Current challenges in photoprotection

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Electromagnetic radiation in the ultraviolet, visible, and infrared ranges all produce biologic effects. Ultraviolet filters are the most well-studied photoprotective measure for the adverse effects of ultraviolet radiation. Because of the reported endocrinologic effects of oxybenzone in animal studies, its effects on coral reefs, and its photocontact allergy potential, its use has been minimized in many countries worldwide. New developments in topical antioxidants and oral and subcutaneous agents (eg, Polypodium leucotomos extract, afamelanotide, nicotinamide) with photoprotective and antiphotocarcinogenic properties could potentially provide addition modalities for protection against the effects of visible light and infrared radiation. (J Am Acad Dermatol 2017;76:S91-9.)

Key words: afamelanotide; antioxidant; nicotinamide; oxybenzone; photoprotection; Polypodium leucotomos extract; sunscreen.

Although the need to prevent acute (erythema) and chronic (skin cancer and photoaging) skin damage resulting from exposure to ultraviolet (UV) radiation (UVR) (UVB and UVA) is well understood, the safest and most effective way to achieve this still presents a number of challenges, specifically, in the practical implementation of sun-protective measures. These include concerns about the safety of some currently available UV filters, whether sunscreens detrimentally affect serum vitamin-D levels, whether new nontopical agents can offer significant additional sun protection, and how to protect against recently identified harmful effects of radiation at frequencies outside the UV range of the solar spectrum.

It should be emphasized that although sunscreen products are excellent means of photoprotection, they should always be part of the total photoprotection package, which includes seeking shade, wearing protective clothing and a wide-brimmed hat, and using sunglasses.

Abbreviations used:

25(OH)D:	25-hydroxyvitamin D
CPD:	cyclobutane pyrimidine dimer
EPP:	erythropoietic protoporphyria
FDA:	Food and Drug Administration
MMP:	matrix metalloproteinase
ROS:	reactive oxygen species
SPF:	sun-protection factor
UV:	ultraviolet
UVR:	ultraviolet radiation

SUNSCREEN SAFETY AND EFFICACY

Oxybenzone

Oxybenzone (benzophenone-3) is an organic filter that absorbs both UVB and short-range UVA (UVA2). Because few other organic UVA filters have been approved by the US Food and Drug Administration (FDA), oxybenzone is widely used in the United States. Concerns were expressed about the safety of oxybenzone after reports of cases of allergic and photoallergic contact dermatitis and

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because of its potential for endocrine disruption reported in an animal model. Oxybenzone is the most common photoallergen among all the UV filters.[1] A 10-year retrospective analysis found that 70.2% of almost 24,000 patients patch-tested with UV filters between 2001 and 2010 had positive reactions to oxybenzone.[2] In 2014, oxybenzone was largely responsible for the naming of benzophenones as contact allergen of the year by the American Contact Dermatitis Society.[3] Potential endocrine effects of oxybenzone were identified in several in vitro studies[4-6] and an in vivo study showed dose-dependent estrogenic activity in 21-day-old rats fed doses of oxybenzone (≥1500 mg/kg/d).[7] It should be noted that the doses of oxybenzone used in the animal study were very high and the estrogenic potency detected was 1 million-fold less than the estradiol control.[8,9] Short-term studies that looked at topical application of UV filters including oxybenzone in human beings found that there were no significant UV filter–related alterations on the endocrinologic effects on either reproductive hormones[10] or thyroid function.[11] Mathematic modeling indicated that it would take 277 years using a sunscreen containing 6% oxybenzone used at 2 mg/cm^2 (the dose recommended for sun-protection factor [SPF] testing by the FDA) or 1 mg/cm^2 (reported real-life use) to achieve the systemic levels of oxybenzone achieved in the study in rats.[12] Oxybenzone has been in use in the United States since at least the early 1970s with no clinical report of estrogenic side effects. Thus, all current data indicate that oxybenzone is safe. Nonetheless, in the European Union the label of a sunscreen containing oxybenzone must include a cautionary statement (“contains benzophenone-3”) if the concentration is over 0.5%.[13] Oxybenzone has also emerged as a potential hazardous environmental contaminant. Water sampling studies have shown that it is not fully eliminated during waste water treatment,[14,15] and oxybenzone and its metabolites have been detected in fish, with antiandrogenic and antiestrogenic effects.[16,17] A genotoxic effect of oxybenzone on coral was recently reported in a laboratory study,[18] supporting earlier evidence of bleaching effects on coral in the Atlantic, Pacific, and Indian oceans,[19] and presenting a hazard to the viability of the reefs.

