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REVIEW

Update on Photoprotection

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Abstract

Photoprotection is the primary preventive and therapeutic strategy against photoaging and skin cancer. This review presents the most important new advances in both topical and systemic photoprotection. Starting with innovations in the traditional physical and chemical filtering agents, we go on to discuss the growing number of antioxidants, the novel strategies for repairing light-induced DNA damage, and current research on substances that stimulate melanogenesis. A final section deals with protection against infrared radiation.

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PALABRAS CLAVE

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Cáncer cutáneo

Novedades en fotoprotección

Resumen

La fotoprotección es una estrategia preventiva y terapéutica fundamental frente al fotoenvejecimiento y el cáncer de piel. Este artículo recopila las novedades más relevantes en sustancias fotoprotectoras, tanto en fotoprotección tópica como sistémica. Comenzando por las nuevas aportaciones a los clásicos filtros químicos y físicos, pasando por la creciente incorporación de sustancias antioxidantes, las novedosas estrategias de reparación del daño solar en el ADN y el estado actual del uso de sustancias estimulantes de la melanogénesis. Por último, se revisa la protección frente a la radiación infrarroja.

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Introduction

Photoprotection in this review refers to preventive and therapeutic measures taken to protect the skin against cancer and photoaging. Recommended measures include avoiding exposure to the sun during the hours of peak UV irradiation, wearing protective clothing, hats, and sun glasses, and applying an appropriate sunscreen prior to exposure.¹ These measures are always necessary for prolonged outdoor activity and are particularly important for individuals with light skin phototypes, multiple or atypical nevi, or a history of skin cancer.

Sunscreen products contain molecules or molecular complexes that can absorb, reflect, or scatter UV photons. Protection against the high-energy photons of UV-B radiation is needed to prevent erythema and sunburn. Photoaging, on the other hand, is primarily caused by low-energy UV-A radiation. Thus, novel sunscreens are those that can prevent, counteract, and even repair UV-induced skin damage. Their protective effects include 1) direct absorption of photons; 2) inhibition of chronic inflammation; 3) modulation of immunosuppression; 4) induction of apoptosis; 5) direct antioxidant activity (for example neutralizing or trapping reactive oxygen species); and 6) indirect antioxidant activity (that is, induction of intrinsic cytoprotective reactions that lead to detoxification of various oxidants).² Finally, sunscreens must be safe, not only for the humans who apply them to any exposed skin but also for the environment, the ultimate repository of the substance.

The principal innovations in photoprotection in recent years have generally fallen into 2 categories: 1) the introduction of new ingredients into traditional topical sunscreens, and 2) the use of oral formulations to provide systemic photoprotection, a novel form. Table 1 lists the main types of photoprotective products and ingredients discussed in this review.

Topical Sunscreens

Topical sunscreens have been shown to prevent and even repair damage caused by exposure to UV radiation in animal models.³ In humans, there is evidence that these products can prevent the acute effects of solar radiation and reduce the incidence of some skin cancers, such as squamous cell carcinoma.⁴⁻⁶ It is still unclear, however, whether they are effective in reducing the risk of basal cell carcinoma, melanoma, and photoaging. What is becoming increasingly clear is the need for adequate protection against both UV-A and UV-B radiation. Seité et al⁷ have shown that the daily use of a broad-spectrum sunscreen can significantly reduce skin damage caused by UV radiation. Furthermore, such sunscreens with an SPF of at least 25 for UV-B and 14 for UV-A radiation not only protect against sunburn but also against UV-induced immunosuppression.⁸ However, a meta-analysis of 11 studies on the risk of melanoma and the use of a sunscreen showed that patients who used protection gained only slight protection.⁹ On the other hand, an analysis of only the more recent studies of more effective sunscreens

Table 1 Main Groups of Photoprotective Agents

- 1 *Topical photoprotective agents*
 - a) Chemical or organic filters
 - b) Physical or inorganic filters
 - c) Antioxidants
 - i) Carotenoids
 - ii) Polyphenols
 - (1) Flavonoids
 - (2) Resveratrol
 - (3) Hydroxycinnamic acids
 - (4) Green tea extract
 - (5) *Polypodium leucotomos* extract
 - (6) Pomegranate extract
 - iii) Other substances
 - (1) Broccoli extract
 - (2) Caffeine
 - (3) *Polygonum multiflorum thunb* root
 - d) DNA repair agents
 - i) Liposome-encapsulated T4 Endonuclease V
 - ii) Photolyase
 - iii) Oxoguanine glycosylase enzyme
 - iv) Thymidine oligonucleotides
 - e) Cyclooxygenase-2 inhibitors
 - f) Iron chelators
 - g) Osmolytes
 - h) Other agents
 - i) Dihydroxyacetone
 - ii) Pityriacitrin
2. *Oral photoprotective agents*
 - a) Botanical dietary substances
 - i) Carotenoids
 - ii) Epigallocatechin 3-gallate
 - iii) Flavonoids
 - iv) *Polypodium leucotomos* extract
 - v) Chocolate
 - vi) Caffeine
 - b) Dietary fats
 - i) Eicosapentaenoic acid
 - ii) Omega-3 fatty acids
 - c) Antioxidant combinations
3. *New photoprotection strategies*
 - a) Stimulation of melanogenesis
 - i) Forskolin
 - ii) α -melanocyte-stimulating hormone analogs

(many of which were effective against both UV-A and UV-B radiation) concluded that these products do appear to have a protective effect.¹⁰

The ideal sunscreen should protect the skin against both UV-B¹¹ and UV-A¹² radiation, scavenge free radicals, and contain enzymes or other active ingredients that will stimulate DNA repair systems. Obviously, these products must also be safe and stable.

