ARTIGO ORIGINAL
ISSN 1677-5090

DOI: 10.9771/cmbio.v23i2.54651

Natural products as new photoprotection strategies

Produtos Naturais como novas estratégias fotoprotetoras

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Abstract
Objective: to investigate the photoprotective efficacy of natural products in *in vivo* models. **Methodology:** this is an integrative literature review based on articles published between 2015 and 2020 in English, found on electronic platforms with the following keywords: natural sunscreens, medicinal plants, ultraviolet radiation (UVR), ultraviolet rays, sunscreens, and plant extracts. **Results:** 96 articles were identified on the electronic platforms Pubmed, Science Direct, Scielo, and Springer, and eight articles were selected for final analysis and discussion. The compiled data showed that experimental animal models stood out from human models. As for UVR-induced damage, the general effects presented by natural products are radiation absorption, erythema, hyperplasia, and induced carcinogenesis reduction; anti-inflammatory and antioxidant effects; and reduction of signs of photoaging, such as wrinkles, rashes, and skin dehydration. Regarding the type of radiation used, UVB studies are prevalent, but some extracts demonstrate protective effects against UVA and UVB, presenting a broad spectrum of protection. Regarding the form of administration, the findings emphasised the topical route, with formulations with plant extracts being the most used. **Conclusion:** despite the low number, *in vivo,* studies prove that using natural products such as sunscreens has benefits in inhibiting, delaying, or preventing oxidative, inflammatory, carcinogenic damage and aesthetic dysfunctions caused by UV radiation. Thus presenting the potential to be used as a multifunctional sun protection system.
Keywords: Medicinal plants; natural compounds; photoprotection; ultraviolet radiation.

Resumo
Objetivo*: investigar a eficácia fotoprotetora de produtos naturais em modelos in vivo.* ***Metodologia:*** *trata-se de uma revisão integrativa da literatura, baseada em artigos publicados entre os anos de 2015 e 2020, em língua inglesa, encontrados nas plataformas eletrônicas com as seguintes palavras-chave: protetores solares naturais, plantas medicinais, radiação ultravioleta (RUV), raios ultravioletas, fotoprotetores e extratos vegetais.* ***Resultados:*** *96 artigos foram identificados nas plataformas eletrônicas Pubmed, Science Direct, Scielo e Springer e 8 artigos foram selecionados para análise final e discussão. Os dados compilados mostraram que modelos experimentais em animais se destacaram dos modelos humanos. Quanto aos danos induzidos por RUV, os efeitos gerais apresentados pelos produtos naturais são absorção de radiação, redução de eritema, hiperplasia e carcinogênese induzida; efeito antiinflamatório e antioxidante; e redução de sinais de fotoenvelhecimento, como rugas, erupções cutâneas e desidratação da pele. Quanto ao tipo de radiação utilizada, há uma prevalência de estudos com UVB, mas alguns extratos demonstram efeitos protetores contra UVA e UVB, apresentando amplo espectro de proteção. Quanto à forma de administração, os achados enfatizaram a via tópica, sendo as formulações com extratos vegetais as mais utilizadas.* ***Conclusão:*** *apesar do baixo número, estudos in vivo comprovam que o uso de produtos naturais como protetores solares tem benefícios em inibir, retardar ou prevenir danos oxidativos, inflamatórios, carcinogênicos e disfunções estéticas causadas pela radiação UV. Assim, apresentando potencial para serem usados como sistemas de proteção solar multifuncionais.*
Palavras-chave*: Plantas medicinais; compostos naturais; fotoproteção; radiação ultravioleta.*

INTRODUCTION

The sun is a vital energy source for living beings. Adequate amounts of ultraviolet (UV) radiation synthesise vitamin D, a beneficial and physiologically necessary factor. Nonetheless, chronic exposure or intermittent overexposure of human skin to UV rays leads to various skin diseases, including immunosuppression, irreversible skin photoaging, and dermal pathologies, including tumorigenesis [1].

