Exploration of Medicine

Open Exploration

Open Access Review

Antioxidant and photoprotective potential of *Polypodium leucotomos*

Rosy Yesela Mancilla Santa Cruz[1,2], Sharon Velásquez Arévalo[3], Anas Rashid[1,4], Marco Rolando Aronés Jara[2], María Segunda Aurora Prado[1]*

[1]Department of Pharmacy, School of Pharmaceutical Sciences, University of São Paulo, São Paulo 05508-000, Brazil
[2]Professional School of Pharmacy and Biochemistry, Faculty of Health Sciences, National University of San Cristóbal of Huamanga, Ayacucho 05001, Peru
[3]Department of Pharmacotechnics, Faculty of Pharmacy and Biochemistry, National University of Trujillo, Trujillo 13011, Peru
[4]School of Medicine and Surgery, University of Torino, Torino 10125, Italy

***Correspondence:** María Segunda Aurora Prado, Department of Pharmacy, School of Pharmaceutical Sciences, University of São Paulo, Av. Prof. Lineu Prestes 580, Block 13, Butanta, São Paulo 05508-000, Brazil. msaprad06@usp.br
Academic Editor: Md Noushad Javed, K.R. Mangalam University, India

Received: September 9, 2022 **Accepted:** November 14, 2022 **Published:** December 29, 2022

Cite this article: Cruz RYMS, Arévalo SV, Rashid A, Jara MRA, Prado MSA. Antioxidant and photoprotective potential of *Polypodium leucotomos*. Explor Med. 2022;3:607–16. https://doi.org/10.37349/emed.2022.00117

Abstract

In recent years, *Polypodium leucotomos* has emerged with a great interest for having medicinal and therapeutic potential. It is producing very promising results due to the presence of antioxidant and photoprotective properties. Electronic libraries and databases, including Scopus, PubMed, Google Scholar, Science Direct, and Web of Science were searched to identify relevant studies; 79 publications contributed to this review regarding *Polypodium leucotomos* botanical aspects, chemical composition, antioxidant and photoprotective activity. It is used in complementary and alternative therapies with various pharmaceutical dosage forms (systemic or topical). Thanks to the composition of phytochemical constituents present in the leaves and rhizomes which confer antioxidant and photoprotective activity that has clinical therapeutic potential to be used as systemic and topical sunscreen of natural origin for the prevention of different types of skin diseases caused by harmful ultraviolet A and ultraviolet B radiations. However, more studies are needed in the future to test the ability and enhance the capacity of sunscreen and sunblock in cosmetic formulations. To conclude, it is recommended to carry out scientific studies based on different analytical methods to evaluate the phytoconstituents potential and to develop stable pharmaceutical formulations according to the skin phototype.

Keywords

Polypodium leucotomos, antioxidant, photoprotective

Introduction

Polypodium leucotomos—a tropical fern belonging to the genus *Polypodium* and to the family Polypodiaceae—originated from South and Central America [1, 2] which was traditionally used due to its anti-tumor and anti-inflammatory properties [3]. In 1788, this species was first introduced in Europe after the botanical

expedition in Peru and Chile by Hipólito Ruiz López (botanist) funded by the Spanish Crown and later spread to other areas [4]. It has been shown to contain saponins [1] and phenolic compounds: vinyl acid, chlorogenic acid, ferulic acid, caffeic acid, and coumaric acid [5–7] extracted from rhizomes [1, 8] and leaves [9, 10]. It is beneficial for specific dermatological pathologies [11] such as skin tumors [3, 12, 13], rash [14], erythema and pigmentation [12, 13, 15], melanoma [16], photodermatosis [13, 17, 18], vitiligo [19, 20], melasma, psoriasis, and atopic dermatitis [2, 21, 22]. It particularly reduces the skin deterioration induced by exposed ultraviolet (UV) rays [11, 23, 24] to minimize photoaging [25], therefore, it gained considerable interest in cosmetic and dermatological research. Further, the research demonstrated the positive effects in tonsillitis [26], trichomoniasis [4], infectious diseases [27], acute colitis [28], scalp keratosis [29, 30], polymorphic light eruption [14, 31] as well as immunomodulation of lymphocytes and cytokines [32] and it was also used as a dietary supplement [33].