Topical sunscreens based on ingredients that, by one means or another, prevent UV radiation from reaching

skin cells have been in use for over 50 years. Rather than focusing on filtering or blocking radiation, the chief innovations in recent years have sought to prevent or counteract the undesirable effects of solar radiation on skin cells through the use of antioxidants and agents such as those that favor the repair of damaged DNA. Below, we will discuss the substances with topical photoprotective effects that have come onto the market in recent years.

Chemical and Organic Filters

The most recently introduced chemical and organic agents have been the Mexoryl and Tinosorb filters, ingredients that have been present in our sunscreens for some years (Table 2). Terephthalylidene dicamphor sulfonic acid (Mexoryl SX) and drometrizole trisiloxane (Mexoryl XL), both developed by L'Oreal, absorb UV-B and UV-A radiation.² Following daily application in humans, a sunscreen containing Mexoryl SX absorbed UV radiation and prevented skin damage caused by both types.¹³ Methylene bis-benzotriazolyl tetramethylbutylphenol (Tinosorb M) and bis-ethylhexyloxyphenol methoxyphenyl triazine (Tinosorb S) both absorb and reflect photons. The latest trend in organic sunscreens is the development of sol-gel glass microcapsules containing photon absorbers encapsulated within a silica shell of approximately 1 μm in diameter.¹⁴ This technology reduces the penetration of the UV filter into the skin while improving photostability and reducing allergenic potential.

Given the role in actinic damage played by free radicals generated through exposure to solar radiation, one way to enhance the protective efficacy of sunscreens is to add ingredients with antioxidant properties. This strategy was used in an innovative formulation that combined the UV-B absorber octyl-methoxycinnamate and the antioxidant piperidine nitroxide (Tempol).¹⁵ This novel sunscreen absorbed photons from both UV-B and UV-A radiation, trapped free radicals, and reduced lipid peroxidation. In another study excellent photoprotective results were obtained when avobenzone and diethylamino hydroxybenzoyl hexyl benzoate, two UV-A absorbers, were added.¹⁶ The combination of octyl-methoxycinnamate and piperidine nitroxide with diethylamino hydroxybenzoyl hexyl benzoate produced a broad spectrum, photostable sunscreen that also attenuated the damage caused by the free radicals generated by UV radiation. The use of such substances in multiactive photoprotective formulations will allow the number of ingredients to be reduced while maintaining or even increasing overall effectiveness.¹⁶

The safety profile of chemical filters is still under investigation. In a study exposing healthy volunteers to whole-body topical application of 2 mg/cm² of a sunscreen formulation (wt/wt) containing benzophenone-3 (BP-3), octyl-methoxycinnamate, and 3-(4-methylbenzylidene) camphor (4-MBC),¹⁷ the mean concentrations in plasma were surprisingly higher at 96 hours than at 24 hours for 4-MBC and octyl-methoxycinnamate in men and for BP-3 and 4-MBC in women. However, the reality is that the amount of sunscreen normally applied by

users is about 50% of the dose used in that study, and, although these substances have deleterious effects, none have been demonstrated in conditions of normal use. The nonpenetrating sunscreens that have recently appeared on the market have chemical characteristics that confine them to the upper stratum corneum where the photoprotective molecules act. They can therefore block solar radiation from reaching the dermis while preventing the sunscreen from entering the bloodstream.¹⁸

Physical, or Nonorganic, Blockers

Physical blocking agents are composed of sizable particles that scatter, reflect, or absorb solar radiation in the UV, visible, and even IR bands. Two inorganic particles widely used in sunscreens are micronized zinc oxide and titanium dioxide. The latest trend is to encapsulate these substances in or combine them with vehicles such as carnauba wax to achieve stable dispersion, ideal viscosity, and a considerable increase in SPF.¹⁹⁻²¹

A strategy used to boost the efficacy of sunscreens is to add materials that reflect or disperse light. Microspheres that remain on the surface of the skin have been developed for use in combination with conventional chemical filters. These spheres (Syntran, Solterra Boost, SolPerform, SunSpheres) reflect sunlight and can increase the SPF by 50% to 70%.

Antioxidants

UV radiation causes DNA damage and protein oxidation and induces the synthesis of matrix metalloproteinases. The use of botanical antioxidants to protect human skin from the harmful effects of UV radiation is a topic that has attracted growing interest in recent years within the world of photoprotection research.²² The antioxidant capacity of these ingredients reduces the damage caused by UV radiation but does not interfere with the synthesis of vitamin D in the skin. Moreover, many of these natural substances have been shown to have other photoprotective properties in addition to their antioxidant effect. The classic antioxidants used in sunscreens include C and E vitamins and β -carotene.²³ The following is a summary of the photochemicals shown in recent years to have photoprotective effects.

Carotenoids

Lutein and astaxanthin are xanthophyll pigments that eliminate peroxy fatty-acid radicals, inhibiting the accumulation of the free polyamines induced by UV-A radiation.^{24,25}

Polyphenols

Polyphenols, a group of chemical substances found in plants, are characterized by the presence of more than one phenol group per molecule. They are generally subdivided into hydrolyzable tannins and phenylpropanoids. The latter group includes the flavonoids and other compounds. Many naturally occurring substances that have a photoprotective effect are polyphenols.