To soften the effects and provide protection against UV rays, the use of sunscreen is essential. Sunscreens are cosmetic preparations that help to protect the skin from sunburn, early skin ageing and skin cancer [2] It can be classified concerning their ability to absorb UV radiation (UVR) as UVA, UVB or broad-spectrum UV filters (UVA and UVB)[3]. The formulations of sunscreens can be composed

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of physical and chemical ingredients. Physical sunscreens act as a physical barrier by scattering or reflecting UV rays. Chemical sunscreens work by absorbing the UV rays [2].

Recent industry demand for naturally derived alternatives for cosmetic formulations has led to a deeper investigation of natural sources for sunscreen application [4]. The use of medicinal plants and natural products has grown significantly in recent decades due to the great diversity of available compounds[5]. Because they have biological activities such as UV radiation absorption and antioxidant and anti-inflammatory capacity, some bioactive compounds have received considerable attention as photoprotection agents, enabling promising strategies to increase the action of available sunscreens[6–8].

In this sense, several studies have been carried out to evaluate the photoprotective capacity of natural compounds. Generally, test substances are evaluated in experimental models of absorption and photoprotection in vitro and/or in vivo from the skin of different species, including rodents, swine and human beings[9]. Despite positive results demonstrating the photoprotective power of natural products, many studies are carried out only in vitro[10–13], using isolated cells or tissues, not guaranteeing that the results can be applied translationally.

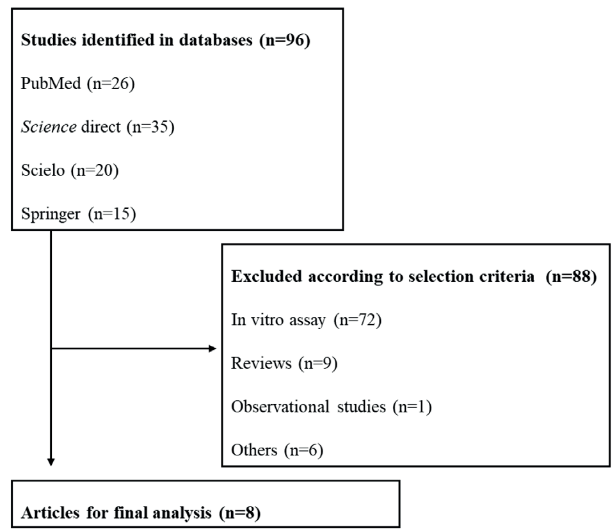
In addition to demonstrating efficacy, in vivo, studies consider variables such as biocompatibility, absorption, interaction with skin components, local and systemic biological effects, as well as possible adverse reactions. They are essential for evaluating the use of natural products in sunscreens. Thus, considering the wide diversity of natural products with the possibility of photoprotection and the different experimental models used, this study aimed to investigate the photoprotective effects of natural products in vivo models through an integrative review and provide the reader with a clearer view of this topic.

METHODOLOGY

This study is an integrative review based on the guiding question: Is the photoprotective efficacy of natural products proven by in vivo tests? In October 2020, we searched the Scielo, Pub Med, Springer, and Science Direct databases for English articles published between January 2015 and October 2020. The following descriptors were used to search for the articles: natural sunscreens, medicinal plants, ultraviolet radiation, ultraviolet rays, photoprotective, and vegetable extracts.

Two researchers independently evaluated the articles identified by the search strategy and selected articles that presented experimental in vivo studies with an animal or human model, evaluating the photoprotective effect exclusively of natural products. Repeated articles were previously deleted. As exclusion criteria, the following were considered: review articles, articles that used in vitro methodology, studies with observational design, studies involving mixtures of chemical or physical sunscreens and natural products, and publications in event proceedings.

After analysing the articles, data extraction was performed (Figure 1).



Source: self-authored

RESULTS

Ninety-six articles were selected from the Scielo, Pubmed, Springer, and Science Direct electronic databases. After evaluation and reading, 08 studies were selected for analysis and final discussion. To extract data from the selected articles, priority was given to the search for the study objectives, experimental model, plant species, form of preparation and application, and exposure to radiation (Table 1). Only the results obtained in in vivo experimental models were discussed in studies with more than one experimental model.

