



What's New in Photoprotection

A Review of New Concepts and Controversies

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KEYWORDS

- Photoprotection • Photoaging • Photocarcinogenesis • Sunscreen • UV filters • Photolyases
- Antioxidants

KEY POINTS

- Recent advances, including the discovery of delayed production of cyclobutane pyrimidine dimers and biologic effects of visible light, have resulted in a more thorough understanding of the mechanisms of photodamage.
- Systemic and topical photoprotective agents, including antioxidants and photolyases, may provide additional protection against both cumulative UV radiation and visible light-induced photodamage.
- Although data are still evolving, the safety and environmental impact of organic/chemical UV filters has been questioned recently.
- Dermatologists play a pivotal role in educating patients and the public on photoprotective strategies.

INTRODUCTION

Cumulative UV radiation (UVR) exposure plays a critical role in photoaging, immunosuppression, photocarcinogenesis and the exacerbation of photodermatoses. UV-A (320–400 nm) penetrates into the dermis and damages DNA by producing reactive oxygen species.^{1,2} It is the major contributor to photoaging. UV-B (290–320 nm), in contrast, is responsible for sunburns it directly damages DNA by the formation of 6-4 cyclobutane pyrimidine dimers (CPDs) and pyrimidine (6-4)pyrimidone photoproducts.² Both UV-A and UV-B exposure increase the risk of basal cell carcinoma, squamous cell carcinoma, and melanoma. According to the Skin Cancer Foundation, 90% of

nonmelanoma skin cancers and 86% of melanomas are related to sun exposure and UVR.²

As a result, photoprotection is one of the most important preventative health strategies, with dermatologists playing a critical role in advising patients to implement protective measures. Photoprotection includes behavioral modifications, such as seeking shade when outdoors and wearing protective clothing, wide-brimmed hats, and sunglasses. The use of sunscreens and other products to prevent or counteract the damaging effects of UVR are also critical. Despite what is known regarding the danger of cumulative UVR exposure, adoption of these practices is not undertaken regularly by a large proportion of patients. Various obstacles exist, including

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lifestyle preferences and common misconceptions regarding sun protective practices. Sunscreens, which are an integral component in all photoprotective regimens, have been questioned recently in terms of their safety for users and their environmental impact. The aim of this article is to provide an overview of new concepts in photoprotection and also address current controversies pertaining to sunscreens.

NEW CONCEPTS IN PHOTOPROTECTION

Dark Cyclobutane Pyrimidine Dimers Formation

Melanin has traditionally been thought to be protective against UVR-induced DNA damage and skin cancer development. However, it has been recently found that, in a murine model, melanin may also be carcinogenic by contributing to the formation of CPDs, even after the completion of UV-A radiation. When melanin is exposed to UV-A, it induces superoxide and nitric oxide production, which causes degradation of melanin and excitation of melanin derivatives into their high-energy state.³ It is postulated that these high-energy melanin derivatives transfer their energy to DNA, creating mutagenic CPDs hours after UV-A exposure. These CPDs that arise hours after UV exposure are referred to as delayed or “dark” CPDs. It was further shown that pheomelanin was a more potent generator of dark CPD formation than eumelanin. Although this study has not been extended to humans, it should be noted that pheomelanin is the predominant melanin in fair skinned individuals, the very skin phototype that is more prone to photocarcinogenesis.³

One of the benefits of the delayed formation of CPDs for up to 3 hours after UV exposure, should this occur in humans, is the opportunity for intervention during this time. A goal of future studies may be to develop products to apply after sun exposure that protect the skin. For example, *in vitro*, the antioxidant vitamin E has been shown to block the formation of light and dark CPDs in keratinocytes when added either before or after UV-A1 exposure.⁴

Photolyases in Sunscreens

Photolyases are enzymes that have the property of repairing CPDs. They are naturally occurring enzymes in bacteria, plants, and animals that experience high UV exposure; these enzymes are absent in humans and other placental mammals.⁵ They repair DNA in the presence of flavonoids, which act as UV chromophores. After absorbing UV photons, flavonoids transfer excited electrons to the damaged DNA segments (ie, CPDs), causing

them to convert to their nucleotide monomers in preparation for their repair by photolyases.⁵