Table 2 List of UV Filters Used in Sunscreens

Substance	Nomenclature	Concentrations Used (%)	Absorption Peak	Safety	Countries Where Permitted
<i>Chemical filters: mainly UV-B PABA and its derivatives</i>					
4-aminobenzoic acid	PABA	5	283-289 nm	Increases DNA defects	EU, USA, AUS
Padimate O	Octyldimethyl PABA	1, 4-8	290-310 nm	Photo-unstable	EU, USA, AUS
		0.5-5			
<i>Ethoxylated 4-aminobenzoic acid ethyl ester</i>	PEG-PABA, Uvinul P25	5	305 nm		EU, AUS
<i>Ethylhexyl triazone</i>	Uvinul T 150	5	292 nm		EU, AUS
<i>Cinnamates</i>					
<i>Cinoxate</i>	2-Ethoxyethyl p-methoxycinnamate	1-3	310 nm		USA, AUS
<i>Octyl-methoxycinnamate</i>	2-Ethylhexyl p-methoxycinnamate	7.5-10	311 nm	Photo-unstable	EU, USA, AUS
	Parsol, MCX				
<i>Isopentyl 4-methoxycinnamate</i>	Neo Heliopan E1000	10	310 nm		EU, AUS
<i>Salicylates</i>					
<i>Homosalate</i>	3,3,5-trimethylcyclohexyl salicylate	4-10	306 nm	Improves photostability of other filters	EU, USA, AUS
<i>Octyl-salicylate</i>	2-ethylhexyl salicylate, octisalate	3-5	305 nm	Good substantivity	EU, USA, AUS
<i>Trolamine salicylate</i>	Triethanolamine salicylate	5-12	298 nm		USA, AUS
<i>Others</i>					
<i>Octocrylene</i>	2-ethylhexyl-2-cyano-3,3-diphenylacrylate	7-10	303 nm	Increases reactive oxygen species Improves the photostability of photolabile filters	EU, USA, AUS
<i>2-Phenyl-5-benzimidazole-5-sulfonic acid</i>	Eusolex 232 or Ensulizole	4 (USA) 8 (EU)	310 nm	Genotoxic in bacteria. Water soluble. Increases the SPF of the final product	EU, USA, AUS
<i>Chemical filters: UV-B and to a lesser degree UV-A</i>					
<i>Benzophenones</i>					
<i>Dioxybenzone</i>	Benzophenone-8	3	288, 352 nm		USA, AUS
<i>Oxybenzone</i>	2-Hydroxy-4-methoxybenzophenone	6 (USA)	288, 325 nm	Most common cause of photoallergic dermatitis in sunscreen	EU, USA, AUS
	Benzophenone-3	10 (EU)			
	Eusolex 4360				
<i>Sulisobenzone</i>	Benzophenone-4	5 (EU) 10 (USA)	288, 366 nm		EU, USA, AUS

Anthralins <i>Meradimate</i>	Menthyl anthramilate	3.5-5	286, 335 nm	USA, AUS
Others				
<i>Iscotrizinol</i>	Diethylhexyl butamido triazone. Uvasorb HEB	10	311 nm	EU
<i>Polyisicone 15</i>	Parsol SLX, dimethyldiethylbenzalmalonate	10	310-360 nm ^a	EU, AUS
Chemical sunscreens, mainly UV-A				
<i>Avobenzone</i>	Butyl methoxydibenzoylmethane	3-5	358, 360 nm	EU, USA, AUS
	Parsol 1789	5		
<i>3-(4-methylbenzylidene)camphor</i>	Eusolox 6300	4	345 nm	
<i>Terephthalylidene dicamphor sulfonic acid</i>	Mexoryl SX	10 (EU) 3 (USA)	345 nm	EU, USA, AUS
<i>Neo Heliopan AP</i>	Disodium phenyl dibenzimidazole tetrasulfonate	10	340 nm	EU, AUS
<i>Aminobenzophenone</i>	Diethylamino hydroxybenzoyl hexyl benzoate	10	354 nm	
Broad spectrum chemical absorbers				
<i>Drometrizole-trisiloxane</i>	Silatrizole	15	303, 341 nm	EU, AUS
	Mexoryl XL			
<i>Tinosorb M</i>	Methylene bis-benzotriazolyl tetramethylbutylphenol	10	303, 368 nm	EU, AUS
	Bisocotrizole			
<i>Tinosorb S</i>	Bis-ethylhexyloxyphenol methoxyphenyl triazine. Bemotrizinol	10	310, 340 nm	EU, AUS
	Anisotriazine			
Physical filters or mineral blockers (UV-A, UV-B, IR)				
<i>Titanium dioxide</i>		2-25	400 nm	EU, USA, AUS
<i>Zinc oxide</i>		20-25	400 nm	EU, USA, AUS

^aIts absorption wavelength depends on the solvent used.

Abbreviations: AUS Australia; EU, European Union; IR, infrared radiation; PABA, para-aminobenzoic acid; PEG, polyethylene glycol; ROS, reactive oxygen species; SPF, sun protection factor; USA, United States.

a. Flavonoids

Flavonoids, which are natural pigments found in vegetables, have a protective effect against the damage caused by oxidizing agents, such as UV radiation and air pollution, among others. Since the human body cannot produce these protective chemical substances, flavonoids must be obtained through food or dietary supplements. They are found in a wide range of plants, fruits, vegetables, and beverages and are substantial constituents of the nonenergetic part of the human diet.

Flavonoids have a variable number of phenolic hydroxyl groups in their chemical structure and are excellent chelators of iron and other transition metals, making them efficient antioxidants. Consequently, they play an essential role in protecting the body against oxidative damage. They also have therapeutic effects in a large number of diseases, including ischemic heart disease, atherosclerosis, and cancer.²⁶ Depending on their structural characteristics, flavonoids are classified into the following groups: 1) flavanols, such as catechin; 2) flavonols, such as quercetin; 3) flavones, such as diosmetin; and 4) anthocyanidins.

Flavonoids have 3 different photoprotective effects: they absorb UV radiation, they have direct and indirect antioxidant properties, and they also modulate several signaling pathways.

More than 5000 flavonoids have been identified,²⁷ and the following is a brief account of those shown to have photoprotective properties.

