The Open Dermatology Journal

Content list available at: https://opendermatologyjournal.com

OPINION ARTICLE

Personalized Medical Photoprotection: Determining Optimal Measures for Susceptible Patient Groups

Salvador González[1,*], María Victoria De Gálvez[2], Magdalena De Troya[3], Azahara Rodríguez-Luna[4,5,*] and Piergiacomo Calzavara-Pinton[6]

[1]*Department of Medicine and Medical Specialties, Alcalá de Henares University, Madrid 28805, Spain*
[2]*Photobiological Dermatology Laboratory, Department of Dermatology and Medicine, Faculty of Medicine, Medical Research Center, University of Málaga, Málaga, Spain*
[3]*Dermatology Department, Hospital Costa del Sol, Marbella, Spain*
[4]*High Performance Research Group in Physiopathology and Pharmacology of the Digestive System NeuGut-URJC, Department of Basic Health Sciences, Faculty of Health Sciences, Campus de Alcorcón, Universidad Rey Juan Carlos, Alcorcón, Spain*
[5]*Department of Pharmacology, Faculty of Pharmacy, Universidad de Sevilla, Seville, Spain*
[6]*Department of Dermatology, University Hospital "Spedali Civili", Brescia, Italy*

Abstract:

Background:

Increasing knowledge regarding the deleterious effects of sun exposure and the mechanisms of photodamage has enabled the development of tailored photoprotection strategies based on skin type and the existence of underlying conditions. Dermatologists play an essential role as they identify the specific skin photoprotection needs of their patients. This translates into specific recommendations of suitable protection measures, both in terms of the length and time of the day these patients can be exposed to the sun and the use of sun protection products.

Purpose:

Our purpose was to overview optimal photoprotection strategies for patients with dermatological pathologies or alterations. Methods: Increasing evidence supports the use of sunscreens containing not only organic and inorganic filters but also non-filtering biological ingredients that can enhance sunscreen protection efficacy. Examples of these biologicals are DNA repair enzymes, antioxidants including vitamins and other biological agents, including those of botanical origin.

Results:

Oral photoprotection is also an area of increasing interest that contributes to an integral protection against sun-related alterations.

Conclusion:

This article provides the skin care specialist with a simple, easy-to-use guide to identify appropriate measures for patients presenting pathologies or conditions requiring specific sun protection needs, including (but not limited to) photodermatoses (polymorphic light eruption, porphyrias); inflammatory dermatoses (atopic dermatitis, rosacea, psoriasis); pigmentation disorders (hyperpigmentation, vitiligo), photoaging, skin pre-cancerous lesions and cancers, and photosensitive or sensitized skin (patients undergoing specific drugs treatments or skin-related procedures), ensuring the choice of personalized protection for susceptible groups within the general population.

Keywords: Photoprotection, Sunscreens, Organic filters, Inorganic filters, DNA repair enzymes, Antioxidants.

Article History	Received: August 12, 2022	Revised: November 25, 2022	Accepted: December 12, 2022

1. INTRODUCTION

In recent years, much progress has been made to better understand the roles of solar wavebands in photocarcinogenesis, photoaging and photodermatoses, and the various biological pathways by which this damage occurs. Ultraviolet B (UVB) light essentially causes erythema and direct damage to DNA and skin immune defenses, while ultraviolet A (UVA) light causes indirect damage to skin structures through the formation of reactive oxygen species (ROS) leading to DNA damage, photodermatoses, melanogenesis, mitochondrial and extracellular damage. Visible light (VL), especially high-energy blue-violet light (HEVL) causes, or aggravates, photodermatoses, skin aging and hyperpigmentation, especially in darker skin phototypes (SPT III-VI), mostly by inducing oxidative stress. Chronic

* Address correspondence to this author at the Department of Basic Health Sciences, Faculty of Health Sciences, Universidad Rey Juan Carlos, Alcorcón, Spain; E-mail: azahararodriguezluna@gmail.com

exposure to infrared A (IR-A) radiation can accelerate skin aging through increased metalloproteinases (MMPs) expression. Due to the various effects exerted by the different wavelengths of the electromagnetic spectrum, photoprotection measures should take into consideration specific measures to contrast these wavelengths and the pathways activated, as well as individual patient physio-pathological skin conditions.

The first step to optimize photoprotection is to obtain an accurate diagnosis of the patient's skin condition and identify factors that could present a risk or promote the worsening of the pathology. Skin phototype is perhaps the single most important factor in determining skin response to solar radiation. However, other aspects such as lifestyle, exposure conditions, environmental factors (weather, climate, environmental contamination in the form of particles in suspension, toxic substances, *etc*.); as well as concomitant dermatological conditions such as inflammatory dermatoses, previous history of dermatological illnesses [1 - 5], hormonal imbalances [6 - 8] and use of photosensitizing drugs [9] need to be taken into consideration (Fig. **1**).

Once an accurate diagnosis of skin conditions and risk factors has been obtained and their biological implications understood, the physician can begin to evaluate photoprotection alternatives suited to the patient's needs. Different recent studies have begun to identify and set out specific UVB-UVA-VL protection measures for different skin phototypes and dermatological illnesses, particularly with respect to sun exposure habits and the use of filtering sunscreens [10, 11]. In addition to avoiding direct sun exposure and wearing photoprotective clothing (including hats and sunglasses), ideal filtering characteristics of sunscreens include very high SPF and lower UVA-PF formulations are required by lighter phototypes, whereas darker phototypes require less SPF, but more UVA-PF (including UVA1) and VL-PF [10, 12].

