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# The latest on skin photoprotection

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**Abstract** UV radiation is the main etiological agent of most types of skin cancer and a key factor responsible for photoaging. Photoprotection is thus critical to avoid these undesired effects. Sunscreens rank among the best photoprotective measures. Sunscreens are the main components of lotions and creams used to prevent UV-induced damage or to ameliorate its harmful effects. There are 3 types of sunscreens: physical photon blockers, antioxidants, and stimulators of repairing mechanisms. This review summarizes current topics in the development of sunscreens, with special emphasis on substances of natural origin bearing photoscreening, antioxidant, or repairing properties. The characterization of different parameters to evaluate the effects of sunscreens, such as the sunscreen protection factor, is discussed. Finally, the effect of public awareness and public health campaigns are also reviewed.


## Introduction

Earth is constantly irradiated by light photons coming from the sun; 56% are infrared light photons (wavelength, 780-5000 nm), 39% visible light (400-780 nm), and 5% UV light (290-400 nm). UV radiation is absorbed by different chromophores in the skin, such as melanin, DNA, RNA, proteins, lipids, water, aromatic amino acids, such as tyrosine and tryptophan; *trans*-urocanic acid; etc. Absorption of UV photons by these chromophores results in different photochemical reactions and secondary interactions involving reactive oxygen species (ROS), which result in harmful effects.[1] DNA is the main target of UV light. Pyrimidines in particular are subject to different photochemical modifications forming cyclobutane dimers, hydration products, adducts, and other photoproducts that are repaired by specific enzymes.[2] Mutations can be transmitted to the cell progeny after mitosis, especially upon alterations of the photoprotective mechanisms based on inhibition of replication, apoptosis, or cell death of the mutation carriers.

Photoprotection is an essential prophylactic and therapeutic element. The development of photoprotection has been stimulated by a change in the behavioral habits of human society. In addition, self-image has become particularly important in modern society, which has bolstered interest in fighting the effects of aging, particularly photoaging. Finally, biological research has unveiled the deleterious effects of these environmental factors on the skin. In this regard, skin oncology research has highlighted UV light as the one of the main etiological factors in the development of skin cancer.[3,4]

In addition, UV light has a profound effect on the eyes. Every year, approximately, 3 million people lose their sight because of UV-related damage such as cataracts, which underlines the need to incorporate photoprotective measures for the care of the eyes.[5]

In conclusion, it is crucial to avoid exposure to harmful UV light, which suggests the use of photoprotective measures, such as limiting the exposure to sunlight and the

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use of sunscreens and other products to prevent and/or counteract the damage induced by UV photons in the skin.

## Sun protection

### Clothing and glasses

Clothing and glasses are the most basic photoprotective tools. Fashion trends reduce their effectiveness. In 1998, the American Society of Photobiology published 2 articles in *ASP news* (1998; 27:11 and 1998; 27:4-5), titled "Solar UV and Health and "UV radiation and photoprotection," respectively. They underlined the importance of the use of appropriate clothing and hat as photoprotective tools. Likewise, the American Academy of Dermatology recommends the use of appropriate clothing and sunglasses if exposure has to be prolonged.

Clothing photoprotective capability depends on thickness, color (dark colors protect more efficiently), and weight. It is also influenced by moisture and tightness. Lately, photoprotective fabrics have been commercialized, of particular interest for outdoors workers and sports practitioners. Hats are particularly useful to protect the scalp, forehead, and neck, whereas gloves are useful preventing the appearance of photoaging signs on the hands.[6]

Regarding sunglasses, it is essential to note their UVA screening capability. Acute injury in the eye presents similar features to those on the skin and includes photoconjunctivitis ("pinkeye"), solar keratitis, and in severe cases, transient loss of vision.[5,7] Chronic exposure, on the other hand, may result in cataracts and macular degeneration,[3,4] the leading causes of loss of vision, but the risk is significantly decreased upon the use of adequate photoprotective measures. The Food and Drug Administration has defined parameters for sunglasses: permissiveness must be less than 0.001 % for wavelengths between 200 and 320 nm and less than 0.01% for wavelengths between 320 and 400 nm. Recently, therapeutic sunglasses provide protection against UV and blue light. Coloring must be dark enough to prevent dazzling but must not affect color and contrast perception.[8]

### Sunscreens

Sunscreen products are primarily designed to protect the skin from the harmful effects of solar UV radiation. They contain molecules or molecular complexes that can absorb, reflect, or scatter UV photons. These are shielding sunscreens. In addition, new sunscreen substances have been recently developed that prevent, ameliorate, or even repair solar-induced skin damage.

Shielding sunscreens are most efficient in protecting from solar erythema and sunburn caused by high-energy UV photons, but their efficacy in preventing photoaging depends on their ability to block low-energy UV light. In this regard, sunscreens that prevent local and systemic immunosupression are particularly useful to inhibit epidermal gene modifications like mutations on p53 gene, thymine dimers formation, and induction of apoptosis or to restore the levels of collagen production.[9-13]

Finally, sunscreens have to be safe not only for humans that apply them on exposed body parts but also for the environment, which indirectly receives them during disposal.

The following section presents an overview of the latest issues on sun protection; the focus is on its effects on aging of the skin.