Both *in vitro* and *in vivo* studies have supported the beneficial properties of photolyases in preventing photodamage.^{6–8} All human studies were done with sunscreen containing chemical (ie, organic) UV filters, with photolyases encapsulated in liposomes to enhance their penetration through stratum corneum. In another study, the efficacy of sun protection factor (SPF) 50 sunscreen, with or without antioxidants (carnosine, arazine, ergothioneine) and/or photolyases in reducing CPD formation was evaluated. It was found that the combined presence of topical antioxidants and photolyases resulted in the greatest reduction in CPDs and free radical-induced protein damage compared with the sunscreen that contained either ingredient alone,⁹ suggesting that antioxidants and photolyases might have a synergistic effects.⁹ In patients being treated with photodynamic therapy for actinic keratoses, treatment with sunscreen containing topical photolyases resulted in longer remission times.^{10,11} The use of photolyase-containing sunscreen in patients with xeroderma pigmentosum resulted in a lower incidence of new actinic keratoses, basal cell carcinomas, and squamous cell carcinomas at 1 year compared with sunscreen alone.¹² It should be noted that photolyase-containing sunscreen available in the United States at the time of writing has zinc oxide as the sole UV filter, whereas these studies were done with a product containing chemical filters.

Role of Visible Light

Historically, the focus of many photoprotection studies was on the effects of UV light. Recently, the visible light spectrum, which includes the wavelengths between 400 and 700 nm, has been found to induce skin pigmentation. UV-B-induced hyperpigmentation is attributed, in part, to increased p53 expression inducing melanogenesis. Interestingly, when compared with UV-B radiation, blue-violet light (part of the visible light spectrum) has not been found to increase p53 expression.¹³ The mechanism of visible light-induced pigmentation and melanogenesis is still being actively investigated.

A study of 22 patients found that, when exposed to visible light, patients with skin types IV to VI developed darker and more sustained pigmentation compared with subjects exposed to pure UV-A1. In addition, visible light-induced pigmentation was observed up to 2 weeks after the radiation, a time point when UV-A1-induced pigmentation had resolved. These pigmentation

effects were not observed in lighter skin patients of skin type II.¹⁴ Histologic specimens in this study found that visible light-induced migration of melanin from the basal layer to the upper layers in the epidermis. This finding could explain the sustained effect of pigmentation for up to 2 weeks after visible light exposure. Visible light-induced pigmentation was irradiance dependent. Furthermore, exposure to a light source emitting visible light and a small amount of UV-A1 (0.5%) resulted in more intense pigmentation compared with exposure to pure visible light.¹⁵

These findings support the concept that visible light may have a role in conditions aggravated by sun exposure, such as postinflammatory hyperpigmentation and melasma, especially in darker skinned individuals. This finding is of great significance because the visible spectrum compromises 38.9% of sunlight that reaches the surface of the earth.¹⁴ Currently available chemical (ie, organic) UV filters are not sufficient to protect the skin from the effects of visible light (Table 1). Similarly, current sunscreens do not provide adequate protection for the UV-A1 spectrum, which acts synergistically with visible light.¹⁵ Although nonmicronized form of zinc oxide or titanium dioxide would physically block visible light transmission, the chalky white appearance of these agents make them aesthetically not acceptable to users. Similar to exposure to UVR, visible light exposure generates reactive oxygen species; therefore, it is possible that antioxidants could play a role in decreasing these pigmentary alterations.¹⁶

Vitamin D and Sunburn

UV-B is responsible for the conversion of epidermal 7-dehydrocholesterol into active vitamin D₃ (cholecalciferol), which has been found to have various immunomodulatory effects. Prior in vitro and animal studies have proven that vitamin D enhances antimicrobial responses, suppresses proinflammatory mediators, and diminishes inflammation after skin injury.¹⁷ Recently, a pilot study of human subjects displayed that high doses of oral vitamin D₃ (cholecalciferol) are beneficial in attenuating the sunburn response. Twenty patients were randomized to receive either placebo or high doses of oral vitamin D₃ 1 hour after being exposed to 3 minimal erythema doses of simulator solar radiation. Compared with the placebo group, subjects who received 200,000 IU of vitamin D₃ had a sustained decrease in skin redness after the experimental sunburn with less epidermal damage noted on skin biopsies. These subjects also had a decreased release of