- *Genistein*, the isoflavone found in soybeans (*Glycine max*), is a potent antioxidant, a tyrosine kinase inhibitor, and a phytoestrogen. There is evidence that it blocks both UV-A and UV-B radiation and reduces photocarcinogenic and photoaging effects.²⁸ Topical application of genistein in experimental animals following exposure to UV radiation reduced inflammation and protected the animals against UV-induced immunosuppression.²⁹ Other studies have shown that topical genistein inhibits tumorigenesis in animals subjected to chronic UV radiation.²⁸ In humans, topical application an hour before exposure reduced erythema and discomfort.²⁸ An interesting characteristic of genistein is that the protective effect against sun damage is available even when the compound is applied 1 to 4 hours after exposure.³⁰
- *Silymarin*, a flavonoid isolated from the seeds of the milk thistle (*Silybum marianum*), is a mixture of 3 flavonoids, namely, silibinin, silidianin, and silicristin. Silymarin has been shown to modulate a number of the acute and chronic effects of UV radiation in mice, providing protection against sunburn, DNA damage, and radiation-induced immune suppression. Studies indicate that it has excellent antioxidant, anti-inflammatory, and immunomodulatory properties and can therefore protect against skin cancer caused by UV-B radiation in animal models.³¹
- *Equol* (4',7-isoflavandiol) is an isoflavonoid metabolized from daidzein by bacterial flora in the intestines of mammals. Topical equol has been shown to protect against inflammation, immunosuppression, and the formation of UV-induced cyclobutane pyrimidine dimers in mice.³² However, its photoprotective effect is lower than that of other flavonoids, such as its precursor daidzein or genistein.³³
- *Quercetin* is the flavonoid with the most potent antioxidant properties. There is scant research on its photoprotective effects, but some topical formulations containing quercetin inhibit the damage induced by UV-B radiation in animals.³²
- *Apigenin* is a bioflavonoid that prevents photocarcinogenesis in mice. This anticarcinogenic effect is, at least in part, mediated by inhibition of UV-B radiation-induced cyclooxygenase-2 protein expression.³⁴ Apigenin also enhances UV-B radiation-induced apoptosis, affecting both intrinsic and extrinsic pathways.

The extracts of various flavonoid-rich plants with photoprotective properties, such as pycnogenol and red clover, have also been investigated.

- *Pycnogenol* is a water-soluble extract of the bark of the French maritime pine (*Pinus pinaster* subsp *atlantica*). It contains a number of phenolic and polyphenolic flavonoids, including monomeric procyanidins (catechin, epicatechin, and taxifolin) and oligomeric procyanidins with varying chain lengths and bonding patterns.³⁵ Topical application of pycnogenol immediately after irradiation significantly reduces both acute and chronic effects of UV exposure (inflammation, immunosuppression, and tumorigenesis) in experimental animals.³⁶ Pycnogenol could be useful in preventing UV-induced skin damage in humans, complementing current sunscreens when applied after sun exposure.
- *Red clover* (*Trifolium pretense*) is a rich source of isoflavones, such as genistein and daidzein. Its photoprotective properties depend, at least in part, on metallothionein, a cutaneous antioxidant that modulates damage induced by UV radiation.³² Widyarani et al²⁹ studied the protective effect against photoimmune suppression of a number of isoflavones found in this plant separately after topical application. They found genistein and the metabolites equol, isoequol and the related derivative dehydroequol to be the isoflavones that most reduced the edema and immunosuppression caused by UV radiation and concluded that this effect was due to their antioxidant properties. Red clover extract, they suggested, might play an important role in protecting the immune system from sun-induced immune suppression rather than from erythema or sunburn, making it an excellent complement to the sunscreens currently on the market.

Few studies have compared the photoprotective effect of the different flavonoids. In a study comparing the topical application on pig skin of 0.5% solutions of 5 isoflavones (genistein, equol, daidzein, biochanin A, and formononetin), Lin et al,³³ found the protective effect of genistein, daidzein, and biochanin A to be superior to

that of equol and formononetin. However, none of the isoflavones were as effective in this respect as a standard antioxidant solution containing 15% L-ascorbic acid, 1% α -tocopherol, and 0.5% ferulic acid.

b. *Resveratrol (Trans-3,5,4'-trihydroxystilbene)*

Resveratrol is a polyphenolic phytoalexin found in grapes and their derivatives, such as wine and grape juice, and in certain foods, including oysters, peanuts and walnuts. It can also be produced by chemical synthesis. Topical application of resveratrol before exposure to UV-B radiation has been found to affect subsequent inflammation, significantly inhibiting edema and reducing leukocytic inflammatory infiltrates and the formation of hydrogen peroxide.³⁷ Resveratrol also has chemopreventive anticarcinogenic effects against multiple exposures to UV-B radiation mediated via the pathways of the cyclin-dependent kinase cyclins and mitogen-activated protein kinase, and it also inhibits survivin, a member of the inhibitor of apoptosis protein family.^{38,39} Aziz et al³⁹ reported that topical application of resveratrol (10 μ mol) on the skin of mice before exposure to UV-B radiation significantly inhibited survivin levels, Ki-67 proliferation, and epidermal levels of cyclooxygenase-2 and ornithine decarboxylase (both markers of tumor promotion). Resveratrol also enhanced induction of UV-B radiation-mediated apoptosis. These findings suggest that resveratrol has a chemopreventive effect on the skin damage caused by UV-B radiation, although to date this effect has only been demonstrated in animal models.

