



Pharmacognosy

Can natural products improve skin photoprotection?

Bruna Galdorfini Chiari-Andréo^{1,2}, Fernanda Borges de Almeida¹, Paulo Renato Yamasaki^{1,3}, Jean Leandro dos Santos¹, Marcos Antonio Corrêa¹, Chung Man Chin¹ & Vera Lucia Borges Isaac^{1,4,5}

Abstract

Due to increased UV radiation on the Earth's surface, caused by depletion of the stratospheric ozone, people have become more susceptible to different types of skin damage, such as erythema, sunburns, and cancer; this is especially of concern in tropical countries. Thus, efforts to improve awareness as well as the use of sunscreen are increasing worldwide. However, synthetic UV filters have been associated with deleterious effects such as photosensitization. Natural products have been used by ancient cultures for several purposes, including protecting the skin from the sun. However, there is still doubt today whether photoprotection is a real phenomenon or whether it is simply tanning of the skin. Plants have self-protective mechanisms and produce secondary metabolites that can protect themselves from UV radiation. Yet, can phytochemical compounds protect human skin? This review discusses the paradoxical effect of chemical UV filters and the influence of phytochemicals in *in vitro* and *in vivo* tests of photoprotection.

Key words: chemical analysis, natural compounds, photoprotection, sunscreen, synergism.

Resumo

Devido ao aumento da incidência da radiação ultravioleta na superfície da Terra causada pelo esgotamento do ozônio estratosférico, a pele humana se torna mais suscetível à danos, como eritema, queimaduras solares e câncer, principalmente em países tropicais. Assim, em todo o mundo os esforços de conscientização estão aumentando, assim como o uso de produtos de proteção solar. No entanto, filtros UV sintéticos têm sido associados a efeitos deletérios, como a fotossensibilização. Os produtos de origem natural foram usados por culturas antigas para diversos fins, incluindo a proteção da pele contra a radiação solar. Contudo, até hoje há uma dúvida se é uma fotoproteção real ou apenas um simples bronzeamento da pele. O fato é que as espécies vegetais apresentam mecanismos de autoproteção e produzem metabólitos secundários para se proteger da radiação UV. Porém, as substâncias de origem vegetal podem proteger a pele humana? A presente revisão discute o efeito paradoxal dos filtros químicos UV e a influência dos metabólitos secundários de origem vegetal nos testes de fotoproteção *in vitro* e *in vivo*.

Palavras-chave: análise química, substâncias naturais, fotoproteção, protetor solar, sinergismo.

Introduction

Natural products have been used in human therapy for centuries and have long been a thriving source for the discovery of new drugs, due to their chemical diversity and ability to act on several biological targets. The longstanding and successful

use of natural product combinations in traditional medicine has generated interest in phytomedicine in recent years (Simões *et al.* 2017).

Sun tanning is synonymous with beauty, good health, and dynamism in some cultures, particularly in tropical countries. South America

See supplementary material at <<https://doi.org/10.6084/m9.figshare.12252350.v1>>

¹ Universidade Estadual Paulista - UNESP, Faculdade de Ciências Farmacêuticas, Rod. Araraquara-Jaú, km 1, 14800-903, Araraquara, SP, Brazil.

² Universidade de Araraquara - UNIARA, Depto. Ciências Biológicas e da Saúde, R. Carlos Gomes 1338, 14800-903, Araraquara, SP, Brazil.

³ Universidade Paulista - UNIP, Inst. Ciências da Saúde - ICS, Av. Alberto Benassi 200, 14804-300, Araraquara, SP, Brazil.

⁴ ORCID: <<http://orcid.org/0000-0001-7402-920X>>

⁵ Author for correspondence: lacos.unesp@gmail.com

natives used *urucum* fruit (*Bixa orellana* L.) to color the skin. While this tradition led the population to believe that *urucum* is a natural sunscreen, there is no evidence to date to support this. Moreover, there is a myth about plant safety in therapeutics, which is disseminated by the population. However, the information about the possibility of harmful adverse effects to human health that can easily occur, such as allergic manifestations, should also be noted (Drew & Myers 1997; Shaw *et al.* 1997).

Many previous reviews and studies regarding phytochemicals are available, including those describing the role of phytochemicals in the photoprotection mechanism of plants (Demmig-Adams & Adams 1992; Gilmore 1997; Liu 2004; Ryan *et al.* 2002; Steyn *et al.* 2002; Treutter 2006). However, further review studies on the use of phytochemical compounds in topical sunscreen in humans are needed, as there is a growing interest in these products (Garcia-Bores & Avila 2008; Choquenet *et al.* 2008; Hübner *et al.* 2016; Martins *et al.* 2016).

Thus, the purpose of this review is to show the photoprotection properties occurring in natural substances and compounds, the importance of the use of these molecules in comparison with synthetic sunscreens, and the possibility of their use in synergistic mechanisms (photoprotection/photoprotection and/or photoprotection/antioxidant activity), thus clarifying the myths and facts on this subject.

Methods

The studies were selected by searching Google Scholar, PubMed, and SciELO databases using the following descriptors: photoprotection, sunscreens, phytochemicals and photoprotection, flavonoids and photoprotection, carotenoids and photoprotection, and sunscreen and synergism. A total of 174 articles were consulted, 36 review and 138 originals. A total of 142 papers were selected to be part of this review.

Results and Discussion

Physiopathology of UV damage to the skin

Ultraviolet (UV) radiation upregulates the activator protein (AP-1) and induces AP-1-regulated matrix-degrading metalloproteinase genes in human skin *in vivo* (Fisher *et al.* 1996, 1998). Matrix metalloproteinases (MMPs) are proteases that degrade collagen and other extracellular matrix

components of the dermis (Lahmann *et al.* 2001), promoting skin aging (Fisher *et al.* 1997).

Ultraviolet A (UVA) and ultraviolet B (UVB) rays induce skin damage, including skin cancer, by different mechanisms (Fig. 1) (Setlow *et al.* 1993; Arthey & Clarke 1995; Ezzedine *et al.* 2007; Neale *et al.* 2007; Brenner & Hearing 2008; Rigel 2008). UVA radiation, ranging from 320 to 400 nm (Helbling *et al.* 1992), causes damage to DNA molecules by reactive oxygen species (ROS) formation (including superoxide anion radicals, hydrogen peroxide, and singlet oxygen). By being absorbed directly by DNA, generating DNA photoproducts (Vile & Tyrrell 1995; Fisher *et al.* 2002) thus, resulting in single-strand breaks and subsequent formation of oxidized pyrimidines, purines, and cyclobutane pyrimidine dimers (CPDs). UVA radiation also induces inflammatory responses through activation of the pro-inflammatory factor NF- κ B (Kvam & Tyrrell 1997; Douki *et al.* 2003; Sander *et al.* 2004; Nash *et al.* 2006).

UVB radiation, ranging from 280 to 320 nm (Helbling *et al.* 1992), acts directly on DNA inducing damage by dimerization reactions between adjacent pyrimidine bases, resulting in the formation of CPDs and (6-4) photoproducts (Berneburg & Krutmann 2000; Fisher *et al.* 2002; Douki *et al.* 2003; Jans *et al.* 2005). UVB radiation also oxidizes guanine residues, resulting in the formation of 8-oxo-7,8-dihydro-20-deoxyguanosine in DNA, a molecule involved in carcinogenesis (Cooke *et al.* 2010; Afaq 2011).

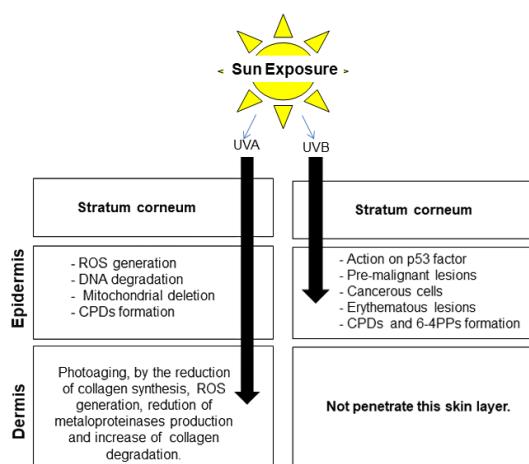


Figure 1 – Damage to skin cells caused by UV radiation [adapted from (Guaratini *et al.* 2007; Scotti *et al.* 2007; Soehnge *et al.* 1997)].