Table 1
Current 17 active sunscreen ingredients approved by the US Food and Drug Administration and their range of protection

Active Ingredient/UV ^a Filter Name	Range of Protection
Organic (chemical) UV filters	
UV-A filters	
Avobenzone	UV-A1
Ecamsule (Mexoryl SX) ^a	UV-A2
Meradimate (menthyl anthranilate)	UV-A2
UV-B filters	
Aminobenzoic acid	UV-B
Cinoxate	UV-B
Ensulizole (phenylbenzimidazole sulfonic acid)	UV-B
Homosalate	UV-B
Octocrylene	UV-B
Octinoxate (octyl methoxycinnamate)	UV-B
Octisalate (octyl salicylate)	UV-B
Padimate	UV-B
Trolamine	UV-B
UV-A and UV-B filters	
Dioxybenzone	UV-A2, UV-B
Oxybenzone	UV-A2, UV-B
Sulisobenzene	UV-A2, UV-B
Inorganic (physical) UV filters	
Titanium dioxide	UV-A2, UV-B
Zinc oxide	UV-A1, UV-A2, UV-B

^a Approved through New Drug Application process.

proinflammatory mediators of tumor necrosis factor-alpha and nitric oxide synthase. This finding was attributed to the upregulation of gene expression in the skin of arginase-1, which is antiinflammatory.¹⁷ Larger clinical trials are needed to support the findings of this proof-of-concept study.

Nontopical Forms of Photoprotection

Other nontopical forms of sun protection have also been gaining interest recently to provide additional protection against UVR exposure. Sunscreens with organic and inorganic UV filters do not protect against visible light. Systemic photoprotective agents may be beneficial for these reasons.

Several studies have shown that oral and a subcutaneously administered agent have been shown to be effective in reducing photodamage, but larger studies are still needed to confirm their efficacy (Table 2).

Polypodium leucotomos extract is derived from a fern plant that is native in Central and South America. It has been shown to have antioxidative and antiinflammatory properties. As an antioxidant, *P leucotomos* extract decreases lipid peroxides and neutralizes superoxide anions and hydroxyl radicals after UV exposure.¹⁸ Its antiinflammatory properties are attributed to reduced UV-induced cyclooxygenase-2 expression, p53 suppressor gene mutations, and formation of CPDs and inflammatory infiltrate in animal models.¹⁸

Human studies have shown that *P leucotomos* extract increases the UV dose required for immediate pigment darkening, minimal erythema dose, and minimal phototoxic dose.^{19,20} It is protective against UV-B and psoralen plus UV-A-induced phototoxicity.²¹ It has also been found to be beneficial in preventing polymorphous light eruption, solar urticarial, and other photodermatoses.²² Current studies are being performed to assess its efficacy in protecting against visible light-induced delayed tanning and persistent pigment

darkening. A review of both human and basic science studies found no significant adverse effects of oral *P leucotomos* extract.²³

Nicotinamide is the active amide form of vitamin B₃ (niacin; nicotinic acid) and is a cofactor for adenosine triphosphate, which is essential in DNA repair in the skin.²⁴ It is safe and widely available over the counter. Unlike niacin, it does not cause a flushing reaction. UVR typically inhibits adenosine triphosphate production and prevents optimal skin immune response and DNA repair. This pathway is ultimately responsible for photocarcinogenesis. In human keratinocytes, nicotinamide blocks the inhibitory effect of UV on adenosine triphosphate production, enhances DNA repair, and decreases the formation of CPDs.²⁴ In a phase II clinical trial, subjects with sun-damaged skin who took 500 mg once or twice daily had 29% and 35%, respectively, fewer actinic keratoses at 4 months.²⁵ A phase III trial demonstrated that nicotinamide might be beneficial as chemoprevention in subjects with a history of 2 or more nonmelanoma skin cancers. Subjects who received nicotinamide 500 mg twice daily had 23% lower rates of new nonmelanoma skin cancers and 11% fewer actinic keratosis compared with placebo at 12 months.²⁶ Notably, consistent with the proposed mechanism of action of

