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REVIEW ARTICLE

New trends on personalized sunscreens

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Abstract

Background/Purpose: Nowadays, there are emerging trends in customized and personalized photoprotection, focusing on the innovative approaches to enhance sun protection efficacy tailored to individual needs.

Methods: We conducted an electronic search of the following databases: MEDLINE, EMBASE, Cochrane Database of Systematic Reviews, Cochrane Skin Group Specialised Skin Register, and TESEO. Specific search terms related to personalized photoprotection and the variables of age, genetic predisposition, skin phototype, photodermatosis, and physiological conditions such as pregnancy, as well as lifestyle habits were used.

Results/Conclusion: The article highlights the challenges and opportunities in adopting personalized photoprotection strategies, aiming to promote skin health and prevent the harmful effects of UV radiation in the era of precision medicine.

KEYWORDS
individualized medicine, photoprotection, sunscreens

1 | INTRODUCTION

Sunscreens are an important aspect of photoprotection, and they were developed to prevent sunburn.[1] Excessive sun exposure has been recognized as a major cause of skin cancer. UVB radiation was the main culprit of photocarcinogenesis, but in the nineties, UVA radiation was discovered as a principal agent not only in the production of reactive oxygen species and an important inductor of photoaging but also in its role in DNA damage.[2–6]

In the last decades, the role of less energetic radiations, such as long UVA, blue light, and near-infrared radiation (i.e., infrared A; IRA), have been highlighted. The participation of IRA in photoaging in a synergistic way with UVA radiation was proposed by Kligman,[7] and later, Krutmann studied its action through the mitochondria.[8]

The more recent finding on the importance of long UVA and visible light/blue light-induced hyperpigmentation in dark-skinned persons suggests the necessity to introduce effective photoprotectors against these radiations in sunscreens.[9]

Globally, there are differing needs for photoprotection, including the use of sunscreens. There are environmental, genetic, and socioeconomic factors (collectively known as exposome) that can influence the need for photoprotection. These include the place of living (latitude and pollution), time of the year, occupation, recreational activities, a proper understanding of side effects of sun exposure, or the financial ability to purchase photoprotective clothing and sunscreens. But also, there are personal circumstances: age, genetics, the capacity to get sunburn known as skin phototype, the constitutive color of the skin, the existence of some dermatoses, the

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presence of photodermatoses, the intake of photosensitizing medications, impairment of the skin barrier, and physiological states such as pregnancy. All these circumstances make it necessary to adapt the photoprotective behavior and the sunscreen based on the specific needs of each individual, a concept of personalize and customized photoprotection.[10]

2 | INDIVIDUAL CHARACTERISTICS

2.1 | Children

The use of sunscreen in younger children and individuals with sensitive skin requires special attention, since absorption and allergen sensitization are of concern.[11]

Regarding active ingredients of sunscreen, oxybenzone (benzophenone 3, BP3) can be detected in human urine up to 48 h after application and also penetrates human skin in vitro.[12] In fact, in a population study, it was found in 97% of the subjects studied, including children over 6 years of age.[13] But there was no evidence of endocrine alteration of the hypothalamic–pituitary–gonadal axis in adults.[14] However, dermal exposure of female rats to BP3 in the concentration of 100 mg/kg, which gives the plasma levels of BP3 comparable to those seen in humans using cosmetics containing this compound,[15] resulted in the increase in lipid peroxidation and a decrease in antioxidant activity in their frontal cortex and hippocampus.[16] BP3 is the most common UV filter causing allergic reactions in many studies. BP3 was named allergen of the year for 2014 by the American Contact Dermatitis Society[17]; in the largest reported series of sunscreen photopatch testing, 4.5% of the children had positive photoallergic reactions to UV filters and mainly to BP3.[18] In a recent research aimed to study the UV filters in sunscreen products labeled specifically for "kids" or as "sensitive/hypoallergenic" and compare these to general sunscreen products, BP3 was not commonly found in sunscreens designated for "kids."[11] It should be noted due to controversies on the environmental and health impacts of BP3, the use of BP3 in sunscreens in EU and the United States has decreased significantly in recent years.