In Brazil, skin cancer cases represent 30% of all malignant tumors reported. In 2016–2017, an estimated 600,000 new cases of cancer was considered, including 180,000 cases of non-melanoma skin cancer (INCA 2016).

However, excessive sun exposure can increase the risk of developing skin cancer, including malignant melanomas. Cutaneous melanoma has a high mortality rate, but a low incidence. It originates from melanocytes and is predominantly found in adult Caucasian individuals. While representing only a small portion of all types of skin cancer, melanoma is of significant concern because of its high possibility of metastasis. Risk factors include sensitivity to sunlight (sunburn without tan), light skin, excessive exposure to UVA and UVB, family history of skin cancer, family history of melanoma, congenital nevus (dark spot), maturity, xeroderma pigmentosum (congenital disorder characterized by the skin's total intolerance to the sun, external burns, chronic injuries, and multiple tumors), and dysplastic nevi (lesions with dark precancerous cell changes on the skin) (INCA 2016). In 2018 it was estimated the emergence of 6260 new cases of melanoma skin cancer in Brazil (INCA 2018).

Awareness of the damaging effects of sun exposure has resulted in increased use of sunscreen products, since these products have been widely recommended as protective against sunburn, photoaging, and skin cancer (Gustavsson Gonzalez *et al.* 2002; Hughes & Stone 2007).

Chemical sunscreens in photoprotection

Chemical UV filters are incorporated into sunscreen products to reduce skin photoaging and prevent skin cancer (Foley *et al.* 1993; Marto *et al.* 2016). The main chemical filters include para-aminobenzoic acid, benzophenones, cinnamates, and benzimidazole sulfonic acids. An example of a more recently developed molecule for this purpose is bis-ethylhexyloxyphenol methoxyphenyl triazine (Chatelain & Gabard 2001; Hüglin 2016) (Fig. 2). However, of late two chemical filters (oxybenzone and octinoxate) have been banned from use in Hawaii due to their ecotoxic potential against coral reefs (Raffa *et al.* 2018).

Sunscreens containing chemical filters are capable of effectively absorbing UV radiation, both through high absorptivity and broad spectral coverage across the UV region, preventing its harmful penetration into the skin (Paye *et al.* 1961). Absorption occurs via promotion of the

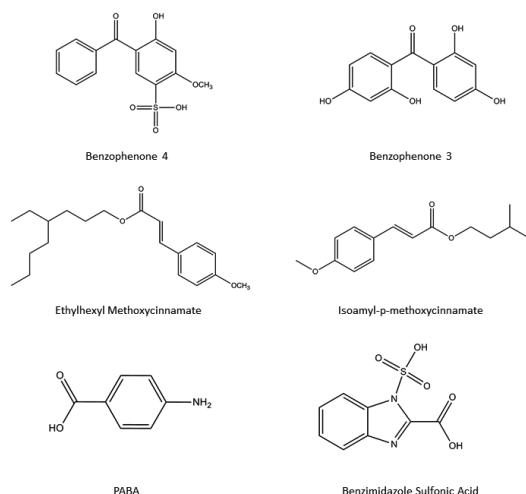


Figure 2 – Chemical structure of the major chemicals used as sunscreens.

sunscreen molecule to its excited state (Fig. 3). However, long-lived excited states can themselves be harmful to the skin due to the generation of ROS or increased reactivity. As such, ideal screening agents will rapidly deactivate their excited states via photophysical processes known as internal conversion or isomerization, both of which convert the photon energy to heat by returning the molecule to its electronic ground state (Corrêa 2012).

One of the universally accepted parameters used to evaluate the efficacy of a sunscreen is the sun protection factor (SPF). The SPF value represents the ratio of the minimal erythematous dose (MED) of the protected skin with the MED of unprotected skin (Schalka & dos Reis 2011).

Phytochemicals in photoprotection

The use of natural products in the prevention of skin damage caused by UV light has gained attention, especially in the case of phytochemicals that exhibit antioxidant, anti-inflammatory, anti-mutagenic, anti-carcinogenic, and immunomodulatory activities and that could act in different cellular and molecular mechanisms (Afaq 2011). Proserpio (1976) described natural products in relation to sunscreen and tanning in 1967. Bobin *et al.* (1994) evaluated 100 different plant extracts to determine if they exhibited sunscreen activity, and Ramos & Santos (1996) evaluated another plant extract with respect to its UV absorption spectra and SPF value. Plants are a good source of molecules that have been used in the development of UV protective agents

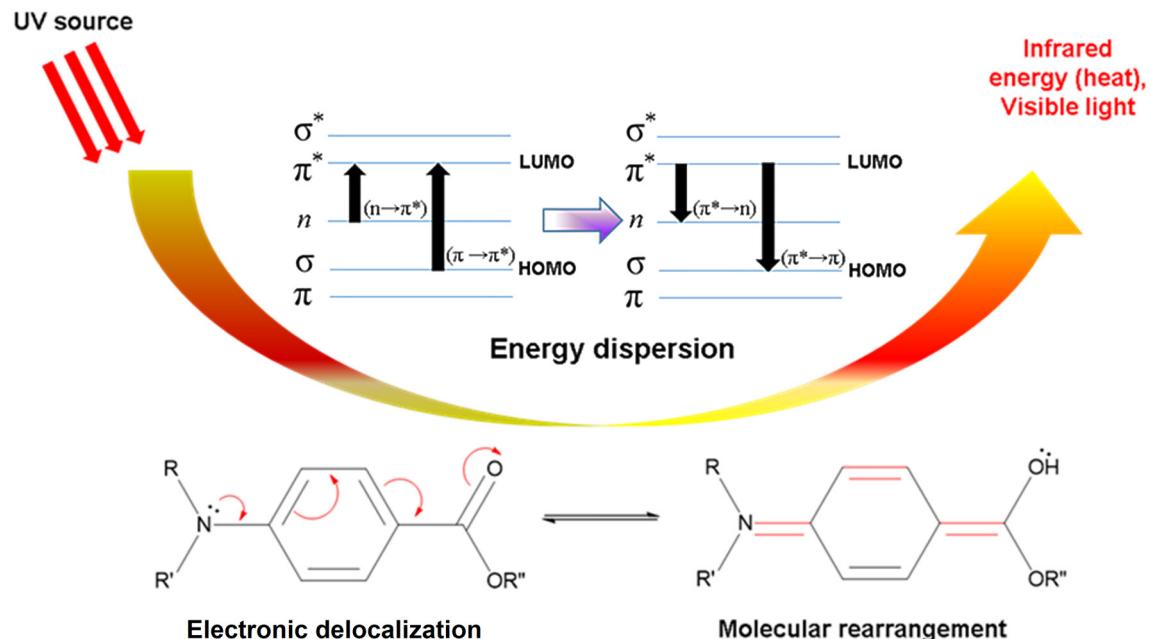


Figure 3 – Possible mechanism of UV absorption by the relocation of electrons of the chemical absorber in sunscreens (Shaath 1986; Wolf *et al.* 2001).

for the skin (Ferrari *et al.* 2007). The interest in the use of secondary metabolites found in plants to develop sunscreens is based on the increased UV radiation resistance of plants compared with mammalian cells and microorganisms, suggestive of the photoprotective effect of phytochemicals (Caldwell *et al.* 1983; Dinkova-Kostova 2008). Because of the importance of these substances, Liu (2004) defined phytochemicals as bioactive non-nutrient plant compounds found in fruits, vegetables, grains, and other plant foods that have been linked to the reduced risk of major chronic diseases.

There are several classes of secondary metabolites including alkaloids, flavonoids, carotenoids, isothiocyanates, lignans, tannins, quinones, saponins and methylxanthines, for example, that are produced by plants according to their necessity, with the stimulus received and stress conditions which are submitted (Gobbo-Neto & Lopes 2007; Dinkova-Kostova 2008; Solovchenko & Merzlyak 2008; Simões *et al.* 2017).