#### Systemic photoprotection

Recently, several oral sunscreens that provide full-body coverage have been commercialized. These products contain several active principles that enable different mechanisms to prevent cutaneous sun damage. Most of them possess antioxidant activities, which replenish the normal antioxidant capability of the body after systemic loss of endogenous antioxidants during UV exposure.[14,15] These products include the following:

***Carotenoids.*** Lycopene is the major carotenoid of tomatoes and is a very efficient singlet oxygen quencher. A significant decrease in sensitivity toward UV-induced erythema has been observed in healthy human volunteers after 10 to 12 weeks of lycopene administration.[16]

***Combination of antioxidants.***

1. Inclusion of *vitamins C and E* in photoprotective compounds increases significantly the photoprotective effects compared with monotherapies[17];
2. *Seresis* is an antioxidative combination containing physiological levels of lipid- and water-soluble compounds, including carotenoids (beta-carotene and lycopene), vitamins C and E, selenium, and proanthocyanidins. A clinical, randomized, double-blind, parallel-group, placebo-controlled study showed that Seresis slowed down the development of UVB-induced erythema and decreased UV-induced expression of matrix metalloproteinase (MMP)-1 and MMP-9.[18]

***Dietary botanicals.*** Dietary botanicals include dietary flavonoids and phenolics. Their photoprotective and anticarcinogenic properties are ascribed to their antioxidant and anti-inflammatory activities. Some of these are:

1. *Polypodium leucotomos extract:* A polyphenol-enriched natural extract from the leaves of the fern *P leucotomos*. It is the only botanical derived agent that has shown photoprotection on human skin after single doses. In this regard, at low dose (7.5 mg/kg), it exerts a photoprotective effect on human skin, reducing erythema, thymine dimers formation, and Langerhans

cell depletion.[19,20] Its beneficial effects include a high antioxidant capability, inhibition of *trans*-urocanic acid photoisomerization,[21] and in vivo and in vitro cellular photoprotection.[22-24] In addition, oral supplementation of *P leucotomos* also inhibited UV-induced cyclooxygenase 2 (COX-2) activation and accelerated photoproduct removal in the XPC+/− mice (unpublished data).

2. *Green tea polyphenols (GTPPs):* Epigallocatechin-3-gallate (EGCG) is the major photoprotective polyphenolic component of green tea. Oral administration prevents UVB-induced skin tumor in mice, which is mediated through the induction of immunoregulatory cytokine interleukin 12, the inhibition of UV-induced immunosuppression, and the inhibition of angiogenic factors and stimulation of cytotoxic T cells in a tumor microenvironment.[25] In addition, oral administration of GTPPs to mice remarkably inhibited UV-induced expression of skin MMPs, suggesting that GTPPs have a potential antiphotoaging effect.[26]

***Genistein.*** Genistein is a soybean isoflavone with potent antioxidant activity. It is also a specific inhibitor of protein tyrosine kinases and a phytoestrogen. It has been shown that orally supplemented genistein in mice inhibits UVB-induced skin carcinogenesis.[27]

***Omega-3 polyunsaturated fatty acid.*** Omega-3 polyunsaturated fatty acid has been recently reported to decrease UVB-induced sunburn and inflammation in a clinical trial; it also reduced UVA-dependent responses after 3 months of fish oil ingestion.[28] It is not widely used because of the relatively large amount of fish oil needed to get the desired effect.

In summary, oral sunscreens have been shown to prevent acute sun damage and some of the deleterious alterations associated to skin aging. Nevertheless, the efficacy of oral sunscreens to prevent photoaging in humans has not been assessed in long-term clinical trials.

## Topical Sunscreens

Topical sunscreens can repair preexisting damage and prevent further damage caused by exposure to ultraviolet radiation in animal models.[29] More recently, a large population study in Australia has provided evidence of the effectiveness of sunscreens (sunscreen protection factor [SPF] 15 or higher) to reduce the incidence of some squamous neoplasias,[30,31] but the risk of basal-cell carcinoma was not reduced.[32] Their efficiency in long-term clinical trials to prevent or diminish photoaging has not been convincingly shown. A randomized trial in humans showed that the use of SPF of 29 for 2 years inhibited photoaging compared with placebo group.[33] Thus, the ideal requirements for a topical sunscreen are the following:

1. Protection against UVB radiation.[34]
2. Protection against long-wavelength UVA radiation.[35]
3. Reactive oxygen species scavenging capability.
4. Inclusion of enzymes or active reagents that activate the cellular DNA repair systems.
5. Stability and safety of the filters.

High-SPF sunscreens always contain a physical filter and at least 2 organic filters: one with optimal screening for UVB wavelengths and the other for UVA photons. The 2 key questions are the persistence and photostability of such filters under UV irradiation.