Methylene bis-benzotrizolyl tetramethylbutylphenol (Tinosorb∅M or MBBT)-based sunscreen agents have been reported to cause allergic contact dermatitis in adults due to excipient, decyl glucoside.[19] The alkyl glucosides family was named allergen of the year for 2017 by the American Contact Dermatitis Society.[20] In children, MBBT was more commonly found in sensitive products than in non-sensitive products.[11]

In one study conducted in the United States, they showed that products marked as suitable for sensitive skin in children had significantly fewer allergens, but a majority of these products still had at least one allergen.[21]

Contact dermatitis can develop following repeated application of aluminum-containing sunscreens (2%) in children with aluminum sensitization and vaccination granulomas; therefore, we must be alert in this group of patients and avoid it.[22]

Oil-based emulsions of inorganic filters such as titanium dioxide and zinc oxide are preferred to organic filters for infants and children because they offer broad-spectrum protection and have minimal irritation, sensitization, and skin penetration potential.[23] Thanks to nanotechnology, smaller molecules, between 20 and 50 nanometers compared with the usual 200–300 nanometers in previous formulations, have been produced. The nanoparticles are easier to apply and are transparent on the skin; however, doubts arise about whether their smaller size (4 and 60 nm) may favor their absorption through the skin and, therefore, their toxicity.[24,25] Titanium dioxide, TiO_2, nanoparticles can remain in an aggregated form in the outermost layers of the epidermis, both in intact skin and in skin irradiated with a solar simulator, so care must be taken in children especially those with atopic dermatitis.[26] It is because exposure to TiO_2 nanoparticles under skin barrier dysfunction/defect can exacerbate atopic dermatitis symptoms through Th2-biased immune responses. Furthermore, TiO_2 nanoparticles can play a significant role in the initiation and/or progression of skin diseases following the barrier dysfunction/defect by histamine release even in the absence of allergen.

2.2 | Elderly

Little has been described about photoprotection in the elderly; however, at this time of life, we must focus not only on photoaging but also on the higher incidence of keratinocyte skin cancer, as well as greater photosensitivity due to a higher probability of taking photosensitizing medications such as hydrochlorothiazide, atorvastatin, simvastatin, telmisartan, and metformin.[27]

The aging process, both intrinsic and extrinsic, is also believed to be influenced by the formation of free radicals, also known as reactive oxygen species. When sunscreen is applied as recommended, it tends to reduce free radical formation by only 55%. However, the reduction in free radicals can be enhanced by adding antioxidants to sunscreen formulations.[28]

There has been a lot of research conducted on anti-aging and sunscreen products to enhance their efficacy, stability, and safety and be more favorable to consumers.[29] So far, sunscreen creams have been incorporating products to prevent photoaging such as microspheres with vitamin E, topical peptides, or fetal stem cells.[29]

Niacinamide has been widely used in halting the features of aging by acting as an antioxidant, not as an ultraviolet filter, but like a DNA repair agent, and by preventing dehydration, but also topical delivery of niacinamide to the skin using hybrid nanogels enhances photoprotection effect.[30]

Not only the addition of active components is important in effectiveness but also the formulation is fundamental in cosmeticity, so nanoparticles are increasingly used in anti-aging and sunscreens. Nanotechnology in sunscreens allows for improved UV protection while maintaining desirable cosmetic properties, making them more effective and appealing for everyday use. Their stability, high entrapment efficiency, and enhanced skin penetration make it

advantageous over the conventional counterparts.[31] Thanks to this, a greater penetration and therefore a greater effect when nanotechnology is used can be reached.