Scientific studies of mutant plants have also been used to demonstrate the role of secondary metabolites in protection against damage caused by UV radiation. Stapleton & Walbot (1994) showed that a type of mutant maize, deficient in flavonoids,

suffered increased DNA damage in leaf tissue. Landry *et al.* (1995) found an increase in DNA damage caused by UVB rays in a mutant strain of *Arabidopsis* that exhibited reduced production of phenolic compounds. The authors of this study concluded that phenolic compounds may be able to absorb UV radiation, thus acting as a sunscreen for the plant. These compounds possess one or more aromatic rings with one or more hydroxyl groups; examples include phenolic acids, flavonoids, stilbenes, coumarins, and tannins (Liu 2004). This behavior was verified by other researchers in *Arabidopsis thaliana* (Chapple 1992; Li *et al.* 1993; Ormrod *et al.* 1995; Shirley 1996; Booij-James *et al.* 2000; Jin *et al.* 2000; Stracke *et al.* 2010; Biever *et al.* 2014; Roepke & Bozzo 2015).

Studies have also shown that plants are able to react to excessive UV radiation by increasing phenolic compound production. Liu *et al.* (1995) showed that *Hordeum vulgare* L. can respond to an increase of UVB and UVA radiation by increasing the flavonoid content in the plant tissue.

According to Kliebenstein (2004), the secondary metabolites found in *Arabidopsis* are glucosinolates, terpenoids, phenylpropanoids, and the alkaloid-like camalexin, as well as other uncharacterized compounds. Phenylpropanoids

are the major class of secondary metabolites that absorb UVB irradiation in plants, and because of that, there is speculation that they could function as a sunscreen. Flavonoids, isoprenoids, and alkaloids correspond to the three major classes of secondary metabolites produced by higher plants (Tian *et al.* 2008). One of the most striking features of flavonoids, among their several physiological functions, is their ability to absorb UV radiation over a wide range of the spectrum (Liu *et al.* 1995; Solovchenko & Schmitz-Eiberger 2003; Julkunen-Tiitto *et al.* 2015).

Bandaranayake (1998) showed that other types of living organisms, such as fungi, algae, and other marine species, also synthesize compounds that protect themselves against UV radiation. These compounds absorb light at wavelengths ranging from 240 to 310 nm, avoiding the damage caused by light in these organisms.

Four possible mechanisms for phytoprotection have been proposed: (1) the ability of the molecule to absorb UVA and UVB rays; (2) the antioxidant effect of the molecule, the chelating activity of transition metals, and/or ROS scavenging through the formation of less reactive structures (applied to polyphenols); (3) inhibition of MMPs, which could damage or destroy the collagen and elastic fibers that constitute the dermis; and (4) modulation of stress-dependent signaling and/or suppression of cellular and tissue responses such as inflammation (Pillai *et al.* 2005; Hinneburg *et al.* 2006; Russo *et al.* 2006; Stahl & Sies 2007; Dinkova-Kostova 2008; Mudit & Katiyar 2010; Nichols & Katiyar 2010; Oresajo *et al.* 2010; Staniforth *et al.* 2012). The last three mechanisms prevent damage that could have been caused by excessive UV radiation in the skin. These mechanisms are described in detail below.

The ability of phytochemicals to absorb UVA and UVB rays represents the ability to filter the UV rays. It can be compared to the effect of sunscreen substances, which either reflect the light and prevent the rays from reaching the skin's surface or absorb them, transforming it into heat. It could be considered a requisite and not a mechanism of photoprotection (Nichols & Katiyar 2010).

The antioxidant activity of phytochemicals helps prevent damage caused by UV rays. UV light promotes the generation of free radicals; however, when phytochemicals are able to react with these unstable radicals, the reaction of UV light with cellular components, such as the

cellular membrane, is avoided. Additionally, UV light causes the depletion of endogenous antioxidants, and phytochemicals can contribute to their regeneration (Pillai *et al.* 2005). It is important to note that this ability is not verified in the SPF determination *in vitro*, since current methodologies are only able to determine how much the substance is able to block the passage of light and not other effects such as the antioxidant activity. The influence of the antioxidant activity in the SPF value has only been measured *in vivo*, and has been shown to retard erythema formation (Pillai *et al.* 2005).

MMPs are able to degrade collagen and other extracellular matrix components of the dermis and thus are directly related to skin aging, more specifically with the acceleration of aging due to sun exposure (photoaging). In this vein, inhibition of these proteases could prevent premature aging due to sun exposure (Lee *et al.* 2018).

Finally, phytochemicals act to modulate stress-dependent signaling and/or suppress cellular and tissue responses such as inflammation. These interferences have been based on alteration of the expression of genes related to cellular signaling pathways. UV light affects, for example, the tumor suppressor p53, resulting in apoptosis. However, when p53 is mutated, the result could be resistance to apoptosis and uncontrolled proliferation of the damaged cell (Liu *et al.* 1995; Bosch *et al.* 2015). The transcription factor NF- κ B and MAPKs are components of other signaling pathways that are modulated by UV exposure and have been linked to inflammation (Cho *et al.* 2003). An advantage of the use of phytochemicals for protection against the sun is based on their "pluripotent character", as termed by Dinkova-Kostova (2008), which is defined as their ability to counteract the multiple damaging effects of UV radiation.

Fresneda *et al.* (2001) demonstrated the photoprotective activity of five plant species (casuarina, pine, mimosa, eucalyptus, and soplillo) and observed that elastase inhibition was caused by the presence of tannins.

Da Silva *et al.* (2005) showed that the *in vitro* SPF value of the crude extract of *Pothomorphe umbellata* L. root was 21, and was attributed to the presence of 4-nerolidylcathecol. Considering that sunscreen formulations available on the market have similar SPF values; *e.g.*, SPF 15 and 30, this result could be promising and possibly even improved by the addition of other phytochemicals or synthetic photoprotector substances (Matsui *et*

al. 2009; Silva *et al.* 2019). Antioxidant activity of *Piper umbellata* L. was reported by Baldoqui *et al.* (2009), and was attributed to the presence of 4-nerolidylcathecol, which exhibits antioxidant activity as potent as that of alpha-tocopherol.

Rosa *et al.* (2008) assessed the photoprotective potential of aqueous extracts of different plants by methodology of Mansur *et al.* 1986. They showed that the presence of phenolic compounds, tannins, flavonoids, coumarins, cardiotonic glycosides, reducing sugars, triterpenes, and steroids in extracts of *Achillea millefolium* L., *Brassica oleracea* var. *capitata* L., *Cyperus rotundus* L., *Plectranthus barbatus* Andrews, *Porophyllum ruderale* (Jacq.) Cass., and *Sonchus oleraceus* (L.) L. resulted in significant increases in SPF values, with SPF 8 for *A. millefolium*; SPF 6 for *S. oleraceus*; SPF 5 for *P. ruderale*, *B. oleracea* var. *capitata*, and *P. barbatus*; and SPF 2 for *C. rotundus* (Rosa *et al.* 2008). In the case of these values, the combination of several of these compounds, or in combination with synthetic sunscreens, may be beneficial as SPF values of 15 or higher are recommended for sun exposure (USFDA 2017, 2019).

Souza *et al.* (2005) observed the photoprotective activity of extracts of *A. millefolium* flowers and leaves. However, the extracts were not effective for the preparation of a sunscreen product, since the wavelengths of maximum absorption shown by these substances did not correspond to UVA and UVB radiation.

Violante *et al.* (2009) assessed the *in vitro* photoprotective activity of plant extracts from the cerrado of Mato Grosso, Brazil. The authors used dried ethanolic extracts to evaluate the absorbance of UV radiation in the region between 260 and 400 nm. However, the extract showed an SPF value of less than 2, which does not characterize a sunscreen product, according to Mansur *et al.* (1986). Table S1 (available on supplementary material <<https://doi.org/10.6084/m9.figshare.12252350.v1>>) summarizes some phytochemicals as well as their sources and activities.

Up until this point in this review, the findings of Surh & Na (2008) were taken into account. According to them, the most critical factors in multistage carcinogenesis are oxidative stress and inflammatory tissue injuries. Thus, much attention has been dedicated to the antioxidant properties of phytochemicals. In addition, these substances can exert chemopreventive effects, acting by distinct mechanisms not easy to elucidate considering structure-activity relationships.