The *Polypodium leucotomos* pharmaceutical preparations are available as oral capsule (act as a systemic antioxidizing agent), topical gel, cream, spray and compact makeup powder to protect the skin from sunlight (or invisible UV rays) exposure [2]. Besides, it is one of the global public health problems. Overexposure to solar radiation has a significant impact on skin health [34] such as sunburn, photoaging, photodermatosis, photosensitivity, immunosuppression and photocarcinogenesis [35, 36]; the latter being of great concern due to the increase in cases [37, 38]. Therefore, it is highly beneficial due to its chemoprotective, immunomodulatory, anti-inflammatory and antioxidant properties. In addition, it is attributed for the inhibition of photoisomerization as well as apoptosis that leads directly to DNA damage, and it also prevents immunosuppression [7, 25, 39, 40] which were proven in *in vitro* and *in vivo* studies, involving human, cell and animal studies [22, 41].

It is necessary to highlight that the harmful biological effects of UV radiation will depend on the energy that it diffuses [42]; while UVA, UVB and UVC spectral ranges of solar radiation comprise from 100 to 400 nm. Among them, UVA and UVB radiations are of great biological importance as they are concerned with mild to chronic skin damage and compromise the skin integrity [43]. Hence, the skin is the primary organ that eventually receives the most exposure [44], as there is a direct relationship between skin and UV radiation and this relationship generates reactive oxygen species that alter the structure and function of the skin [45]. For this reason, the dermatological studies carried out on *Polypodium leucotomos* have demonstrated its potential antioxidant activity [5, 10] due to the presence of phenolic compounds. Since, they have the ability to bind with free radicals, which are agents that prevent or delay oxidation by inhibiting the initiation of oxidative reactions and thus producing beneficial effects on human health [46, 47].

Free radicals are highly reactive unstable species and when reacting with UV rays, they can even lead to cell death [48] which implies they are responsible for photoaging, immunosuppression, phototoxicity, photoallergic and photocarcinogenesis [9, 47, 49, 50]. To avoid these damages, strategies are sought out such as photoprotection with natural antioxidants to limit them thus preventing erythema, inflammation, wrinkles, photoaging and skin cancer [51].

The area of cosmetic science has emerged in the last three decades to maintain cutaneous homeostasis and to neutralize the free radicals induced by damaging UV rays. The researchers are trying their best to formulate the skin preparation without causing toxicity or unwanted effects [52]. Some traditional sunscreen contains inorganic compounds such as titanium dioxide and zinc oxide [33] that dissociate UVA and UVB rays. Perhaps they are often visible as an undesirable opaque layer on the skin, though these are metallic particles that are considered highly toxic for the skin [53].

Therefore, researchers have been studying the compounds present in the *Polypodium leucotomos* which is considered as a UV protector. In recent years, there is a very high demand for its oral formulation as antioxidant capsules [41]. It should be important to highlight that the *Polypodium leucotomos* extract has been patented with the name Fernblock® XP [54].

The aim of this review is to gather the information from published studies to evaluate the antioxidant and photoprotective properties. The databases of Scopus, PubMed, Google Scholar, Science Direct and Web of Science were searched and an exhaustive review was carried out with publications from the year 2010

to 2022. A total of 117 reviews and research articles were collected, 79 contributing to this review with a topic of interest to carry out this work. In English, the following search words were used and mentioned here: "*Polypodium leucotomos*"; and other word combinations were also made like "*Polypodium leucotomos*" with "antioxidant", "photoprotective", "cancer", "anti-inflammatory", "photoaging", "UV radiation", "phenolic compounds", "reactive oxygen species", "skin" and "Fernblock". After thorough evaluation, a discussion was held to highlight its antioxidant and photoprotective properties.

Taxonomy

The taxonomic classification is shown in Table 1.

Table 1. Taxonomic classification of *Polypodium leucotomos*

Kingdom	Plantae
Class	Equisetopsida
Order	Polypodiales
Suborder	Polypodiineae
Family	Polypodiaceae
Genus	*Polypodium*
Species	*leucotomos*

Distribution

The geographical distribution ranges from Central America to South America, mainly in Bolivia, Brazil, Mexico and Peru [10, 26]. Besides, it cultivates in humid environment, and it grows on developed tree trunks. Its adaptation and vegetation reach the height of 1,200 to 2,200 meters above sea level [8].

Phytochemical constituents

The phytochemical constituents are presented in Table 2 and the chemical structures are shown in Figure 1.