Table 1 – Summary of the selected studies and variables of interest.

Title	Author	Model Experimental/ Radiation	Natural product and administration route	Objective of the study	Main results	Conclusion	Data base
The photoprotective and anti-inflammatory activity of red propolis extract in rats	Batista et al.14 2018	Wistar rats, albinos, males, adults, exposed to UVB radiation	Hydroalcoholic extract of red propolis. Gel emulsion, topical (3.5%) and oral (6%) application	Evaluate the photoprotective effects of topical and oral formulations of red propolis extract	Oral: it did not increase the protection against burns, but it had a chemoprotective, anti-inflammatory effect and inhibited the formation of reactive species. Topical: Decreased erythema as much as the oxybenzone containing protectant.	Red propolis has shown to have a photoprotective effect that may be related to the antioxidant and anti-inflammatory characteristics of the extract, being promising for incorporation in cosmetic products and sunscreens.	PubMed
Evaluation of photoprotective potential and percutaneous penetration by photoacoustic spectroscopy of the Schinus terebinthifolius raddi extract	Bulla et al.15 2015	Wistar rats, albinos, males, adults, exposed to UVB radia-tion	Ethanol extract of Schinus terebinthifolius (Aroeira- Vermelha). Gel emulsion, topical application at 10%	Evaluate the photoprotective potential and ex vivo percutaneous penetration of Schinus terebinthifolius leaf extract	The extract showed radiation absorption with photoprotective potential in the UVB region, increased antioxidant capacity, decreased erythema and no changes histologics after ex-posure	The strong antioxidant activity of the extract suggests that the plant has photoprotective activity, with the possibility of incorporation in photoprotectors.	PubMed
The chemical compositions of Angelica pubescens oil and its prevention of UV-B radiation-induced cutaneous photoaging	Chen et al.16 2018	Mice exposed to UVB radiation	Angelica pubescens essential oil (AP) Topical application diluted in ethanol (1, 5 and 10%) (v/v)	To analyze the chemical composition of Angelica pubescens essential oil and its bioactivity against photoaging in hairless mice induced by UVB radiation	AP improved UVB-damaged skin and the mechanism of action was related to inhibition of inflammatory cytokine production. It also demonstrated photoprotective effects in the treated groups, including reduced signs of erythema	Angelica pubescens can protect the skin from UVB radiation and photoaging due to its anti-inflammatory and photoprotective properties, enabling a therapeutic and preventive option	PubMed
Blackberry extract inhibits UVB-induced oxidative damage and inflammation through MAP kinases and NF-κB signalling pathways in SKH-1 mice skin	Divya et al.17 2015	Mice SKH-1 exposed to UVB radiation	Extract diluted in acetone of fresh blackberry. Topical application at 10% and 20%	Investigate whether blackberry extract reduces inflammatory responses induced by UVB irradiation in mouse skin	The extract suppressed UVB-induced hyperplasia and reduced inflammatory cell infiltration. It reduced glutathione (GSH), lipid peroxidation (LPO) and myeloperoxidase (MPO) depletion. Decreased the level of pro-inflammatory cytokines IL-6 and TNF-α in UVB-exposed skin	Data indicate that Blackberry extract protects against UVB-induced oxidative damage and inflammation by modulating MAP kinase and NF-κB signaling pathways, serving as a protective agent against this type of radiation.	PubMed