Genistein

Wei *et al.* (1998) conducted a complete study of genistein, the most abundant isoflavone soy-derived phytoestrogen. They demonstrated that it potently inhibits UVB-induced carcinogenesis and photodamage in animals. They proposed that genistein is able to scavenge ROS, block oxidative and photodynamic damage of DNA, promote inhibition of tyrosine protein kinases, downregulate EGF-receptor phosphorylation and MAPK activation, and suppress oncoprotein expression in UVB-irradiated cells and mouse skin. In addition, they investigated the effect of topical application of genistein on UVB-induced erythema (sunburn) in the dorsal skin of men with phototypes II to IV. The results showed that 5 µmol genistein/cm² applied on the human skin substantially blocked erythema induced by different doses of UVB radiation, whereas post-UVB application showed little protection of cutaneous erythema. However, lower doses of genistein (0.1 µmol) effectively inhibited erythema induced by one erythema dose of UVB. In addition, the results of pre-UVB application of genistein significantly inhibited both cutaneous erythema and discomfort whereas post-UVB application improved the discomfort score with a minimal effect on erythema (Wei *et al.* 1998). Moore *et al.* (2006) confirmed the potent antioxidant and anti-photocarcinogenic effects of genistein.

In 2010, Wang *et al.* studied the effect of genistein on skin senescence. They performed experiments using subcytotoxic doses of UVB in human diploid fibroblasts (HDFs), which induced the expression of senescence-associated beta-galactosidase (CCS) that caused apoptosis and cell cycle arrest of HDFs. They observed potent activity of genistein, supporting the hypothesis that genistein protects skin fibroblasts against senescence by inducing antioxidant enzymes and preventing intracellular oxidative stress in the mitochondria. Genistein treatment increased intracellular superoxide dismutase activity and decreased intracellular levels of malondialdehyde in HDFs. The study also revealed that genistein treatment decreased the relative copy number of a common deletion (4,977 bp deletion) and 3,895 bp deletion of mitochondrial DNA in UVB-exposed HDFs. Genistein treatment also reduced the expression of p66Shc and FKHL1 in UVB-exposed HDFs.

Carotenoids

Carotenoids are natural pigments found in several vegetables. Studies performed with

these compounds have focused on carotenoid supplementation to increase the antioxidant concentration in human serum and protect against UV light-induced erythema (Stahl *et al.* 2000; Gammon *et al.* 2017). A study performed by Junghans *et al.* (2001) showed that these compounds are efficient blue light filters.

Red and green propolis

Nascimento *et al.* (2009) evaluated the increase in SPF of sunscreen formulations by the addition of red and green propolis extracts. The authors used ethanolic and glycolic extracts of propolis and found that there was a significant increase in the SPF value when the ethanolic extract of propolis was added. They observed a higher increase in SPF when the green propolis extract was used, which is higher when the red propolis is used.

Curcumin

In the field of suppression of cellular and molecular mechanisms induced by UV radiation, Cho *et al.* (2005) studied the potential of curcumin to inhibit the expression of COX-2 in UVB-irradiated human keratinocytes (HaCaTs), since UVB irradiation induces acute inflammation. They suggested that curcumin may inhibit COX-2 expression by suppressing the activities of two kinases of the MAPK family, p38 MAPK and JNK, in UVB-irradiated HaCaTs and that curcumin could be applied as an effective and novel sunscreen drug for protection against photoinflammation. Curcumin could be effective in the chemoprevention of skin cancer since COX-2 expression plays an important role in UV-induced carcinogenesis (Chen *et al.* 2001).

Quercetin

Ding *et al.* (2010) studied the role of quercetin in inhibition of MAPK and AP-1 pathways and in activation of the Nrf2/ARE pathway based on the antioxidant and anti-carcinogenic activity of this flavonoid. The results obtained provide evidence that quercetin contributes to the inhibition of neoplastic transformation by blocking activation of the MAPK pathway and stimulating signaling pathways linked to cellular protection.

Myricetin

Kang *et al.* (2011) reported that myricetin could inhibit the activity of MEK, JAK1, Akt, and MKK4 kinases. In addition, this substance could attenuate the expression of COX-2 in UVB-

irradiated mice and mediate the inactivation of Akt in the UVB response that plays a role in regulating UVB-induced carcinogenesis.

Proanthocyanidins

Sharma *et al.* (2007) showed that proanthocyanidins, derived from dietary grape seed, have the potential to attenuate UVB-induced oxidative stress and to inhibit activation of cellular signaling cascades involving the MAPK and NF- κ B pathways. Thus, proanthocyanidins can reduce the risk of photocarcinogenesis.

Synergism between natural products and synthetic sunscreens

To date, studies have shown that the roles of phytochemicals could be exploited in dermatological products, mainly to prevent the occurrence of skin cancers and other dermatological pathologies promoted by the sun and/or free radicals (Bosch *et al.* 2015; Dzialo *et al.* 2016; Martins *et al.* 2016; Bose *et al.* 2017; Andrade *et al.* 2019).

Another important subject that should be explored is the synergism between natural products and synthetic photoprotector products. Ramos & Santos (1996) prepared liquid and dry extracts of *Hamamelis virginiana* L., *Matricaria recutita* L., *Aesculus hippocastanum* L., *Rhamnus purshiana* DC., and *Cinnamomum zeylanicum* Blume by different methods, such as repercolation, maceration, and microwave oven heating. Afterwards, they evaluated the UVB absorption spectra (290–320 nm) and SPF values using the spectrophotometric method described by Mansur *et al.* (1986). They tested three concentrations (3%, 10%, and 40%) of these extracts and the association with a synthetic sunscreen (ethylhexyl methoxycinnamate). The results revealed photoprotective activity superiority with the combination of natural products compared with single constituents, as described by Wagner (2011). The macerated extract of *A. hippocastanum* does not exhibit UVB absorption (Tab. 1). However, the SPF value increases to 6 when it is mixed with a synthetic photoprotector. The synergism between phytochemical and synthetic sunscreens was also observed by Velasco *et al.* (2008). Plant extracts present low SPF values, however, in some cases, when added to synthetic sunscreens, the photoprotection factor of the formulation was improved (Tab. 2).

The therapeutic superiority of multidrug combinations of traditional medicine with natural products over single constituents has been

Table 1 – SPF values of different plant extracts isolated and associated with ethylhexyl methoxycinnamate determined by Ramos & Santos (1996).

Plant species	Kind of extract										FPS values					
	EF extract	Dry extract	3% R	3% MO	3% M	10% R	10% MO	10% M	10% R + 2% MCX	10% MO + 2% MCX	10% M + 2% MCX	40% R	40% MO	40% M		
<i>H. virginiana</i>	X		0	0		0	1								1	3
		X				2	3		6	6						
<i>R. purshiana</i>	X		0	0		1	0								1	1
		X				2	4		7	7						
<i>C. zeytlanicum</i>	X		0	1		0	1								1	2
		X				4	2		7	6						
<i>M. recutita</i>	X		0			0									0	
		X				2			5							
<i>A. hippocastanum</i>	X			0				0							0	
		X						0								

EF extract = Ethanolic fluid extract; R = Reperculation; MO = Microwave oven extraction; M = Maceration; MCX = ethylhexyl methoxycinnamate.

Table 2 – FPS values of different natural products.

Natural product	Product assessed	Extract concentration	SPF	Reference
<i>Achillea millefolium</i>	Aqueous extract	1 µL/mL	8	(Rosa <i>et al.</i> 2008)
Green propolis and red propolis	Ethanolic and glycolic extract in a gel	0.2 µL/mL	2.2–5.8	(Nascimento <i>et al.</i> 2009)
<i>Pothomorphe umbellata</i> root	Crude ethanol-water extract	0.2 µg/mL	21	(Da Silva <i>et al.</i> 2005)
<i>Sonchus oleraceus</i>	Aqueous extract	1 µL/mL	6	(Rosa <i>et al.</i> 2008)
<i>Brassica oleracea</i>	Aqueous extract	1 µL/mL	5	(Rosa <i>et al.</i> 2008)
<i>Porophyllum ruderale</i>	Aqueous extract	1 µL/mL	5	(Rosa <i>et al.</i> 2008)
<i>Plectranthus barbatus</i>	Aqueous extract	1 µL/mL	2	(Rosa <i>et al.</i> 2008)
<i>Cyperus rotundus</i>	Aqueous extract	1 µL/mL	1	(Rosa <i>et al.</i> 2008)
Rutin	-	0.1%	1.1	(Velasco <i>et al.</i> 2008)
<i>Passiflora incarnata</i>	Dry extract	1.68%	1.2	(Velasco <i>et al.</i> 2008)
<i>Plantago lanceolata</i>	Hydroglycolic extract	2.78%	1.1	(Velasco <i>et al.</i> 2008)
<i>Dracocephalum moldavica</i>	Ethyl acetate extract	2 mg/mL	24.79	(Khazaeli & Mehrabani 2008)
<i>Viola tricolor</i>	Ethyl acetate extract	2 mg/mL	25.69	(Khazaeli & Mehrabani 2008)
<i>Moringa oleifera</i>	Aqueous extract	4.0%	2.01	(Baldisserotto <i>et al.</i> 2018)
<i>Capnophyllum peregrinum</i>	Crude methanolic extract	2 mg/mL	35.21	(Lefahal <i>et al.</i> 2018)

demonstrated by several previous studies (Wagner 2011).