However, there is an active debate on the alarming impact that TiO_2 NP seepage into bodies of water can cause on the environment and aquatic life, and the effect that it can have on human skin and health, in general, especially if it penetrates into the human body and the bloodstream.[25] Examples include the formulation of epigallocatechin-3-gallate and hyaluronic acid in transferosomes or the use of cationic liposomes to ensure intercellular delivery of antioxidants including vitamin C and E for deeper penetration into the dermis layer.[32]

Instead, the term "active photoprotection" has been suggested to refer to therapy and protection; these are photoprotectors that contain DNA photolyase, as complementary therapy for the management of the field cancerization disease, which is more common in the elderly. Photolyase is an enzyme that recognizes and directly repairs UV-induced DNA damage. It has been shown that the application of a SPF >100 sunscreen with photolyase for 3 months significantly reduced the number of actinic keratoses (AKs), and improved Baseline Severity Index (BSI) and Total Clinical Score (TCS). Clinical studies evaluating the histological and cellular effects of a sunscreen containing DNA photolyase have shown a potential benefit in the treatment of the cancerization field in AK patients.[33–35]

Recent clinical studies have shown that the addition of DNA repair enzymes (photolyase and endonuclease) to traditional sunscreens may reduce ultraviolet radiation (UVR)-induced molecular damage to the skin to a greater extent than sunscreens alone.[35,36]

2.3 | Skin of color

All individuals, regardless of skin phototype, are subject to the potential adverse effects of ultraviolet radiation and will benefit from sunscreen use.[23]

Dark skin has specific characteristics that protect it against ultraviolet radiation (UVR), such as a higher concentration of melanin, its distribution in more superficial layers, a higher eumelanin/pheomelanin ratio, and a more efficient DNA repair following UVB exposure (compared with light skin).[37] This is manifested in individuals with high phototypes to have lower rates of skin cancer and later signs of photoaging than individuals with low phototypes.[38,39] For that reason, individuals with high phototypes practiced fewer photoprotection measures, and dermatologists tended to recommend the practice of photoprotection less frequently.[40,41] It is partly a misperception; dark-skinned individuals do need to practice photoprotection, but we need to give them a different recommendation than light-skinned individuals, hence the importance of "personalized photoprotection."

However, in higher phototypes there is a higher incidence of pigmentary disorders, such as post-inflammatory hyperpigmentation and melasma. In fact, visible light induces more durable hyperpigmentation than UVA irradiation in dark phototypes.[42] At a mechanistic level, blue light induces melanin production by activating the photoreceptor opsin-3, which acts on the transcription factor Mitf, controlling tyrosinase expression and thus melanin production. In addition, blue light also generates reactive oxygen species (ROS), which causes photo-oxidative damage to DNA and cellular structures, for example, by inducing matrix metalloproteinases (MMPs) secretion.[43]

In this group when photoprotection is recommended, those with a broad spectrum with a high index against UVA and protection against visible light are effective in various hyperpigmentation disorders, including melasma.[9]

Colored sunscreens based on pigments (iron oxides) and pigmentary, non-nanosized inorganic filters (zinc oxide and titanium dioxide) can also be recommended. Colors sunscreens protect not only against UVB and UVA (including UVA1 and UVA2) but also against light visible, showing up to 85% attenuation of UVR with wavelengths from 415 to 465 nm (visible light).[44] These products should preferably be color-matched to the constitutive skin color of the user to maximize compliance.[44] Universal shade-tinted sunscreens are usually acceptable to dark-skinned individuals; however, they are still quite noticeable in those with very light or very dark skin.[40]

The use of broad-spectrum photoprotectors containing depigmenting agents is a novel strategy for the treatment of hyperpigmentation disorders and could increase therapeutic adherence. Among the potentially useful active ingredients are the tyrosinase inhibitors that have been shown to be useful in the management of melasma such as some derivatives of resorcinol, tetrapeptide-30, and niacinamide. Based on current data, the treatment of melasma using niacinamide 4% or isobutylamidothiazolyl-resorcinol 0.2% has achieved similar results to those reached after treatment with hydroquinone 4%.[45,46]

Recently, the practical recommendations for individuals with skin of color from an expert panel are the use of a sunscreen with SPF30+, broad-spectrum [ultraviolet (UV)B/UVA] protection with high sun protection factor, as well as protection against long-wave UVA (UVA1) and visible light, as these wavelengths are capable of inducing or augmenting pigmentary disorders.[47] They may also contain depigmenting agents for patients with pigmentary disorders.[9]

2.4 | Pregnancy

Pregnancy is associated with many rapid biological adaptations that support the healthy development of the growing fetus.