c. *Hydroxycinnamic Acids*

Hydroxycinnamic acids are a group of compounds found in plant cell walls whose principal representatives are ferulic and caffeic acid, the former being more abundant in nature. Applied topically in healthy volunteers, both ferulic and caffeic acid reduced erythema caused by UV-B radiation.⁴⁰ Two interesting studies have demonstrated the photoprotective role of ferulic acid in combination with vitamins C and E and phloretin.^{41,42} In the first of these, a formulation with 15% L-ascorbic acid, 1% α -tocopherol, and 0.5% ferulic acid applied to human skin before exposure to solar-simulated UV radiation for 4 days afforded significant photoprotection, and in particular reduced the formation of thymine dimers.⁴¹ This study showed that topical application of a combination of 2 endogenous antioxidants—vitamins C and E—stabilized by ferulic acid, a potent botanical antioxidant, can supplement the inherent antioxidant capacity of human skin to counteract UV-induced oxidative damage. The second study used a different combination of topical antioxidants, a mixture of vitamin C, ferulic acid, and phloretin.⁴² Topical application of this formulation to the skin of healthy volunteers prior to solar-simulated irradiation on 4 consecutive days led to an increase in the minimum erythema dose that correlated linearly with the antioxidant concentration used. On the cellular and molecular level, the application reduced sunburn-cell and thymine dimer formation, metalloproteinase-9

expression, and p53 protein expression, and attenuated the suppression of Langerhans cells. The authors concluded that phloretin, in addition to being a potent antioxidant, may also stabilize and increase the availability in skin of topical vitamin C and ferulic acid.

d. *Green Tea Extract*

Several studies have demonstrated the benefits of green tea polyphenols in terms of both photoprotection and the prevention of photocarcinogenesis.^{43,44} However, high concentrations of these polyphenols can be toxic,⁴⁵ and they rapidly oxidize and lose their activity. The addition of 0.1% butylated hydroxytoluene to 10% epigallocatechin 3-gallate, the most active of the green tea polyphenols, has been shown to significantly increase stability.⁴⁶ A recent study showed that topical application of green and white tea extracts at a concentration of 2.5 mg/cm² to human skin 15 minutes before exposure to UV irradiation significantly reduced oxidative damage to keratinocyte DNA and radiation-induced depletion of Langerhans cells.⁴⁷ White tea is the least processed of all teas and its polyphenol content may therefore be greater. Green and black teas also contain catechins, which are flavonoids.

e. *Extract of Polypodium leucotomos*

A polyphenol-rich extract obtained from the fronds of the *P leucotomos* fern is included in some photoprotective formulations because of its antioxidant properties. It blocks the generation of reactive oxygen species and inhibits UV-induced cell death and the photoisomerization and photodecomposition of the isomer trans-urocanic acid.^{48,49} On the cellular level, it prevents UV-induced apoptosis and necrosis as well as degradation of the extracellular matrix,^{50,51} thereby reducing solar elastosis,⁵² the principal cause of the clinical signs of premature aging. Moreover, topical application of this extract after irradiation significantly reduced the development of tumors related to chronic UV-B radiation in experimental animals.⁵²

f. *Extract of Pomegranate (Punica granatum)*

Pomegranate extract is a source of anthocyanins and hydrolyzable tannins. It is a potent antioxidant with anti-inflammatory properties.⁵³ Pomegranate extract has been shown to protect skin against the adverse effects of UV-B and UV-A radiation. Pretreatment of reconstituted human skin (EpiDerm) with pomegranate extract before UV-B irradiation inhibited the induction of cyclobutane pyrimidine dimers, the formation of 8-dihydro-2-deoxyguanosine, as well as protein oxidation and cell proliferation. It also inhibited the synthesis of several UV-B radiation-induced matrix metalloproteinases. At the molecular level, it reduced the protein expression of c-Fos and phosphorylation of c-Jun induced by UV-B radiation.⁵³ In an in vitro study of its role as a defense against UV-A radiation, pomegranate extract was shown to inhibit increases in keratinocyte proliferation and promote apoptosis of cells in which the cell cycle had been arrested by UV-A radiation, thereby reducing cell damage.⁵⁴

Other Substances

a. *Broccoli Extract*

Topical application of broccoli extract to the skin of healthy volunteers resulted in a 40% mean reduction in UV-induced erythema.⁵⁵ This effect was not attributed to the absorption of UV radiation but rather to the production of protective intracellular enzymes that defend cells against UV damage. Thus, the effect of this extract lasts longer, up to several days, persisting even after the extract is no longer present on the skin. The chemical agent responsible for this effect is sulforaphane, an organic sulfur compound with anticarcinogenic, antidiabetic, and antimicrobial properties.⁵⁶

b. *Caffeine*

Caffeine and caffeine sodium benzoate have photoprotective properties. Their topical application accelerates UV-B radiation-induced apoptosis and inhibits tumorigenesis.⁵⁷

c. *Polygonum multiflorum thunb* root

Root of *P multiflorum thunb* is used in traditional oriental medicine for its antibacterial and antifungal effects and also its antiaging properties, which are associated with cellular antioxidant activity. In animal models, topical application of the extract thirty minutes before UV irradiation strongly inhibited oxidative stress, specifically the destruction of the superoxide dismutase enzyme.⁵⁸

To summarize, a considerable number of botanical substances have excellent photoprotective properties. However, many problems are still unresolved, such as the fact that antioxidants tend to be unstable⁵⁹ and, of course, much less effective than physical filters in the prevention of sunburn.⁶⁰

DNA Repair Agents

Since photoaging is in part due to DNA damage caused by UV radiation, enhancing the skin's ability to repair DNA damage will reduce actinic damage. This is the basis for the photoprotective use of DNA repair enzymes, which are active irrespective of whether they are applied before or after exposure to UV radiation. The following are some examples.