The SPF value is dependent on the molecule(s) present in the extracts that exhibit photoprotection ability, the method of extraction, the concentration of the substances, and the solvent or system in which it is incorporated. In the determination of SPF values *in vivo*, the quality of the film formed under the skin is important for yielding high SPF values. Therefore, it is difficult to make a detailed comparison between different studies in relation to the photoprotective capacity of different phytochemicals, since they all use different conditions. However, it is possible to confirm that the phytochemicals cited in this report can potentially be used as photoprotectors. For a detailed comparison, it is necessary to evaluate the concentration of all constituents of the extract by high performance liquid chromatography, for example. However, the comparison between the extracts will not be exact due to their complex composition.

Health and safety

Another important subject related to the level of photoprotection provided by phytochemicals is how safe is the use of these substances. The use of synthetic sunscreens could cause a cutaneous manifestation, mediated by light, called photosensitization (Isaac & Corrêa 2002). Chemical synthetic sunscreens have the ability to absorb radiation by forming molecules that can be transformed into new compounds, which are inactive (*i.e.*, do not absorb UV radiation) and have the ability to degrade biocomponents of the skin. Because of this, they are potential agents for photosensitization (Bonda & Steinberg 2000; Xu *et al.* 2001; Isaac & Corrêa 2002; Armeni *et al.* 2004; Brezová *et al.* 2005; Herzog *et al.* 2009; Vallejo *et al.* 2011). Usually in the case of phytochemicals, substances that exhibit photoprotection activity simultaneously display antioxidant activity, which neutralizes the photoreactivity.

Moreover, sunscreens which are used to protect the skin from the deleterious effects of solar radiation, and more specifically, to protect the skin against the carcinogenic effect of UV radiation (Lautenschlager *et al.* 2007), are not completely efficient in these tasks because they depend on a variety of factors. These include the impossibility of creating a stable and thick film on the skin (Chistiakov *et al.* 2009). Therefore, according to Chistiakov *et al.* (2009), a defense against these

deleterious effects should be based on a complex approach using various mechanisms. In this context, the use of phytochemical sunscreens, isolated or in combination with synthetic sunscreens, could be an interesting alternative in the battle against UV radiation. This could be achieved by two different mechanisms: absorption of UV radiation and antioxidant activity. This approach is in accordance with increased interest in the use of plants to treat or prevent diseases. Twilley *et al.* (2008) have reinforced this desire, particularly with respect to the treatment of complex diseases such as cancer.

Conclusions

According to this research, it is possible to note the potential of the use of substances derived from plants, called phytochemicals, to prevent UV damage to cell constituents and human skin in a healthy individual. It is also possible to confirm that the photoprotective effect of these phytochemicals is strongly related to the resonance structure present in all of the molecules and synthetic sunscreens studied. Some studies have shown that conjugated bonds are able to absorb UV radiation and transform them into heat. In this way, it is possible to infer that phytochemicals absorb radiation using the same mechanism. On the other hand, phytochemicals also display antioxidant activity and, thus, they are able to suppress the cellular and molecular reactions triggered by the action of UV radiation on the skin, which enhances the photoprotective effect. This property prevents cell damage, especially of the epidermis and the extracellular matrix of the dermis. Therefore, many phytochemicals are able to increase the SPF value of synthetic sunscreens without increasing toxicity, thus offering a great alternative for photoprotection.

Acknowledgments

The authors want to thank Capes - Coordenação de Aperfeiçoamento de Pessoal de Nível Superior; FAPESP - Fundação de Amparo à Pesquisa do Estado de São Paulo; and CNPq - Conselho Nacional de Desenvolvimento Científico e Tecnológico.

References

- Afaq F (2011) Natural agents: cellular and molecular mechanisms of photoprotection. *Archives of Biochemistry and Biophysics* 508: 144-151.
- Andrade BA, Corrêa AJC, Gomes AKS, Neri PMS, Sobrinho TJSP, Araújo TAS, Castro VTJNA & Amorim ELC (2019) Photoprotective activity of

- medicinal plants from the caatinga used as anti-inflammatories. *Pharmacognosy Magazine* 15: 356-361.
- Armeni T, Damiani E, Battino M, Greci L & Principato G (2004) Lack of in vitro protection by a common sunscreen ingredient on UVA-induced cytotoxicity in keratinocytes. *Toxicology* 203: 1-3.
- Arthey S & Clarke VA (1995) Suntanning and sun protection: a review of the psychological literature. *Social Science & Medicine* 40: 265-274.
- Baldissarro A, Buso P, Radice M, Dissette V, Lampronti I, Gambari R, Manfredini S & Vertuani S (2018) Moringa oleifera leaf extracts as multifunctional ingredients for “natural and organic” sunscreens and photoprotective preparations. *Molecules* 23: 1-16.
- Baldoqui DC, Bolzani VDS, Furlan M, Kato MJ & Marques MOM (2009) Flavonas, lignanas e terpeno de *Piper umbellata* (Piperaceae). *Química Nova* 32: 1107-1109.
- Bandaranayake WM (1998) Mycosporines: are they nature's sunscreens? *Natural Product Reports* 15: 159-172.
- Berneburg M & Krutmann J (2000) Photoimmunology, DNA repair and photocarcinogenesis. *Journal of Photochemistry and Photobiology B: Biology* 54: 87-93.
- Biever JJ, Brinkman D & Gardner G (2014) UV-B inhibition of hypocotyl growth in etiolated *Arabidopsis thaliana* seedlings is a consequence of cell cycle arrest initiated by photodamage accumulation. *Journal of Experimental Botany* 65: 2949-2961.
- Bobin MF, Raymond M & Martini MC (1994) UVA/UVB absorption properties of natural products. *Cosmetics & Toiletries* 109: 63-70.
- Bonda C & Steinberg DC (2000) A new photostabilizer for full spectrum sunscreens. *Cosmetics & Toiletries* 115: 37-45.
- Booij-James IS, Dube SK, Jansen MA, Edelman M & Mattoo AK (2000) Ultraviolet-B radiation impacts light-mediated turnover of the photosystem II reaction center heterodimer in *Arabidopsis* mutants altered in phenolic metabolism. *Plant Physiology* 124: 1275-1283.
- Bosch R, Philips N, Suárez-Pérez JA, Juarranz A, Devmurari A, Chalenouk-Khaosaat J & González S (2015) Mechanisms of Photoaging and Cutaneous Photocarcinogenesis, and Photoprotective Strategies with Phytochemicals. *Antioxidants* 4: 248-268.
- Bose B, Choudhury H, Tandon P & Kumaria S (2017) Studies on secondary metabolite profiling, anti-inflammatory potential, *in vitro* photoprotective and skin-aging related enzyme inhibitory activities of *Malaxis acuminata*, a threatened orchid of nutraceutical importance. *Journal of Photochemistry and Photobiology B: Biology* 173: 686-695.
- Brenner M & Hearing V (2008) The protective role of melanin against UV damage in human skin. *Photochemistry and Photobiology* 84: 539-549.
- Brezová V, Gabčová S, Dvoranová D & Staško A (2005) Reactive oxygen species produced upon photoexcitation of sunscreens containing titanium dioxide (an EPR study). *Journal of Photochemistry and Photobiology B: Biology* 79: 121-134.
- Caldwell MM, Robberecht R & Flint SD (1983) Internal filters: prospects for UV-acclimation in higher plants. *Physiologia Plantarum* 58: 445-450.
- Chapple C (1992) An arabidopsis mutant defective in the general phenylpropanoid pathway. *The Plant Cell* 4: 1413-1424.
- Chatelain E & Gabard B (2001) Photostabilization of butyl methoxydibenzoylmethane (Avobenzone) and ethylhexyl methoxycinnamate by bis-ethylhexyloxyphenol methoxyphenyl triazine (Tinosorb S), a New UV Broadband Filter. *Photochemistry and Photobiology* 74: 401-406.
- Chen W, Tang Q, Gonzales MS & Bowden GT (2001) Role of p38 MAP kinases and ERK in mediating ultraviolet-B induced cyclooxygenase-2 gene expression in human keratinocytes. *Oncogene* 20: 3921-3926.
- Chistiakov VA, Sazykina MA, Kolenko MA, Cherviakov GG & Usatov AV (2009) Methylene blue as a suppressor of the genotoxic effect of ultraviolet radiation with a wavelength of 300-400 nm. *Russian Journal of Genetics* 45: 304-307.
- Cho JW, Park K, Kweon GR, Jang BC, Baek WK, Suh MH, Kim CW, Lee KS & Suh S (2005) Curcumin inhibits the expression of COX-2 in UVB-irradiated human keratinocytes (HaCaT) by inhibiting activation of AP-1: p38 MAP kinase and JNK as potential upstream targets. *Experimental & Molecular Medicine* 37: 186-192.
- Cho SY, Park SJ, Kwon MJ, Jeong TS, Bok SH, Choi WY, Jeong WI, Ryu SY, Do SH, Lee CS, Song JC & Jeong KS (2003) Quercetin suppresses proinflammatory cytokines production through MAP kinases and NF-κB pathway in lipopolysaccharide-stimulated macrophage. *Molecular and Cellular Biochemistry* 243: 153-160.
- Choquenet B, Couteau C, Paparis E & Coiffard LJM (2008) Quercetin and rutin as potential sunscreen agents: determination of efficacy by an *in vitro* method. *Journal of Natural Products* 71: 1117-1118.
- Cooke MS, Loft S, Oliniski R, Evans MD, Bialkowski K, Wagner JR, Dedon PC, Møller P, Greenberg MM & Cadet J (2010) Recommendations for standardized description of and nomenclature concerning oxidatively damaged nucleobases in DNA. *Chemical Research in Toxicology* 23: 705-707.
- Corrêa MA (2012) Cosmetologia: ciência e técnica. Medfarma, São Paulo. 492p.
- Da Silva VV, Ropke CD, De Almeida RL, Miranda DV, Kera CZ, Rivelli DP, Sawada TCH & Barros SBM