There is increasing evidence, however, that not all sun damage can be prevented with the use of sunscreens. Additional factors include incorrect and insufficient sunscreen application; lack of regular re-application; sunscreen inability to prevent the formation of every type of ROS; lack of photostability of some sun filters; non-uniform spectral filtering activity over the whole UVB, UVA and VL spectrum; inadequacy of SPF & UVA-PF designations to accurately consider all types of damage; damage caused by sub-erythemal doses of UV radiation, and scarce protection against visible light and IR-A. Many conventional organic and inorganic filters display one or several of these deficiencies, requiring the inclusion of other non-filtering biological actives and oral photoprotection to ensure optimal protection, especially in highly sensitive patient groups.

Our purpose was to overview optimal photoprotection strategies for patients with dermatological pathologies or alterations.

2. METHODS

An international panel of 5 experts in clinical dermatology, clinical photobiology, photoprotection and pharmacological pathways conducted a narrative review of the literature. We developed a comprehensive search with PubMed (2002 onward) including the keywords (non-MeSH) "photoprotection", "sensitive skin", "pathological skin", "biological filters", "photodermatoses", "inflammatory dermatoses", "pigmentation disorders", "sunscreen" and "oral photoprotection". The search was restricted to English and Spanish language articles.

3. RESULTS AND DISCUSSION

As indicated above, after conducting an extensive literature review, Chen and co-workers concluded that topical filters were not sufficient to provide complete protection and that "sunscreens with broad-spectrum UV protection only reduce free radical formation by 55% [13]." They suggested that topical delivery of antioxidants could "provide additional benefit to complement the protection from UV filters". In 2020, Schalka and Coelho Donato demonstrated that the presence of Fernblock®, a standardized extract from the fern *Polypodium leucotomos*, could significantly increase sunscreen efficacy with respect to DNA and immunoprotection, aging and pigmentation [14]. In 2021, Aguilera and co-workers demonstrated that this fern plant extract could increase HIF (Human Immunoprotection Factor) provided by UVA and UVB filters by 18% [15]. DNA repair enzymes such as endonuclease, photolyase and glycosylase have demonstrated important DNA repair activity *in vitro* [16 - 19]. Moreover, Fernblock® can provide biological protection against VL [20 - 22]; while tinted titanium dioxide and iron oxide provide a physical shield against VL radiation [23, 24]. The well-described DNA repair and lightening activities of niacinamide also make it an interesting component of sunscreen formulations [25, 26]. Based on patient skin characteristics and needs, physicians can improve prevention measures by seeking topical formulations which combine UVA and UVB filters with these non-filtering biological agents.

Due to often incomplete protection provided by sunscreen formulations (even those containing additional biological activities), oral sun protection can provide a useful tool to boost protection against skin damage, particularly important in patients with important photo-aggravated conditions. Oral photoprotection can help increase the natural resistance of the skin against sun damage, reducing erythema and preventing and/or repairing DNA and oxidative damage. Oral photoprotective actives with demonstrated efficacy include antioxidants (*e.g*. carotenoids), niacinamide [27] and Fernblock® [14, 28, 29]. Studies have shown that the use of Fernblock® can improve both the prevention and treatment of hyperpigmentation [30] and reduce relapse in patients with Actinic Keratosis (AK) [31]. It has also been shown to be a useful adjuvant in the treatment of photodermatoses [32] and vitiligo [33].

Table **1** provides a brief, but comprehensive, overview of optimal photoprotection strategies for patients with dermatological pathologies or alterations, including photodermatoses, photo-aggravated inflammatory dermatoses (lupus, dermatomyositis, atopic dermatitis, rosacea, acne and psoriasis), pigmentation disorders (hyperpigmentation, vitiligo), photoaging, photo-induced skin pre-cancer and cancer, and photosensitive or sensitized skin (drugs, procedures). Recommendations include filter selection, the use of additional non-filtering biological actives and the main features of specific cosmetic formulations, that were outlined in Table **2**. Also, we have illustrated strategies based on sun protection needs for healthy skin and patients with dermatological pathologies or alterations.

Table 1. Photoprotection strategies for patients with dermatological pathologies or alterations.