***Organic or chemical filters.***

1. *UVB filters*:[36] They are the most effective, blocking 90% of UVB radiation. Cinnamates are the most frequently used, but they have poor substantivity and thus are usually combined with other agents. Encapsulation of ethylhexyl-*p*-methoxycinnamate into nanoparticles consisting of poly-D,L-lactide-co-glycolide resulted in decreased photodegradation.[37] Another study showed that glyceridic esters of octinoxate have more persistent photoprotective properties in vivo compared with the native molecule.[38] Salicylates are exceptionally stable, nonsensitizing, and water-insoluble, leading to high substantivity. They are also useful as solvents for other poorly soluble sunscreen ingredients, such as benzophenones. Trolamine salicylate is used as a photoprotective agent in hair cosmetics.[1]
2. *UVA filters:* Most commercially available sunscreens provide excellent protection against UVB, but not all of them are equally effective against UVA. On the other hand, most of the UVA filters absorb some of UVB radiation. Oxybenzone (Bp-3; Eusolex 4360) absorbs most efficiently in the UVB and UVA2 ranges (Table 1). It is very sensitive to oxidation. Avobenzone (Parsol 1789) is a dibenzoylmethane with high UV absorption (wavelengths up to 380 nm), but it is very unstable and can undergo photoisomerization to inert, nonphotoprotective compounds.[36]
3. *Dual UVB/UVA filters:* Some filters absorb both UVB and UVA radiations. For example, terephtalylidene dicamphor sulfonic acid (Mexoryl SX) possesses durable photostability and is frequently included in formulations with avobenzone and other UVB acceptors, constituting a broad-spectrum sunscreen. In humans, Meroxyl SX protects from UVA exposure and its deleterious effects including pigmentation, epidermal hyperplasia, decrease of skin hydration, and elasticity.[39,40] Drometrizol trisiloxane (Mexoryl XL) absorbs UVB and UVA2 radiation, and when combined with Mexoryl SX, its protective effect increases.[40] A clinically controlled study showed that a daily use cream containing a photostable combination of UVB and UVA absorbers (octocrylene, avobenzone, and Mexoryl SX) reduces UV-induced skin damage, demonstrating the benefit of daily

**Table 1** Main sunscreen ingredients

| Compound | Maximum concentration (%) | Absorption (nm) |
|---|---|---|
| UVB organic filters | | |
| PABA and derivatives | | |
| PABA (*p*-aminobezoic acid) | 5 | 283-289 |
| Octyldimethyl PABA (Padimate O) | 1, 4-8 | 290-310 |
| *p*-Amyldimethyl PABA (Padimate A) | 1-3 | |
| Ethyl 4[*bis*(hydroxyprolyl)] aminobenzoate [a] | 1-5 | 312 |
| Glyceryl PABA [a] | 2-3 | 297 |
| Cinnamates | | |
| Octinoxate (octyl methocycinnamate, Parsol MCX) | 7.5 | 311 |
| Cinoxate | 3 | 289 |
| Isopentil-4-metoxicinamato [a] | 8-10 | 288-290, 325 |
| Salicilates | | |
| Octisalate (octyl salicylate) | 5 | 307 |
| Homosalate | 15 | 306 |
| Trolamine salicylate | 12 | 260-355 |
| Others | | |
| Digalloyl trioleate [a] | 2-5 | |
| Octocrylene | 10 | 303 |
| Ensulizole (2-phenylbenzimidazole-sulfonic acid) | 4 | 310 |
| UVB and less UVA organic filters | | |
| Benzofenones | | |
| Dioxybenzone (benzophenone-8) | 3 | 288, 352 |
| Oxybenzone (benzophenone-3) | 6 | 288, 325 |
| Sulisobenzone (benzophenone-4) | 10 | 288, 366 |
| Anthralines | | |
| Meradimate (menthyl anthralinate) | 3.5-5 | 286, 335 |
| UVA organic filters | | |
| Butyl methoxydibenzoyl methane (Avobenzone) | 3 | 360 |
| 3-(4-metilbencilideno) alcanfor (Eusolex 6300) (only in Europe) | 4 | 345 |
| Terephtalylidene dicamphor sulfonic acid (Mexoryl SX, Mexoryl SX) | 10 | 345 |
| Broadband organic filters | | |
| Drometrizol-trisiloxano (Mexoryl XL) | 15 | 303, 344 |
| Bisethylhexyloxyphenol methoxyphenyl triazene (Tinosorb) | 10 | 303. 368 |
| Inorganic absorbers | | |
| $TiO_2$ | 25 | 400 (depending on particle size) |
| ZnO | 25 | 400 (depending on particle size) |

Modified from Kullavanijaya and Lim. [1]

[a] Retired by the Food and Drug Administration due to safety concerns.

photoprotection to prevent the biological changes associated with photoaging.[9] Mexoryl filters are registered trademarks developed by L'Oreal (Clichy, France), and this company has made the referenced studies available. Methylene-*bis*-benzotriazolyl tetramethylbutylphenol (Tinosorb M) is a broad-spectrum sunscreen made of microfine organic particles dispersed in the aqueous phase of sunscreen emulsions.[1] Bisethylhexyloxyphenol methoxyphenyl triazene (Tinosorb S) is a high–molecular weight, broadband sunscreen filter (280-380 nm) that does not penetrate the skin. Its mechanism of action is dual: it absorbs photons and also reflects them. In addition, it confers photostability to 2-ethylhexyl-4-methoxycinnamate (OMC) and avobenzone-containing sunscreens.[41] All these properties made tinosorbs good candidates in the prevention of photoaging. The latest development in organic sunscreens is the production of UV photon absorbers entrapped in sol-gel glass microcapsules.[42] The active UV filter is encapsulated within a silica shell of approximately 1-$\mu$m diameter. The potential advantages of these cutting edge sunscreens are a marked reduction of the penetration of the UV filter, improved photostability, and lower allergenic potential (Table 1).

