vitamin C found in foods and supplements have been used to prevent UV-induced erythema,[10] not only through their antioxidant properties but also by interfering with cellular signaling induced by UVR.[29,30] Several groups of phytochemicals have been described, including carotenoids, phenolics, alkaloids, nitrogen-containing compounds, and organosulfur compounds.[11]

Garlic Extract

Garlic *(Allium sativum)* has been used universally as a flavoring ingredient, functional food, and traditional medicine. Specific constituents found in garlic and its extracts may account for garlic's medical and beneficial properties, and many studies suggest that organosulfur compounds are responsible for its biological activities.[31] Some components of garlic have been shown to alter activation of carcinogens and to cause inhibition of tumor cells.[32] Aged garlic extract (AGE) is manufactured by a natural long-term process called the *aging extraction process,* which takes more than 10 months at room temperature and contains water-soluble allyl amino acid derivatives. AGE contains organosulfur compounds, including *S*-allylcysteine and *S*-allylmercaptocysteine. *S*-allylcysteine and *S*-allylmercaptocysteine have been reported to show a variety of biological activities, including antioxidant function,[33,34] cancer prevention,[35] antiatherogenic activity,[36] and antiplatelet aggregation activity. The antioxidant effects of these compounds were determined using in vitro assay systems. Reeve et al[37] incorporated lyophilized AGE at concentrations of 0.1%, 1%, and 4% into semipurified powdered diets of hairless mice. Under moderate UVB exposure conditions resulting in 58% suppression of the systemic contact hypersensitivity response in control-fed mice, a dose-responsive protection was observed in the AGE-fed mice; contact hypersensitivity in the UVB-exposed mice fed 4% AGE was suppressed by only 19%. Mice fed a diet containing 4% AGE were protected from all concentrations of urocanic acid. AGE contains an ingredient(s) that protects from UVB-induced suppression of contact hypersensitivity, suggesting that the mechanism of action is through antagonism of the cis-urocanic acid mediation of this form of immunosuppression.[37] Garlic also contains several carotenoids and other phytochemicals, including β-carotene, caffeic acid, ferulic acid, p-coumaric acid, phytic acid, and quercetin. These components have been shown to have photoprotectant effects as well.

Currently, there are no ongoing human studies evaluating garlic as a photoprotective agent. Therefore, future studies in humans are warranted to determine the likely photoprotective properties and other possible benefits of garlic.

Carotenes

β-*Carotene*—A carotenoid-rich diet or β-carotene supplementation at doses ranging from 15 to 180 mg/d for 10 weeks or longer has been shown to moderately protect against UVR.[38] In a placebo-controlled, parallel study, Heinrich et al[38] compared the erythema-protective effect, after exposure to a solar light simulator, of 24 mg/d of β-carotene obtained from an algal source; of 24 mg/d of a carotenoid mix containing the 3 principal dietary carotenoids, including β-carotene, lutein, and lycopene; and of placebo. Compared with baseline, there was a 4-fold increase in serum β-carotene concentration in the β-carotene group, while there was only a 1- to 3-fold increase in serum concentration of each of the 3 carotenoids after 6 and 12 weeks. No changes were observed in the placebo group. In both supplemented groups, the intensity of erythema 24 hours after irradiation was significantly lower after 12 weeks compared with baseline, whereas a slight increase in the intensity of erythema was noted in the control group. There was no difference in the intensity of erythema between the β-carotene group and the carotenoid mix group; there was no difference in the intensity of erythema from week 0 to week 6 and from week 0 to week 12. High doses of β-carotene have been associated with pro-oxidant reactions and with an increased risk of developing cancer, as reported by Albanes et al[39] and Omenn et al,[40] where β-carotene supplements, either alone or in combination with α-tocopherol or retinol, applied for several years at doses of 20 and 30 mg/d, increased the incidence of lung cancer by 20%. β-Carotene has been found to enhance UVA induction of proinflammatory interleukin (IL)–6 and hemeoxygenase-1, a sensitive marker for oxidative stress, in cultured human skin fibroblasts. This effect was not observed with UVB radiation.[41] To prevent this effect, β-carotene doses have been lowered, and β-carotene combinations with other carotenoids have been developed for sun protection.[10] Studies by Greenberg et al,[42] Green et al,[43] and Darlington et al[22] have demonstrated no effect of vitamin A in the prevention of skin cancers.