Two studies by FDA scientists studied sunscreen application among healthy participants. In this study, six filters (avobenzone, oxybenzone, octocrylene, homosalate, octisalate, and octinoxate) were administered in four different sunscreen formulations. All filters were absorbed systemically and had plasma concentrations that surpassed the FDA threshold for potentially waiving some of the additional safety studies for sunscreens.[48,49] However, these findings

do not indicate that pregnant women should refrain from using sunscreen, because melanoma can arise at any age and approximately one-third of female patients diagnosed with melanoma are of childbearing age.[50]

Oxybenzone (BP-3), with a molecular weight of 228 g/mol, can be systemically absorbed through the skin, may pass through the placental barrier, and can be found in breast milk.[49]

Studies performed in animal models showed that after topical application, BP-3 can penetrate into bloodstream, blood–brain barrier, and blood-placental barrier and may induce reproductive toxicity and abnormal development of the fetus, endocrine system disruption, and neurotoxicity.[49,51] This fact has generated a controversy,[52] since it has been reported a possible relation between Hirschsprung disease and BP-3.[53] In vitro studies showed that BP-3 exposure was associated with the inhibition of cell migration and a dose–response correlation was observed between BP-3 exposure dose and tyrosine-protein kinase receptor expression.[53,54] However, it is unclear whether this directly causes these effects, especially since the association in real-life situations was based on a single urine sample taken at an unspecified time after pregnancy, and the suggested mechanisms were only observed in laboratory studies. Human studies on this are limited and conflicting.[55,56]

Until this situation is clarified, pregnant women and children should pay special attention to the composition of sunscreens. For their own safety, they should look for the alternative photoprotection including sunscreens with mineral/inorganic UV filters, protective clothing, and avoidance of sun exposure during midday hours.

We must pay attention to the use of titanium dioxide nanoparticles in sunscreens, since in a study using a murine model, D'Errico et al.[57] identified the systemic distribution and placental accumulation of Ti after nano-TiO_2 aerosol inhalation in a pregnancy model with adverse pregnancy outcomes, even with biological impacts that persist in at least two generations[58] However, no data have been reported in humans although TiO_2 has been used in sunscreens since 1952.

2.5 | Photodermatoses

Sunscreens are an integral component of photoprotection in the management of photodermatoses.

Mexoryl 400 and TriAsorb are two new filters, especially useful for visible/UVA light-induced photodermatoses such as solar urticaria/solar angioedema or porphyria in which the action spectrum lies in the visible range at 400–410 nm (Soret band).[59,60]

Furthermore, the sun filter (TriAsorB) remained mainly on the skin surface after topical application, without being absorbed even with damaged skin such as it could happen in patients with photodermatosis.[61]

Additionally, these two filters, Mexoryl 400 and TriAsorb, can be very useful in polymorphous light eruption (PLE), lupus erythematosus, dermatomyositis, and drug-induced phototoxicity since the clinical guidelines indicate that sunscreens with high SPF and high UVA-PF, with an SPF/UVA-PF ratio close to 1, are necessary for the management of these photosensitivity disorders.[9]

The latest developments to prevent PLE consist of adding other components to sunscreens. A high broad-spectrum sunscreen medical device, containing a very high protection complex of UVB and UVA filters and 1% of ectoin, a naturally occurring molecule, classified as a compatible solute or osmoprotectant, which means it helps organisms maintain cellular function and stability under stressful conditions, and also, ectoin may be effective in preventing UVA-induced PLE.[62] Another possibility is the simultaneous administration of acetyl-11-keto-β-boswellic acid (AKBA), a derivative of boswellic acid, loaded ZnO nanoparticles of which drug release behavior is UV-controlled has been successfully synthesized. Such nanoparticles can not only reflect UV but also transfer the energy to release AKBA, which presents excellent antioxidant and anti-inflammatory effects.[63]

All the tips on personalized photoprotection according to individual characteristics are summarized in Figure 1.