Table 2. Phytochemical constituents

Phytochemical constituents	Chemical compound	Plant part	Refs.
Saponins	Osladin, calagualine	Rhizome	[8, 55]
Phenolic compounds	Caffeic acid: 3,4-dihydroxycinnamic acid, Ferulic acid: 3-methoxy-4-hydroxycinnamic acid	Leaves	[56]
Biological acid molecules	Shikimic acid, glucuronic acid, malic acid, coumaric acid: 4-hydroxycinnamic acid, vanillic acid: 3-methoxy-4-hydroxybenzoic acid, chlorogenic acid: 3-caffeoylquinic acid, lactic acid, protocatechuic acid: 3,4-dihydroxybenzoic acid, citric acid	Rhizome and leaves	[56]
Monosaccharides	Fructose, glucose	Rhizome and leaves	[56]
Steroids	Ecdysone	Rhizome	[8]
Others	Oleoresin, deoxyhexose, potassium nitrate	Rhizome	[8]

Antioxidant activity

Antioxidants are substances that can neutralize the actions of oxidants that cause free radicals, thus endogenous cellular antioxidants are released into the bloodstream that is subsequently trapped by free radicals, which maintains oxidant-antioxidant homeostasis [57]. The free radical is an atom that has an unpaired (free) electron; this characteristic makes them very reactive to capture an electron from molecules to become stable, thus reaching their electrochemical stability. Usually, the free radical tends to initiate a chain reaction and lead to the destruction and damage to cell membranes and tissues. In our body, this action occurs continuously and we need antioxidants to control this process [48, 58]. It will not be beneficial for health when our body has to tolerate excess free radicals that are produced by endogenous and exogenous

oxidant species such as solar radiation [57, 59, 60]. The latter is considered as the major source of free radical production that causes inflammation, acceleration of cellular aging, and initiation of skin cancer [61].

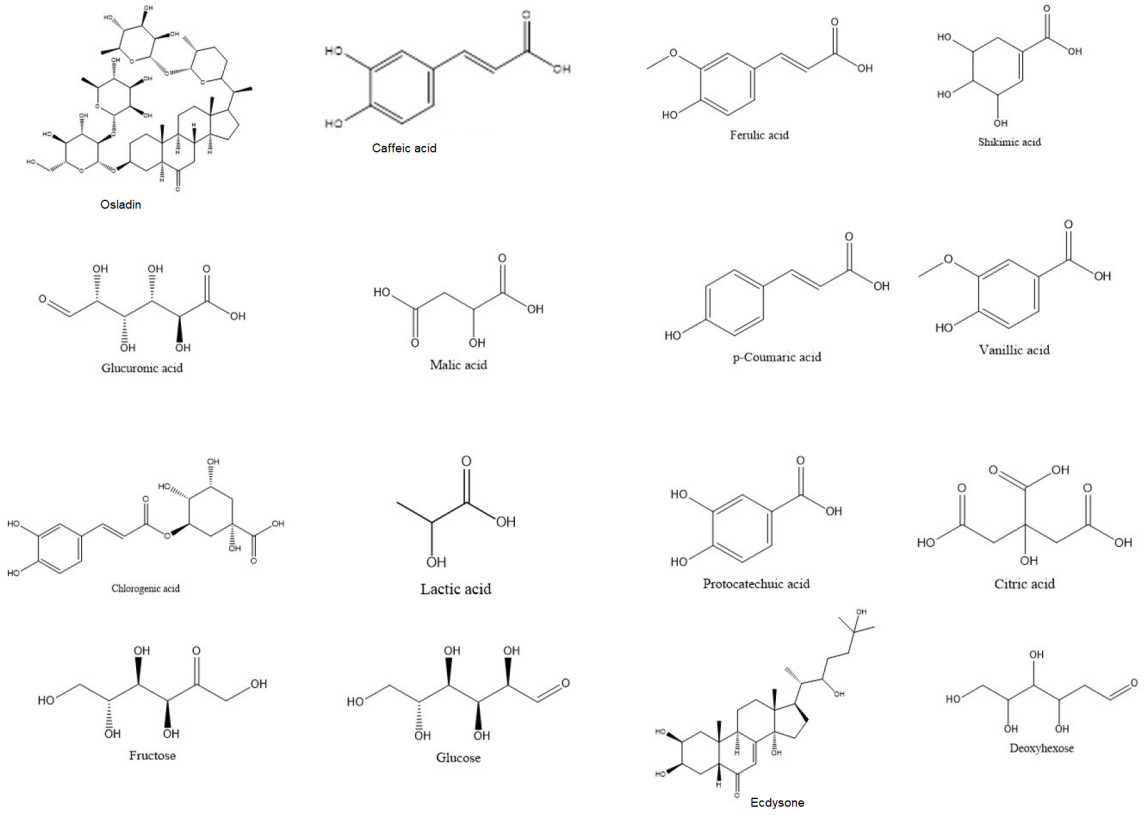

Figure 1. Chemical structure

The phytochemical extracts were demonstrated to have antioxidant activity and photoprotective properties [6]. However, if we compare the activities between the rhizomes and the leaves, the leaves showed high activity due to the presence of phenols, tannins and flavonoids [8, 13, 62], which was determined using oxygen radical scavenging methods such as ferric reducing antioxidant power (FRAP), 2,2-azino-bis-3-ethylbenzothiazoline-6-sulfonic acid (ABTS), and oxygen radical absorbance capacity (ORAC) [3, 11, 63]. Of note, health benefits of polyphenols using human skin cells demonstrated to be good skin photo protectors and photocarcinogenesis inhibitors, therefore, widely incorporated in medicinal and cosmetic products [64, 65].