Outside the United States oxybenzone has been replaced in many sunscreens by other UV filters. These include broad-spectrum filters such as bemotrizinol and bisoctrizole, which are not currently available in the United States, and ecamsule, which is available in the United States only in products approved though the New Drug Application process. In 2015 the FDA announced that ecamsule, bemotrizinol, bisoctrizole, and 5 other sunscreen ingredients that had been awaiting approval in the United States through the Time and Extent Application process were not generally recognized as safe and effective, despite approval by regulatory agencies in many parts of the world.[20]

CAPSULE SUMMARY

- In addition to application of sunscreen, proper photoprotection consists of seeking shade, wearing photoprotective clothing and hat, and using sunglasses.
- Ultraviolet filters have been well established to be effective against the adverse effects of ultraviolet radiation.
- With increased understanding of the effect of visible light and infrared radiation, studies on antioxidants and oral and subcutaneous topical forms of photoprotection are ongoing.

Antioxidants

Traditional sunscreens provide effective protection against erythema but not similarly effective protection against the generation of reactive oxygen species (ROS) in the skin after exposure to UVR, especially UVA.[21] Therefore, antioxidants are incorporated in many sunscreen products because of their ability to scavenge and reduce levels of ROS, the primary mediator of oxidative damage to the skin.[22-24] Compared with sunscreen alone, the addition of antioxidants has been shown to suppress ROS formation by an additional 1.7-fold for SPF 4, and 2.4-fold for SPF 15 and 50 formulas, respectively.[25] Sunscreen with added antioxidant has been shown to be more efficient than sunscreen alone in suppressing other changes in the skin known to be induced to exposure to UVR such as development of pigmentation, depletion of Langerhans cells, and induction of matrix metalloproteinase (MMP)-9.[22-24] These and other data indicate that addition of antioxidants to sunscreens represents a potentially effective strategy to minimize UV damage. The antioxidants that have been studied include vitamins A (retinol), C (ascorbic acid), and E (α-tocopherol), and (−)-epigallocatechin-3-gallate, a polyphenol component of green tea. Antioxidants are inherently unstable compounds, however, so are difficult to formulate in an acceptable, stable, and biologically active composition for sunscreen products. A 2011 analysis of 12 commercially available US sunscreens

with added antioxidants listed in their labels indicated that 10 had no antioxidant power at all (measured as the compound's capacity to remove a certain number of free radicals in certain time intervals) and the other 2 had only low power.[26]

Nanoparticles

The safety of sunscreens containing inorganic UV filters of titanium dioxide and zinc oxide nanoparticles (single particles of diameter <100 nm) came into question after both were shown to induce formation of free radicals in vitro on exposure to UVR, which could potentially damage viable cells in vivo.[27] However, it should be noted that when used in sunscreen, nanoparticles are coated with materials to almost completely block emission of ROS into the skin and to reduce cytotoxicity by preventing adherence of the nanoparticles to cells. A number of recent reviews concluded there is no evidence of any related adverse consequences for human health.[27-30] Concerns that nanoparticles could penetrate the skin were investigated and—based on current evidence—nanoparticles appear to remain on the surface of the intact human skin.[27] Although they can lodge in hair follicles, they appear confined to the stratum corneum after topical application and do not penetrate the dermoepidermal junction. Although there is no evidence of percutaneous absorption or penetration of intact skin, there are insufficient data on inflamed skin where the epidermal barrier function has been altered, so care should be taken in applying nanoparticles in sunscreen in the individuals with altered skin barrier function. Other methods of photoprotection (eg, staying in the shade, wearing photoprotective clothing) is more appropriate for individuals in whom the skin barrier has been severely compromised, eg, in those with very severe eczema.

VITAMIN D

It has been suggested that blocking UVB with sunscreen could lead to vitamin-D deficiency by preventing the conversion of 7-dehydrocholesterol (also known as provitamin D) in the skin to previtamin D_3, the precursor of the biologically active vitamin D. Vitamin-D insufficiency/deficiency, defined variously as total serum 25-hydroxyvitamin D [25(OH)D] of 20 ng/mL or less (≤50 nmol/L)[31] or 30 ng/mL or less (≤75 nmol/L),[32] is associated with increased risk for fractures, falls, cardiovascular disease, cancer, diabetes, depression, cognitive decline, and death.[33,34] Deficiency in vitamin D can arise from insufficient production in the skin from UVB exposure and inadequate dietary intake, but may also be a result of genetic predisposition.[35,36] Several studies reported low serum 25(OH)D levels associated with sunscreen application.[37-39] However, a 2009 review of the available evidence concluded that although sunscreens can significantly reduce the production of UVB-induced previtamin D_3 when applied under strictly controlled conditions, in real life, normal use does not generally result in vitamin-D deficiency.[40] This is mainly because of inadequate application of sunscreen to the skin; most people do not apply it at the dose recommended for SPF testing (2 mg/cm^2), resulting in an in-use SPF that is a few-fold lower than the SPF on the label.