3 | LIFESTYLE

3.1 | Outdoor workers

In the last years, there has been an increasing interest in the occupational UVR exposure and there are many articles that evidence a higher risk of keratinocyte carcinomas in outdoor workers, such as mountain guides, farm workers, or workers of ski resorts.[64–66] This circumstance makes it necessary to adapt the photoprotection behavior and the sunscreen used to different outdoor workers' situations.

Of course, the first and most important photoprotection measures for this group of population are clothes and hats. Regarding the sunscreen, used as a complement to the previous ones, it should equally protect against UVB and UVA. There are no studies showing a superiority of higher vs lower SPF in outdoor workers. When applied properly, a SPF 15 or higher decreases the risk of skin cancer and early skin aging caused by the sun. However, most of the Dermatological Societies recommend to use at least a SPF 30 considering that the amount of sunscreen applied is lower than the tested one, which decreases significantly the SPF in real life (High-SPF sunscreens (SPF > 70)) may provide ultraviolet protection above minimal recommended levels by adequately compensating for lower sunscreen user application amounts.[67] Instead, considering the clinical trials performed in situation of intense sun exposure, such as the beach or ski resorts, a SPF 100 is better than SPF 50 to prevent sunburn, therefore maybe for workers in these environments.[68,69] Regarding photoprotection against UVA radiation, it is recognized that UVA contributes to skin cancer formation, and it is the main radiation involved in photoaging and also hyperpigmentation[70]; in addition, the amount of UVA radiation received is more constant and abundant throughout the day and during all seasons of the year than UVB radiation; therefore, a very good UVAR protection is necessary for outdoor workers.[71]

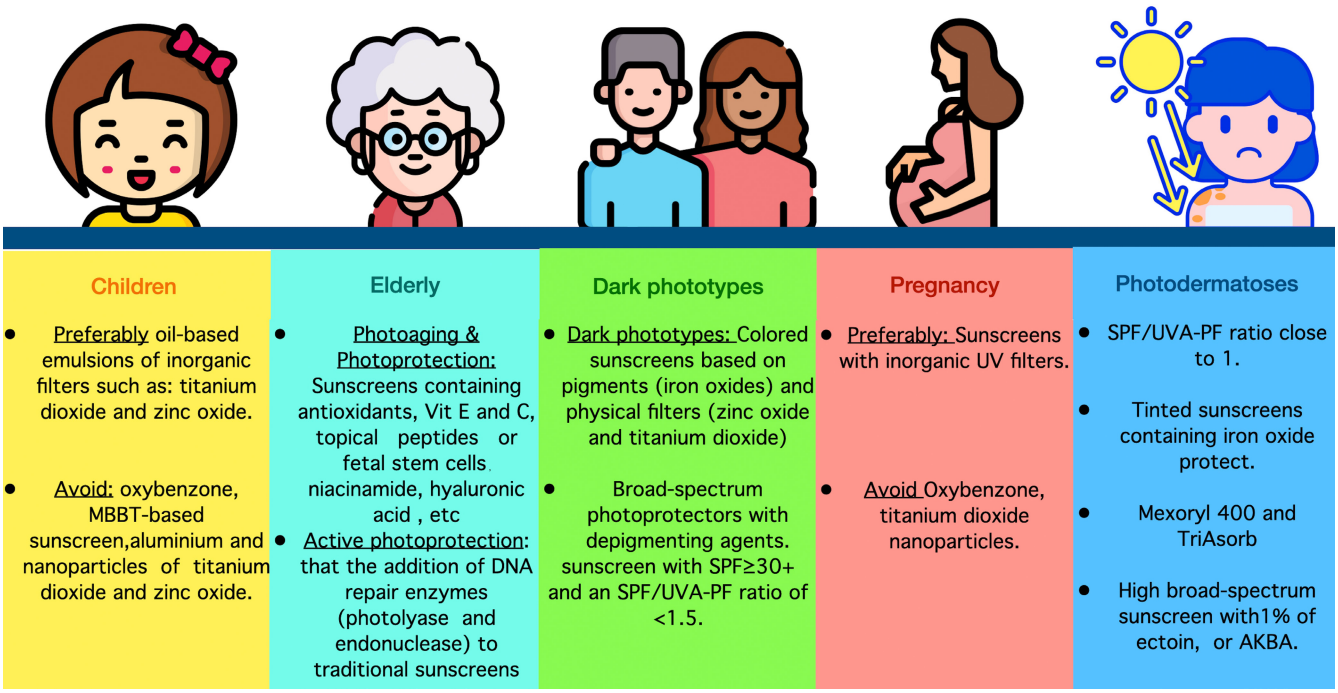

FIGURE 1 Personalized photoprotection strategies according to individual characteristics.