Table 2
Nontopical forms of photoprotection

Product	Source	Mechanism	Clinical Uses
<i>Polypodium leucotomos</i> extract	Tropical fern	Neutralization of superoxide anions, lipid peroxides and hydroxyl radicals Reduced cyclooxygenase-2 expression, p53 suppressor gene mutations, cyclobutane pyrimidine dimers, sunburn cells, and inflammatory infiltrate	Reducing immediate pigment darkening Increasing minimal erythema dose and minimal phototoxic dose Preventing polymorphous light eruption and other photodermatoses
Nicotinamide	Active form of vitamin B ₃ (niacin)	Prevent UVR-induced intracellular depletion of adenosine triphosphate Boosts cellular energy and enhances DNA repair	Chemoprevention of actinic keratosis and nonmelanoma skin cancers
Afamelanotide	Analogue of alpha-melanocyte-stimulating hormone	Stimulates eumelanin production in the epidermis without UV-induced cellular damage Results in eumelanin that absorbs UV light, reduces free radicals and reactive oxygen species	Photoprotective in patients with erythropoietic protoporphyria Possible role in polymorphous light eruption, actinic keratosis in organ transplant patients and solar urticaria

Abbreviations: UVR, UV radiation.

preventing UV-induced suppression of adenosine triphosphate production, this response is not sustained once nicotinamide is discontinued.

Afamelanotide is a structural analogue of alpha-melanocyte-stimulating hormone and acts as an agonist of melanocortin-1 receptor. It promotes the synthesis of melanin (eumelanin) without the UV-induced cellular damage that occurs with UV exposure.²⁷ It has been found to be photoprotective in patients with erythropoietic protoporphyria and solar urticaria by stimulating melanogenesis and acting as an antioxidant.^{28,29} In phase II and phase III trials in Europe and the United States, patients with erythropoietic protoporphyria were administered 16 mg subcutaneously every 60 days; they had an improved quality of life and longer pain-free periods after sun exposure.³⁰ In combination with narrowband UV-B phototherapy, it has also been demonstrated to accelerate repigmentation in vitiligo.²⁷

CONTROVERSIES ON SUNSCREENS

UV Blocked Versus Transmitted

SPF is a well-known term used to communicate how effective a sunscreen is in protecting against erythema-induced radiation (EIR). An incorrect misconception made by many is generalizing that SPF 30 provides only minimal additional protection.^{31,32} This misconception might stem from the way that SPF is commonly presented as percent of EIR absorbed and not percent of EIR transmitted. This approach is misleading because only photons that are transmitted are absorbed and have biologic effects. For example, when comparing percent absorbed of SPF 30 with SPF 60, it is 96.7% EIR absorbed compared with 98.3% EIR absorbed. However, if comparing the number of photons transmitted when exposed to 60 photons, SPF 30 allows 2 photons to be transmitted, and SPF 60, 1 photon.

Notice that the photons transmitted are halved despite the seemingly small difference in the percent of EIR absorbed (**Table 3**).

A recent survey found that, when sunscreen SPF is presented as percent of EIR absorbed compared with percent transmitted, dermatologists underestimated the increased protection provided by the higher SPF sunscreen.³³ It is photobiologically and clinically more relevant to assess the amount of UV photons transmitted, especially in the setting of chronic sun exposure. Higher SPF sunscreens are more beneficial for long-term cumulative photoprotection.

Safety of Oxybenzone and Other Sunscreen Active Ingredients

Oxybenzone (benzophenone-3) is a widely used broad-spectrum organic filter that is protective against UV-B and UV-A2 (see **Table 1**).³⁴ In a 2018 report, it was estimated to be in two-thirds of nonmineral sunscreens in the United States.³⁴ However, concerns have been raised about its photoallergic potential, systemic absorption, endocrine side effects, and environmental impact.³⁵

In 2014, benzophenones were named the American Contact Dermatitis Society's Contact Allergen of the Year. Of all the UV filters, it is the most common cause of photoallergy and contact allergy reactions.³⁶ In a large 10-year retrospective study, a review of the patients who listed an allergy to sunscreen found that 70.2% had a positive patch test reaction to oxybenzone.³⁶ In the European Union, oxybenzone has been largely replaced with other broad-spectrum UV filters. Unfortunately, this replacement cannot be easily done in the United States because many of those filters are not yet approved by the US Food and Drug Administration to be used in the United States.