Supporting evidence that the use of sunscreens in real-life settings does not decrease serum 25(OH)D levels came from an analysis of data from 5920 adults in the 2003 to 2006 National Health and Nutrition Examination Survey, which concluded that frequent sunscreen use has no effect.[41] In contrast, seeking out shade and wearing long sleeves were significantly associated with lower 25(OH)D levels and vitamin-D deficiency [25(OH)D ≤20 ng/mL], especially in white individuals, but wearing a hat and using sunscreen use were not (Fig 1). These associations were much weaker in Hispanic and black adults. The authors suggested that the lack of association between frequent sunscreen use and lower serum 25(OH)D levels might be a result of application of sunscreen only before intentional prolonged sun exposure, which was reported in 2 studies in which use of sunscreens was associated with prolonged sun exposure[42] and sunburns.[43] Patients who practice rigorous photoprotection, such as those with lupus erythematosus,[44] erythropoietic protoporphyria (EPP),[45] or photosensitivity,[46] have low 25(OH)D levels (≤20 ng/mL). Similarly, in a recent investigation, 21 patients with xeroderma pigmentosum were found to have significantly suppressed levels of 25(OH)D (median 19 nmol/L).[47]

The American Academy of Dermatology cautions against obtaining vitamin D from unprotected exposure to UVR,[48] and supports recommendations from the Institute of Medicine for vitamin-D supplementation in individuals at risk for vitamin-D insufficiency, which include adults aged 71 years or older; individuals with limited sun exposure, with dark skin or fat malabsorption, and who are obese, because vitamin D is a fat-soluble vitamin; and breast-fed infants, because human milk is a poor source of vitamin D. According to recent US Preventive Services Task Force guidelines, although vitamin-D testing is widely available, current evidence is insufficient to assess the balance of benefits and harms of screening for vitamin-D deficiency in asymptomatic adults.[49]

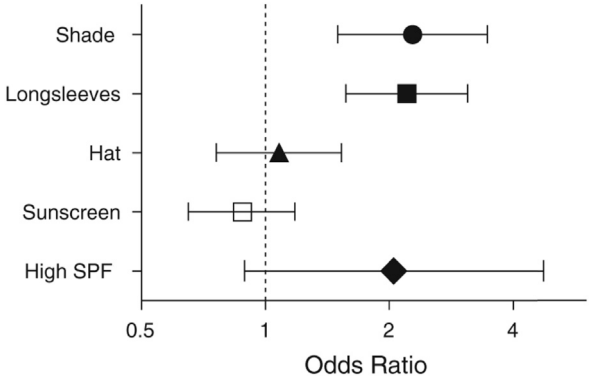

Fig 1. Odds ratio of vitamin-D deficiency comparing frequent with rare users according to sun-protective behaviors among US white individuals. *SPF*, Sun-protection factor. © Springer Science+Business Media B.V. 2011. With permission of Springer.[41]

ORAL AND SUBCUTANEOUS PHOTOPROTECTION

There is growing interest in the potential for oral and subcutaneous agents to provide additional protection against exposure to UVR and to further reduce damage that ordinarily would lead to photoaging and skin cancer. These agents are different from sunscreens in their mechanism of action, in the different end points important in measuring efficacy, and in the benefits of their use. Several orally and subcutaneously administered agents have been shown to have the potential to reduce the severity of a sunburn, decrease photosensitivity, and prevent photodamage; however, larger studies need to be done to confirm efficacy and safety. Several of these agents are in late stages of clinical development.