	PATHOLOGY		RISK FACTORS	MAIN PATHWAYS INVOLVED	SPECIFIC PHOTOPROTECTION INCLUDING NON-FILTERING BIOLOGICAL ACTIVES
PATHOLOGICAL SKIN	PHOTO-INDUCED SKIN PRECANCER AND CANCER AK/NMSC/CANCER/XERODERMA PIGMENTOSUM		- UVB, UVA - phototypes I-II - moderate / high sun exposure - pollution - previous history AK/NMSC	- DNA damage (P53, 8-OH-dG, CPDs & Dark-CPDs) - Immunosupression	- very high, broad spectrum protection - antioxidants & DNA repair actives - immunomodulating actives - oral photoprotection
	PIGMENTATION DISORDERS	HYPERPIGMENTATION	-phototypes III-V - moderate / intense sun / device exposure (UVA, VL) - pollution - hormones - inflammatory pathologies	- Opsin 3 - Tyrosinase activity - Oxidative stress: (NRF2/FOXO) - melanin photo-oxidation	- very high UVA, VL protection (incl. *e.g.* non-nano mineral filters, iron oxide, ...) - antioxidants - specific pigment-control actives - oral photoprotection
		VITILIGO	- genetics - autoimmunity - stress - antioxidant disturbance	- macrophage activation - Th17 type immune response - oxidative burst	- narrow-band UVB sun protection - anti-oxidant actives & specific pigment-control actives - immunomodulating actives - oral photoprotection
	PHOTOAGING		- UVA, IR - phototypes I-III - moderate / intense exposure - pollution	-Oxidative stress: (NRF2/FOXO Sirtuin 1, mTOR) - ECM alterations (fibrillins, elastin, MMP-1, cathepsin K) - Mitochondria damage	- very high broad spectrum + IR protection VL protection - antioxidants - oral photoprotection
	PHOTOAGGRAVATED INFLAMMATORY DERMATOSES	ATOPIC DERMATITIS	- pollution - barrier skin - Inflammation - dry climate	- Inflammation: IL1a - Filaggrin, loricrin, involucrin - Th imbalance: Th1 (IFN gamma), Th2 (IL31), Th17 (IL17), Th22 (IL-22), - cathelicidin LL37 (IL-1ß); ICAM and VCAM - microbiome imbalance	- high tolerability mineral filters or chemical filters - high, broad spectrum protection - anti-inflammatory & calming actives
		ROSACEA	- pollution - hot climate - alcohol - Stress -small intestinal bacterial overgrowth (SIBO) - Microbiome disturbance (Demodex)	- Inflammation (cathelicidin LL-37, NLRP3) - Neurovascular dysregulation (TRPV1, substance P)	- high tolerability mineral filters - very high, broad spectrum protection, incl IR to minimise heat - anti-inflammatory & calming actives - interference pigments - non-comedogenic, lightweight, non-greasy
		ACNE	- pollution - unsuitable cosmetic products (comedogenic, oily, occlusive, …) - Microbiome disturbance (*C. acnes*)	- Inflammation (NLRP3, NFKB, IL-12, IL-17). - IFG-1 - Akt/mTOR	- non-comedogenic, lightweight, non-greasy - high / very high broad spectrum protection (according to acne therapy being used) + VL protection to avoid PIH - matte finish
		PSORIASIS	- stress - pollution - smoking - alcohol - genetics	- Inflammation (IL-17A, IL-22, IFN gamma, TNF-a)	- high, broad spectrum protection - anti-inflammatory & calming actives - antioxidants
		OTHER: LUPUS, DERMATOMIOSITIS, …			- very high, broad spectrum protection incl. Vis protection (incl. *e.g.* Fernblock®, non-nano mineral filers, iron oxide, ...) - oral photoprotection
	PHOTODERMATOSES	Polymorphus light eruption, Chronic Actinic Dermatitis, Actinic Prurigo, Hydroa Vacciniforme	- phototypes I-III - moderate / intense sun exposure (UVB-UVA-VL)	Th1/Th2 imbalance Inmunosupression (UCA, Langerhans cells)	- very high, broad spectrum protection, incl. VL protection - anti-inflammatory actives - immunomodulating actives - oral photoprotection
		Solar Urticaria		- type I hypersensitivity response (chromophores. Production of neoAg recognized by IgE)	
SENSITIVE SKIN	"REACTIVE SKIN"		- UVB, UVA, VL	- skin barrier alterations - Neuropeptides (TRPV1, substance P) - vasodilatation - Inflammation (IL-1, IL-8 prostaglandin E2, F2, TNF-α)	- very high, broad spectrum protection incl. VL protection (incl. *e.g.* non-nano mineral filers, iron oxide, ...) - mineral filters - antioxidant & anti-inflammatory actives - oral photoprotection
	DRUG-INDUCED SENSITIVITY		- UVB, UVA, VL	- Inflammation (IL-1B, TNF-α) - Th1/Th2 imbalance - Oxidative stress: NRF2	
	POST-PROCEDURE		- UVA, VL - dark phototypes III-V	- Oxidative stress - Inflammation - skin barrier damage	
NON-FILTERING BIOLOGICAL ACTIVES	* Pigment-control actives		Fernblock® [20], Niacinamide [34], vitamin E [35] 25, Vitamin C [36], kojic acid [37], arbutin [38], caffeic acid [39], ferulic acid [40], Gluthatione [41], afamelanotide [42], Forskolin [43], among others.		
	*Antioxidant actives		Resveratrol [44], Fernblock® [45], Pomegranate fruit extract [46], Green tea extract [47], Genistein [48], vitamin D [49], Vitamin E [35], Vitamin C [50], curcumin [51], quercetin [52], Apigenin [53], Pycnogenol [54], Carotenoids [55], Coenzyme Q10 [56], among others.		
	* Anti-inflammatory & calming actives		Phytocannabinoids [57], Ectoin [58], Hyaluronic acid [54], Niacinamide [59], among others.		
	*Visible light protection actives		Carotenoids [60], Fernblock® [20], Flavonoids [61], Mycosporine-like amino acids (MAAs) [62]		
	* Molecules and compounds with DNA-repair activity		Repair enzymes [63], niacinamide [59], Fernblock® [64], among others.		
	* Immunomodulating actives		Vitamin D [50, 65], Silymarin [66], Fernblock® [15], Equol [67], among others.		

