Natural products and their mechanisms in potential photoprotection of the skin

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Exposure to solar radiation can generate different types of damage to the skin, including skin cancer. Depending on the duration of the exposure, sun damage can present as sunburn, photoaging, and photoinmunosuppression, among other effects. Using natural products on the skin may aid in preventing the damage caused by exposure to solar radiation, in addition to reducing the adverse side effects of common sunscreens, such as irritation, allergies, phototoxic reactions, photosensitivity, and generation of reactive oxygen species. On the other hand, the UV light absorption capacity of natural products has been reported to be due to the presence of chromophores in their structure, which, when added to the beneficial effects they have on the skin, makes them attractive candidates for use as photoprotectors. The present work gathers updated information regarding skin damage caused by prolonged sun exposure. It also describes the photoprotective effect of several natural products, their mechanism of action, and their preventive and therapeutic potential. For this purpose, the scientific literature was searched using PubMed, Science Direct, and Google Scholar.

Keywords. Natural products; phenolic compounds; photoprotector; skin damage; UV light

1. Introduction

In modern society, we are constantly exposed to several factors that damage deoxyribonucleic acid (DNA) (Whanger 1983; Khaidakov et al. 2001; Montgomery et al. 2002). Among these, one of the most damaging factors is UV light, which is mainly produced by solar radiation; in addition, the main exposed organ, the skin, is the body’s largest organ (Bernstein et al. 2002).

Limiting sun exposure could reduce the amount of sun damage and the number of cancer cases. For this, a series of lifestyle changes, such as avoiding overexposure, maintaining a healthy lifestyle, and attending to any changes in the skin that could be considered premalignant lesions (since early detection can contribute to a better prognosis and management of the disease), could reduce or delay the appearance of skin cancer. In addition, using natural products as preventive formulations against sun damage could be a strategy to
reduce the incidence of certain types of skin cancer (Janakiram et al. 2016; Zubair et al. 2017).

2. Sunlight composition

Natural sunlight is composed of 62.7% visible, 31.9% infrared, and 5.4% UV rays, of which 0.3% corresponds to UVB and 5.1% to UVA. The spectrum of UV radiation is divided into three bands or regions: UVA (320 to 400 nm), UVB (280 to 320 nm), and UVC (100 to 280 nm). UVB is approximately 5% of the UV light we are exposed to, while UVA light is the remaining 95%; however, the biological damage caused by exposure to sunlight is attributed mainly to UVB light (González et al. 2009; Stevanato et al. 2014).

2.1 The effect of UV radiation on the skin

Long UV exposure induces visible responses in the skin, such as the development of erythema, edema, telangiectasias, burns, hyperplasia, immunosuppression, DNA damage, photoaging, inflammation, and melanogenesis. In addition, UV exposure changes the expression of genes such as cyclooxygenase-2 (COX-2) and retinoblastoma (RB) and induces mutations in several genes, which may be directly or indirectly related to the development of cancer (González et al. 2009; Palareti et al. 2016).

UV radiation is absorbed by chromophores in the skin which initiate a series of photochemical reactions that damage the skin. These photochemical reactions involve the oxidation of nucleic acids and modification of proteins and lipids, which affect the functionality of these biomolecules (Simon 2000; Trautinger 2001; Ghersetich et al. 2007; Bilaç et al. 2014).

UVB light can change the pyrimidine bases of DNA strands, forming pyrimidine cycle dimers. Conversely, UVA (320–400 nm) generates thymine dimers (Hannah 1972; Sage 1993; Kielbassa et al. 1997; McCready 1999; Kielbassa and Epe 2000). Moreover, urocanic acid can absorb UV light, generating the highly reactive singlet oxygen molecule that can chemically attack cellular structures and generate reactive oxygen species (ROS). Accumulating damage caused by UV light exposure leads to the accumulation of mutations that can subsequently trigger skin cancer (Simon 2000; Barclay et al. 2007; Menon et al. 2007).