Reactive oxygen species (superoxide anion, hydroxyl radical, hydrogen peroxide, and singlet oxygen) are important oxidizing agents that have been considered to be involved in skin aging and various diseases such as cerebrovascular, Parkinson's, multiple sclerosis, heart, cancer, and others [57, 66, 67]. This plant demonstrated its antioxidant effect by eliminating reactive species [6, 68] while inactivating the oxidative stress response that is a precursor of inflammation, aging, androgenic alopecia and skin cancer [68]. Further, it is not limited to reactive oxygen species, but it also prevents the synthesis of nitric oxide that participates in cell damage [69].

Photoprotective activity

The skin is highly sensitive to UV rays which cause sunburn, photoaging, immunosuppression and photocarcinogenesis. It has caught the attention of researchers to develop alternatives in photoprotection that may have a filtering system for UVA and UVB radiations [35]. We are familiar that our body undergoes series of preventive mechanisms to counteract short- and long-term solar damage, but they are not enough due to the increase in intensity and duration of solar radiation exposure, whether due to the environmental pollution or ozone layer thinning that is subsequently responsible for skin cancer which considered a global health problem [70, 71].

In this scenario, the most affected people are those that have fair skin and even more if they live in the regions closest to the earth equator that has a higher solar irradiance [72]. The use of sunscreen and sunblock is one of the protective measures. Hence, the efficient development of skin products should be with high protection factors that are less irritating, with lower amounts of synthetic agents and above all easy accessibility in the market [73]. The skin products should not cause adverse reactions such as dermatitis or causing skin sensitivity and thinning. The adverse reaction usually happens when we use sunscreens in a very concentrated way that have phototoxic effects and thus a high risk for consumers [74]. To resolve this problem, the researchers are trying to introduce phytocosmetics from natural compounds that have proven scientific quality, safety and efficacy established during different studies [75].

This has been proven to successfully inhibit skin damage induced by UVA and UVB rays by reducing DNA mutations, inhibiting inflammation, improving the immune response and ultimately decreasing the photo-induced erythema. Recently, *in vitro* and *in vivo* studies that include animal models and human clinical trials proved that phytotherapeutic treatments are of great interest and hence beneficial for humans [38, 40, 76].

Polypodium preparation

The Polypodium preparations are mentioned in Table 3.

Table 3. Polypodium preparation

Polypodium preparation	Result of interest	Photoprotective activity (assays)	Radiation type	Route and dose	Refs.
Capsule	Significant reduction of cutaneous reaction and symptoms/photoprotection treatment in idiopathic photodermatosis	*In vivo*—human	UVA/UVB	Oral Used dose: 480 mg/day	[18]
Capsule	Decreased erythema/increased minimal erythema dose (MED)	*In vivo*—human	UVB	Oral Used dose: 120–1,080 mg/day	[16, 40, 77]
Hydrophilic extract	Prevention and delay of typical lesions (eruptions) caused by UVR	*In vivo*—human	UVA/UVB	Oral Used dose: 720, 960, 1,200 mg/day	[14]
Extract	Inhibition of elastase activity/stimulation of cell expression/strengthening cell matrix/prevention in photoaging	*In vitro*—enzymes and substrate	UVA/UVB	Enzyme (starting concentration of 1 µg/µL) with its substrate 0.5 mM	[78]
Extract	Negative photobiological effects/ reduction of UVB rays	*In vivo*—human	UVB	Oral Used dose: 480 mg/day	[7]
Hydrophilic extract (Fernblock)	Cell damage prevention/ increased expression of matrix metalloproteinase-1 and cathepsin K/ slowing expression of fibrillin 1, 2 and elastin	*In vitro*—cell cultures (human dermal fibroblasts)	Infrared A and visible light	Incubation	[11]
Extract	Decrease in darkening, cyclooxygenase-2 (marker of cell damage)	*In vivo*—human	Visible light	Oral Used dose: 480 mg/day	[79]
Extract (Fernblock)	Protective activity against oxidative stress and aging	*In vitro*—non-tumorigenic human keratinocyte cells	UVB	Incubation	[68]

Conclusions

Different studies have demonstrated that this plant extract possesses anti-inflammatory, antioxidant, photoprotective and immunomodulatory activities making this species a powerful agent against solar induced aging and skin cancer. The capsule dosage form is very popular, widely accessible, and viable for all people around the globe. Hence, its antioxidant activity greatly facilitates its usage and thus preventing the skin damage caused by harmful UV radiation.