- (2005) Chemical stability and SPF determination of pothomorphe umbellata extract gel and photostability of 4-nerolidylcatechol. International Journal of Pharmaceutics 303: 125-131.
- Demmig-Adams B & Adams WW (1992) Photoprotection and other responses of plants to high light stress. Annual Review of Plant Physiology and Plant Molecular Biology 43: 599-626.
- Ding M, Zhao J, Bowman L, Lu Y & Shi X (2010) Inhibition of AP-1 and MAPK signaling and activation of Nrf2/ARE pathway by quercitrin. International Journal of Oncology 36: 59-67.
- Dinkova-Kostova AT (2008) Phytochemicals as protectors against ultraviolet radiation: versatility of effects and mechanisms. Planta Medica 74: 1548-1559.
- Douki T, Reynaud-Angelin A, Cadet J & Sage E (2003) Bipyrimidine photoproducts rather than oxidative lesions are the main type of DNA damage involved in the genotoxic effect of solar UVA radiation. Biochemistry 42: 9221-9226.
- Drew K & Myers SP (1997) Safety issues in herbal medicine: implications for the health professions. The Medical Journal of Australia 19: 538-541.
- Dzialo M, Mierziak J, Korzun U, Preisner M, Szopa J & Kulma A (2016) The potential of plant phenolics in prevention and therapy of skin disorders. International Journal of Molecular Science 17: 160.
- Ezzedine K, Guinot C, Mauger E, Pistone T, Rafii N, Receveur MC, Galan P, Hercberg S & Malvy D (2007) Expatriates in high-UV index and tropical countries: Sun exposure and protection behavior in 9,416 French adults. Journal of Travel Medicine 14: 85-91.
- Ferrari M, Oliveira MSC, Nakano AK & Rocha-Filho PA (2007) Determinação do fator de proteção solar (FPS) *in vitro* e *in vivo* de emulsões com óleo de andiroba (*Carapa guianensis*). Revista Brasileira de Farmacognosia 17: 626-630.
- Fisher GJ, Datta SC, Talwar HS, Wang ZQ, Varani J, Kang S & Voorhees JJ (1996) Molecular basis of sun-induced premature skin ageing and retinoid antagonism. Nature 379: 335-339.
- Fisher GJ, Kang S, Varani J, Bata-Csorgo Z, Wan Y, Datta S & Voorhees JJ (2002) Mechanisms of photoaging and chronological skin aging. Arch Dermatology 138: 1462-1470.
- Fisher GJ, Talwar HS, Lin J, Lin P, McPhillips F, Wang Z, Li X, Wan Y, Kang S & Voorhees JJ (1998) Retinoic acid inhibits induction of c-Jun protein by ultraviolet radiation that occurs subsequent to activation of mitogen-activated protein kinase pathways in human skin *in vivo*. The Journal of Clinical Investigation 101: 1432-1440.
- Fisher GJ, Wang Z, Datta SC, Varani J, Kang S & Voorhees JJ (1997) Pathophysiology of premature skin aging induced by ultraviolet light. The New England Journal of Medicine 337: 1419-1429.
- Foley P, Nixon R, Marks R, Frown K & Thompson S (1993) The frequency of reactions to sunscreens: Results of a longitudinal population-based study on the regular use of sunscreen in Australia. British Journal of Dermatology 128: 512-518.
- Fresneda YG, Sánchez MP, Álvarez S & Santana JL (2001) Taninos de diferentes especies vegetales en la prevención del fotoenvejecimiento. Revista Cubana de Investigaciones Biomédicas 20: 16-20.
- Gammone MA, Pluchinotta FR, Bergante S, Tettamanti G & D'Orazio N (2017) Prevention of cardiovascular diseases with carotenoids. Frontiers in Bioscience Scholar 9: 165-171.
- Garcia-Bores AM & Avila JG (2008) Natural products: molecular mechanisms in the photochemoprevention of skin cancer. Revista Latinoamericana de Química 36: 83-99.
- Gilmore AM (1997) Mechanistic aspects of xanthophyll cycle-dependent photoprotection in higher plant chloroplasts and leaves. Physiologia Plantarum 99: 197-209.
- Gobbo-Neto L & Lopes NP (2007) Plantas medicinais: fatores de influência no conteúdo de metabólitos secundários. Química Nova 30: 374-381.
- Guaratini T, Medeiros MHG & Colepicolo P (2007) Antioxidantes na manutenção do equilíbrio redox cutâneo: Uso e avaliação de sua eficácia. Química Nova 30: 206-213.
- Gustavsson Gonzalez H, Farbrot A & Larkö O (2002) Percutaneous absorption of benzophenone-3, a common component of topical sunscreens. Clinical and Experimental Dermatology 27: 691-694.
- Helbling EW, Villafane V, Ferrario M & Holm-Hansen O (1992) Impact of natural ultraviolet radiation on rates of photosynthesis and on specific marine phytoplankton species. Marine Ecology Progress Series 80: 89-100.
- Herzog B, Wehrle M & Quass K (2009) Photostability of UV absorber systems in sunscreens. Photochemistry and Photobiology 85: 869-878.
- Hinneburg I, Kempe S, Rüttinger HH & Neubert RHH (2006) Antioxidant and photoprotective properties of an extract from buckwheat herb (*Fagopyrum esculentum* MOENCH). Die Pharmazie 61: 237-240.
- Hübner AA, Vetore Neto AV, Sobreira F, Pinto C, Dario MF, Lourenço FR, Baby AR & Bacchi EM (2016) Phytochemistry, antioxidant activity, and sunscreen efficacy of hydroethanolic extract of Cabernet Sauvignon grape pomace (*Vitis vinifera* L.). Planta Medica 82.
- Hughes TM & Stone NM (2007) Benzophenone 4: an emerging allergen in cosmetics and toiletries? Contact Dermatitis 56: 153-156.
- Hüglin D (2016) Advanced UV absorbers for the protection of human skin. Chimia 70: 96-101.
- INCA - Instituto Nacional de Cancer José Alencar Gomes da Silva (2016) Estimativa 2016: incidência de câncer no Brasil. Ministério da Saúde, Instituto