Skin cancer is among the 10 most frequent cancers in the world. This type of cancer is classified into two groups: melanomas and non-melanomas, which in turn are subdivided into squamous cell and basal cell carcinomas (Franco 2003; Jemal et al. 2004; Imokawa 2008; Henley et al. 2020).

Basal cell carcinoma (BCC) is the most frequent type of skin cancer, constituting 80% to 90% of all skin cancer types. It has relatively low malignancy, but if not detected early, it can lead to severe aesthetic changes, which may have psychological repercussions. This carcinoma is slow growing, usually originating in the keratinocytes of the epidermis near the basal layer. BCC usually presents as a papule or superficial nodule and is locally destructive, but in some rare cases, it can present metastasis and affect organs such as the brain, lung, and bone (Figueiredo Kopke and Schmidt 2002; Vilchez-Márquez et al. 2020).

Squamous cell carcinoma (SCC), by contrast, is generated in the epidermal keratinocytes and subsequently invades the dermis. It shows rapid growth and usually appears in premalignant lesions such as actinic keratoses, and chronic ulcers, among others. SCC usually presents with extensive damage and possibly produces metastasis to regional lymph nodes. It has a mortality rate of 25% (Hernández-Gil Sánchez et al. 2006; Muñoz and López-Bran 2018).

Melanoma, another common type of skin cancer, has the highest mortality rate. It originates in melanocytes and usually starts without previous lesions, frequently metastasizing to the lungs, liver, brain, bones, skin, or lymph nodes, although it can spread to any part of the body. Early diagnosis is crucial in this type of cancer to have a good prognosis (Fagundo et al. 2011; Rodrigo Schwartz 2011).

2.2 Photoprotection and natural products in the treatment of skin damage

Several actions have been recommended to reduce the damage caused by sun exposure; these include: (1) avoiding prolonged exposure to the sun between 10 am and 4 pm, (2) using protective accessories such as hats and sunglasses, (3) using sunscreens with a sun protection factor (SPF) greater than or equal to 15, (4) implementing child education activities to teach them to protect themselves from the sun, (5) avoiding tanning in sun booths, (6) examining the skin regularly to detect lesions early, and (7) receiving frequent medical examinations to remove premalignant lesions such as sun freckles, sunspots, and sun moles (Mallory and Watts 1987; Schaefer et al. 1998; DeBuys et al. 2000; Gil and Kim 2000; Yoon and Baek 2005).
Although sunscreens effectively prevent sunburn and DNA and skin damage, their components can also have adverse side effects such as irritation, allergies, phototoxic reactions, inhibition of vitamin D synthesis, and generation of ROS. In addition, they can act as photosensitizers (Kullavanijaya and Lim 2005).

The photochemopreventive effects of natural products (figures 1, 2, 3) have recently been studied to prevent skin damage. These substances can absorb UV rays and act as filters to prevent DNA damage, skin damage, and photoimmunosuppression (Mallory and Watts 1987; Schaefer et al. 1998; DeBuys et al. 2000; Kullavanijaya and Lim 2005).

In this regard, several studies have evaluated the potential photoprotective effect of natural products. These compounds can absorb UV radiation due to the presence of chromophores in their chemical structure, which prevents solar radiation from penetrating the skin. Examples of such chromophores are stilbenes, flavonoids, and hydroxycinnamic acids. (Potapovich et al. 2013). Some of these compounds exhibit a high UV absorption, with sun protection factors ranging from 7 to 29. For example, quercetin has a protection factor of 10.3; resveratrol, 19.2; apigenin, 28.8; caffeic acid, 28; and ferulic acid, 11.9 (Gregoris et al. 2011).

In addition, Park et al. (2010) have evaluated the therapeutic potential of a polyphenol extract from Punica granatum bark, which confers photoprotection against UVB light damage in human fibroblasts by inhibiting photoaging. This protection was attributed to catechin, which promotes the overexpression of collagen and negatively regulates the expression of extracellular matrix metalloproteinase-1 (MMP-1), both of which are involved in aging, dermal fibrosis, tumor invasion, or blistering (Pérez-García 2004).