Lycopene—Lycopene is a carotenoid red pigment abundant in tomatoes and their products and represents 50% of the carotenoids found in human serum.[44] It has the highest capacity for eliminating singlet oxygen in vitro among dietary carotenoids and demonstrates potent activity against oxidation of proteins, lipids, and DNA. It can be found in particularly high concentrations in the prostate and adrenal glands, testes, skin, liver, and kidneys.[45] The inverse relationship between the levels of lycopene and the risk of developing certain cancers, including cancer of the prostate, pancreas, and stomach, has been reported.[44] Other types of tumors that have been reduced by lycopene intake include lung adenomas and carcinomas, colon cancer, mammary tumors, endometrial cancer, lung cancer, and human promyelocytic leukemia cell line growth.[45]

Lycopene has also been shown to have photoprotective activity in UVB-exposed human skin.[46-49] Both oral supplementation and topical application of lycopene for long periods of time[50] have demonstrated a protective effect against human skin erythema caused by UV exposure.[45] An animal study by Fazekas et al[45] on topical lycopene application reported a dose-dependent inhibition by lycopene of UVB-induced ornithine decarboxylase and myeloperoxidase and significantly reduced skin thickness after acute UVB light source irradiation, which induces inflammatory reactions, including elevation of ornithine decarboxylase and myeloperoxidase. In a study by Stahl et al,[51] an oral tomato paste (40 g) was given to volunteers receiving 16 mg/d of lycopene; erythema was induced with a solar light simulator at baseline, week 4, and week 10. Elevated serum levels of lycopene were detected in supplemented subjects, whereas no changes were obtained in carotenoid serum levels in the control group. Both groups differed at week 4 and week 10 in dorsal erythema formation. There was no difference in the development of erythema between the 2 groups at week 4. However, at week 10 the erythema was 40% lower in the supplemented group than in the control group.

Lutein and zeaxanthin—Lutein and zeaxanthin are potent antioxidant xanthophyll carotenoids found in green leafy vegetables such as broccoli, spinach, and cabbage. They are also found in the fovea centralis of the human retina, where they prevent age-related macular degeneration. Lutein is structurally related to β-carotene but has superior antioxidant properties.[52] Female hairless mice received a 0.4% or 0.04% lutein plus zeaxanthin–enriched diet for 2 weeks and were exposed to single doses of UVB radiation. Lutein plus zeaxanthin significantly decreased UVB-induced skin thickening, reduced the percentage of proliferating cell nuclear antigen and bromodeoxyuridine, and decreased the number of apoptotic keratinocytes measured by the reduction of the amount of terminal deoxyribonucleotidyl transferase–mediated dUTP nick-end labeling assay–positive cells at a dose of 0.04%, with a 210% greater reduction at a dose of 0.4%. These findings demonstrated the role of lutein plus zeaxanthin in the reduction of acute inflammatory and hyperproliferative cellular responses induced by UVB radiation.[52]

Lutein plus zeaxanthin also protects the skin against UVB-induced photoaging and photocarcinogenesis[53] through mechanisms that include the inhibition of the ratio of matrix metalloproteinases (MMPs) to tissue inhibitors of metalloproteinases in dermal fibroblasts and melanoma cells and the inhibition of cell loss, membrane damage, and elastin expression in UVR-exposed fibroblasts.[54]

Phenolics

Phenolics, also known as polyphenols when more than one aromatic ring is present in the molecule, are the second most common dietary phytochemicals, following carotenoids, found in nature. Cranberry has the highest concentration of phenolics, followed by apple, red grape, strawberry, pineapple, and grapefruit. Of the vegetables, broccoli has the highest concentration of phenolics, followed by spinach, yellow onion, red pepper, carrot, and cabbage. Phenolics can also be found in large amounts in tea and red wine.