Liposome-Encapsulated T4 Endonuclease V

After the bacterial phage enzyme T4 endonuclease V identifies cyclobutane pyrimidine dimers, the main DNA photolesions produced by UV-B radiation, this enzyme initiates their repair and stimulates their removal.⁶¹ T4 endonuclease V also reduces the synthesis and expression of immunosuppressive cytokines that contribute to the risk of skin cancer, such as tumor necrosis factor- α and interleukin-10.⁶² Thus, it protects the skin against sunburn and sunlight-induced immunosuppression and enhances the proper functioning of the endogenous DNA repair system. Encapsulation of this enzyme in liposomes facilitates its distribution throughout the skin. A number of clinical trials have been done in patients with xeroderma pigmentosum because this treatment has been shown to be particularly useful in that setting.⁶³

Photolyase

Photolyase is found in plants, bacteria, reptiles, amphibians, and marsupials, and even in the placenta of mammals; it absorbs visible light and uses the energy to disrupt the cyclobutane ring in a mechanism of action called "photoreactivation." In vivo and in vitro studies of liposome-encapsulated photolyase derived from the cyanobacteria *Anacystis nidulans* have demonstrated a 50% reduction in both apoptosis and the production of cyclobutane pyrimidine dimers.⁶⁴

Oxoguanine Glycosylase 1 Enzyme

The oxoguanine glycosylase 1 enzyme catalyzes the first step in the process of base excision repair, the process that removes guanine bases with oxidative damage—8-hydroxy-2-deoxy guanosine—from DNA. The application of this botanical enzyme encapsulated in liposomes following exposure to UV-B radiation in mice chronically exposed to such radiation reduced the size and progression of skin cancers.⁶⁵

Thymidine Oligonucleotides

Thymidine oligonucleotides are DNA fragments, specifically thymidine dinucleotides homologous to the sequence that repeats in one third of the telomere (TTAGGG), which is the most common substrate for the photoproducts of UV irradiation. Application of these oligonucleotides triggers the SOS-like response normally initiated to rescue cells exposed to UV radiation, involving processes such as melanogenesis, but it does so without any irradiation taking place, thereby improving the skin's capacity to repair DNA damage without prior UV exposure.⁶⁶

These oligonucleotides have been shown to reduce the development of squamous and basal cell carcinomas in mice by decreasing cyclooxygenase-2 expression, inhibiting cell proliferation, increasing apoptosis, and significantly reducing cyclobutane pyrimidine dimers and the expression of 8-hydroxy-2'-deoxyguanosine.⁶⁷

In short, topical application of oligonucleotides and DNA repair enzymes increases the body's endogenous capacity for DNA repair, thereby enhancing protection against UV radiation and reducing photocarcinogenesis.

Cyclooxygenase-2 Inhibitors

In animal models, topical celecoxib reduces the inflammation and acute oxidative damage produced by UV-B radiation and inhibits the formation of carcinomas induced by chronic exposure to such radiation.⁶⁸ However, these substances are not currently used in photoprotective products.

Iron Chelators

Exposure of the skin to UV radiation results in high intracellular iron levels, favoring the production of reactive oxygen species; this finding is the basis for including iron chelators in photoprotective products.⁶⁹ N-(4-pyridoxy/methylene)-l-serine (PYSerine), an antioxidant whose action is mediated by iron sequestration, has been shown

to attenuate UV-B radiation-induced skin damage in mice: its topical application resulted in a histologic reduction in epidermal hyperplasia and lymphocyte infiltrates and inhibited the production of glycosaminoglycans in the dermis, thereby reducing and delaying wrinkle formation.⁶⁹

Osmolytes

Osmolytes are organic solutes whose chief function is to maintain cell volume. However, they also appear to protect cells against harmful agents, such as reactive oxygen species. Both UV-A and UV-B radiation stimulated the uptake of specific osmolytes by keratinocytes, and pretreatment of cultured keratinocytes with the osmolyte taurine inhibited the synthesis of tumor necrosis factor- α and interleukin-10.⁷⁰ Topical application of the bacterial osmolyte ectoin following exposure to UV-B radiation prevents depletion of Langerhans cells and the formation of sunburn cells.⁷¹ The results of in vitro studies have demonstrated that ectoin reduces UV-induced DNA mutations in fibroblasts. Based on these findings, osmolytes could prove to be a very interesting ingredient in future photoprotective products.

Other Topical Photoprotective Agents

Dihydroxyacetone

Dihydroxyacetone is the substance most commonly used in sunless tanning products. It has also been shown to have a weak photoprotective effect, providing an SPF of between 1.5 and 3.5.⁷² This photoprotection depends on the concentration used and the number of applications (for example, 20% dihydroxyacetone applied once or a 5% solution applied 3 times will provide the same photoprotection, an SPF of 1.6).⁷³ The greatest advantage of dihydroxyacetone is that its photoprotective effect can last 1 to 2 weeks.

Pityriacitrin

Pityriacitrin is a potent indole synthesized naturally by *Malassezia furfur*. It is a substance that absorbs UV radiation, and at a concentration of 5% applied in vivo to human skin it has been shown to afford an SPF of 1.7.⁷⁴

Conclusion

There are a large number of promising substances that can defend the skin against the damaging effects of sun following topical application. However, since many of them have only been investigated in vitro and in animal models, studies are needed to provide evidence to support their use in humans. It is difficult to ensure complete and safe photoprotection with topical products because they are affected after application by washing, sweating, wiping, and rubbing. Oral photoprotective products that can be used to complement topical sunscreens have been developed to address this problem.

Oral Photoprotection

There is evidence that a number of substances when taken orally exercise a preventive effect against UV-induced skin damage without adverse effects. The mechanisms of action are highly varied, affecting diverse signaling pathways and resulting in antioxidant, anti-inflammatory, and immunomodulatory activity. The following is a review of the substances for which there is the most evidence of oral photoprotective effect.

Botanical Dietary Substances

Many of the botanical substances used as topical sunscreens also have a similar effect when taken orally. This group includes dietary alkaloids such as caffeine, *Pleurotomos* extract, epigallocatechin 3-gallate, genistein, and the carotenoids (β -carotene, lycopene).