Title	Author	Model Experimental/ Radiation	Natural product and administration route	Objective of the study	Main results	Conclusion	Data base
A Specific melon concentrate exhibits photoprotective effects from antioxidant activity in healthy adults	Egoume-nides18 et al. 2018	Humans and human skin explants exposed to UVA and UVB radiation*	Melon juice concentrate pulp Oral: Capsules 20 mg Topic: Neutral vegetable cream (14U SOD/mg)	To characterize the potential photoprotective effects of food supplementation and the topical application of a melon concentrate	The application or supplementation of melon concentrate increased the minimum erythematous dose and the endogenous antioxidant enzymes	It is suggested that the administration of melon concentrate (oral and/or topical) may be a useful strategy for photoprotection due to its antioxidant properties	PubMed
Citral prevents UVB-induced skin carcinogenesis in hairless mice	Kremer et al.19 2019	Hairless male HRS mice exposed to UVB radiation	Citral Methanol Extract (in Gel a 0.1; 0.5 and 1.0%) by topical route	Evaluate the chemoprotective effect of citral during UVB-induced skin carcinogenesis	The 1% citral methanol extract was able to completely inhibit UVB-induced skin carcinogenesis by reducing the levels of oxidative stress and pro-inflammatory cytokines, increasing the rate of apoptosis in the skin	Citral is a promising molecule with effective protection against UVB-induced carcinogenesis	PubMed
Red raspberry extract protects the skin against UVB-induced damage with antioxidative and anti-inflammatory properties	Wang et al.20 2019	Mice strain ICR--Foxn and Human ke-ratonocytes exposed to UVB radiation*	Ethanol extract of red raspberry, applied topically at 750 ug/ml	Investigate the preventive effects and molecular mechanisms of red raspberry extract on UVB damage	The extract prevented skin damage caused by radiation. It also reduced wrinkles, rashes and skin dehydration caused by UVB radiation	Red raspberry extract can reduce photodamage caused by exposure to UVB rays, allowing the development of new strategies to protect skin exposed to UVB radiation.	PubMed
Protective effect of super-critical carbon dioxide fluid extract from flowers and buds of Chrysanthemum indicum Linne´n against ultraviolet-induced photo-aging in mice	Zhang et al.21 2015	Mice exposed to UVA and UVB radiation	Supercritical extract of chrysanthemum flowers and buds by topical route containing 10 mg/ml, 30 mg/ml and 100 mg/ml	To investigate the photoprotective effect of Chrysanthemum indicum extract by topical application to the skin of mice exposed to UV radiation	The extract reduced skin thickness and UV-induced wrinkles in a dose-dependent manner. Furthermore, it reduced UV-induced inflammation by inhibiting the production of inflammatory cytokines and antioxidant indicators and down-regulated MMP-1 and MMP-3 levels	The extract proved to be a new photoprotective agent obtained through natural resources against UV irradiation	PubMed

** Studies with multiple experimental models. Only the in vivo results were included. Source: The author*

Source: research data

DISCUSSION

Evidence from selected studies reports different types of natural products with potential use as photoprotection agents against UV rays. These products also demonstrate to be an alternative with low cost and no, or rare, adverse effects.

As for the types of experimental models, it was observed that most studies were conducted with an animal model of rats[14,15] and mice[16,17,19–21] which can be explained by the fact that the surroundings have physiology skin similar to humans and this affinity can increase the significance of the results[9].

In prominence, the study by Egoumenides et al.[18] (2018), which characterised the potential photoprotective effects of food supplementation and/or topical administration of a concentrated melon juice, was the only article selected with an experimental model in humans. In this study, the Minimum Erythematous Dose (MED) increase can be observed after application and/or supplementation with concentrated melon juice, compared to the placebo group, indicating a photoprotective effect of this juice on the skin. MED consists of the lowest irradiation dose capable of initiating erythema and determining the Sun Protection Factor (SPF) of the formulations, indicating how long there can be sun exposure to UVB radiation without burns[22,23].

As for the type of radiation used in the experimental models, it was observed that five of the studies used only exposure to UVB radiation[14–17,20]. In fact, UVB radiation is identified as more carcinogenic, as it is more erythematous and responsible for burns, predisposing individuals with phototypes I and II to skin cancer. Because they have a mean wavelength between 290 and 320 nm, UVB rays have less penetration into the skin (only in the epidermis). Still, they are capable of causing changes in the chemical structures of DNA through the formation of reactive oxygen species (ROS) and increased oxidative stress[5], which can cause DNA breaks and inflammation, disrupting cell signalling pathways and predisposing to the development of tumours[24–26].