After an exhaustive review, no studies have been found for this plant based on its phytochemical performance, whether taken from leaves or rhizomes. It is recommended to carry out these studies for better evaluation of this plant. Likewise, it is worth mentioning that no scientific study carried out to determine the antioxidant capacity by 2,2-diphenyl-1-picryl-hydrazyl-hydrate (DPPH) free radical electron-transfer method, while stability studies are required for different pharmaceutical formulations as there is no widely approved dose according to the skin phototype. Hence, nowadays it is necessary to carry out these studies on damaging UVC rays to make better formulations with other active ingredients to produce synergy in the photoprotective and antioxidant capacity.

Abbreviations

UV: ultraviolet

Declarations

Author contributions

RYMSC and SVA: Investigation, Methodology, Formal analysis, Visualization, Writing—original draft. MRAJ: Supervision. AR and MSAP: Conceptualization, Methodology, Formal analysis, Writing—review & editing, Project administration, Supervision.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical approval

Not applicable.

Consent to participate

Not applicable.

Consent to publication

Not applicable.

Availability of data and materials

Not applicable.

Funding

Not applicable.

References

1. Horvath A, Alvarado F, Szöcs J, de Alvardo ZN, Padilla G. Metabolic effects of calagualine, an antitumoral saponine of *Polypodium leucotomos*. Nature. 1967;214:1256–8.
2. Choudhry SZ, Bhatia N, Ceilley R, Hougeir F, Lieberman R, Hamzavi I, et al. Role of oral *Polypodium leucotomos* extract in dermatologic diseases: a review of the literature. J Drugs Dermatol. 2014;13:148–53.
3. Efectos del extracto de *Polypodium leucotomos* sobre la tumorogénesis inducida por la radiación ultravioleta [Internet]. Theses and Dissertations Online; [cited 2022 Sep 9]. Available from: http://hdl.handle.net/10803/8754
4. Nogal-Ruiz JJ, Gómez-Barrio A, Escario JA, Martínez-Fernández AR. Effect of Anapsos in a murine model of experimental trichomoniasis. Parasite. 2003;10:303–8.

5. Garcia F, Pivel JP, Guerrero A, Brieva A, Martinez-Alcazar MP, Caamano-Somoza M, et al. Phenolic components and antioxidant activity of Fernblock, an aqueous extract of the aerial parts of the fern *Polypodium leucotomos*. Methods Find Exp Clin Pharmacol. 2006;28:157–60.
6. Gombau L, García F, Lahoz A, Fabre M, Roda-Navarro P, Majano P, et al. *Polypodium leucotomos* extract: antioxidant activity and disposition. Toxicol Vitr. 2006;20:464–71.
7. Kohli I, Shafi R, Isedeh P, Griffith JL, Al-Jamal MS, Silpa-Archa N, et al. The impact of oral *Polypodium leucotomos* extract on ultraviolet B response: a human clinical study. J Am Acad Dermatol. 2017;77:33–41.e1.
8. Saorin DCM, inventor. Transformação de *Polypodium leucotomos* extrato seco das raízes no fotoprotetor oral sob forma de cápsulas. Portuguese patent PI 0904487-6 A2. 2011 Jan 4.
9. Bhatia N. *Polypodium leucotomos*: a potential new photoprotective agent. Am J Clin Dermatol. 2015;16:73–9.
10. Parrado C, Mascaraque M, Gilaberte Y, Juarranz A, Gonzalez S. Fernblock (*Polypodium leucotomos* extract): molecular mechanisms and pleiotropic effects in light-related skin conditions, photoaging and skin cancers, a review. Int J Mol Sci. 2016;17:1026.
11. 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;19:2250.
12. Schalka S, Vitale-Villarejo MA, Agelune CM, Bombarda PCP. Benefícios do uso de um composto contendo extrato de *Polypodium leucotomos* na redução da pigmentação e do eritema decorrentes da radiação ultravioleta. Surg Cosmet Dermatol. 2014;6:344–8. Portuguese.
13. Schalka S, Steiner D, Ravelli FN, Steiner T, Terena AC, Marçon CR, et al.; Brazilian Society of Dermatology. Brazilian consensus on photoprotection. An Bras Dermatol. 2014;89:1–74.
14. 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;66:58–62.
15. Charoo NA. Hyperpigmentation: looking beyond hydroquinone. J Cosmet Dermatol. 2022;21:4133–45.
16. Aguilera P, Carrera C, Puig-Butille JA, Badenas C, Lecha M, González S, et al. Benefits of oral *Polypodium leucotomos* extract in MM high-risk patients. J Eur Acad Dermatol Venereol. 2013;27:1095–100.
17. Caccialanza M, Percivalle S, Piccinno R, Brambilla R. Photoprotective activity of oral *Polypodium leucotomos* extract in 25 patients with idiopathic photodermatoses. Photodermatol Photoimmunol Photomed. 2007;23:46–7.
18. Caccialanza M, Recalcati S, Piccinno R. Oral *Polypodium leucotomos* extract photoprotective activity in 57 patients with idiopathic photodermatoses. G Ital Dermatol Venereol. 2011;146:85–7.
19. Middelkamp-Hup MA, Bos JD, Rius-Diaz F, Gonzalez S, Westerhof W. Treatment of vitiligo vulgaris with narrow-band UVB and oral *Polypodium leucotomos* extract: a randomized double-blind placebo-controlled study. J Eur Acad Dermatol Venereol. 2007;21:942–50.
20. Searle T, Al-Niaimi F, Ali FR. *Polypodium leucotomos* as an adjunct to the treatment of vitiligo. J Am Acad Dermatol. 2022;86:e65.
21. Szczurko O, Boon HS. A systematic review of natural health product treatment for vitiligo. BMC Dermatol. 2008;8:2.
22. Berman B, Ellis C, Elmets C. *Polypodium leucotomos*--an overview of basic investigative findings. J Drugs Dermatol. 2016;15:224–8.
23. Gonzalez S, Gilaberte Y, Philips N. Mechanistic insights in the use of a *Polypodium leucotomos* extract as an oral and topical photoprotective agent. Photochem Photobiol Sci. 2010;9:559–63.