Phenolics are subdivided into phenolic acids, flavonoids, stilbenes, coumarins, and tannins. Flavonoids represent approximately two-thirds, while phenolic acids account for the remaining one-third, of phenolics in the human diet.[10,11] Phenolics are efficient and powerful antioxidants and modulate multiple enzymes influencing anti-inflammatory and cell division reactions.[10,11] The antioxidant effect of polyphenols appears to be greater than that of vitamin C. Among polyphenol-containing foods with photoprotective properties, we will discuss green tea and grape seed extract.

Green tea—There are 3 main varieties of tea: green, black, and oolong. The difference among the teas is in their processing. Green tea is made from unfermented leaves and reportedly contains the highest concentration of polyphenols. Studies have shown that topical application of green tea extract protects against UVB rays and provides broad-spectrum protection against skin aging. Polyphenols contained in teas are classified as catechins. Green tea contains 6 primary catechin compounds: catechin, gallocatechin, epicatechin, epigallocatechin, epicatechin 3-gallate, and epigallocatechin-3-gallate (EGCG). EGCG is the most studied and most active polyphenol component in green tea and is probably responsible for its protective effect. Green tea also contains alkaloids, including caffeine, theobromine, and theophylline, which provide its stimulant effect.

Recent research has shown that the green tea included in many natural sun-protection products is an effective sunscreen. It has also been reported that EGCG is the most effective chemopreventive agent against cutaneous inflammatory and carcinogenic responses among the catechins.[55,56] Antioxidant compounds in green tea have been shown to exhibit antimutagenic activity in vitro and to inhibit carcinogens and UV-induced skin carcinogenesis in vivo. Morley et al[57] demonstrated that green tea, and particularly EGCG, can offer some degree of protection against UVR-induced DNA damage in human cell cultures and also in human peripheral blood in samples taken post–green tea ingestion. Studies in mouse models have shown that topical application or oral consumption of a polyphenolic fraction isolated from green tea provides protection against inflammation, chemical carcinogenesis, and photocarcinogenesis. The majority of the studies have been conducted in a mouse skin tumor model system, where tea is fed either as a water extract through drinking water or as purified green tea. Green tea has also been shown to provide protection against chemical carcinogen–induced stomach, lung, esophagus, duodenum, pancreas, liver, breast, and colon cancer in specific bioassay models. Epicatechin derivatives, specifically EGCG, have also shown anticarcinogenic activity.

The mechanisms of tea's antitumor effects are not completely understood; different theories proposed include inhibition of UV- and tumor promoter–induced ornithine decarboxylase, cyclooxygenase, and lipoxygenase activities; antioxidant and free radical scavenging activity; enhancement of antioxidant (glutathione peroxidase, catalase, and quinone reductase) and phase II (glutathione *S*-transferase) enzyme activities; inhibition of lipid peroxidation; and anti-inflammatory activity. These properties of tea polyphenols make them effective agents against the initiation, promotion, and progression stages of multistage carcinogenesis.[58]

Recent evidence indicates that EGCG has the potential to reduce UVB-induced erythema and block the UVB-induced infiltration of leukocytes and the subsequent generation of ROS. Bi et al[59] have shown that EGCG may prevent the signal transduction of photodamage induced by UV irradiation. Some of the mechanisms of photoprotection of EGCG demonstrated by flow cytometry analysis include the reduction of UVB-induced keratinocyte apoptosis and UVA-induced fibroblast apoptosis by increasing the bcl-2 protein and decreasing Fas messenger RNA (mRNA). EGCG can recover UV-induced loss of bcl-2 expressed in cultured human keratinocytes and also inhibits NF-κB translocation to the nucleus and IL-6 secretion in cultured human keratinocytes. EGCG also reduced UVB-induced skin damage by decreasing the secretion of tumor necrosis factor α (TNF-α) and IL-1β and their mRNA expression. In addition, EGCG protected human fibroblasts against UVB damage by down-regulating the transcription activity of the c-Jun protein and the expression of MMP-1. The ratio of MMP-1 to tissue inhibitors of metalloproteinase-1 plays a major role in human photoaging. UVA radiation can inhibit collagen synthesis in cultured dermal fibroblasts, whereas EGCG can reverse this inhibition. EGCG may also increase the levels of type I and type III procollagen mRNA expression in the cultured fibroblasts. Different dosages of UVA decreased levels of hydroxyproline in the fibroblast-cultured medium, whereas EGCG is able to increase these levels by inhibiting MMP synthesis and decreasing collagen I, collagen II, and hydroxyproline degradation. Therefore, the method by which EGCG acts to avoid