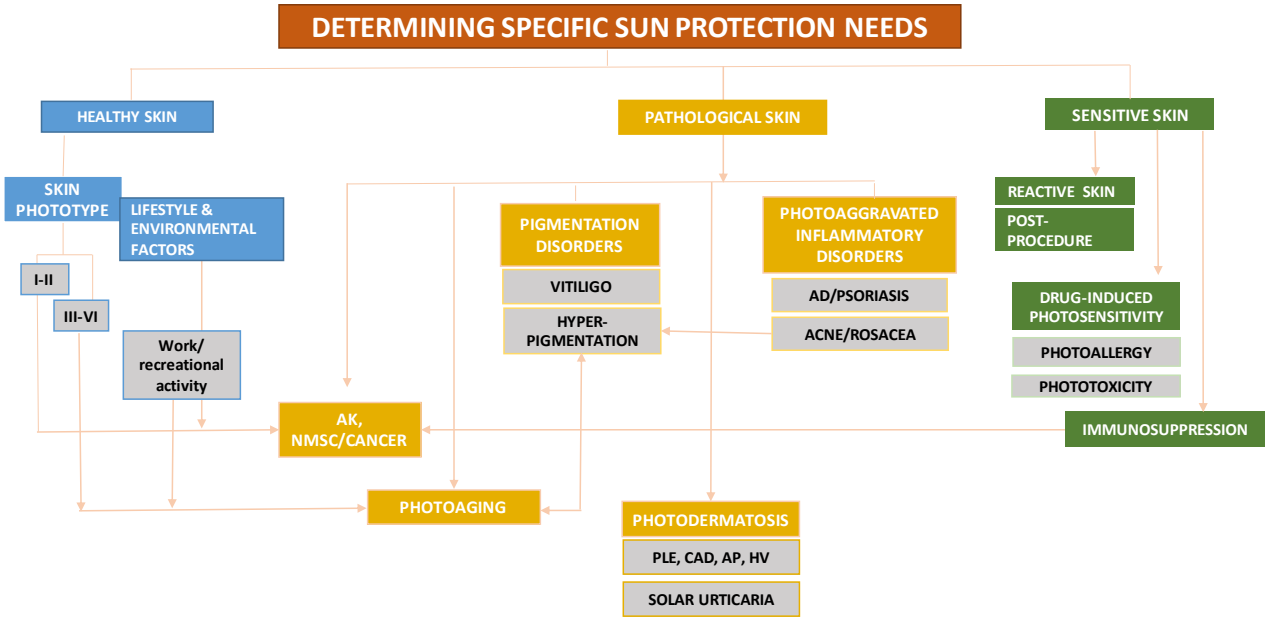

Fig. (1). Strategies based on sun protection needs for healthy skin and patients with dermatological pathologies or alterations.

Table 2. Specific photoprotection including filtering and non-filtering biological actives.

PATHOLOGY	FILTERING INGREDIENTS					NON-FILTERING INGREDIENTS						
	Very High, Broad Spectrum Protection	Specific VL Protection	Specific IR Protection	Narrow-band UVB Sun Protection	High Tolerability Mineral Filters	Antioxidants	DNA repair Actives	Immune-modulating Actives	Anti-inflammatory & Calming Actives	Specific Pigment-control Actives	Non-greasy	Oral Photoprotection
PHOTO-INDUCED SKIN PRECANCER AND CANCER	✓	-	-	-	-	✓	✓	✓	-	-	-	✓
HYPERPIGMENTATION	✓	✓	✓	-	✓	✓	-	-	-	✓	-	✓
VITILIGO	-	-	-	✓	-	✓	-	✓	-	✓	-	✓
PHOTOAGING	✓	✓	✓	-	-	✓	-	-	-	-	-	✓
ATOPIC DERMATITIS	✓	-	-	-	✓	-	-	-	✓	-	-	-
ROSACEA	✓	✓	✓	-	✓	-	-	-	✓	-	✓	-
ACNE	✓	✓	-	-	-	-	-	-	-	-	✓	-
PSORIASIS	✓	-	-	-	-	✓	-	-	✓	-	-	-
OTHER: LUPUS, DERMATOMIOSITIS, …	✓	✓	-	-	-	-	-	-	-	-	-	✓
PHOTODERMATOSES	✓	✓	-	-	-	-	-	✓	✓	-	-	✓
SENSITIVE SKIN	✓	✓	-	-	✓	✓	-	-	✓	-	-	✓

CONCLUSION

Patients with skin alterations and sun-induced pathologies can benefit from personalized photoprotection strategies targeting specific wavelengths and biological pathways. A correct diagnosis of the patient's needs together with the expert recommendation of appropriate sun exposure behavior, photoprotective filters, biological actives, cosmetic formulations, and oral photoprotection can provide an optimal level of protection even for the most photosensitive groups, reducing the deleterious effects of sun exposure and thus increasing the patient's quality of life.

AUTHORS' CONTRIBUTIONS

SG: conceptualization. SG, AR-L, MVdeG, MdeT, P C-P: discussion, original draft preparation and writing, review and editing.

LIST OF ABBREVIATIONS

DNA	=	Deoxyribonucleic Acid
UVB	=	Ultraviolet B
UVA	=	Ultraviolet A
ROS	=	Reactive Oxygen Species
VL	=	Visible Light
HEVL	=	High-energy Blue-violet Light
IR-A	=	Infrared A
MMPs	=	Metalloproteinases
SPF	=	Sun Protection Factor
HIF	=	Human Immunoprotection Factor

CONSENT FOR PUBLICATION

Not applicable.

FUNDING

None.

CONFLICT OF INTEREST

S.G. has a consultant role for Cantabria Labs. The remaining authors declare no conflict of interest.

ACKNOWLEDGEMENTS

Declared none.