24. Torricelli P, Fini M, Fanti PA, Dika E, Milani M. Protective effects of *Polypodium leucotomos* extract against UVB-induced damage in a model of reconstructed human epidermis. Photodermatol Photoimmunol Photomed. 2017;33:156–63.
25. Parrado C, Gilaberte Y, Philips N, Juarranz A, Gonzalez S. Chapter 34 - Fern extract, oxidative stress, and skin cancer. In: Preedy VR, Patel VB, editors. Cancer (second edition): oxidative stress and dietary antioxidants. San Diego: Academic Press; 2021. pp. 387–98.
26. Sánchez-Rodríguez C, Peraza Cruces KR, Rodrigáñez Riesco L, García-Vela JA, Sanz-Fernández R. Immunomodulatory effect of *Polypodium leucotomos* (Anapsos) in child palatine tonsil model. Int J Pediatr Otorhinolaryngol. 2018;107:56–61.
27. Solivellas BM, Martín TC. *Polypodium leucotomos* extract use to prevent and reduce the risk of infectious diseases in high performance athletes. Infect Drug Resist. 2012;5:149–53.
28. Gálvez J, Sánchez de Medina F, Romero J, Zarzuelo A. Effect of *Polypodium leucotomos* on acute, chronic and reactivated trinitrobenzene sulphonic acid colitis in rats. Inflammopharmacology. 2000;8:89–105.
29. 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? Dermatol Surg. 2015;41:898–902.
30. Piaserico S, Mazzetto R, Sartor E, Bortoletti C. Combination-based strategies for the treatment of actinic keratoses with photodynamic therapy: an evidence-based review. Pharmaceutics. 2022;14:1726.
31. Stump M, Dhinsa H, Powers J, Stone M. Attenuation of actinic prurigo eruptions with *Polypodium leucotomos* supplementation. Pediatr Dermatol. 2022;39:145–6.
32. Sempere-Ortells JM, Campos A, Velasco I, Marco F, Ramirez-Bosca A, Diaz J, et al. Anapsos (*Polypodium leucotomos*) modulates lymphoid cells and the expression of adhesion molecules. Pharmacol Res. 2002;46:185–90.
33. Thompson KG, Kim N. Dietary supplements in dermatology: a review of the evidence for zinc, biotin, vitamin D, nicotinamide, and polypodium. J Am Acad Dermatol. 2021;84:1042–50.
34. Dedios M, Ninell J. Niveles de radiación ultravioleta, fenotipos e infraestructura de protección solar en instituciones educativas de Piura, Perú. Rev Colomb Enfermería. 2017;15:40–9. Spanish.
35. Garnacho Saucedo GM, Salido Vallejo R, Moreno Giménez JC. Efectos de la radiación solar y actualización en fotoprotección. An Pediatr (Engl Ed). 2020;92:377.e1–9. Spanish.
36. Subhadarshani S, Athar M, Elmets CA. Photocarcinogenesis. Curr Derm Rep. 2020;9:189–99.
37. García-Malinis AJ, Gracia-Cazaña T, Zazo M, Aguilera J, Rivas-Ruiz F, de Troya Martín M, et al. Hábitos y conocimientos sobre fotoprotección y factores de riesgo para quemadura solar en corredores de maratones de montaña. Actas Dermo-Sifiliogr. 2021;112:159–66. Spanish.
38. Gracia-Cazaña T, González S, Parrado C, Juarranz Á, Gilaberte Y. La influencia del exposoma en el cáncer de piel. Actas Dermo-Sifiliogr. 2020;111:460–70. Spanish.
39. Palomino OM. Current knowledge in *Polypodium leucotomos* effect on skin protection. Arch Dermatol Res. 2015;307:199–209.
40. Parrado C, Nicolas J, Juarranz A, Gonzalez S. The role of the aqueous extract *Polypodium leucotomos* in photoprotection. Photochem Photobiol Sci. 2020;19:831–43.
41. Nestor MS, Berman B, Swenson N. Safety and efficacy of oral *Polypodium leucotomos* extract in healthy adult subjects. J Clin Aesthet Dermatol. 2015;8:19–23.
42. Narayanan DL, Saladi RN, Fox JL. Ultraviolet radiation and skin cancer. Int J Dermatol. 2010;49:978–86.
43. Corrêa Mde P. Solar ultraviolet radiation: properties, characteristics and amounts observed in Brazil and South America. An Bras Dermatol. 2015;90:297–313.
44. Bharath AK, Turner RJ. Impact of climate change on skin cancer. J R Soc Med. 2009;102:215–8.