- Nacional de Cancer José Alencar Gomes da Silva, Rio de Janeiro.
- INCA - Instituto Nacional de Cancer José Alencar Gomes da Silva (2018) Estimativa 2018: incidência de câncer no Brasil. Ministério da Saúde, Instituto Nacional de Cancer José Alencar Gomes da Silva, Rio de Janeiro.
- Isaac VLB & Corrêa MA (2002) Fotoproteção. Cosmetics & Toiletries 14: 88-95.
- Jans J, Schul W, Sert YG, Rijken Y, Rebel H, Eker APM, Nakajima S, Van Steeg H, De Gruijl FR, Yasui A, Hoeijmakers JHJ & Van Der Horst GTJ (2005) Powerful skin cancer protection by a CPD-photolyase transgene. Current Biology 15: 105-115.
- Jin H, Cominelli E, Bailey P, Parr A, Mehrtens F, Jones J, Tonelli C, Weisshaar B & Martin C (2000) Transcriptional repression by *AtMYB4* controls production of UV-protecting sunscreens in *Arabidopsis*. The EMBO Journal 19: 6150-6161.
- Julkunen-Tiitto R, Nenadis N, Neugart S, Robson M, Agati G, Vepsäläinen J, Zipoli G, Nybakken L, Winkler B & Jansen MAK (2015) Assessing the response of plant flavonoids to UV radiation: an overview of appropriate techniques. Phytochemistry Reviews 14: 273-297.
- Junghans A, Sies H & Stahl W (2001) Macular pigments lutein and zeaxanthin as blue light filters studied in liposomes. Archives of Biochemistry and Biophysics 391: 160-164.
- Kang NJ, Jung SK, Lee KW & Lee HJ (2011) Myricetin is a potent chemopreventive phytochemical in skin carcinogenesis. Annals of the New York Academy of Sciences 1229: 124-132.
- Khazaeli P & Mehrabani M (2008) Screening of sun protective activity of the ethyl acetate extracts of some medicinal plants. Iranian Journal of Pharmaceutical Research 7: 5-9.
- Kliebenstein DJ (2004) Secondary metabolites and plant/environment interactions: a view through *Arabidopsis thaliana* tinged glasses. Plant Cell Environment 27: 675-684.
- Kvam E & Tyrrell RM (1997) Induction of oxidative DNA base damage in human skin cells by UV and near visible radiation. Carcinogenesis 18: 2379-2384.
- Lahmann C, Bergemann J, Harrison G & Young AR. (2001) Matrix metalloproteinase-1 and skin ageing in smokers. The Lancet 357: 900-901.
- Landry LG, Chapple C & Last RL (1995) Arabidopsis mutants lacking phenolic sunscreens exhibit enhanced ultraviolet-B injury and oxidative damage. Plant Physiology 109: 1159-1166.
- Lautenschlager S, Wulf HC & Pittelkow MR (2007) Photoprotection. The Lancet 370: 528-537.
- Lee HJ, Im AR, Kim SM, Kang HS, Lee JD & Chae S (2018) The flavonoid hesperidin exerts anti-photoaging effect by downregulating matrix metalloproteinase (MMP)-9 expression via mitogen activated protein kinase (MAPK)-dependent signaling pathways. BMC Complementary and Alternative Medicine 18: 1-9.
- Lefahal M, Zaabat N, Ayad R, Makhloufi E, Djarri L, Benahmed M, Laouer H, Nieto G & Akkal S (2018) Contents, antioxidant and photoprotective activities of crude methanolic extract of aerial parts of growing in Algeria. Medicines 26: 1-10.
- Li J, Ou-Lee T, Raba R, Amundson RG & Last RL (1993) Arabidopsis flavonoid mutants are hypersensitive to UV-B irradiation. The Plant Cell 5: 171-179.
- Liu L, Gitz DC & McClure JW (1995) Effects of UV-B on flavonoids, ferulic acid, growth and photosynthesis in barley primary leaves. Physiologia Plantarum 93: 725-733.
- Liu RH (2004) Potential synergy of phytochemicals in cancer prevention: mechanism of action. The Journal of Nutrition 134: 3479-3485.
- Mansur JS, Breder MNR & Mansur MC d'Ascenção (1986) Determinação do fator de proteção solar por espectrofotometria. Anais Brasileiros de Dermatologia 61: 121-124.
- Martins FJ, Caneschi CA, Vieira JLF, Barbosa W & Raposo NRB (2016) Antioxidant activity and potential photoprotective from amazon native flora extracts. Journal of Photochemistry and Photobiology B: Biology 161: 34-39.
- Marto J, Gouveia LF, Gonçalves L, Chiari-Andréo BG, Isaac V, Pinto P, Oliveira E, Almeida AJ & Ribeiro HM (2016) Design of novel starch-based Pickering emulsions as platforms for skin photoprotection. Journal of Photochemistry & Photobiology B: Biology 162: 56-64.
- Matsui MS, Hsia A, Miller JD, Hanneman K, Scull H, Cooper KD & Baron E (2009) Non-sunscreen photoprotection: antioxidants add value to a sunscreen. Journal of Investigative Dermatology Symposium Proceedings 14: 56-59.
- Moore JO, Wang Y, Stebbins WG, Gao D, Zhou X, Phelps R, Lebwohl M & Wei H (2006) Photoprotective effect of isoflavone genistein on ultraviolet B-induced pyrimidine dimer formation and PCNA expression in human reconstituted skin and its implications in dermatology and prevention of cutaneous carcinogenesis. Carcinogenesis 27: 1627-1635.
- Mudit V & Katiyar SK (2010) Molecular mechanisms of inhibition of photocarcinogenesis by silymarin, a phytochemical from milk thistle (*Silybum marianum* L. Gaertn.) (Review). International Journal of Oncology 36: 1053-1060.
- Nascimento CS, Nunes LCC, De Lima AAN, Grangeiro Júnior S & Rolim Neto PJ (2009) Incremento do FPS em formulação de protetor solar utilizando extratos de própolis verde e vermelha. Revista Brasileira de Farmácia 30: 334-339.
- Nash JF, Tanner PR & Matts PJ (2006) Ultraviolet a radiation: testing and labeling for sunscreen products. Dermatologic Clinics 24: 63-74.
- Neale RE, Davis M, Pandeya N, Whiteman DC & Green