Polypodium leucotomos extract

Polypodium leucotomos is a fern plant (botanically known as *Phlebodium aureum*, *Polypodium aureum*, or *Polypodium leucotomos*) that is native to Central and South America, where it is used in traditional medicine. Extract of the plant is commercially available in many parts of the world as over-the-counter oral and topical formulations.[50] Studies with the oral formulation have shown it to be photoprotective against UVB- and psoralen plus UVA–induced toxicity,[51,52] development of polymorphous light eruption,[53-55] and possibly also solar urticaria.[53,54] Polypodium leucotomos extract increases the UV dose required for immediate pigment darkening, minimal erythemal dose, and minimal phototoxic dose.[51] A recently concluded short-term study of oral Polypodium leucotomos extract administered at 240 mg twice daily for 60 days in healthy individuals resulted in suppression of UVB-induced erythema.[56] The primary activities of Polypodium leucotomos extract appear to be antioxidative and antiinflammatory; it has a low SPF (3-8).

Nicotinamide

Nicotinamide is an active amide form of vitamin B_3 (niacin; nicotinic acid) widely available as an oral dietary supplement. It is a precursor of nicotinamide adenine dinucleotide, an essential cofactor for production of adenosine triphosphate, which is essential for skin immune response and DNA repair. Unlike niacin, oral nicotinamide does not have vasodilatory effects and is not associated with a cutaneous flushing reaction. Nicotinamide has been shown to prevent UVR-induced intracellular depletion of adenosine triphosphate,[57] boosting cellular energy and enhancing DNA repair[58,59] and preventing immunosuppression.[60] In 2 phase II trials, subjects with sun-damaged skin who took 500 mg of oral nicotinamide once or twice daily had, respectively, 29% and 35% fewer actinic keratoses at 4 months compared with patients on placebo.[61] In a recently reported phase III, double-blind, randomized controlled trial, Oral Nicotinamide to Reduce Actinic Cancer, patients with a history of 2 or more nonmelanoma skin cancers who were given nicotinamide 500 mg twice daily had 23% lower rates of new nonmelanoma skin cancers and 11% fewer actinic keratoses than the placebo group after 12 months (Fig 2).[62] This broad chemopreventive effect persisted with continuous treatment, but not after discontinuation of nicotinamide. There were no differences in side effects between the treatment and the control groups.

Afamelanotide

Afamelanotide is a structural analog of α-melanocyte-stimulating hormone that was shown to be beneficial as an adjunctive photoprotective agent in patients with EPP and solar urticaria. As an agonist of the melanocortin-1 receptor, afamelanotide promotes synthesis of melanin (eumelanin), which is photoprotective, and acts as an antioxidant. In clinical trials, it was administered as a controlled-release, subcutaneous implant that released the drug over approximately 2 weeks; melanin concentration was increased after 2 days, with the effect lasting up to 2 months.[63] After undergoing phase II and III clinical trials in Europe and the United States,[64-66] afamelanotide, administered as 16 mg subcutaneously every 60 days, received regulatory approval in Europe for prevention of phototoxicity in adult patients with EPP. In 2 randomized, double-blind, placebo-controlled phase III studies, in 74 European patients with EPP and in 94 US patients with EPP who each received 5 or 3 subcutaneous implants,

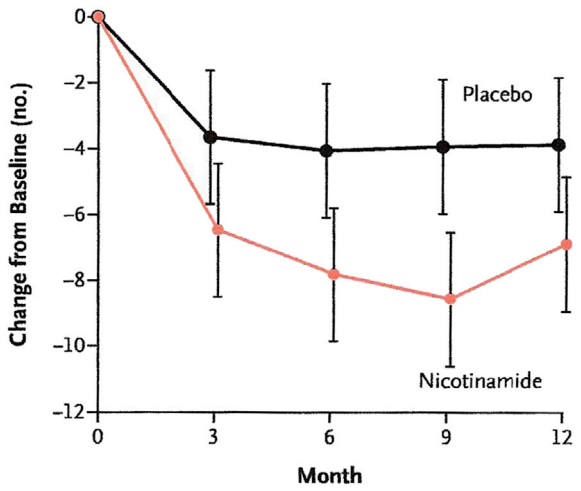

Fig 2. Change from baseline to month 12 in number of actinic keratoses, adjusted for center: 11% lower in the nicotinamide group than in the placebo group at 3 months (P = .01), 14% lower at 6 months (P < .001), 20% lower at 9 months (P < .001), and 13% lower at 12 months (P = .001). Copyright © 2015 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.[62]

respectively, every 60 days, those who received afamelanotide experienced significant improvements in duration of pain-free time under direct sun exposure compared with placebo.[66] Quality of life was also improved in both treatment groups, and adverse effects were mostly mild (consisting of headache, nausea, nasopharyngitis, and back pain). In the longer European study, phototoxic reactions were significantly less severe, with shorter recovery time in patients on afamelanotide. Afamelanotide has also been investigated as treatment of solar urticaria in a small study of 5 patients; it resulted in increased synthesis of melanin and an increase in tolerance to artificial light exposure.[67] It should be noted that a phase III trial with afamelanotide in polymorphous light eruption was started in 2007 and completed in 2010 (NCT00472901), and a phase II trial against actinic keratosis in organ transplant recipients was started in 2009 with unreported study conclusion (NCT00829192). The results of these 2 trials have not been published to date.