photodamage and its underlying value have been proposed in previous studies to be accepted as a prevention and treatment of photoaging.[59]

EGCG has been proven to prevent the signal transduction of photodamage induced by UV irradiation in different ways. The prevention and treatment of photodamage by green tea could be a valid strategy to prevent skin carcinogenesis, photoaging, or both in the future.

To better understand the protective effect of EGCG, it is necessary to learn the photobiologic description of the mechanism by which UV irradiation causes skin damage. Regarding photocarcinogenesis, UVB exposure results in the direct absorption of UVB photons by DNA, inducing the production of structural changes, including the formation of cyclobutane pyrimidine dimers, the most abundant and probably most cytotoxic DNA lesions, and 6-4 photoproducts pyrimidine adducts, which are converted to Dewar isomers by UVB radiation. UVB-induced DNA damage also leads to induction of immunosuppressive cytokines, including TNF-α, IL-10, and IL-6.[60] UVB-induced DNA damage is a crucial event in UVB-mediated apoptosis. However, the complex biological process of photoaging affects various layers of the skin, including the damage seen in the dermal connective tissue.

Following irradiation with UVA and UVB, ROS generation and severe oxidative stress in skin cells require the absorption of photons by endogenous chromophore photosensitizer molecules. Previous literature has identified the epidermal UVA-absorbing chromophore as trans-urocanic acid, which quantitatively accounts for the spectrum of action of UVA in photoaging,[61] resulting in transient and permanent genetic damage and in the activation of cytoplasmic signal transduction pathways that are related to growth, differentiation, replicative senescence, and connective tissue degradation. Collagen type I, which constitutes the major structural component of the dermal connective tissue, has been found to be diminished in photoaged skin. Studies have revealed that various MMPs, serine, and other proteases responsible for the breakdown of various connective tissue components were dose-dependently induced in vitro and in vivo by UVA and UVB irradiation.[62-64] MMP-1 (interstitial collagenase) cleaves collagen type I, whereas MMP-2 is able to degrade elastin as well as basement membrane constituents, including collagen type IV and type VII. MMP-3 reveals the broadest substrate specificity for proteins, such as collagen type IV, proteoglycans, fibronectin, and laminin. Elastin accumulation and collagen degradation are prominent hallmarks in photodamaged skin.

Exposure of fibroblast monolayer cultures to ROS-generating systems or UV irradiation at different spectra in the presence and absence of ROS–quenching/scavenging agents or substances that specifically inhibit ROS-detoxifying enzymes allows ROS to increase or decrease intracellularly and pericellularly. Based on this approach, evidence was provided that singlet oxygen and H_2O_2 are the major ROS involved in the UVA-dependent induction of MMP-1, MMP-2, and MMP-3 on mRNA and protein levels, whereas the hydroxyl radical and intermediates of lipid peroxidation play a major role in the UVB induction of MMP-1 and MMP-3.[65]

Previous data suggest that UVA-generated singlet oxygen may initiate membrane-dependent signaling pathways involving c-Jun amino-terminal kinase (JNK) and p38 members of the mitogen-activated protein kinases and interrelated autocrine cytokine loops of IL-1α IL-1β, and IL-6, leading to the enhanced expression of MMPs.[66,67] There is in vitro evidence from fibroblast monolayer cultures that the UVB-initiated, iron-driven Fenton reaction, with subsequent generation of hydroxyl radicals and lipid peroxidation end products such as malondialdehyde and 4-hydroxy-2(E)-nonenal, stimulates the JNK2, representing an additional family of the mitogen-activated protein kinases. UVB-induced JNK2 leads to the phosphorylation and activation of the c-Jun protein that up-regulates its own expression. Elevated c-Jun, in combination with constitutively expressed c-Fos, increases the transcription of MMPs. It has been described that DNA damage–dependent FKBP12-rapamycin-associated protein kinase and the p70 ribosomal S6 kinase are critically involved in the UVB induction of MMPs in fibroblast monolayer cultures, suggesting that ROS-induced DNA damage may play a role in the UVB-initiated signal transduction pathway, resulting in MMP induction.[68]