Table 3
Comparison of 2 different ways to display SPF protection: percent transmitted versus percent absorbed

	% EIR Transmitted	% EIR Absorbed
SPF 1	100% transmitted × 60 photons = 60 photons transmitted	0% absorbed × 60 photons = 0 photons absorbed
SPF 15	6.7% transmitted × 60 photons = 4.02 photons transmitted	93.3% absorbed × 60 photons = 55.98 photons absorbed
SPF 30	3.3% transmitted × 60 photons = 1.98 photons transmitted	96.7% absorbed × 60 photons = 58.02 photons absorbed
SPF 60	1.7% transmitted × 60 photons = 1.02 photons transmitted	98.3% absorbed × 60 photons = 58.98 photons absorbed

Abbreviations: EIR, erythema-induced radiation; SPF, sun protection factor.

Studies have found that when SPF data are presented as %EIR absorbed, their protective effects are underestimated.

In addition, oxybenzone has been found to have endocrinologic effects in fish and rats.^{37–39} In fish it has been shown to have antiandrogenic and anti-estrogenic effects. Chronic exposure to oxybenzone in fish resulted in decreased egg production and egg hatchings. In rats, a dose-dependent estrogenic effect was observed when these animals were given high doses of oxybenzone (≥ 1500 mg/kg/d) in their drinking water.³⁹ In humans, it has been estimated that, if one applies sunscreen at 2 mg/cm^2 , which is the dose used for SPF testing, to 100% of their body surface, it would take almost 35 years of daily application to achieve the serum levels detected in rats used in that study.⁴⁰ Short-term studies that evaluated topical application of UV filters including oxybenzone in humans found that there were no significant UV filter-related alterations in endocrinologic, reproductive, or thyroid function.^{40,41} It should also be emphasized

that although oxybenzone has been in use in the United States since 1978, no adverse systemic effects have been reported in humans.

There are also concerns regarding the potential for many UV filters to damaging marine environments; these filters include oxybenzone, octocrylene, octinoxate, and ethyl hexyl salicylate.³⁵ In vitro, oxybenzone has shown to cause bleaching of coral reefs, inducing ossification and deforming DNA in the larval stage.⁴² A study measuring the concentrations of oxybenzone in seawater in various locations, including Hawaii and the US Virgin Islands, found varying detectable levels from $0.8 \text{ }\mu\text{g/L}$ to 1.4 mg/L . This study also reported that the coral cell median lethal concentration of oxybenzone for 7 different coral species ranges from 8 to $340 \text{ }\mu\text{g/L}$ over 4 hours of exposure.⁴² These concerns have led to Hawaii to pass a legislative bill that prohibits the sale