Likewise, Giampieri et al. (2012) showed that anthocyanins present in strawberries granted dermal protection to fibroblasts in a model of UVA damage. Other studies have identified several families of protective phytochemicals, including

**Figure 1.** Structures of the phenolic compounds caffeic acid, ferulic acid, gallic acid, apigenin, and catechin.
phenolic compounds, phenolic acids, flavonoids, stilbenes, terpenes, and organosulfates. These compounds can also be classified as the following depending on their mechanism of action: oxidative stress reducers, anti-metastatic, oncogene blockers, UV protective, anti-angiogenic, anti-proliferative, and anti-inflammatory (Kashif et al. 2017; Wang et al. 2017; Ijaz et al. 2018; Ng et al. 2018; Iqbal et al. 2019). Chinembiri et al. (2014) added one more classification: apoptotic promoters, which include quercetin, resveratrol, and curcumin. These compounds could also be categorized into other classes because they have antioxidant, anti-proliferative, or anti-inflammatory actions. In summary, secondary metabolites act as UV radiation protectors, while phenolic compounds act as anti-aging, antioxidant, anti-inflammatory, and immune system activators.

2.3 Ultraviolet radiation and cyanobacteria

Cyanobacteria are a group of photosynthetic prokaryotic organisms that synthesize specific metabolites, such as scytonemin, which absorb UV light to protect themselves from damage to cellular DNA and various biochemical and physiological processes (Rastogi et al. 2014). Scytonemin is a pigment produced exclusively by cyanobacteria (300 species) and is brownish-yellow in color, dimeric, and lipid-soluble, with a molecular weight of 544 Da, characterized by having the effect of a sunscreen, because the complex structures of its rings generate a specific pattern that absorbs UV light; it has an absorption maximum of 370 nm, although it also absorbs significantly at 252, 278, and 300 nm. This compound allows cyanobacteria to survive lethal UVA/B radiations in environments with intense sunlight (Bultel-Poncé et al. 2004). This property makes
scytonemin useful as natural photoprotectants in commercial sunscreens for protection from burns and skin cancer (Rastogi and Sinha 2009; Rastogi et al. 2015).

2.4 **Melanin as photoprotection**

Melanin is a pigment produced by melanocytes; it is distributed from dendritic prolongations to keratinocytes present in the epidermis. The photoprotection function of this pigment is due to its ability to scatter and absorb UV radiation. There are two types of melanin: eumelanin, responsible for dark skin, has a greater ability to absorb UV rays; and pheomelanin, responsible for light skin, unlike eumelanin, is not as efficient for photoprotection. In this sense, melanosomes in dark skin are resistant to degradation due to lysosomal enzymes, which allow them to remain intact in the epidermis, grouping around the cell nucleus for protection. On the other hand, in light skin, the melanosomes are degraded, with melanin remaining only in the epidermis; this reduction of melanosomes is an essential factor in requirement for the photoprotection of skin (Marín and Pozo 2005; Van Den Bossche et al. 2006; Ando et al. 2012; Carletti et al. 2014).

3. **Compounds with anti-aging properties**

Collagen and elastin are proteins that help maintain the firmness and elasticity of the skin. However, upon sun exposure, these proteins are degraded by the action of catalase, stromelysin, and elastase. In addition, sun exposure activates metalloproteinases, further promoting aging. Moreira et al. (2017) evaluated the anti-collagenase and anti-elastase activities of quercetin and gallic acid, phenolic compounds present in *Eugenia dysenterica*, and demonstrated that these compounds...
have an anti-aging effect. Other studies have shown that topical application of the aqueous extracts of *Zingiber officinale* (Rosc.) notably protects against photoaging in both clinical studies and animal models (Imokawa 2008). In other studies, hyaluronidase, an enzyme that breaks down hyaluronic acid present in the extracellular matrix, was shown to decrease inflammation, fluid retention, erythema and loss of skin function, suggesting its potential use in photoprotection (Kuiper et al. 1998; Chompoo et al. 2012; Kumar and Mandal 2019; Madan and Nanda 2018) (figure 4).