The damage caused by UVB radiation in the experimental models of the selected studies corroborates studies that have already demonstrated an increase in free radicals, inflammatory cytokines, and erythema as a consequence of excessive exposure to UV rays, culminating in irreversible cellular and molecular changes[5,27,28].

Two studies were conducted with combined exposure to UVB and UVA radiation[18,21]. UVA radiation, with a longer wavelength (320 to 400 nm)[29], is responsible for skin pigmentation and has greater penetration, reaching the reticular dermis. This causes oxidative damage to fibroblasts, the main cause of photoaging[30–32].

Thus, studies that use the association of UVA and UVB radiation mimic the natural effects of sun exposure. The association of both radiations in the experimental models used potentiated the erythema index and skin burns, increased oxidative stress and the abnormal expression of p53. When there is an abnormal production of the p53 protein due to mutations in the gene that encodes it, it ceases to act as a suppressor, allowing the wrong encoding of the DNA and predisposing it to cancer development[18,21]. In these studies, the supercritical extract of chrysanthemum flowers and buds and melon juice concentrate pulp were able to minimise these effects, contributing to an effective photoprotection against damage caused by UVB and UVA radiation. These effects must be related to botanical compounds present in vegetal extracts, like the flavonoids, which have aromatic rings that show a broader UV absorption spectrum covering a wavelength range of 200–400 nm[1].

Regarding the plant products that were the subject of the studies, differences can be observed among the extracts tested and their ways of obtaining and using vehicles. Among the plants used, the ethanol extract of Schinus terebinthifolius (Red Aroeira)[15], essential oil of Angelica Pubescens[16] and supercritical extract of Chrysanthemum indicum (chrysanthemum flowers and buds)[21] were tested. Regarding the fruits, studies were found using ethanol extract of Rubus idaeus (red raspberry)[20], extract of Morus nigra (Blackberry) [17] and concentrated pulp of Cucumis melo L (melon juice)[18]. Still, studies were found with hydroalcoholic extract of Dalbergia ecastophyllum (red propolis)[14] and 3,7-dimethyl-2,6-octadienal (citral)[19]. Although the different types of extracts studied present significant photoprotective effects, the extraction conditions of plant metabolites define their final concentrations in extracts, impacting final product preparation and performance; thus, extracts from natural sources must be previously standardised according to official methods and specialised literature before large scale use[33].

Regarding administration routes, it was found that five studies had topical application[15–17,19,] and two studies used combined oral and topical administration[14,18]. Although most sunscreens are applied topically, the oral route is a type of rapid administration with minimal risk of adverse reactions, providing the additional benefits of systemic distribution compared to the topical route[34,35]. Oral sunscreens generally have active principles whose photoprotection mechanisms are characterised by antioxidant actions[36], enhancing the body's antioxidant efficacy against mechanisms that cause damage after exposure to UV radiation. In this context, agents such as essential vitamins and minerals, isolated or combined with plants that contain polyphenols, selenium, and carotenoids, have also already exhibited antiphotocarcinogenic effects by the oral route. Although oral photoprotection has benefits against damage caused by UV radiation, it does not directly protect the skin when used alone and, therefore, oral photoprotectors do not replace the use of topical filters[37,38].

This can be seen in the study by Egoumenides et al.[18] (2018) with concentrated melon juice, which demonstrated that while an increase in MED was achieved within

Rev. Ciênc. Méd. Biol., Salvador, v. 23, n. 2, p. 338-345, mai./ago. 2024

four days after application of the topical active cream, an equivalent increase in MED was observed only after 30 days of oral supplementation. Also, at the end of the study, the increase in MED was greater with the combined treatment (topical + oral) than with the isolated treatment (only topical or oral). The study by Batista et al.[14] (2018), on the other hand, demonstrated in a murine model that the topical application of red propolis extract presented photoprotective and anti-inflammatory activity against damage induced by UV radiation and that the joint application of the oral and topical formulation did not show a superior protective effect. This result is possibly related to the short time of oral supplementation, as the capsules were administered 1 hour before exposure to UVB radiation for six days.