REFERENCES

[1] Rutter KJ, Watson REB, Cotterell LF, Brenn T, Griffiths CEM, Rhodes LE. Severely photosensitive psoriasis: a phenotypically defined patient subset. J Invest Dermatol 2009; 129(12): 2861-7. [http://dx.doi.org/10.1038/jid.2009.156] [PMID: 19536141]

[2] Ros AM, Eklund G, D O. Photosensitive psoriasis. J Am Acad Dermatol 1987; 17(5): 752-8. [http://dx.doi.org/10.1016/S0190-9622(87)70258-8] [PMID: 3680654]

[3] Rutt VL, Reed KX, Liu X, Richard eg, Purcell SM. Photosensitive atopic dermatitis exacerbated by UVB exposure. Cutis 2017; 100(3): 180-4. [PMID: 29121122]

[4] Ellenbogen E, Wesselmann U, Hofmann SC, Lehmann P. Photosensitive atopic dermatitis - a neglected subset: Clinical, laboratory, histological and photobiological workup. J Eur Acad Dermatol Venereol 2016; 30(2): 270-5. [http://dx.doi.org/10.1111/jdv.13451] [PMID: 26523351]

[5] ten Berge O, van Weelden H, Bruijnzeel-Koomen CAFM, de Bruin-Weller MS, Sigurdsson V. Throwing a light on photosensitivity in atopic dermatitis: a retrospective study. Am J Clin Dermatol 2009; 10(2): 119-23. [http://dx.doi.org/10.2165/00128071-200910020-00004] [PMID: 19222251]

[6] Ferrer Guillén B, Giácaman MM, Valenzuela Oñate C, Magdaleno Tapial J, Hernández Bel P, Pérez Ferriols A. Pirfenidone-induced photosensitivity confirmed by pathological phototest. Photodiagn Photodyn Ther 2019; 25: 103-5. [http://dx.doi.org/10.1016/j.pdpdt.2018.11.015] [PMID: 30468899]

[7] Mobasher P, Foulad DP, Raffi J, *et al.* Catamenial Hyperpigmentation: A Review. J Clin Aesthet Dermatol 2020; 13(6): 18-21. [PMID: 32884614]

[8] Reddy H, Carmichael AJ, Wahie S. Severity of polymorphic light eruption in pre- and post-menopausal women: a comparative study. J Eur Acad Dermatol Venereol 2015; 29(1): 97-101. [http://dx.doi.org/10.1111/jdv.12470] [PMID: 24684752]

[9] Zhao X, Liu J, Fan J, Chao H, Peng X. Recent progress in photosensitizers for overcoming the challenges of photodynamic therapy: from molecular design to application. Chem Soc Rev 2021; 50(6): 4185-219. [http://dx.doi.org/10.1039/D0CS00173B] [PMID: 33527104]

[10] Passeron T, Lim HW, Goh CL, *et al.* Photoprotection according to skin phototype and dermatoses: practical recommendations from an expert panel. J Eur Acad Dermatol Venereol 2021; 35(7): 1460-9. [http://dx.doi.org/10.1111/jdv.17242] [PMID: 33764577]

[11] Schalka S, Lim HW, Krutmann J, Passeron T, Dréno B, Ocampo Candiani J, *et al.* Revolution in photoprotection: How to recommend and adapt photoprotection according to skinphototype and dermatoses. 30th European Academy of Dermatology and Venereology (EADV) Congress 2022: EMJ Dermatol. 2-8.

[12] González S, Aguilera J, Berman B, *et al.* Expert recommendations on the evaluation of sunscreen efficacy and the beneficial role of non-filtering ingredients. Front Med (Lausanne) 2022; 9: 790207. [http://dx.doi.org/10.3389/fmed.2022.790207] [PMID: 35433750]

[13] Chen L, Hu JY, Wang SQ. The role of antioxidants in photoprotection: A critical review. J Am Acad Dermatol 2012; 67(5): 1013-24. [http://dx.doi.org/10.1016/j.jaad.2012.02.009] [PMID: 22406231]

[14] Schalka S, Coelho Donato L. Evaluation of effectiveness of a sunscreen containing Polypodium leucatomos extract in reducing the sun damage to the skin. Surg Cosmet Dermatol 2019; 11(4): 310-8.

[15] Aguilera J, Vicente-Manzanares M, de Gálvez MV, Herrera-Ceballos E, Rodríguez-Luna A, González S. Booster effect of a natural extract of *Polypodium leucotomos* (Fernblock®) that improves the UV barrier function and immune protection capability of sunscreen formulations. Front Med (Lausanne) 2021; 8: 684665. [http://dx.doi.org/10.3389/fmed.2021.684665] [PMID: 34150816]

[16] Yarosh DB, Rosenthal A, Moy R. Six critical questions for DNA repair enzymes in skincare products: a review in dialog. Clin Cosmet Investig Dermatol 2019; 12: 617-24. [http://dx.doi.org/10.2147/CCID.S220741] [PMID: 31695467]

[17] Luze H, Nischwitz SP, Zalaudek I, Müllegger R, Kamolz LP. DNA repair enzymes in sunscreens and their impact on photoageing—A systematic review. Photodermatol Photoimmunol Photomed 2020; 36(6): 424-32. [http://dx.doi.org/10.1111/phpp.12597] [PMID: 32772409]

[18] Leccia MT, Lebbe C, Claudel JP, Narda M, Basset-Seguin N. New Vision in Photoprotection and Photorepair. Dermatol Ther (Heidelb) 2019; 9(1): 103-15. [http://dx.doi.org/10.1007/s13555-019-0282-5] [PMID: 30674003]