Grape seed extract—Grapes are rich in polyphenols, including proanthocyanidins, with 60% to 70% of these compounds found in the seeds. Grape seed proanthocyanidins (GSPs) are potent antioxidants, serving as free radical scavengers. Previous studies have demonstrated that GSPs can suppress the UVR-induced production of DNA photoproducts, reactive oxygen intermediates, and immunosuppressive cytokines, such as IL-10.[69] Furthermore, GSPs inhibit the depletion of endogenous antioxidant enzymes, including glutathione peroxidase and catalase.[70] Mittal et al[71] have shown that oral GSPs significantly inhibit UVR-induced skin tumor incidence, multiplicity, and size in mouse models. Topical GSP treatment has also been shown to inhibit carcinogenesis in mice. In addition, GSPs were shown in vitro to have antiproliferative and proapoptotic effects on skin cancer cells by interfering with cell cycle progression. GSPs appear promising in mouse models, but more clinical trials in humans are needed.

Oral grape seed extract is available as 50- or 100-mg capsules or tablets. Cough, headache, and nausea are

among the adverse effects reported by participants in clinical studies.[72] Grape seed extract may reduce the clotting time in people taking antiplatelet or anticoagulant medications and herbal products, including aspirin, garlic, ginseng, ginkgo, papain, and saw palmetto.

Cocoa—Heinrich et al[73] demonstrated the effectiveness of a cocoa beverage rich in flavonols (eg, epicatechin and catechin) in decreasing human skin sensitivity to UVR as compared with baseline, with a reduction of 15% after 6 weeks and 25% after 12 weeks in the degree of erythema after exposure to a solar light simulator. This effect is comparable with that associated with carotenoid supplements.[39] A beverage containing a low concentration of flavonols failed to induce changes in skin sensitivity to UVR after the same light source exposure.

OTHER NATURAL COMPOUNDS

Polypodium leucotomos

Native Americans have long believed that the tropical fern *Polypodium leucotomos* (PL) has antitumoral and anti-inflammatory effects.[74] Both in vivo and in vitro studies have shown that PL extract can prevent acute sunburn and minimize photoaging parameters, including immediate pigment darkening, minimal erythema dose, minimal melanogenic dose, and minimal phototoxic dose by solar radiation.[75,76] The photoprotective activity of PL involves a combination of antioxidant, photoprotective, and photoimmunoprotective effects. Some suggested mechanisms include preventing inflammation[77] and ROS formation,[78] inhibiting UV-induced photoisomerization of trans-urocanic acid,[79] decreasing UV-induced mast cell infiltration of the skin, reducing the loss of epidermal Langerhans cells,[80,81] suppressing the induction of TNF-α expression and production of NO, and preventing apoptosis in human keratinocytes and fibroblasts after UV light exposure.[82,83]

In a study of 26 patients with idiopathic photodermatoses, Caccialanza et al[84] reported improvement in 49% of patients who took PL 480 mg/d for 2 weeks. No adverse reactions were reported in the study patients. Capote et al[79] described the beneficial effects of PL in preventing acute psoralen and UVA-induced phototoxic skin reactions in human subjects and in minimizing photoaging changes in mice. Middelkamp-Hup et al[81] demonstrated that oral administration of 2 doses of PL led to decreases in DNA damage, erythema, sunburn cells, UV-induced epidermal hyperproliferation, and mast cell infiltration in human skin.