Topical sunscreens are formed by chemical and physical filters, capable of reflecting, scattering or absorbing radiation[39,40]. In this context, new strategies for developing photoprotectors, such as incorporating bioactive agents from natural products in topical formulations and using oral formulations with systemic protective action in a complementary way, have been highlighted[35]. The topical administration route of sunscreen promotes rapid efficacy due to its direct, specific, and localised action on the skin as a target organ. On the other hand, oral administration provides benefits via systemic distribution[34], but a long period of supplementation seems necessary to obtain the desired effects.

In the studies analysed, the tested extracts were isolated [16,17,20,21] or incorporated into formulations[14,15,18,19], showing similar effects regarding skin thickness reduction, erythema index, damage reduction oxidative and other damage caused by UV radiation. Previous studies show that the sunscreen vehicle is essential for its effectiveness and absorption during use, as it guarantees stability, ease of penetration and spreadability on the skin. In general, the water in oil emulsion is the recommended formulation for sunscreens to achieve the highest SPF and water resistance[41,] but none of the studies evaluated used this vehicle.

Clinically, skin exposure to UV radiation results in unsightly consequences such as solar keratoses and pigmentation disorders[42–44]. Such characteristics include thinner and opaque skin, decreased sweat and sebaceous gland activity, which leads to loss of moisture and natural lubrication, leaving the skin dehydrated, susceptible to the appearance of deep wrinkles, erythema, telangiectasias, loss of elasticity and resistance and non-uniform pigmentation, characteristic of photoaging[45].

In the studies reviewed that involved the topical administration of natural products, red propolis[14], Schinus terebinthifolius[15], Angelica pubescens[16] and melon juice[18] were able to reduce erythema; Chrysanthemum indicum[21] decrease skin thickness, and the classification of wrinkles; Schinus terebinthifolius[15] and Angelica pubescens[16] showed UV radiation absorption capacity and photoprotective potential; Schinus terebinthifolius[15], melon juice[18] and chrysanthemum[21] reduced oxidative damage, inflammatory cytokines and increased antioxidant capacity. These results are in line with studies that have shown that natural components have photoprotective effects on the skin, not only through direct UV-absorption properties but also through their antioxidant effects (scavenging ROS), as well as by regulation of UV light-induced gene expression, modulation of stress-dependent signalling, and/or suppression of cellular and tissue responses like inflammation[46]. Thus, considering the multiple effects of natural compounds against UV radiation, we observed that the in vivo studies presented in this review demonstrated a high potential for using natural products tested in multifunctional sunscreen systems.

To the best of our knowledge, during the period studied, the number of in vivo studies evaluating the effectiveness of sunscreens based on natural products was very low, especially involving human beings. Despite the complications of in vivo testing, such as the use of participants or animals, approval by research ethics committees, as well as risks for volunteers regarding UV exposure, it is remarkably important to assess the actual efficacy of natural sunscreens as results obtained via in vitro methods could not always be confirmed in vivo[33]. Furthermore, the diversity of tests carried out to evaluate the effectiveness of natural sunscreens makes it very difficult to compare results and identify plant species with the most significant prospecting potential. Therefore, there are still many future studies to be carried out to prove the photoprotective properties demonstrated in vitro by natural products, in addition to the development of standard methodologies that allow the comparative evaluation of such compounds.

CONCLUSION

Despite the low number, in vivo studies prove that using natural products such as sunscreens has benefits in inhibiting, delaying or preventing oxidative, inflammatory, carcinogenic damage and aesthetic dysfunctions. They have potential for topical or oral application, with local and systemic effects, and can be used in different formulations, presenting potential for innovative cosmetics as multifunctional sun protection systems.

Still, considering the great diversity of natural products available, future studies should clarify their photoprotective mechanisms in standardised in vivo studies.

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Submetido em: 29/12/2023
Aceito em: 03/08/2024