***Physical blockers.*** Physical blocking agents are made of sizeable particles that scatter, reflect, or absorb solar radiation in the UV, visible, and even infrared ranges. These agents are micronized and coated, but those procedures diminish their broad-spectrum protection. Two inorganic particulates are widely used in sunscreens: microfine zinc oxide (ZnO) and titanium dioxide ($TiO_2$). It has been shown that ZnO is a better blocker than microfine

$TiO_2$,[43] especially in the long-wave UVA spectrum. In addition, ZnO is not photoreactive and has a better aesthetic appearance than microfine $TiO_2$ because of its lower reflectance. Both micronized $TiO_2$ and ZnO can undergo photochemical reactions that may compromise their efficiency, cause RNA and DNA damage, or alter cellular homeostasis.[44] To avoid this, $TiO_2$ and ZnO particles are coated with dimethicone or silica, which stabilize them.[45] Recently, modern approaches such as encapsulation have allowed the development of high-quality inorganic sunscreens. One of them is the combination with carnauba wax. Carnauba wax contains cinnamates, which synergize with $TiO_2$ resulting in stable dispersion, ideal viscosity, and a significant increase in SPF up to about 50.[46,47] In addition, this increases protection against UVA-induced erythema.[48]

***Antioxidants.*** Skin damage due to UV light may also result from increased ROS production. Topical antioxidants are a successful strategy for diminishing UV-related damage of the skin. Classical antioxidants comprising sunscreen formulations include vitamin C, vitamin E, and beta-carotene, whose photoprotective effects against UVB and UVA are well characterized.[49] In addition, there are new substances under investigation:

1. *Astaxanthin:* It is a xantophilic pigment particularly efficient in the elimination of peroxilipidic radicals and inhibiting the concentration of free polyamines induced by UVA radiation, protecting fibroblasts from photoinduced damage.[50]
2. *Polyphenolics:* Polyphenolic compounds are an important part of human diet. Flavonoids and phenolic acids are the most abundant in food. Some of them have photoprotective properties because they have antioxidative, anti-inflammatory, and anticarcinogenic activities.[51] They include the following:
   - *Green tea polyphenols:* The protective properties of GTPP against UV light possess potential value against photoaging. EGCG induces a 3-fold reduction of UVB-induced lipid peroxide levels, prevents UVA-induced skin damage (roughness and sagginess), inhibits the expression of collagenase in cultured human epidermal fibroblasts as well as the activities of both AP-1 and NF-$\kappa$B, and reduces collagen cross-linking.[52] Standardized delivery systems for topical application of GTPPs have not been yet established. High concentrations of GTPPs or EGCGs can induce toxicity.[53] In addition, they are highly reactive; they are easily oxidized and lose activity if not used immediately after preparation. It has been suggested that the addition of 0.1% butylated hydroxytoluene to 10% EGCG in an hydrophilic ointment significantly enhanced its stability.[54]
   - *Resveratrol:* Resveratrol is a polyphenolic phytoalexin found in the peels and seeds of grapes, nuts, fruits, and red wine. Topical application of resveratrol to hairless mice before UVB irradiation significantly inhibited edema and decreased the generation of hydrogen peroxide and leukocyte infiltration[55] and significantly inhibited tumor incidence, delaying the onset of tumorigenesis.[56] The effect of resveratrol on photoaging remains to be examined.
3. *Flavonoids:* Flavonoids are plant-derived isoflavones with antioxidant and weak estrogenic properties. They are currently receiving attention as potential anticarcinogenic compounds.
   - *Genistein:* Genistein effectively blocks UVB-induced skin burns in humans,[27] as well as psoralen plus UVA (PUVA)-induced photodamage and molecular alterations in hairless mouse skin.[57] In addition, it has a potent antiphotocarcinogenic and antiphotoaging effects.[27]
   - *Silymarin:* Silymarin is a plant flavonoid isolated from the seeds of milk thistle (*Silybum marianum*). It consists of a mixture of 3 flavonoids, namely silybin, silydianin, and silychristin. Current experimental observations indicate that it protects against sunburn, DNA damage, nonmelanoma skin cancer, and immunosuppression.[58]
   - *Equol:* Red clover (*Trifolium pratense*) is a rich source of primary isoflavones like genistein and daidzein. Equol is a natural metabolite of the latter. It strongly protects against UV irradiation and inhibits tumor promotion during photocarcinogenesis[59] and photoaging.[60] Its photoprotective action in mouse and human skin seems to be dependent on metallothionein, a cutaneous antioxidant that modulates UV photodamage.[61]
   - *Quercetin:* It is a promising flavonoid that possesses the higher antioxidant activity among flavonoids. Topical formulations containing quercetin successfully inhibit UVB-induced skin damage in mice.[62]
   - *Apigenin:* It is a nonmutagenic bioflavonoid that prevents mouse skin carcinogenesis induced by UV exposure, which could be mediated in part by inhibition of COX-2 protein expression induced by UVB.[63]
4. *Caffeic and ferulic acids:* They are hydroxycinnamic acids of vegetal origin. Upon topical application, both protect against UVB-induced erythema in vivo and in vitro.[64] They are frequently used in skin lotions and sunscreens.
5. *Pomegranate:* Pomegranate (*Punica granatum*, fam. Punicaceae) is a rich source of 2 types of polyphenolic compounds: anthocyanidins (such as delphinidin, cyanidin, and pelargonidin) and hydrolyzable tannins. It possesses strong antioxidant and anti-inflammatory

properties.[65] Pomegranate protects against the adverse effects of UVB radiation, inhibiting UVB-dependent activation of NF-κB and mitogen-activated protein kinase pathways. It also provides protection against the deleterious effect of UVA light.