Vitamin D

Vitamin D is produced in skin by UVB radiation (290–320 nm) acting on 7-dehydrocholesterol.[85] The photoprotective effect of $1,25(OH)_2D_3$ has been shown both in vitro and in vivo. Gupta et al[85] showed that the UVR-induced production of cyclobutane pyrimidine dimers are reduced after $1,25(OH)_2D_3$ treatment and proposed a novel mechanism involving the enhanced elevation of nuclear p53 post-UVR and the suppression of the NO pathway. They also demonstrated that an increase in cell survival and a reduction in DNA damage were observed in the skin of UV-radiated hairless mice after topical treatment with $1,25(OH)_2D_3$. Lee et al[86] demonstrated that although irradiated cultured human keratinocytes could not survive in the presence of UVB, cell survival was noted in the presence of $1,25(OH)_2D_3$. Immunohistochemical staining revealed that $1,25(OH)_2D_3$ induced the expression of metallothionein, a potent radical scavenger. It was found that $1,25(OH)_2D_3$ did not inhibit peroxidation of plasma lipids, interact with superoxide, or remove hydrogen peroxide. UVB-induced photodamage of human epidermal keratinocytes was significantly decreased with the pretreatment of vitamin D_3 when the cells were irradiated with 30 to 40 mJ/cm^2 of UVB. At a higher UVB dose (ie, 50 mJ/cm^2), human epidermal keratinocyte viability was decreased regardless of $1,25(OH)_2D_3$ concentrations. Therefore, $1,25(OH)_2D_3$ exerted its photoprotective effect against a moderate range of UVB irradiation by induction of metallothionein and its capacity to prevent ROS-related damage.[86]

Excessive avoidance of sun exposure, age-related decreases in cutaneous synthesis, and inadequate low levels of dietary intake can result in vitamin D deficiency. The skin is the only site where vitamin D is synthesized and therefore plays a central role in obtaining sufficient vitamin D.[87,88] It is important to recognize that all of the beneficial effects of UVR exposure do not occur only through UVR-induced vitamin D synthesis. This understanding has led researchers to reconsider current sun-avoidance policies. Also, supplementing food with vitamin D may not be sufficient to avoid the risks of inadequate exposure to UVR.[89]

Caffeine

Caffeine is a xanthine alkaloid compound that acts as a psychoactive stimulant in humans and has been shown to prevent UVB-induced skin cancer.[90] Treatment with topical caffeine has been reported in animal model studies to significantly diminish nonmalignant and malignant tumors by 44% and 72%, respectively. The proposed mechanism of tumorogenesis inhibition is through the induction of apoptosis. One possible mediator of this effect is ataxia-telangiectasia and Rad3 related, which belongs to a family of large protein kinases that are related in sequence to phosphatidylinositol kinase and are involved in sensing various cellular stresses, including UV DNA damage, and in halting replication so that the cell has time to repair its DNA.[90] Koo et al[90] found

TABLE 1

Comparison of Phytochemicals

Compound Tested	Subjects	Exposure	Results	Author
Garlic extract, lyophilized powder (0.1%, 1%, 4%)	Hairless mice	UVB (to 58% systemic contact hypersensitivity suppression in control mice).	Dose-responsive protection. Hypersensitivity suppression was 19% in mice fed 4% garlic extract	Reeve et al[37]
Carotenes				
β-Carotene, dietary	Humans (N=36, 12 men and 24 women)	UVB	Erythema response to UVB was significantly lower at 6 weeks ($P<.05$) and 12 weeks ($P<.001$) compared to baseline and control	Heinrich et al[38]
Lycopene, topical	Female SKH-1 mice	UVB	Dose-dependent inhibition of UVB-induced ODC, ($P<.05$), MPO ($P<.05$), and bifold skin thickness ($P<.05$)	Fazekas et al[45]
Lutein/ zeaxanthin, dietary	Hairless mice	UVB exposure	Decreased UVB-induced epidermal hyperproliferation and acute inflammation	González et al[52]
Phenolics				
Green tea (EGCG)	In vitro keratinocytes and fibroblasts	UVB, UVA exposure	Reduction of keratinocyte and fibroblast apoptosis	Bi et al[59]
Grape seed extract	Mice	UVB exposure	Suppression of UV-induced production of DNA photo-products, ROS, and immuno-suppressive cytokines such as IL-10. Inhibited depletion of endogenous antioxidant enzymes, including glutathione peroxidase and catalase	Katiyar[69]
Cocoa (flavonols, epicatechin and catechin), dietary	Humans (N=24 females)	UV radiation (solar light simulator)	Reduction in erythema by 25% after 12 weeks compared to baseline	Heinrich et al[73]