Carotenoids

The results of studies in humans who followed a carotenoid-rich diet over an extended period provide evidence that such diets improve photoprotection in that they result in a slight increase in minimum erythema dose.⁷⁵

Polyphenols in Tea and Wine

Animal studies have shown that continuous oral administration of epigallocatechin 3-gallate increases minimum erythema dose and reduces UV-B radiation-induced photocarcinogenesis and photoaging.⁷⁶ These effects appear to be mediated, at least in part, by interleukin-12, which reduces skin inflammation.⁷⁷ The photoprotective capacity of red wine polyphenols has also been investigated recently. While topical application of red wine has not demonstrated any photoprotective effect, oral intake did significantly increase minimum erythema dose.⁷⁸ However, the dose and duration of wine consumption required to achieve this effect has not yet been determined.

Flavonoids

Oral genistein has also been shown to reduce carcinogenesis induced by UV-B radiation in animal models.²⁸ Furthermore, oral administration of quercetin reduces the systemic oxidative stress produced when the animals are exposed to either UV-B⁷⁹ or UV-A⁸⁰ radiation.

Pleurotomos Extract

In humans, consumption of single doses of *Pleurotomos* extract not only has an antioxidant effect and inhibits the lipid peroxidation of cutaneous cell membranes,⁸¹ but it also reduces UV-induced inflammation,^{82,83} prevents the isomerization of trans-urocanic acid to its cis form,⁴⁹ and protects against radiation-induced immunosuppression.⁸⁴ A particularly important effect of oral *Pleurotomos* extract is the induction and activation of the p53 gene, which directly accelerates removal of DNA photoproducts, especially the highly mutagenic thymine dimers. *Pleurotomos* extract has also been shown to prevent DNA oxidative damage, inhibiting the conversion of guanosine to 8-deoxyguanosine and reducing UV-induced mutagenesis.⁸¹

Chocolate

Cocoa beans are very rich in polyphenols and therefore have potent antioxidant properties. The main phenolic phytochemicals in cocoa are epicatechin and catechin together with the procyanidins. However, a large part of the cocoa bean's antioxidant capacity is lost during the chocolate manufacturing process.⁸⁵ The authors of a recent study reported that daily consumption for 12 weeks of chocolate specially processed to preserve its flavonols almost doubled minimum erythema dose as compared to a control group who consumed conventional dark chocolate (70%).⁸⁶

Caffeine

Several epidemiologic studies support the experimental evidence that caffeine consumption has a protective effect against skin cancer.⁸⁷ Experimentally, both topical and oral caffeine promote the apoptosis of the keratinocytes irradiated with UV-B, which means that it could play a role in preventing photocarcinogenesis.⁸⁸

Dietary Fats

The results of studies in both mice and humans indicate that low-fat diets protect and even inhibit the development of actinic keratosis. However, certain fats appear to have a photoprotective effect. For example, eicosapentaenoic acid and omega-3 fatty acids inhibit the development of skin cancer in murine models.²² They also reduce levels of proinflammatory mediators and immunosuppressants, such as prostaglandin E₂, interleukin-8, interleukin-6, and tumor necrosis factor- α , and the expression of cyclooxygenase-2, thereby attenuating the cutaneous inflammatory response.⁸⁹

Both these lipids have been shown to reduce UV-induced DNA damage and to increase the sunburn threshold. The main disadvantage is that the daily dose of fish oil administered in these studies was relatively large (4-10 g/d).⁹⁰

Antioxidant Combinations

Like topical sunscreens, oral photoprotective agents tend to contain a combination of substances, mainly antioxidants, that enhance the overall photoprotective effect. For example, it is now well known that vitamins C and E in combination significantly increase the photoprotective effect obtained with administration of either vitamin alone.⁹¹ Seresis is an antioxidant combination containing physiological levels of lipid and water-soluble compounds, including carotenoids (β -carotene and lycopene), vitamins C and E, selenium, and proanthocyanidins. Administration of repeated doses of Seresis reduced erythema induced by UV-B radiation and expression of matrix metalloproteinase-1 and -9.⁹² Another antioxidant combination studied in animal models during chronic exposure to UV-B radiation was a mixture of vitamins C and E, pycnogenol, and evening primrose oil.⁹³ Oral administration of this preparation inhibited the expression of matrix metalloproteinase and enhanced collagen synthesis, thereby reducing wrinkle formation.

New Strategies in Photoprotection

Stimulation of Melanogenesis

Tanning is the principal physiologic photoprotective response of the skin. Tanned skin is thought to provide an SPF of between 2 and 4 and to reduce light-induced DNA damage. In fact, an inverse relationship exists between the melanin content of our skin and said DNA photoproducts. It would appear that UV-induced DNA damage and its repair are some of the initial triggers of melanogenesis. From this we can deduce that stimulating the production of melanin without exposure to the sun would reduce cutaneous DNA damage.⁹⁴

Forskolin

A good way of increasing skin pigmentation is to intervene in any of the cell signals that induce melanogenesis. Forskolin is a diterpene that penetrates the cell and activates adenylate cyclase. This enzyme mediates the effect of α melanocyte-stimulating hormone in melanocytes, bypassing the melanocortin 1 receptor and thereby obviating the need for prior UV exposure. A recent study demonstrated that topical application over 3 months of forskolin in mice induced eumelanin production and resulted in a resistant photoprotective effect evidenced by an increase in minimal erythema dose.⁹⁵ Moreover, this effect was accompanied by an increase in epidermal melanocytes and thickening of the epidermis due to an accumulation of nucleated keratinocytes. The additional advantage of this photoprotective substance is its ability to stimulate photoprotection in individuals with a functional disruption of the melanocortin 1 receptor, who are characterized by blonde or red hair and fair skin that does not tan. This effect has been demonstrated in transgenic mouse models.⁹⁶