6. *Pycnogenol:* It is a standardized extract of the bark of the French maritime pine, *Pinus pinaster* Ait., which possesses potent antioxidant, anti-inflammatory, and anticarcinogenic properties. Topic application of Pycnogenol resulted in significant and dose-dependent protection from UV radiation-induced acute inflammation, immunosuppression, and carcinogenesis. Pycnogenol has photoprotective potential as a complement to sunscreens, possessing demonstrable activity when applied to the skin after, rather than before, UV exposure.[66]
7. *Polypodium leucotomos extract:* Topical treatment with this hydrophilic extract inhibits erythema produced in vivo by UVB light and PUVA therapy.[23] This effect is mediated not only by its antioxidant capability but also by its capability to inhibit the production of proinflammatory cytokines such as tumor necrosis factor-α or interleukin-6.[67] It also preserves the number and morphology of Langerhans cells during UV light exposure as well as during PUVA therapy.[2,19,20] *P leucotomos* also reduces chronic UVB-induced elastosis and appears to prevent photoinduced skin tumors.[68]

Oral administration of antioxidants protects the entire skin surface without being affected by washing, perspiration, or rubbing. In addition, topical application is limited by poor diffusion into the epidermis. Antioxidants tend to be unstable.[1] On the other hand, antioxidants are less potent than physical filters in preventing sunburn.[69] In a search to overcome these problems, a new compound has been recently described. It is a combination of the UVB photon absorber OMC and the antioxidant piperidine nitroxide TEMPOL. This de novo synthesized molecule has shown very promising preliminary results in photoprotection,[70] but its applicability in human subjects still remains under scrutiny.

### *Other photoprotective agents.*

1. *Dihydroxyacetone:* It produces temporary staining of the skin but only offers an SPF of 3 to 4, conferring protection at the low end of the visible spectrum and limited UVA wavelengths. In addition, its effects last only for several hours after application.[71]
2. *DNA repair enzymes:* A new approach to photoprotection is to enhance repair of DNA damage after UV exposure. The following are some examples:

   - *Photolyase:* It is an enzyme derived from the cyanobacteria *Anacystis nidulans*. Upon immediate application after UVB exposure, it induces a 50% decrease in the number of UVB-induced dimers in human skin.[72]
   - *T4 endonuclease:* Apart from its employment in patients with xeroderma pigmentosum,[73] treatment with T4 endonuclease V liposomes immediately after UV exposure protects against sunburn, local suppression of contact- and delayed-type hypersensitivy. It has little or no effect on UV-induced skin edema.[73]

3. *DNA oligonucleotides:* Pretreatment consisting of topical application of DNA fragments (thymidine dinucleotides) enhances the cellular response to subsequent UV irradiation, regardless the existence of previous DNA damage.[74] Application of DNA oligonucleotides homologous to the telomere 3-prime overhang sequence (T-oligos) on intact human skin or paired skin explants enhances melanogenesis, prolongs epidermal arrest, and increases the rate of DNA repair after UV irradiation, thus decreasing the severity of acute and chronic photodamage in human skin.[75] This is consistent with an inducible SOS-like response, including increased melanogenesis and DNA repair.
4. *Caffeine and caffeine sodium benzoate:* They possess sunscreen properties and also enhance UVB-induced apoptosis when applied to the skin. Additional studies have shown that caffeine sodium benzoate strongly inhibited UVB-induced tumor formation.[76]
5. *Polygonum multiflorum thumb:* The root of *P multiflorum* thumb is used in Oriental medicine because it is believed to possess antibacterial, antifungal, and antiaging properties. Topical administration of *P multiflorum* extracts after UVB irradiation sustained superoxide dismutase 1 immunoreactivity and protected against UVB-induced stress. These results indicate that topical application of *P multiflorum* extracts strongly inhibits oxidative stress induced by UVB irradiation and suggest that *P multiflorum* extract may have an antiphotoaging effect.[77]
6. *N-(4-pyridoxylmethylene)-l-serine (PYSer):* PYSer is an antioxidant that suppresses iron-catalyzed ROS generation due to its iron-quenching activity. Topical application of PYSer significantly delayed and decreased formation of visible wrinkles induced by chronic UVB irradiation and inhibited UVB-induced increase in glycosaminoglycans.[78] These results indicate that PYSer is a promising antioxidant in the prevention of chronic skin photoaging due to its iron-sequestering activity.
7. *Pityriacitrin:* It is a potent UV absorber indole compound naturally occurring in *Malassezia furfur.* Pityriacitrin exhibits UV-protective activity on *Candida albicans* and staphylococci with no detectable toxicity.[79]
8. *Creatine:* Exogenous creatine was readily up-taken by keratinocytes and increased creatine kinase activity,

mitochondrial function, and protected against the effect of ROS, suggesting its efficacy against a variety of cellular stress conditions, including oxidative and UV damage in vitro and in vivo. This has further implications in other modulating processes involved in premature skin aging and skin damage.[80]

9. *Cyclooxygenase 2 inhibitors:* COX-2 is an important metabolic enzyme up-regulated in different types of cancer. Celecoxib, a selective inhibitor, decreased UVB-mediated inflammation, including edema, dermal neutrophil infiltration, and activation, prostaglandin E2 levels, and the formation of sunburn cells.[81] Celecoxib also inhibited acute oxidative damage and UVB-induced papilloma/carcinoma formation in long-term studies.[82]