[19] Megna M, Lembo S, Balato N, Monfrecola G. "Active" photoprotection: sunscreens with DNA repair enzymes. Italian J Dermatol Venereol 2017; 152(3): 302-7. [http://dx.doi.org/10.23736/S0392-0488.17.05567-5]

[20] Portillo M, Mataix M, Alonso-Juarranz M, *et al.* The aqueous extract of *Polypodium leucotomos* (Fernblock®) regulates opsin 3 and prevents photooxidation of melanin precursors on skin cells exposed to blue light emitted from digital devices. Antioxidants 2021; 10(3): 400. [http://dx.doi.org/10.3390/antiox10030400] [PMID: 33800784]

[21] Mohammad TF, Kohli I, Nicholson CL, *et al.* Oral polypodium leucotomos extract and its impact on visible light-induced pigmentation in human subjects. J Drugs Dermatol 2019; 18(12): 1198-203. [PMID: 31859468]

[22] Zamarrón A, Lorrio S, González S, Juarranz Á. Fernblock prevents dermal cell damage induced by visible and infrared a radiation. Int J Mol Sci 2018; 19(8): 2250. [http://dx.doi.org/10.3390/ijms19082250] [PMID: 30071607]

[23] Lyons AB, Trullas C, Kohli I, Hamzavi IH, Lim HW. Photoprotection beyond ultraviolet radiation: A review of tinted sunscreens. J Am Acad Dermatol 2021; 84(5): 1393-7. [http://dx.doi.org/10.1016/j.jaad.2020.04.079] [PMID: 32335182]

[24] Bernstein EF, Sarkas HW, Boland P. Iron oxides in novel skin care formulations attenuate blue light for enhanced protection against skin damage. J Cosmet Dermatol 2021; 20(2): 532-7. [http://dx.doi.org/10.1111/jocd.13803] [PMID: 33210401]

[25] Snaidr VA, Damian DL, Halliday GM. Nicotinamide for photoprotection and skin cancer chemoprevention: A review of efficacy and safety. Exp Dermatol 2019; 28(Suppl. 1): 15-22. [http://dx.doi.org/10.1111/exd.13819] [PMID: 30698874]

[26] Hakozaki T, Minwalla L, Zhuang J, *et al.* The effect of niacinamide on reducing cutaneous pigmentation and suppression of melanosome transfer. Br J Dermatol 2002; 147(1): 20-31. [http://dx.doi.org/10.1046/j.1365-2133.2002.04834.x] [PMID: 12100180]

[27] Surjana D, Halliday GM, Martin AJ, Moloney FJ, Damian DL. Oral nicotinamide reduces actinic keratoses in phase II double-blinded randomized controlled trials. J Invest Dermatol 2012; 132(5): 1497-500. [http://dx.doi.org/10.1038/jid.2011.459] [PMID: 22297641]

[28] Kohli I, Shafi R, Isedeh P, *et al.* The impact of oral Polypodium leucotomos extract on ultraviolet B response: A human clinical study. J Am Acad Dermatol 2017; 77(1): 33-41.e1. [http://dx.doi.org/10.1016/j.jaad.2017.01.044] [PMID: 28341348]

[29] Nestor MS, Berman B, Swenson N. Safety and efficacy of oral polypodium leucotomos extract in healthy adult subjects. J Clin Aesthet Dermatol 2015; 8(2): 19-23. [PMID: 25741399]

[30] Goh CL, Chuah SY, Tien S, Thng G, Vitale MA, Delgado-Rubin A. Double-blind, placebo-controlled trial to evaluate the effectiveness of *Polypodium Leucotomos* extract in the treatment of melasma in asian skin: A pilot study. J Clin Aesthet Dermatol 2018; 11(3): 14-9. [PMID: 29606995]

[31] Auriemma M, Di Nicola M, Gonzalez S, Piaserico S, Capo A, Amerio P. Polypodium leucotomos supplementation in the treatment of scalp actinic keratosis: could it improve the efficacy of photodynamic therapy? Dermatologic surgery 2015; 41(8): 898-902.

[http://dx.doi.org/10.1097/DSS.0000000000000425]

[32] Tanew A, Radakovic S, Gonzalez S, Venturini M, Calzavara-Pinton P. Oral administration of a hydrophilic extract of Polypodium leucotomos for the prevention of polymorphic light eruption. J Am Acad Dermatol 2012; 66(1): 58-62. [http://dx.doi.org/10.1016/j.jaad.2010.09.773] [PMID: 21696853]

[33] Pacifico A, Damiani G, Iacovelli P, Conic RRZ, Gonzalez S, Morrone A. NB-UVB plus oral *Polypodium leucotomos* extract display higher efficacy than NB-UVB alone in patients with vitiligo. Dermatol Ther 2021; 34(2): e14776. [http://dx.doi.org/10.1111/dth.14776] [PMID: 33433041]

[34] Brito S, Baek JM, Cha B, *et al.* Nicotinamide mononucleotide reduces melanin production in aged melanocytes by inhibiting cAMP/Wnt signaling. J Dermatol Sci 2022; 106(3): 159-69. [http://dx.doi.org/10.1016/j.jdermsci.2022.05.002] [PMID: 35610161]

[35] Saleh MM, Lawrence KP, Jones SA, Young AR. The photoprotective properties of α-tocopherol phosphate against long-wave UVA1 (385 nm) radiation in keratinocytes *in vitro*. Sci Rep 2021; 11(1): 22400. [http://dx.doi.org/10.1038/s41598-021-01299-y] [PMID: 34789788]