4. Compounds that act as antioxidants

One factor contributing to the skin’s degenerative process is the presence of free radicals. Antioxidants such as phenolic compounds can block these effects. The antioxidant activity of these compounds is due to their phenolic nucleus, chemical structure (specifically, the number and position of hydroxyl groups), and the presence of the aromatic ring (figures 1–3). Phenolic compounds attract ROS but also reduce and chelate the ferric ions that catalyze lipid peroxidation. Likewise, they have the ability to inactivate free radicals by transferring hydrogen atoms or donating an electron to the radical (Moreno-Garrido 2008; Epstein 2009; Roohbakhsh et al. 2014; Brglez Mojzer et al. 2016; Pullar et al. 2017; Xu et al. 2017; Paun et al. 2018; Guo et al. 2020) (figure 5).

5. Protective effects of vitamins C and E

The skin typically contains a high concentration of vitamin C, which serves as a powerful antioxidant and protects against photoaging, immunosuppression due to UV rays, and photocarcinogenesis. In addition, vitamin C regulates collagen synthesis by increasing and stabilizing its production and reducing its degradation. Abnormalities in the synthesis of collagen besides causing aging can lead to an abnormality in the structure of blood vessels, decreasing their resistance.

Vitamin C also mitigates photopigmentation by reducing melanin production, and acts synergistically with vitamin E, the main lipid-soluble vitamin in the skin. One of the main factors responsible for the decrease in vitamins C and E is the activity of free radicals (mainly the precursors of oxidative processes) since both vitamins are sensitive to oxidation. Phenolic compounds, especially flavonoids, possess high antioxidant activity; therefore, these molecules can prevent or reduce the oxidation of vitamins, providing protection (Kelly et al. 1996; Ronchetti et al. 1996;
6. Compounds with phytoestrogen activity

Flavonoids have a wide range of biological activity due to their affinity towards proteins (Havsteen 2002; Dangles and Dufour 2006; Aguilar and Bonilla 2009).
and protein receptors of the nervous system, as well as enzymes such as oxygenase, cyclooxygenases, oxidases, and mono-oxygenases. In the skin, flavonoids have affinity to α and β-type estrogen receptors. The isoflavones genistein and estradiol have biological effects similar to estrogens in the skin, namely, hydration, thickening of the skin, and stimulation of the production of collagen and elastin, which creates a rejuvenating effect, since the loss of collagen and elastin is an aging factor. Finally, flavonoids have a vasodilating effect, improving blood circulation in the skin (Kuiper et al. 1998; Matthews et al. 2000; Kostelac et al. 2003; Velásquez and Fernández Michelena 2004) (figure 7).

7. Compounds with protective effect on blood vessels and platelet aggregation

Skin damage activates platelets and their adherence to collagen fibers, which seal the walls of blood vessels. If platelet aggregation increases, it can lead to increased pressure and subsequent rupture of blood vessels, harming the skin (redness, petechiae, and telangiectasias). Flavonoids may protect against telangiectasias and petechiae (both associated with sun damage) because they increase blood vessel resistance. In this way, flavonoids improve blood flow by acting on blood vessel walls, decreasing their susceptibility to present ruptures and, consequently, decreasing subcutaneous blood extravasation. Flavonoids, especially rutin, catechin, epicatechin, and hesperetin, show a protective effect on blood vessel walls. Furthermore, a synergistic effect between these and vitamin C has been demonstrated (Bena- vente-García et al. 1997; Garg et al. 2001; Londoño-Londoño et al. 2010; Roohbakhsh et al. 2014; Li and Schluesener 2017) (figure 8).