## Evaluation of the SPF

Although controversial, SPF is the most reliable indicator of the efficacy of sunscreen filters. Erythema protection factor is more accurate than SPF because the test protocol only takes into account the erythematous response after 24 hours. Erythema measurement is an easy and noninvasive protocol that evaluates the efficacy of sunscreens. The question remains whether erythema induction as measured by SPF is a bona fide indicator of long-term UV damage. In fact, inflammation and loss of elasticity in photoaging is induced by suberythematous doses of ultraviolet radiation. It has been recently reported that suberythemous UVB radiation not only alters Langerhans cells number and antigen-presenting function but also induces pyrimidine dimer formation and affects p53 expression.[83,84]

***UVA protection.*** Some studies have suggested the possibility of using sunscreens capable of inhibiting elastase activation to reduce UVA-dependent photoaging.[85] No definitive methodology has been yet described to measure the biological effect of UVA on the skin. The most frequent techniques are in vivo tests, such as the Persistent Pigment Darkening and the Immediate Pigment Darkening tests.[86] There are a few in vitro methods, like the Australian standard testing or the critical wavelength value.[87] Finally, it has been reported that mutations (mainly deletions) of mitochondrial DNA in dermal fibroblasts play a critical role in UVA-induced photoaging and can be used as sensors for protection.[88]

***Infrared protection.*** Despite its low energy, infrared radiation cannot be considered totally harmless. In fact, infrared exposure and subsequent tissue heating can promote UV-dependent carcinogenesis.[89] Infrared radiation also seems to be involved in photoaging.[90] In fact, decreased collagen and increased MMP-1 levels in chronic infrared-irradiated skin have been associated with connective tissue damage in human skin.[91] Physical blockers usually protect against infrared radiation, but no standard method has been suggested to evaluate this fact.

***Other photoprotective requisites.***

1. *Photoimmunoprotection:* Erythema is a poor indicator of immunosuppression. Current methods to determine immunosupression include the sunscreen ability to inhibit UV-induced local suppression of contact- or delayed-type hypersensitivity responses, using either the induction or the elicitation arms of these responses. The induction arm of the contact hypersensitivity response is sensitive to a single suberythemal exposure of solar-simulating radiation, which enables direct comparison with SPF, but it requires a large number of volunteers and is not cost-effective.[92] On the other hand, the elicitation arm exploits prior sensitization to contact or recall antigens and can be applied to small groups of volunteers. Some protocols, however, require repeated solar simulation exposures, which invalidates direct comparisons with SPF based on a single exposure. In conclusion, candidate sunscreens should not substantially alter the relationship between UVR-induced erythema and immune modulation.
2. *Antimutagenic activity:* The mutation protection factor is defined as the ability of a sunscreen to inhibit p53 mutations, that is, induced by UVB irradiation.[87] Standardized techniques to calculate the mutation protection factor as well as the immune protection factor are yet to be developed.

In general and despite its limitations, SPF is bound to remain as the primary indicator of sunscreen efficacy, and broad-spectrum labeling should be used to reflect UVA protection.[86] In this regard, SPF 30 or higher is recommended as a safe and good level of protection.

## Side effects and controversies about sunscreens

Sunscreens provide many health benefits, but the definitive sunscreen has yet to be made. There are controversies, concerns, and challenges about the use of sunscreens. Some of these are outlined below.

***Contact reactions.*** Chemical UV filters are now routinely included in many cosmetic products as either sunscreens or as photoprotectives, increasing population exposure to these reagents. Although bona fide allergic reactions to the active ingredients of sunscreens are rare, almost 20% of the individuals using a sunscreen with SPF 15 or higher over a 7-month period have reported irritation reactions.[93] Photoallergic contact dermatitis and allergic contact dermatitis are equally uncommon.[94] The most frequent photoallergens are benzophenones, PABA, Eusolex 8020,[95] and octyl triazone.[94]

***Photostability.*** Sunscreens must be photostable to maintain their UV protective capability, as well as to prevent formation of potentially photooxidant-reactive intermediates

on the skin, because these can lead to genotoxic events and photoaging.[96] Photostability is usually achieved through combination of filters. Recent efforts have described adequate combinations, that is, OMC, benzophenone-3, and octocrylene; OMC, avobenzone, and octocrylene; OMC, benzophenone-3, and octyl salicylate. In addition, octocrylene improved the photostability of OMC, avobenzone, and benzophenone-3.[97] Newly developed filters such as Mexoryl SX, Mexoryl XL, Tinosorb M, and Tinosorb S possess improved photostability and enhance the photostability and efficacy of sunscreens containing avobenzone and ethylhexyl methoxycinnamate.[41]

***Safety.*** Assessments on human safety for topically applied sunscreens are the result of identification of hazards and exposure evaluation. For topical exposure, they focus on effects on skin and dermal penetration, including reproductive and developmental toxicity. Recently, a review describing the efficacy and safety of 6 chemical classes and a miscellaneous category of UV filters has been published.[98] The main findings are the following:

1. *Aminobenzoates:* The main concern is photoallergy and phototoxicity.
2. *Benzophenones:* They are absorbed after dermal application and appear in blood and urine in significant concentrations. Benzophenone-3 is rapidly metabolized and has a favorable toxicity profile based on repeated exposure in rodents. The market experience with benzophenones is positive overall, although skin reactions are the highest among general UV filters.
3. *Cinnamates:* OMC is the most common UV filter used worldwide. It possesses a favorable human safety profile based on acute and repeated dose toxicity studies. According to this study, it is the safest UV filter.
4. *Dibenzoylmethane:* Avobenzone has been extensively evaluated in toxicological studies resulting in a favorable profile. Photostability issues have improved after carrier modifications to its formulation.
5. *Salicylate:* Octyl salicylate and homosalate are weak UVB filters with favorable toxicological profiles and reputable market experience.
6. *Metal oxides:* The in vitro demonstration of photogenotoxicity of $TiO_2$ is controversial because the opposite effect is observed in vivo.[99] On the other hand, ZnO is nonirritating and has no sensitization potential, and the absence of demonstrable dermal penetration greatly diminishes any concerns related to systemic toxicity.[43]
7. *2-phenylbenzymidazole-5-sulphonic acid:* Available information supports its safety, although it is not as detailed compared with the previous filters.
8. *Octocrylene:* Available data support the human safety of this UV filter.[100]

In summary, there is evidence of the safety of the 9 UV filters present in the formulations of more than 98% of sunscreen products sold in the United States.

***Vitamin D synthesis.*** UV radiation causes DNA damage leading to skin cancer, but the same part of the UV spectrum is required for vitamin D photosynthesis. Thus, the beneficial and deleterious effects of UV irradiation are inseparable. Approximately 90% of synthesized vitamin D is derived from casual exposure to sunlight,[101] which emphasizes the need of maintaining an appropriate balance between sun avoidance and exposure to minimize skin cancer and promote vitamin D synthesis, respectively. Public awareness has recently increased due to the publication of several studies correlating the levels of 25-OH vitamin D (the measurable precursor form of the vitamin D) with beneficial health effects (reviewed in Wolpowitz and Gilchrest[102]). There is epidemiological evidence of the inverse correlation between solar UVB exposure and mortality from several cancers, including colon, breast, prostate, and non-Hodgkin lymphoma.[103-105] Other studies suggest that such evidence is inconclusive due to the lack of clinical trials demonstrating the efficacy and safety of vitamin D supplementation in cancer chemoprevention.[106] This controversy is caused in part by lack of information regarding the biological pathways underlying these empirical observations. In this regard, in vitro data suggested a photoprotective effect for active vitamin D.[107-109] It is hypothesized that UVB-induced cutaneous production of vitamin D may represent an evolutionary conserved feedback mechanism to protect the skin from the hazardous effects of solar UV radiation.[110] Proper use of sunscreens with a SPF 15 or higher reduces the capacity of the skin to produce vitamin D by greater than 98%.[111] Nevertheless, sunscreens used to reduce actinic damage did not cause vitamin D deficiency or adversely affect markers of bone remodeling and skeletal homeostasis.[102] It is difficult to establish the exact threshold of radiation necessary for healthy bone growth and development without increasing the risk of skin cancer. It has been suggested that one third of a minimal erithematogenic dose to 15% of the body (eg face, arms, and hands) most days of the week would be sufficient to maintain adequate vitamin D absorption to reduce osteoporosis.[112] Endocrinologists and nutritionists recommend 5 to 10 minutes of exposure of the arms, legs, and/or face 2 to 3 times per week.[111] Finally, dermatologists recommend an exposure less than 0.25% minimum erythema dose of UVB radiation to the face and backs of the hands 3 times per week and the use of dietary supplements to increase vitamin D uptake (200-1000 IU/d).[102]

***Systemic absorption.*** Usually added to consumer-grade sunscreen products are 3 to 8 UV filters to ensure appropriate UV protection and enhance photostability. The lipophilic nature of many UV filters may cause bioaccumulation in fish and humans, leading to environmental levels of UV filters similar to those of polychlorinated biphenyls and dichloro-

diphenyl-thichloroethane. For example, 0.5% of the total amount of benzophenone-3 topically applied could be detected in the urine of human volunteers for up to 48 hours.[113] Factors influencing the systemic absorption and chronic toxicity of common sunscreens are still under intense debate. In addition, the demand for water-resistant sunscreens encourages the research for more lipophilic substances, which could enhance their dermal absorption. Finally, long-term use of microfine metallic oxides could potentially lead to health effects if significant amounts were absorbed through the skin. It has been shown that neither zinc or titanium ions, nor ZnO or $TiO_2$ particles, were capable of penetrating the porcine stratum corneum.[114-116]

***Hormonal activity.*** Some UV filters may have estrogenic effects, but their activity and interactions in mixtures are largely unknown. One in vitro study showed that 19 different UV filters elicited multiple hormonal activities. Most possessed pronounced antiestrogenic and antiandrogenic activities: phenyl and benzyl salicylate, benzophenone-1 and benzophenone-2, and of 4-hydroxybenzophenone.[117] On the other hand, some filters and combinations of filters activated estrogen receptors: these included benzophenone-3, homosalate, OMC, octyl dimethyl PABA, and 4-methyl-benzilidene canphor,[118] as well as combined benzophenone-3 and 2,4-dihidroxy benzophenone (BP-1), and the mixture of BP-1, BP3, OMC, and 3-(4-methyl-benzylidene)-camphor.[119] Nevertheless, the European Union cosmetics advisory committee stated that the organic sunscreen products allowed in the EU market do not exhibit estrogenic effects.[87]