Topical endonuclease

Topical application of bacteriophage T4 endonuclease 5 in a liposomal lotion in patients with xeroderma pigmentosum was shown to decrease photocarcinogenesis process.[68] Studies are still ongoing.

PHOTODAMAGE

For a long time, the focus of photoprotection was prevention of the immediate effects of UVB/UVA. However, it is now known that chronic exposure to UVR, particularly UVA, and infrared (760-4000 nm) spectra, particularly those in the near infrared range (infrared A; 760-1400 nm), can result in photoaging changes. In addition, exposure to visible light (400-760 nm) results in pigmentary alterations lasting a few weeks in melanocompetent individuals. Consideration should therefore be given to photoprotection against visible light and infrared A.

Delayed photodamage

Until recently, generation of cyclobutane pyrimidine dimers (CPDs) was believed to only occur within picoseconds after irradiation with UVA or UVB. However, a 2012 study suggested that there might be 2 pathways for CPD generation in melanocytes when it revealed that CPDs could be readily detected in the skin of both albino and black mice irradiated with UVB (280-320 nm), but not with UVA (320-400 nm).[69] CPDs and 6-4 photoproducts were comparable in albino and black animals after UVB irradiation, but after UVA irradiation only thymine-thymine-CPD lesions were detected, at lower levels compared with UVB irradiation, and no 6-4 photoproducts were found. A more recent study showed that CPD production continues for several hours in melanin-containing murine melanocytes after UVA irradiation, whereas in melanocytes from albino mice, peak CPD induction is seen immediately after UVA exposure.[70] The CPDs produced later after irradiation were termed "dark CPDs." In mice with melanocytes containing red-yellow pheomelanin, rates of formation of both initial and dark CPDs were twice those in black mice, suggesting that pheomelanin is both a poorer protection against normal CPD formation and a more potent generator of dark CPDs. This is consistent with the observation that individuals with Fitzpatrick skin type I or II, who have high ratios of pheomelanin to eumelanin, are at higher risk for skin cancer. The proposed mechanism for the formation of dark CPD is that UVR induces ROS and nitrogen species that excite electrons in melanin to a high-energy triplet state moiety that transfers energy to DNA hours after UV exposure. This indicates that melanin may be carcinogenic and protective against cancer and underlines the importance of the use of sunscreen or physical protective agents. Systemic or topical antioxidants may be beneficial in preventing dark CPD formation.[70]

Visible light

Visible light (400-760 nm) accounts for 40% to 45% of the electromagnetic radiation that reaches the earth's surface. Few investigators have reported its

biological effects on human skin, but it has been reported to cause changes in pigmentation and erythema,[71-75] thermal damage and free radical production, and production of ROS.[24] In 2010, investigators using a light source emitting 98.3% visible light on skin types IV to VI showed that pigmentation induced by visible light was darker than that induced by long-wave UVA (UVA1, 340-400 nm, 20 J/cm^2) and at higher doses, surrounded by erythema that disappeared within 2 hours of exposure.[73] In contrast to UVA1, pigmentation induced by visible light was sustained over the 2-week period of the study and did not fade away even at lower doses. No pigmentation could be induced in skin type II, suggesting that the response to visible light and UVA is dependent on skin type. This suggests that visible light plays a role in conditions aggravated by sun exposure such as melasma and postinflammatory hyperpigmentation, which is especially common in darker-skinned individuals (skin phototypes III-VI). A subsequent study showed that pigmentation was induced in individuals with skin types III and IV with 415-nm, but not 630-nm radiation; the pigmentation lasted 3 months.[76]