Analogs of α -Melanocyte-Stimulating Hormone

Melanogenesis can also be stimulated through the use of α -melanocyte-stimulating hormone analogs. Three analog fragments (melanotans I, II, and III) have been shown in vitro to be agonists of the melanocortin 1 receptor and to stimulate melanogenesis. Two of them also promote the repair of DNA damage resulting from sun exposure and reduce levels of UV-induced reactive oxygen species.⁹⁷ It is thought that melanotans induce tanning by simulating the action of α -melanocyte-stimulating hormone at melanocortin 1 receptors.^{98,99} Curiously, subcutaneous injection of melanotan I stimulates the synthesis of eumelanin in humans, inducing a tan that lasts for a prolonged period (almost 1 month).¹⁰⁰ Melanotan I (the generic name for afamelanotide) is in phase III clinical trials as a photoprotective drug for patients with photodermatoses, such as erythropoietic protoporphyria and polymorphic light eruption (Clinuvel Pharmaceuticals Limited, Annual report 2008, www.clinuvel.com/resources/pdf/annual_reports/2008/annual_report_2008.pdf). In fact, melanotan I administered at a dose of 20 mg twice daily for 60 days has been shown to increase sun tolerance and decrease the adverse effects of exposure in patients with erythropoietic protoporphyria.¹⁰¹

The risks associated with the pharmacological effects of melanocortin analogs are unclear. To date, facial flushing, nausea, and vomiting have been reported.¹⁰² However, one of the major concerns is that these substances are not specific to the melanocortin receptor and interact with other physiologic systems. Moreover, some authors have reported the development of eruptive melanocytic nevi in patients who had self-administered injections of melanotan over a period of weeks.¹⁰³⁻¹⁰⁶

Photoprotection Against Infrared Radiation

Finally, and as a separate subject, we will discuss the question of protection against infrared (IR) radiation. IR radiation (λ 760 nm-1 mm), which accounts for more than half the solar energy that reaches the human skin, has been divided into A, B, and C spectra. While IR-B and IR-C radiation do not penetrate deeply into the skin, over 65% of IR-A radiation reaches the dermis and 17% penetrates to the subcutaneous tissue. Furthermore, it should be borne in mind that one third of the radiation that reaches us from the sun is in the IR-A spectrum.

Recent research has shown that exposure to IR radiation or to heat induces angiogenesis and inflammatory cell infiltration, disrupts the dermal extracellular matrix by inducing matrix metalloproteinases, and alters dermal structural proteins, thereby contributing to premature aging of the skin.¹⁰⁷ For this reason, it appears that complete photoprotection should include protection against IR radiation, and specifically against IR-A rays.

There are currently no specific physical or chemical filters against IR radiation although some of the available filters may provide such protection and this is currently being investigated.

Antioxidants, especially those that target the mitochondria, including epigallocatechin gallate and the coenzyme Q derivative mitoquinone (MitoQ, Antipodean Pharmaceuticals), may offer an approach to protection against IR radiation. Topical application of these antioxidants to human skin prior to exposure has been shown to attenuate the detrimental effect on dermal gene expression associated with IR radiation.¹⁰⁷

In view of the above, some photoprotective products have included protection against IR radiation according to their labels. However, it is difficult to interpret such assertions in the absence of any standardized method for measuring the index of protection against these rays. Some authors have proposed the minimal heating dose of the skin as a measurement method,¹⁰⁸ but this approach does not appear very useful since IR-A, the most damaging portion of IR radiation, unlike IR-B and IR-C, does not generate heat.

Conclusions

As we have seen, a large number of substances of very different kinds and through different mechanisms exercise a photoprotective effect on the skin, mitigating the damaging effects of solar radiation. However, many questions remain concerning the type of photoprotection

we need. There is no doubt that excessive exposure to the sun is harmful to the skin and eyes. In fact, UV radiation has been included in the Tenth Report on Carcinogens published by the National Institute of Environmental Health Sciences.¹⁰⁹ On the other hand, sunlight is also vital to our wellbeing, conferring important health benefits, many of which are mediated by the synthesis of vitamin D.¹¹⁰ Modern sunscreens are very useful in protecting against sunburn and probably in preventing photoaging and certain skin cancers. Nonetheless, improvements are needed to provide better protection against UV-A and IR radiation. Furthermore, it is imperative to ensure that sunscreens are safe. No effort should be spared to guarantee their photostability and lack of mutagenicity, to minimize their systemic absorption, and to make sure that they are safe for the environment. Finally, it is important to consider that while many of the substances discussed in this review have been shown to have significant photoprotective effects in animal models and in vitro, the safety and effectiveness of their use in humans must be demonstrated before they can be widely used. For all these reasons, we must educate the public on how to make proper use of the sunscreens currently available and stress the importance of wearing appropriate clothing and avoiding exposure during peak sunlight hours. Based on the evidence currently available, this is the message that all associations of dermatologists are transmitting to the general public.

Photoprotection is not, however, necessary at all times (for example when the UV index is below 3) or for all skin types (people with the darkest skin prototypes are at greater risk of vitamin D deficiency). There is growing evidence that vitamin D is essential for many processes in the human organism and that its synthesis in the skin and its intake, whether in food or in dietary supplements, must provide us with the quantities we need. This review highlights the emergence of new substances and strategies for photoprotection that use more physiologic and intelligent methods to protect us from the damaging effects of sunlight. We must seek a balance between protection from and exposure to the sun's rays that will allow us to avoid skin cancer while at the same time obtaining all the beneficial effects that sunlight provides.

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Conflict of Interest

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