[36] Zerbinati N, Sommatis S, Maccario C, *et al.* The anti-ageing and whitening potential of a cosmetic serum containing 3-*O*-ethyl-l-ascorbic acid. Life (Basel) 2021; 11(5): 406. [http://dx.doi.org/10.3390/life11050406] [PMID: 33946734]

[37] Mitani H, Koshiishi I, Sumita T, Imanari T. Prevention of the photodamage in the hairless mouse dorsal skin by kojic acid as an iron chelator. Eur J Pharmacol 2001; 411(1-2): 169-74. [http://dx.doi.org/10.1016/S0014-2999(00)00873-6] [PMID: 11137872]

[38] Wang YS, Yang WH, Gao W, Zhang L, Wei F, Liu H, *et al.* Combination and efficiency: preparation of dissolving microneedles array loaded with two active ingredients and its anti-pigmentation effects on guinea pigs. Eur J Pharm Sci 2021; 160: 105749. [http://dx.doi.org/10.1016/j.ejps.2021.105749]

[39] Jo H, Choi M, Sim J, *et al.* Synthesis and biological evaluation of caffeic acid derivatives as potent inhibitors of α-MSH-stimulated melanogenesis. Bioorg Med Chem Lett 2017; 27(15): 3374-7. [http://dx.doi.org/10.1016/j.bmcl.2017.06.011] [PMID: 28619537]

[40] Cavalcanti GR, Duarte FIC, Converti A, de Lima ÁAN. Ferulic acid activity in topical formulations: technological and scientific prospecting. Curr Pharm Des 2021; 27(19): 2289-98. [http://dx.doi.org/10.2174/1381612826666201020163331] [PMID: 33081675]

[41] Wahab S, Anwar AI, Zainuddin AN, Hutabarat EN, Anwar AA, Kurniadi I. Combination of topical and oral glutathione as a skin-whitening agent: A double-blind randomized controlled clinical trial. Int J Dermatol 2021; 60(8): 1013-8. [http://dx.doi.org/10.1111/ijd.15573] [PMID: 33871071]

[42] Lim HW, Arellano-Mendoza MI, Stengel F. Current challenges in photoprotection. J American Academy of Dermatology 2017; 76(3S1): S91-. [http://dx.doi.org/10.1016/j.jaad.2016.09.040]

[43] Bautista RM, Carter KM, Jarrett SG, *et al.* Cutaneous pharmacologic cAMP induction induces melanization of the skin and improves recovery from ultraviolet injury in melanocortin 1 receptor-intact or heterozygous skin. Pigment Cell Melanoma Res 2020; 33(1): 30-40. [http://dx.doi.org/10.1111/pcmr.12817] [PMID: 31398282]

[44] Cui B, Wang Y, Jin J, *et al.* Resveratrol treats UVB-induced photoaging by Anti-MMP Expression, through anti-inflammatory, antioxidant, and antiapoptotic properties, and treats photoaging by upregulating VEGF-B expression. Oxid Med Cell Longev 2022; 2022: 1-19. [http://dx.doi.org/10.1155/2022/6037303] [PMID: 35028009]

[45] Gonzalez S, Gilaberte Y, Philips N, Juarranz A. Fernblock, a nutriceutical with photoprotective properties and potential preventive agent for skin photoaging and photoinduced skin cancers. Int J Mol Sci 2011; 12(12): 8466-75. [http://dx.doi.org/10.3390/ijms12128466] [PMID: 22272084]

[46] Park HM, Moon E, Kim AJ, *et al.* Extract of *Punica granatum* inhibits skin photoaging induced by UVB irradiation. Int J Dermatol 2010; 49(3): 276-82. [http://dx.doi.org/10.1111/j.1365-4632.2009.04269.x] [PMID: 20465664]

[47] Li H, Jiang N, Liu Q, Gao A, Zhou X, Liang B, *et al.* Topical treatment of green tea polyphenols emulsified in carboxymethyl cellulose protects against acute ultraviolet light B-induced photodamage in hairless mice. Photochem Photobiol Sci 2016; 15(10): 1264-71.

[48] Tang SC, Hsiao YP, Ko JL. Genistein protects against ultraviolet B–induced wrinkling and photoinflammation in *in vitro* and *in vivo* models. Genes Nutr 2022; 17(1): 4. [http://dx.doi.org/10.1186/s12263-022-00706-x] [PMID: 35209841]

[49] Hanada K, Sawamura D, Nakano H, Hashimoto I. Possible role of 1,25-dihydroxyvitamin D3-induced metallothionein in photoprotection against UVB injury in mouse skin and cultured rat keratinocytes. J Dermatol Sci 1995; 9(3): 203-8. [http://dx.doi.org/10.1016/0923-1811(94)00378-R] [PMID: 8664218]

[50] Aguilera J, de Gálvez MV, Sánchez C, Herrera-Ceballos E. Changes in photoinduced cutaneous erythema with topical application of a combination of vitamins C and E before and after UV exposure. J Dermatol Sci 2012; 66(3): 216-20. [http://dx.doi.org/10.1016/j.jdermsci.2012.03.010] [PMID: 22537614]

[51] Liu X, Zhang R, Shi H, *et al.* Protective effect of curcumin against ultraviolet A irradiation□induced photoaging in human dermal fibroblasts. Mol Med Rep 2018; 17(5): 7227-37. [http://dx.doi.org/10.3892/mmr.2018.8791] [PMID: 29568864]

[52] Rajnochova Svobodova A, Rysava A, Cizkova K, Roubalova L, Ulrichova J, Vrba J, *et al.* Effect of the flavonoids quercetin and taxifolin on UVA-induced damage to human primary skin keratinocytes and fibroblasts. Photochem Photobiol Sci 2022; 21(1): 59-75.