45. Bosch R, Philips N, Suárez-Pérez JA, Juarranz A, Devmurari A, Chalensouk-Khaosaat J, et al. Mechanisms of photoaging and cutaneous photocarcinogenesis, and photoprotective strategies with phytochemicals. Antioxidants (Basel). 2015;4:248–68.
46. Scalbert A, Johnson IT, Saltmarsh M. Polyphenols: antioxidants and beyond. Am J Clin Nutr. 2005;81:215S–7S.
47. Khatoon M, Islam E, Islam R, Rahman AA, Alam AH, Khondkar P, et al. Estimation of total phenol and *in vitro* antioxidant activity of *Albizia procera* leaves. BMC Res Notes. 2013;6:121.
48. San-Miguel A, Martin-Gil FJ. Importancia de las especies reactivas al oxigeno (radicales libres) y los antioxidantes en clinica. Gac Med Bilbao. 2009;106:106–13. Spanish.
49. Esteva E. Fotoprotección. Offarm. 2005;24:64–72. Spanish.
50. Seto Y, Ohtake H, Sato H, Onoue S. Phototoxic risk assessment of dermally-applied chemicals with structural variety based on photoreactivity and skin deposition. Regul Toxicol Pharmacol. 2020;113:104619.
51. Taylor JH, Rosen CF. Correction to: systemic photoprotection. Curr Derm Rep. 2020;9:362.
52. Dunaway S, Odin R, Zhou L, Ji L, Zhang Y, Kadekaro AL. Natural antioxidants: multiple mechanisms to protect skin from solar radiation. Front Pharmacol. 2018;9:392.
53. Smijs TG, Pavel S. Titanium dioxide and zinc oxide nanoparticles in sunscreens: focus on their safety and effectiveness. Nanotechnol Sci Appl. 2011;4:95–112.
54. Serini S, Guarino R, Ottes Vasconcelos R, Celleno L, Calviello G. The combination of sulforaphane and Fernblock® XP improves individual beneficial effects in normal and neoplastic human skin cell lines. Nutrients. 2020;12:1608.
55. González S, Pathak MA. Inhibition of ultraviolet-induced formation of reactive oxygen species, lipid peroxidation, erythema and skin photosensitization by *Polypodium leucotomos*. Photodermatol Photoimmunol Photomed. 1996;12:45–56.
56. 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;12:8466–75.
57. Herrera MC, León SV, Tolentino RG, Francisca MV, Vázquez CCR. Antioxidantes: perspectiva actual para la salud humana. Marcela Rev chil nutr. 2015;42:2. Spanish.
58. Avello M, Suwalsky M. Radicales libres, antioxidantes naturales y mecanismos de protección. Atenea. 2006:161–72. Spanish.
59. Salido FP, Fernández JJR. Influencia de los radicales libres en el envejecimiento celular. Offarm. 2002;21:96–100. Spanish.
60. Addor FAS. Antioxidants in dermatology. An Bras Dermatol. 2017;92:356–62.
61. Silva SAME, Michniak-Kohn B, Leonardi GR. An overview about oxidation in clinical practice of skin aging. An Bras Dermatol. 2017;92:367–74.
62. González S, Lucena SR, Delgado P, Juarranz A. Comparison of several hydrophilic extracts of *Polypodium leucotomos* reveals different antioxidant moieties and photoprotective effects *in vitro*. J Med Plants Res. 2018;12:336–45.
63. Capote R, Alonso-Lebrero JL, García F, Brieva A, Pivel JP, González S. *Polypodium leucotomos* extract inhibits trans-urocanic acid photoisomerization and photodecomposition. J Photochem Photobiol B. 2006;82:173–9.
64. Nichols JA, Katiyar SK. Skin photoprotection by natural polyphenols: anti-inflammatory, antioxidant and DNA repair mechanisms. Arch Dermatol Res. 2010;302:71–83.
65. Afaq F, Katiyar SK. Polyphenols: skin photoprotection and inhibition of photocarcinogenesis. Mini Rev Med Chem. 2011;11:1200–15.