Substantivity is also something important for outdoor workers, since many workers may not be able to reapply the sunscreen every 2 h.

Instead, there are people who work in contact with water, such as sailors, or have a physical work and as a consequence they sweat; therefore, water-resistant sunscreen are recommended. Puccetti et al. measured the water resistances in the UVA and UVB radiation and considered as representative of the respective active filters in each spectral range, being the UVA results dominantly due to avobenzone and zinc oxide, whereas UVB values mainly stem from octocrylene, homosalate, and octisalate filters, although most products show lower water resistances in salt water than in tap water which is due to the destabilizing effect of salt ions on the sunscreen films on skin.[72]

There are no studies on drivers, who also have shown to be more susceptible to suffer the effect of mostly UVA radiation, which is photoaging and in a lesser degree skin cancer.[73,74] In this population, a sunscreen with good protection against short and long UVA, besides visible light, would be the best option.

Finally, it has shown a high prevalence of photodamage and actinic keratoses in some of these outdoor workers,[66] the use of "active photoprotection," with DNA photolyase is a good option to this group since they would be treating the cancerization field.[75]

Considering that outdoor workers should apply sunscreen every day for many years, the minimum necessary number of filters, at the lowest concentration and those with less capacity of penetration and more respectful with the environment should be recommended. Therefore, Meroxyl S and XL, tinosorb M and S, and inorganic filters (e.g., zinc oxide) are preferable compared with oxybenzone, octocrylene, octinoxate, and ethylhexyl salicylate.[76]

3.2 | Sports

There are some similarities between the groups of outdoor workers and the athletes: They spend a lot of time exposed to UVR training or playing sports, and they can be exposed to water and clearly to sweat, and some studies have shown an increased risk for skin cancer.[77]

Perspiration negatively affects the performance of a sunscreen film by weakening its substantivity and uniformity by sunscreen wash-off and sunscreen redistribution.[77] Keshavarzi et al.[78] found that using a combination of hydrophobic film formers, which increase water resistance, and small water-absorbing particles, which change the wetting behavior, can make sunscreen formulations more sweat-resistant and to have better substantivity.

Gilaberte et al. based on a review of the literature of photoprotection in sports recommended applying sunscreen irrespective of the UV index (UVI); sunscreen should be at least SPF 30; however, they recommended SPF 50 and up to 100 for snow sports and water sports such as surfing or sailing. Also, secondary performance attributes matter, such as sunscreens that are easy to spread, non-greasy, non-sticky, suitable for use on wet skin, non-irritating to the eyes, sweat resistant, and not causing loss of grip are more likely to be used consistently.[79]

Worth noting that in watersports, the sunscreens can contaminate the water. It has been shown that the concentration of organic filters has seasonal variations[80] and also has been identified in chlorinated water. Organic filters can react with chlorine to create hazardous by-products called brominated transformation products. Manasfi et al.[81] examined chlorinated saltwater pools for the presence of dioxybenzone, oxybenzone, avobenzone, octinoxate, and

octocrylene and the only UV filter studied that did not react with chlorine was octocrylene. In the last years, the worry about coral reefs worldwide has increased, being oxybenzone named a threat to these coral reefs and has been implicated in coral reef bleaching[82]; however, this is still controversial, therefore, a closer examination of all available evidence on the causes of coral reef bleaching needs to be undertaken, including a more thorough appraisal of studies conducted under artificial conditions using higher concentrations of sunscreen ingredients.