[53] Li L, Li M, Xu S, Chen H, Chen X, Gu H. Apigenin restores impairment of autophagy and downregulation of unfolded protein response regulatory proteins in keratinocytes exposed to ultraviolet B radiation. J Photochem Photobiol B 2019; 194: 84-95. [http://dx.doi.org/10.1016/j.jphotobiol.2019.03.010] [PMID: 30933875]

[54] Neves JR, Grether-Beck S, Krutmann J, *et al.* Efficacy of a topical serum containing L-ascorbic acid, neohesperidin, pycnogenol, tocopherol, and hyaluronic acid in relation to skin aging signs. J Cosmet Dermatol 2022; 21(10): 4462-9. [http://dx.doi.org/10.1111/jocd.14837] [PMID: 35150043]

[55] Balić A, Mokos M. Do we utilize our knowledge of the skin protective effects of carotenoids enough? Antioxidants 2019; 8(8): 259. [http://dx.doi.org/10.3390/antiox8080259] [PMID: 31370257]

[56] Ayunin Q, Miatmoko A, Soeratri W, Erawati T, Susanto J, Legowo D. Improving the anti-ageing activity of coenzyme Q10 through protransfersome-loaded emulgel. Sci Rep 2022; 12(1): 906. [http://dx.doi.org/10.1038/s41598-021-04708-4] [PMID: 35042910]

[57] Łuczaj W, Domingues MR, Domingues P, Skrzydlewska E. Changes in lipid profile of keratinocytes from rat skin exposed to chronic UVA or UVB radiation and topical application of cannabidiol. Antioxidants 2020; 9(12): 1178. [http://dx.doi.org/10.3390/antiox9121178] [PMID: 33255796]

[58] Kauth M, Trusova OV. Topical ectoine application in children and adults to treat inflammatory diseases associated with an impaired skin barrier: A systematic review. Dermatol Ther (Heidelb) 2022; 12(2): 295-313. [http://dx.doi.org/10.1007/s13555-021-00676-9] [PMID: 35038127]

[59] Camillo L, Gironi LC, Zavattaro E, Esposto E, Savoia P. Nicotinamide attenuates UV-induced stress damage in human primary keratinocytes from cancerization fields. J Invest Dermatol 2022; 142(5): 1466-1477.e1. [http://dx.doi.org/10.1016/j.jid.2021.10.012] [PMID: 34695410]

[60] Freitas JV, Junqueira HC, Martins WK, Baptista MS, Gaspar LR. Antioxidant role on the protection of melanocytes against visible light-induced photodamage. Free Radic Biol Med 2019; 131: 399-407. [http://dx.doi.org/10.1016/j.freeradbiomed.2018.12.028] [PMID: 30590132]

[61] Lorrio S, Rodríguez-Luna A, Delgado-Wicke P, *et al.* Protective Effect of the Aqueous Extract of *Deschampsia antarctica* (EDAFENCE®) on Skin Cells against Blue Light Emitted from Digital Devices. Int J Mol Sci 2020; 21(3): 988. [http://dx.doi.org/10.3390/ijms21030988] [PMID: 32024276]

[62] Zaytseva A, Chekanov K, Zaytsev P, *et al.* Sunscreen effect exerted by secondary carotenoids and mycosporine-like amino acids in the aeroterrestrial chlorophyte *Coelastrella rubescens* under high light and UV-A irradiation. Plants 2021; 10(12): 2601. [http://dx.doi.org/10.3390/plants10122601] [PMID: 34961072]

[63] Bhatia N, Berman B, Ceilley RI, Kircik LH. Understanding the role of photolyases: Photoprotection and beyond. J Drugs Dermatol 2017; 16(5): 61-6. [PMID: 28628693]

[64] Portillo-Esnaola M, Rodríguez-Luna A, Nicolás-Morala J, *et al.* Formation of cyclobutane pyrimidine dimers after uva exposure (dark-

cpds) is inhibited by an hydrophilic extract of *Polypodium leucotomos*. Antioxidants 2021; 10(12): 1961. [http://dx.doi.org/10.3390/antiox10121961] [PMID: 34943064]

[65] Tongkao-on W, Carter S, Reeve VE, *et al.* CYP11A1 in skin: An alternative route to photoprotection by vitamin D compounds. J Steroid Biochem Mol Biol 2015; 148: 72-8. [http://dx.doi.org/10.1016/j.jsbmb.2014.11.015] [PMID: 25448743]

[66] Katiyar S. Treatment of silymarin, a plant flavonoid, prevents ultraviolet light-induced immune suppression and oxidative stress in mouse skin. Int J Oncol 2002; 21(6): 1213-22. [http://dx.doi.org/10.3892/ijo.21.6.1213] [PMID: 12429970]

[67] Widyarini S, Domanski D, Painter N, Reeve VE. Photoimmune protective effect of the phytoestrogenic isoflavonoid equol is partially due to its antioxidant activities. Photochem Photobiol Sci 2012; 11(7): 1186-92. [http://dx.doi.org/10.1039/c2pp25022e]