8. Compounds with anti-inflammatory effects

Inflammation is a bodily response to injury; its manifestations are swelling, redness, pain, and fever (Larsen and Henson 1983; Schmid-Schönbein 2006; Serhan 2007; Ashley et al. 2012; Arulselvan et al. 2016). The inflammatory process is a microcirculatory reaction characterized by the movement of serum proteins and leukocytes from the blood to the damaged tissue. Phenolic compounds regulate inflammation through their interaction with central target molecules involved in anti-inflammatory activities, for example, by

![Figure 7. Phytoestrogenic effect of flavonoids as photoaging activity.](image-url)
inhibiting proinflammatory enzymes such as cyclooxygenase-2 (COX-2), lipoxygenase (LOX), and nitric oxide synthase (iNOS), which allows cells to release large amounts of NO in response to cytokines such as interferon-gamma (IFN-\(\gamma\)), tumor necrosis factor-alpha (TNF-\(\alpha\)) and interleukin-1 (IL-1). Moreover, phenolic compounds modulate cell survival genes and also function through the activation of peroxisome proliferator-activated receptor R-gamma (PPAR-\(\gamma\)), peroxisome proliferation receptor-gamma (PPR-\(\gamma\)), mitogen-activated protein kinases (MAPK), protein kinase C (PKC), protein kinase serine/threonine (AKT/PKB), and other antioxidant enzymes (Calixto et al. 2004; Fresco et al. 2006; Biesalski 2007; Santangelo et al. 2007; Novoselova et al. 2009; Piesche et al. 2020). In addition, other flavonoids such as quercetin, kaempferol, and myricetin have been shown to inhibit the release of proinflammatory cytokines such as interleukin-8 (IL-8) and tumor necrosis factor (TNF) from mast cells, as well as to inhibit the release of prostaglandins and histamine, which are released during inflammatory processes (Middleton et al. 2000; Park et al. 2008; Weng et al. 2012; Mleek et al. 2016; Jafarinia et al. 2020; Sierra et al. 2020) (figure 9).

9. Immune activity

The immune system is highly complex, and its function is vital to maintain health. It is regulated by various cell types. Immune response is produced by cell–cell interactions through cellular messengers such as hormones, cytokines, and autacoids such as histamine, kinins, leukotrienes, prostaglandins, and serotonin. Different phenolic compounds target one or several immune cell receptors, triggering different signaling pathways that modulate the immune response. In addition, phenolic compounds enhance the generation of regulatory T cells (Martínez et al. 2019). Conversely, polyphenols trigger epigenetic mechanisms that modify key immune factors such as DNA methylation, histone modification, and microRNA-mediated post-translation (Cuevas et al. 2013). Flavonoids affect the function of enzyme systems involved in generating inflammatory processes, especially tyrosine and serine-threonine protein kinase. These enzymes are involved in signal transduction in immune cells and other cells that can be activated by hormones, autacoids, neurotransmitters, and growth factors (Aguilar and Bonilla 2009). Polyphenols significantly increase the level of

**Figure 8.** Protective effect of flavonoids on blood vessels.
interleukin 21 (IL-21) and decrease the release of IL-1-β and IL-6 (Ding et al. 2018). Some compounds, such as resveratrol, stimulate innate and adaptive immunity (including activation of macrophages, lymphocytes, and dendritic cells) and also decrease the expression of activating receptors CD28 and CD80 on immune cells, which ultimately increases the immunosuppressive action of IL-10 (Švajger and Jeras 2012). Resveratrol can also hamper tumor growth by inhibiting the transcription factor Sp1 and inducing apoptosis (Lee et al. 2012). The ability of some phenolic compounds to stimulate immunity suggests that these compounds

Figure 9. Anti-inflammatory effect of phenolic compounds.

Figure 10. Immunological activity of phenolic compounds.
could be of great therapeutic value for photoimmuno-
suppression caused by extensive exposure to solar
radiation (figure 10).

10. Conclusion

This article discusses, in a general sense, the important
effects that solar radiation may have on the skin and the
relevance of natural products in protecting against
exposure to solar radiation. Due to their numerous
benefits, many unexplored and unexploited natural
resources could be proposed as treatment and preven-
tion against skin damage.

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