66. García LAEZ. El envejecimiento y el estrés oxidative. Rev Cubana Invest Bioméd. 2002;21:3. Spanish.
67. Vaquero-Raya EC, Molero-Richard X. Especies reactivas de oxígeno en las enfermedades inflamatorias del páncreas: ¿una posible diana terapéutica? Gastroenterol Hepatol. 2005;28:473–84. Spanish.
68. Delgado-Wicke P, Rodríguez-Luna A, Ikeyama Y, Honma Y, Kume T, Gutierrez M, et al. Fernblock® upregulates NRF2 antioxidant pathway and protects keratinocytes from $PM_{2.5}$-induced xenotoxic stress. Oxid Med Cell Longev. 2020;2020:2908108.
69. El-Haj N, Goldstein N. Sun protection in a pill: the photoprotective properties of *Polypodium leucotomos* extract. Int J Dermatol. 2015;54:362–6.
70. Bosqueta LG. Los peligros de la radiación solar. Fotoprotección. Offarm. 2001;20:75–84. Spanish.
71. Marcos FV. La Contaminación ambiental como factor determinante de la salud. Rev Esp Salud Publica. 2005;79:117–27. Spanish.
72. Sanmartín Jimenez O. The rising incidence of melanoma and nonmelanoma skin cancer obliges us to persevere with primary and secondary prevention campaigns. Actas Dermo-Sifiliográficas. 2017;108:324.
73. Ramos MFS, Santos EP, Dellamora-Ortiz GM. Avaliação da atividade antisolar e estudos preliminares de fotodegradação da propolis. Rev Fitos. 2010;5:3. Portuguese.
74. Nascimento LF, Santos EP, Aguiar AP. Fotoprotetores orgânicos: pesquisa, inovação e a importância da síntese organic. Rev Virtual Quim. 2014;6:190–223. Portuguese.
75. Vieira CBS, Orlanda JFF. Atividade antioxidante e fotoprotetora do extrato etanólico de *Ocimum gratissimum L.* (alfavaca, Lamiaceae). Rev Cubana Plant Med. 2018;23:3. Portuguese.
76. Korman AM, Reynolds KA, Nabhan F, Konda B, Shah MH, Kaffenberger BH. Vandetanib-induced phototoxic drug eruption treated with *Polypodium leucotomos* extract: a case report and review of the literature. J Clin Aesthet Dermatol. 2019;12:35–8.
77. Emanuele E, Bertona M, Biagi M. Comparative effects of a fixed *Polypodium leucotomos*/Pomegranate combination *versus Polypodium leucotomos* alone on skin biophysical parameters. Neuro Endocrinol Lett. 2017;38:38–42.
78. Philips N, Gonzalez S. Beneficial regulation of elastase activity and expression of tissue inhibitors of matrixmetalloproteinases, fibrillin, transforming growth factor-*β*, and heat shock proteins by *P. leucotomos* in nonirradiated or ultraviolet-radiated epidermal keratinocytes. ISRN Oxidative Med. 2013;2013:257463.
79. Mohammad TF, Kohli I, Nicholson CL, Treyger G, Chaowattanapanit S, Nahhas AF, et al. Oral *Polypodium leucotomos* extract and its impact on visible light-induced pigmentation in human subjects. J Drugs Dermatol. 2019;18:1198–203.