- AC (2007) Basal cell carcinoma on the trunk is associated with excessive sun exposure. Journal of the American Academy of Dermatology 56: 380-386.
- Nichols JA & Katiyar SK (2010) Skin photoprotection by natural polyphenols: anti-inflammatory, antioxidant and DNA repair mechanisms. Archives of Dermatological Research 302: 71-83.
- Oresajo C, Yatskayer M, Galdi A, Foltis P & Pillai S (2010) Complementary effects of antioxidants and sunscreens in reducing UV-induced skin damage as demonstrated by skin biomarker expression. Journal of Cosmetic and Laser Therapy 12: 157-162.
- Ormrod DP, Landry LG & Conklin PL (1995) Short-term UV-B radiation and ozone exposure effects on aromatic secondary metabolite accumulation and shoot growth of flavonoid-deficient *Arabidopsis* mutants. Physiologia Plantarum 93: 602-610.
- Paye M, Barel AO & Maiback HI (1961) The handbook of cosmetology. 2nd ed. Informa Health Care, New York.
- Pillai S, Oresajo C & Hayward J (2005) Ultraviolet radiation and skin aging: roles of reactive oxygen species, inflammation and protease activation, and strategies for prevention of inflammation-induced matrix degradation - a review. International Journal of Cosmetic Science 27: 17-34.
- Proserpio G (1976) Natural sunscreens: vegetable derivatives as sunscreens and tanning agents. Cosmetics & Toiletries 91: 34-36.
- Ramos M & Santos E (1996) Preliminary studies towards utilization of various plant extracts as antisolar agents. International Journal of Cosmetics Science 18: 87-101.
- Rigel DS (2008) Cutaneous ultraviolet exposure and its relationship to the development of skin cancer. Journal of the American Academy of Dermatology 58: S129-S132.
- Roepeke J & Bozzo GG (2015) *Arabidopsis thaliana* β -glucosidase BGLU15 attacks flavonol 3-O- β -glucoside-7-O- α -rhamnosides. Phytochemistry 109: 14-24.
- Rosa MB, Oliveira TG, Carvalho CA, Silva FD, Carvalho LM, Nascimento PC & Peres RL (2008) Estudo espectrofotométrico da atividade fotoprotetora de extratos aquosos de *Achillea millefolium*, *brassica oleracea* var. *capitata*, *cyperus rotundus*, *plectranthus barbatus*, *porophyllum ruderale* (jacq.) cass e *sonchus oleraceus*. Revista Eletrônica de Farmácia 5: 101-110.
- Russo A, Cardile V, Lombardo L, Vanella L & Acquaviva R (2006) Genistin inhibits UV light-induced plasmid DNA damage and cell growth in human melanoma cells. The Journal of Nutritional Biochemistry 17: 103-108.
- Ryan KG, Swinny EE, Markham KR & Winefield C (2002) Flavonoid gene expression and UV photoprotection in transgenic and mutant Petunia leaves. Phytochemistry 59: 23-32.
- Sander CS, Chang H, Hamm F, Elsner P & Thiele JJ (2004) Role of oxidative stress and the antioxidant network in cutaneous carcinogenesis. International Journal of Dermatology 43: 326-335.
- Schalka S & Reis VMS (2011) Fator de proteção solar: significado e controvérsia. Anais Brasileiros de Dermatologia 86: 507-515.
- Scotti L, Scotti MT, Cardoso C, Pauletti P, Castro-Gamboa I, Bolzani VS, Velasco MVR, Menezes CM de S & Ferreira EI (2007) Modelagem molecular aplicada ao desenvolvimento de moléculas com atividade antioxidante visando ao uso cosmético. Revista Brasileira de Ciências Farmacêuticas 43: 153-166.
- Setlow RB, Grist E, Thompson K & Woodhead AD (1993) Wavelengths effective in induction of malignant melanoma. Proceedings of the National Academy of Science 90: 6666-6670.
- Shaath NA (1986) The chemistry of sunscreens. Cosmetics & Toiletries 101: 55-70.
- Sharma SD, Meeran SM & Katiyar SK (2007) Dietary grape seed proanthocyanidins inhibit UVB-induced oxidative stress and activation of mitogen-activated protein kinases and nuclear factor-B signaling in *in vivo* SKH-1 hairless mice. Molecular Cancer Therapeutics 6: 995-1005.
- Shaw D, Leon C, Kolev S & Murray V (1997) Traditional remedies and food supplements. A 5-year toxicological study (1991-1995). Drug Safety 17: 342-356.
- Shirley BW (1996) Flavonoid biosynthesis: "new" functions for an "old" pathway. Trends in Plant Science 1: 377-382.
- Simões CMO, Schenkel EP, Mello JCP, Mentz LA & Petrovick PR (2017) Farmacognosia: do produto natural ao medicamento. Artmed, Porto Alegre.
- Silva ACP, Paiva JP, Diniz RD, Anjos VM, Silva ABSM, Pinto AV, Santos EP, Leitão AC, Cabral LM, Rodrigues CR, Pádua M & Santos BAMC (2019) Photoprotection assessment of olive (*Olea europaea* L.) leaves extract standardized to oleuropein: *In vitro* and *in silico* approach for improved sunscreens. Journal of Photochemistry and Photobiology B. Biology 193: 162-171.
- Soehnge H, Ouhtit A & Ananthaswamy ON (1997) Mechanisms of induction of skin cancer by UV radiation. Frontiers in Bioscience: a journal and virtual library 1: 538-551.
- Solovchenko A & Schmitz-Eiberger M (2003) Significance of skin flavonoids for UV-B-protection in apple fruits. Journal of Experimental Botany 54: 1977-1984.
- Solovchenko AE & Merzlyak MN (2008) Screening of visible and UV radiation as a photoprotective mechanism in plants. Russian Journal of Plant Physiology 55: 719-737.
- Souza TM, Santos LE, Moreira RRD & Rangel VLBI (2005) Avaliação da atividade fotoprotetora de

- Achillea millefolium* L. (Asteraceae). Revista Brasileira de Farmacognosia 15: 36-38.
- Stahl W, Heinrich U, Jungmann H, Seis H & Tronnier H (2000) Carotenoids and carotenoids plus vitamin E protect against ultraviolet light-induced erythema in humans. The American Journal of Clinical Nutrition 71: 795-798.
- Stahl W & Sies H (2007) Carotenoids and flavonoids contribute to nutritional protection against skin damage from sunlight. Molecular Biotechnology 37: 26-30.
- Staniforth V, Huang WC, Aravindaram K & Yang NS (2012) Ferulic acid, a phenolic phytochemical, inhibits UVB-induced matrix metalloproteinases in mouse skin via posttranslational mechanisms. The Journal of Nutritional Biochemistry 23: 443-451.
- Stapleton AE & Walbot V (1994) Flavonoids can protect maize DNA from the induction of ultraviolet radiation damage. Plant Physiology 105: 881-889.
- Steyn WJ, Wand SJE, Holcroft DM & Jacobs G (2002) Anthocyanins in vegetative tissues: A proposed unified function in photoprotection. New Phytologist 155: 349-361.
- Stracke R, Jahns O, Keck M, Tohge T, Niehaus K, Fernie AR & Weisshaar B (2010) Analysis of production of flavonol glycosides-dependent flavonol glycoside accumulation in *Arabidopsis thaliana* plants reveals MYB11-, MYB12- and MYB111-independent flavonol glycoside accumulation. New Phytologist Trust 188: 985-1000.
- Surh YJ & Na HK (2008) NF-κB and Nrf2 as prime molecular targets for chemoprevention and cytoprotection with anti-inflammatory and antioxidant phytochemicals. Genes & Nutrition 2: 313-317.
- Tian L, Wan SB, Pan QH, Zheng YJ & Huang WD (2008) A novel plastid localization of chalcone synthase in developing grape berry. Plant Science 175: 431-436.
- Treutter D (2006) Significance of flavonoids in plant resistance: a review. Environmental Chemistry Letters 4: 147-157.
- Twilley D, Rademan S & Lall N (2018) Are medicinal plants effective for skin cancer? Medicinal Plants for Holistic Health and Well-Being Pp. 13-75.
- USFDA (2017) Sunscreen: how to help protect your skin from the sun. U.S. Food and Drug Administration. Available at <<https://www.fda.gov/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/UnderstandingOver-the-CounterMedicines/ucm239463.htm>>. Access on 30 Nov 2019.
- USFDA (2019) FDA proposed rule: sunscreen drug products for over-the-counter-human use; proposal to amend and lift stay on monograph. U.S. Food and Drug Administration. Available at <<https://www.fda.gov/about-fda/economic-impact-analyses-fda-regulations/sunscreen-drug-products-over-counter-human-use-proposal-amend-and-lift-stay-monograph-preliminary>>. Access on 30 Nov 2019.
- Vallejo JJ, Mesa M & Gallardo C (2011) Evaluation of the avobenzone photostability in solvents used in cosmetic formulations. Vitae 18: 63-71.
- Velasco MVR, Sarruf FD, Salgado-Santos IMN, Haroutiounian-Filho CA, Kaneko TM & Baby AR (2008) Broad spectrum bioactive sunscreens. International Journal of Pharmaceutics 363: 50-57.
- Vile GF & Tyrrell RM (1995) Uva radiation-induced oxidative damage to lipids and proteins in vitro and in human skin fibroblasts is dependent on iron and singlet oxygen. Free Radical Biology and Medicine 18: 721-730.
- Violante IMP, Souza IM, Venturini CL, Ramalho AFS, Santos RAN & Ferrari M (2009) Avaliação in vitro da atividade fotoprotetora de extratos vegetais do cerrado de Mato Grosso. Revista Brasileira de Farmacognosia 19: 452-457.
- Wagner H (2011) Synergy research: approaching a new generation of phytopharmaceuticals. Fitoterapia 82: 34-37.
- Wang YN, Wu W, Chen HC & Fang H (2010) Genistein protects against UVB-induced senescence-like characteristics in human dermal fibroblast by p66Shc down-regulation. Journal of Dermatological Science 58: 19-27.
- Wei H, Bowen R, Zhang X & Lebwohl M (1998) Isoflavone genistein inhibits the initiation and promotion of two-stage skin carcinogenesis in mice. Carcinogenesis 19: 1509-1514.
- Wolf R, Tüzün B & Tüzün Y (2001) Sunscreens. Dermatologic Therapy 14: 208-214.
- Xu C, Green A, Parisi A & Parsons PG (2001) Photosensitization of the sunscreen octyl p-dimethylaminobenzoate by UVA in human melanocytes but not in keratinocytes. Photochemistry and Photobiology 73: 600-604.