Table 4
Additional topical antioxidant agents

Antioxidant	Function and Use
Soy (<i>Glycine soja</i>) extract	Genistein phytoestrogen compound in soy causes dose-dependent UV-induced DNA damage and pyrimidine dimer formation. ⁴⁸
Vitamin C (L-ascorbic acid)	Topical concentrations of at least 10% are photoprotective, reducing erythema and immunosuppression. Protects from UV-B and UV-A-induced erythema and sunburn cell formation. ⁴⁹
Vitamin E (tocopherols and tocotrienols)	Protects against UV-induced lipid peroxidation, UV-induced photoaging, immunosuppression and photocarcinogenesis. Inhibits UV-induced CPD formation and inhibits melanogenesis. ⁴⁹
Grape seed extract (<i>Vitis vinifera</i>)	Inhibition of UV-mediated edema and inflammation. Inhibits inflammatory mediation cyclooxygenase-2, reduces hydrogen peroxide and causes decrease lipid peroxidation. Rapid metabolism makes it challenging for topical use unless encapsulated in lipid nanoparticles. ⁵⁰
Tea polyphenols	Epigallocatechin-3-gallate inhibits UV-B-induced release of hydrogen peroxide, and prevents phosphorylation of mitogen-activated protein kinase. ⁵¹ Reduces inflammation through nuclear factor kappa B pathway. Dose dependent inhibitor of UVR-induced erythema. ⁵¹
Selenium	Protects against UV-induced DNA oxidation, IL-10 expression and lipid peroxidation. Protects against UV-induced erythema and skin cancer in mice. In humans, caused a dose-dependent increase in minimal erythema dose. ⁴⁹
Melatonin	Protects against UV-induced erythema, decreased production of reactive oxygen species, enhanced p53 expression, improved DNA repair and decreased CPD generation. ⁴⁹
Algae extract	Stimulates proteasome peptidase activity in irradiated human keratinocytes, reducing the extent of protein oxidative damage. ⁵²
Silymarin milk thistle (<i>Silybum marianum</i>)	Enhances repair of UV-B-induced DNA damage through the nucleotide excision repair pathway. Accelerates DNA repair in human dermal fibroblasts after UV-B irradiation through a p53-dependent repair pathway. ⁵³
Aloe vera leaf extracts	Reduces UV-A-induced redox imbalance, decrease UV-A-associated lipid membrane oxidation and increase overall cell survival. ⁵⁴

Abbreviations: CPD, cyclobutane pyrimidine dimers; UVR, UV radiation.

and distribution of oxybenzone and octinoxate. The bill was signed into law by the governor on July 3, 2018, and will take effect in January 2021.

Nanoparticle Free Radical Damage to the Skin

The safety of broad-spectrum inorganic UV filters or physical sunscreens, titanium dioxide, and zinc oxide has also been questioned. Titanium oxide and zinc oxide are formulated as nanosized products that blend more easily into the skin. When exposed to UV light *in vitro*, titanium oxide and zinc oxide emit electrons and generate free radicals and reactive oxygen species.⁴³ The major concern is that, when exposed to UVR, these nanoparticles may have the potential to damage proteins, lipids, and DNA. It should be noted that all nanoparticles used in sunscreens are coated (usually with silica), greatly limiting the amount of free radicals that are released into the microenvironment. Furthermore, many studies have found that these nanoparticles do not penetrate through intact healthy skin and are mostly limited to the stratum corneum.⁴⁴ One recent study using porcine skin found that UV-B-damaged skin slightly enhanced both titanium and zinc oxide penetration into the epidermis but no transdermal or systemic absorption was seen.⁴⁴ Additionally, toxicity studies of titanium oxide and zinc oxide nanoparticles used subcutaneous and intravenous administration and showed low general toxicity.⁴⁵

Antioxidants in Sunscreen

Sunscreens containing topical antioxidants have been found to reduce the production of reactive oxygen species, cytokines, and matrix metalloproteinase-1 expression after irradiation by UV and visible light.¹⁶ Combining broad-spectrum sunscreen with antioxidants has been found to be superior to just sunscreen alone in suppressing UV-induced pigmentation, depletion of Langerhan cells, and induction of matrix metalloproteinases.^{46,47} However, topical antioxidants are limited by their diffusion into the epidermis and their stability. Incorporation of stabilized antioxidants into sunscreens has gained popularity recently among pharmaceutical and cosmeceutical companies (Table 4).^{48–54}

SUMMARY

Recent advances in photomedicine, including the discovery of delayed production of CPDs and biologic effects of visible light, have resulted in a more thorough understanding of the mechanisms of photodamage. These discoveries open the

door for additional therapeutic options, including systemic photoprotective agents and additional topical agents including antioxidants and photolyases. Proper education of the public should continue to be done on photoprotection, which includes seeking shade when outdoors, wearing photoprotective clothing, wide brimmed hats and sunglasses and applying broad spectrum, with an SPF 30 or greater sunscreen. Although data are still evolving, for those who are concerned about the environmental impact of organic/chemical UV filters, sunscreens with inorganic/physical filters can be used.

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