***Mutagenicity.*** Several in vitro studies have reported ROS generation upon irradiation of several sunscreens with UV light, such as octocrylene, octylmethoxycinnamate, or benzophenone-3.[120,121] The levels of UV-induced ROS generated in nucleated epidermis depended on the skin persistence of the sunscreens.[122] At present, these effects have only been demonstrated in vitro or in animal models, but they provide an experimental basis to question the role of sunscreens in inducing the development of skin cancer instead of preventing it. On the other hand, sunscreens are routinely used to extend the periods of sun exposure, but this may not protect against skin cancers because they possess limited efficacy against UVA radiation.[123] Different surveys have addressed the clinical evidence for sunscreen protection against skin cancer (reviewed in Gallagher[124]). Epidemiological evidence supports that, when applied consistently, sunscreens can play a significant role in reducing the risk of squamous cell carcinoma.[125] Data supporting sunscreen use to reduce the risk of basal-cell carcinoma are not so conclusive.[32] There is conflicting evidence regarding the role of sunscreens in protection against melanoma. According to a meta-analysis case study, sunscreen use does not increase the risk on melanoma[126]; finally, a clinical trial reported that broad-spectrum sunscreen (SPF >30) modestly attenuated short-term (<3 years) development of nevi in children, especially in those with multiple freckles.[127]

***Sunscreen and the risk for the environment.*** The presence of significant amounts of UV filters has been detected in surface water, wastewater, but their role as environmental hazards is under study, except their estrogenic activities in fish, reported both in vivo and in vitro.[128]

## Sun protection in public health: sun safety programs

Prevention against the harmful effects of the sun requires the implementation of protective measures, but the use of sunscreens alone is not enough. Other measures include public education campaigns underlining the need of routine sun protection behaviors, including limitation of exposure during the peak periods of UV radiation, use of protective clothing and wide-brimmed hats, and application of sunscreens; they also recommend minimizing sunburns, avoiding tanning beds, and wearing sunglasses to prevent eye damage.[129] All these strategies must start early, not only because skin sun damage is accumulative.[130] but also because habits and practices about health are easier to acquire during childhood.[131] Besides, community-wide interventions are needed to reach the majority of the population and to remind the importance of sun safety in high-risk situations.[132] The long-term goal of these campaigns is to reduce the incidence of skin cancer. Photoaging awareness can widen the target audience in modern societies, in which self-image and physical appearance are highly regarded. For example, case-scenario photographic intervention and information about photoaging have shown to be a cost-effective approach to motivate an increase in sun protective practices in college students.[133] Other interventions incorporate an attempt to change the current fashion standards (that promote tanning and dark-toned skin), using inspirational community leaders (ie, media figures, fashion models) approving paleness. These have proven very successful to decrease sunbathing and artificial tanning, especially in females.[133]

The Cancer Council Victoria in Australia has recently issued a statement on the risks and benefits of sun exposure. It concludes that skin cancer campaigns need to state that there are beneficial and deleterious effects associated to sun exposure and that an appropriate and healthy balance needs to be achieved.[134] This is underlined by recommendations encouraging moderate sun exposure in the absence of photoprotective measures when the UV levels are low (<3), which is aimed to improve vitamin D synthesis. Finally, high-latitude countries, in which UV levels remain low for a significant proportion of the year, should recommend dietary supplementation of vitamin D, especially under special conditions, such as pregnant women, elders, patients with malabsorption syndromes, organ transplant recipients, and those with individual risk factors of skin cancer.[134,135]

## Conclusions

Many questions remain regarding photoprotection. It seems clear that excessive solar exposition is harmful for the eyes and the skin, inducing photoaging and skin cancer. In fact, UV light is included in the Tenth Report on Carcinogens from the National Institute of Environmental Health Sciences.[136] On the other hand, solar radiation is a vital requirement and poses many health benefits, most of them mediated by the synthesis of vitamin D. At present, sunscreens are very useful to prevent sunburn and probably skin cancer and photoaging. Nevertheless, they need to be improved in terms of protection against UVA and infrared radiations. Finally, safety is essential for any preventive measure. For this reason, efforts cannot be spared to guarantee sunscreen photostability, lack of absorption, and nonmutagenicity. Development of new substances, oral or topical, must demonstrate their safety in addition to their efficacy to increase the protective effect of sunscreens or help to restore sun damages.

Recommended photoprotective measures include sun avoidance during the peak UV radiation hours (a practical clue is when shadows are shorter than those casting them) and the use of photoprotective clothing, wide-brimmed hats, and sunglasses, complemented with the use of broad-spectrum sunscreens. High SPF should be preferred because common application technique results in lower actual SPF (the median quantity of sunscreen applied is less than half the amount needed to achieve the labeled SPF[31]). These measures are critically important for people with low phototypes, with multiple or atypical moles, or with personal history of skin cancer. They are also important for individuals working or practicing sports outdoors under long or intense UV exposition.

A balance is required between avoiding increased susceptibility to skin cancer and maintaining adequate vitamin D levels. Sun protection campaigns need to steer away from the notion that protection is required under all circumstances (not when UVI <3), emphasize rational joy under the sun, avoiding sunburns, and getting moderate tans, which results in low-risk beneficial effects from sun exposure.

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