Abbreviations: EGCG, epigallocatechin-3-gallate; IL, interleukin; MPO, myeloperoxidase; ODC, ornithine decarboxylase; ROS, reactive oxygen species.

that topical application of caffeine after UVB exposure diminished cumulative photodamage as assessed visually by treatment-blinded investigators and was associated with histologic changes, including a marked increase in the fraction of DNA-damaged keratinocytes deleted after UVB exposure. Some consumer products, such as soaps, are marketed with the inclusion of caffeine in their formulations. However, almost no data have been published on the effects of the topical application of caffeine on human skin.

Caffeine is generally well tolerated and relatively safe topically and systemically.

Probiotics

Probiotics are defined as live microorganisms that, when administered in adequate amounts, confer a health

TABLE 2

Comparison of Natural Compounds

Compound Tested	Subjects	Exposure	Results	Reference
Polypodium leucotomos, 480 mg/d orally for 2 wk	Human subjects (N=26) with idiopathic photodermatoses	Normal sunlight	Improvement of photodermatoses in 49% of patients; normalization of photodermatoses in 31% of patients	Caccialanza et al[84]
Vitamin D	In vitro keratinocytes	UVB	Improved keratinocyte cell survival after UVB exposure; effect attributed to induction of MT, a potent free radical scavenger	Lee et al[86]
Caffeine, topical	SKH-1 hairless mice	UVB	Diminished cumulative photodamage as assessed visually by treatment-blinded investigators. Histologically showed marked increase in the deletion of DNA-damaged keratinocytes after UVB	Koo et al[90]
Probiotics (lactic acid bacteria)	Humans (N=17)	UVB	Probiotic creams increased lipid ceramide levels in the stratum corneum, improving the skin's lipid barrier and helping to resist xerosis, scaling, and pruritus	Di Marzio et al[92]

Abbreviation: MT, metallothionein.

benefit on the host. Strains of the genera *Lactobacillus* and *Bifidobacterium* are the most widely used probiotic bacteria. Probiotics are most commonly administered orally, with the goal of maintaining healthy gut flora by populating the gut with symbiotic bacterial species. This may be necessary after antibiotic therapy, excess alcohol ingestion, disease, or exposure to toxic substances. Orally ingested Lactobacilli have been shown to protect against UVR-induced cutaneous immunosuppression in mouse models through protection against the suppression of contact hypersensitivity, decreased epidermal Langerhans cell density, and increased IL-10 serum levels, which may assist in reducing the development of skin tumors.[91] Although no similar human studies have been published, the use of probiotics offers a promising new direction in sun protection that should attract future research.

SUMMARY

Photoprotection is a leading preventive health strategy used by physicians involved in skin care. Considerable interest has been generated recently concerning the use of natural compounds as complementary measures to other sun protection approaches. Systemic endogenous compounds have been demonstrated to be important adjunctive tools against UV effects. In vitro and in vivo animal and human studies suggest that many natural compounds are photoprotective in nature and may be valuable pharmacologic agents in the prevention of solar UVB light–induced skin disorders, including photoaging and melanoma and nonmelanoma skin cancers. However, these natural compounds do not replace clothing and sunscreen but rather act as adjunctive tools against UV effects. The results of different studies performed on animals and humans are summarized in Tables 1 and 2. More clinical trials in humans are needed to determine the safety and efficacy of these promising compounds. The studies presented in this article confirm the utility of natural compounds as photoprotectants but also highlight the importance of combining them with known sunscreens and appropriate clothing to maximize photoprotection.

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