Currently available organic (chemical) UV filters are not sufficient to protect the skin from the effect of visible light; only optically opaque filters such as nonmicronized form of zinc oxide and titanium dioxide, and iron oxide, are able to block visible light.[77] These compounds scatter and reflect visible light. Recent studies demonstrated that addition of these compounds to sunscreens provide greater protection in terms of decrease in Melasma Area and Severity Index score.[78,79] However these compounds are matt white or red in color, water-insoluble, and leave a white or tinted coating on the skin, which is unacceptable to many patients. Topically applied antioxidants may also be beneficial against the effects of visible light, as suggested by the findings that use of a photostable UVA/UVB sunscreen containing an antioxidant combination significantly reduced the production of ROS, cytokines, and expression of MMPs in vitro, and decreased oxidative stress in human skin after visible light irradiation.[24]

Infrared radiation

More than 50% of the solar radiation/energy that reaches earth is infrared radiation (infrared, 760 nm-1 mm). The most widely studied wavelength band is near infrared (infrared A, 760-1400 nm), which represents about one third of total solar energy and can penetrate human skin, directly affecting cells located in the epidermis, dermis, and subcutis. Exposure to infrared produces a perceptible increase in skin temperature.[80] Infrared is now recognized as having biological effects on human skin.[81,82] Infrared A irradiation include the activation of mitochondrial ROS via up-regulation of MMP-1, -3, and -13, without concomitant up-regulation of tissue inhibitor of metalloproteinase-1, resulting in collagen degradation.[83] Repeated exposure to infrared A is associated with the appearance of coarse wrinkling, a characteristic of photoaging, in the skin of mice[83] and human beings.[84] In mouse skin, wrinkle formation was greater with infrared A plus UVR than with either infrared A or UVR alone, indicating that infrared A causes photoaging through different mechanisms. Infrared A has also been shown to reduce type 1 collagen expression by inhibiting the production of procollagen-1-stimulating transforming growth factor-β1, -β2, and -β3,[85] and to induce angiogenesis in human skin through increased expression of vascular endothelial growth factor,[86] and it has been shown to increase numbers of mast cells. Infrared A has been shown to confer resistance to UV-induced apoptosis via reduction of DNA damage and up-regulation of antiapoptotic proteins.[87] Some studies of the effects of infrared A have been criticized for using artificial infrared A sources of higher intensity than real-life daily exposure with the result that skin damage caused by infrared A at real-world intensities has not been conclusively demonstrated.[88]

Currently there are no organic (ie, chemical) or inorganic (ie, physical) filters specifically directed against infrared A; claims that sunscreens protect against infrared A–induced skin damage are not regulated. Sunscreens with infrared A-reflecting inorganic filters such as titanium dioxide would be effective, but it is unlikely that they would be widely used (see Young et al). The demonstration that ROS plays a crucial role in the pathogenesis of infrared A–induced skin damage has led to the testing of antioxidant agents. Topical application of β-carotene (2 mg/cm^2) was reported to protect human skin exposed to infrared radiation.[89] In a proof of principle study, topical application of a commercially available antioxidant mixture containing vitamin C, vitamin E, ubiquinone (coenzyme Q10), and a grape (Vitis vinifera) seed extract effectively prevented infrared A–induced MMP-1 messenger RNA expression in vivo in human skin.[84] The same mixture added to SPF 30 sunscreen applied by 30 healthy volunteers significantly reduced MMP-1 messenger RNA expression compared with SPF 30 sunscreen alone.[90] Grape seed extract includes several flavonols (catechin and epicatechin), procyanidins, and phenolic acids, all of which have been reported to act as antioxidants.[91] Grape seed extract is marketed

widely as a dietary supplement. Another combination being tested is a mixture of topical ferulic acid and vitamins C and E, which was reported to reduce infrared A–induced MMP-1 up-regulation in human skin by 60%.[92] Ferulic acid was shown to inhibit the expression of MMPs and decreases the degradation of collagen fibers.[93] However, further studies of these agents are needed, as are defined criteria by which consumers can judge the efficacy of infrared A protection of a product from its label.

Summary

Electromagnetic radiation in the UV, visible, and infrared ranges all produce biologic effects. UV filters are the most well-studied photoprotective measure for the adverse effects of UVR. Because of reported endocrinologic effects in animal studies, adverse effects on coral reefs, and its photocontact allergy potential, oxybenzone use has been minimized in many countries worldwide and other UV filters introduced. New developments in topical antioxidants and oral and subcutaneous agents (eg, Polypodium leucotomos extract, afamelanotide, nicotinamide) with photoprotective and antiphotocarcinogenic properties could potentially provide addition modalities for protection against the effects of visible light and infrared radiation. It should be emphasized that although sunscreen products are excellent means of photoprotection, they should be used in conjunction with other protective measures including seeking shade and wearing protective clothing.

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