4 | PLACE OF LIVING

4.1 | Urban photoprotection

It has shown that people exposed to highly polluted environments, pollutants, and sunlight may synergistically damage the skin, requiring a specific protection, considering the effects of pollution an emerging aspect of the "skin exposome."[83] Recent studies suggest that pollution accelerates the occurrence of wrinkles and dark spots on the face, having the pollution an impact on extrinsic aging.[84]

Vierkötter et al. investigated signs of skin aging in 400 Caucasian women aged over 70, living either in a polluted industrial area (Germany) or in a rural area, and they found a significant association between traffic-related airborne particles and signs of skin aging such as pigment spots and wrinkles.[85] Similarly, Peng et al.[86] studied skin aging symptoms in 400 Chinese women living in two zones of Beijing differing in their average levels of fine particulate matter (low vs high PM2.5), showing that senile lentigo on the cheeks and the backs of the hands was 1.48 and 2.8 times more prevalent in the population exposed to particulate matter.

There are new studies focusing on this aspect, which are looking for new molecules that can reduce skin damage due to pollution. Because oxidative damage generated by the interaction of pollutants and sunlight is thought to be the major mediator of skin damage, antioxidants that can scavenge ROS could be good candidates to incorporate into sunscreens (i.e., GA, polyphenols, licochalcone, and polypodium leucotomos extract) (PLE).[87]

Fernblock®, a standardized aqueous extract of the fern PLE, has been widely administered both topically and orally with a strong safety profile. Fernblock® as a part of topical sunscreen can prevent the increased oxidative stress and DNA damage produced by the synergistic effect between BaP and UVA radiation, and promote the overexpression of the opsin-3 photoreceptor, a protein that is directly related to melanogenic cellular pathways.[88]

4.2 | Latitude, altitude, and season

The UVR varies depending on the latitude, altitude, and season; the sunscreens used have to be adapted to all conditions. The amount of UVR exposure increases in latitudes closer to the equator, and consequently the incidence of skin cancer.[89] At higher latitudes, the sun is lower in the sky, so UV radiation must travel a greater distance through ozone-rich portions of the atmosphere and, in turn, less UVR is received.[90] Regarding altitude, for every 1000 m increase in elevation, the UVR intensity increases by 10–12%.

FIGURE 2 Graphical representation of customized photoprotection according to the lifestyle and the place of living.

During summer, the sun is higher in the sky, and less UVR is absorbed during its passage through the atmosphere, so the UVR exposure in higher.[90] Finally, the UVR not only depends on the latitude, altitude, or season, which are stable parameters, the UVR can be affected by weather conditions, fog, haze, clouds, and pollutants, which reduce ultraviolet levels by 10–90%. Finally, it is important to consider that snow, sand, and metal can reflect up to 90% of UVR, and seawater can reflect up to 15%, whereas little reflection occurs on still water.[90] All these situations should influence in the SPF and UV PF factor of the sunscreen used.

Recommendations on customized photoprotection according to the lifestyle and the place of living are illustrated in Figure 2.

5 | CONCLUSION

Everybody needs photoprotection! Some to protect their skin from sunburn, others to prevent skin cancer, those with dark phototypes to avoid hyperpigmentation, persons with photodermatoses as a fundamental part of their treatment, and many as part of their esthetic routine to minimize photoaging. Sunscreens have become essential in daily life, from childhood to elderly, in cities, beaches and mountains, in summer and winter, working or practicing sports outside, etc., almost always. Therefore, photoprotection can neither be the same in all these circumstances nor for all types of individuals.

In this review, we have summarized the main concept of personalized topical photoprotection, which is providing recommendations on the use of different types of sunscreens. It should be emphasized that comprehensive photoprotection includes avoiding sun exposure in the mid part of the day, seeking shades when outdoors, and using parasol, photoprotective clothing, wide-brimmed hat, and sunglasses, and applying sunscreen with SPF≥30 to SPF50+, with good UVA and VL protection, depending on skin phototypes, live style, occupation, and place of residence.

AUTHOR CONTRIBUTIONS

TGC, JA, ANB, HL, SG, and YG contributed to the preparation of the manuscript and critically modified it. ANB and TGC contributed to the preparation of figures. All authors contributed to the article and approved the submitted version.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflict of interest to declare.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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