



# Marine macroalgae: A source of chemical compounds with photoprotective and antiaging capacity—an updated review

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## ABSTRACT

The biological effects of ultraviolet radiation (UVR) on the skin have been known for years, which is why there has been an increase in the use of sunscreen products, whose purpose is to protect the skin from these effects through the action of sunscreens that absorb, disperse, or reflect radiation. Sunscreens contain sun filters that act to protect human skin from the harmful biological effects of UVR. However, due to problems related to the effectiveness and safety of sunscreens in recent years, we have resorted to the search for potential photoprotective molecules from natural sources, among which are marine macroalgae which in turn are a source of molecules with potential antiaging effects. The present review shows the current state of sun filters, the mechanisms that trigger aging, and several compounds present in marine macroalgae with photoprotective and antiaging capacity with potential use in cosmetic products. The review was carried out in ScienceDirect, PubMed, and ACS, among other, databases.

## INTRODUCTION

The electromagnetic spectrum covers the wavelengths ( $\lambda$ ) of all existing electromagnetic radiation, from gamma radiation to radio waves. Within this broad spectrum, solar radiation includes ultraviolet radiation (UVR, 100–400 nm), visible light (VL, 400–760 nm), and infrared radiation (IR, 760–3,000 nm) (Sklar *et al.*, 2013). It is important to mention that the solar radiation that reaches the surface of the earth depends on different factors, such as altitude, latitude, state of the ozone layer, environmental and atmospheric conditions, time of day, and seasons, which can increase or decrease its intensity and, therefore, the exposure of humans to it (Bais *et al.*, 2015; McKenzie *et al.*, 2003).

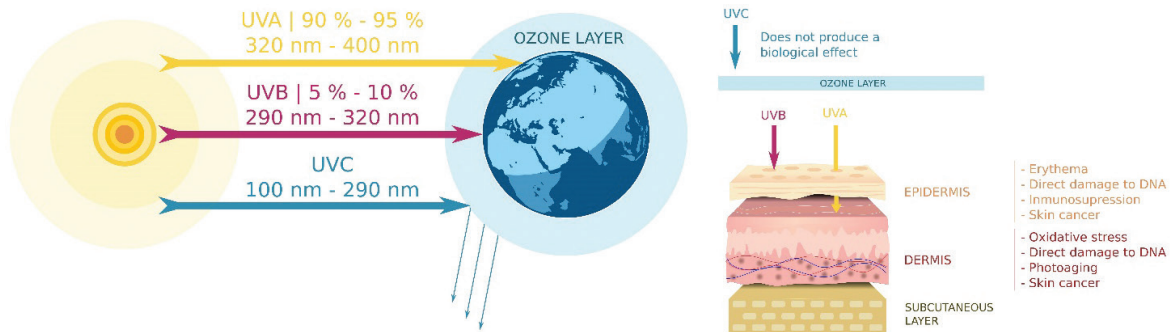
For the study of its biological effects, ultraviolet radiation is divided into three regions according to the wavelength range: Ultraviolet C (UVC) (100–290 nm), Ultraviolet B (UVB) (290–320 nm) and Ultraviolet A (UVA) (320–400 nm), the latter being subdivided into UVA II (320–340 nm) and UVA I (340–400 nm) (International Organization for Standardization, 2010).

UVC is the most energetic UVR; however, its harmful effects in humans are considered negligible because it is absorbed almost entirely by the ozone layer; UVB constitutes 5%–10% of the UVR that reaches the earth and is less energetic than UVC but can cause direct cellular damage; finally, UVA corresponds to the remaining 90%–95% of the total UVR and has deeper penetration into the skin than UVB (Fig. 1) (Dalmay *et al.*, 2018; Lorigo *et al.*, 2018).

Repeated and prolonged exposure of the skin to UVA and UVB radiation can cause undesirable short-term and long-term biological effects, such as inflammation, erythema, direct and indirect DNA damage, oxidative stress, immunosuppression, pigmentation, and skin cancer (Sarkany, 2019). For this reason, the use of topical sunscreens, using chemical and physical sun filters as active ingredients, has been recommended and used as a preferred mechanism to counteract and/or protect against the harmful effects of UVR on the skin. However, the use of these ingredients is questioned in terms of efficacy and safety due to some factors, such as their degradation by photolysis, trigger contact, photocontact, and/or allergic dermatitis, presenting systemic absorption of themselves or their degradation products and thus generating systemic responses, such as acting as endocrine disruptors, allergen, or hapten, which has led to some withdrawals from the market (Jansen *et al.*, 2013; Lorigo *et al.*, 2018).

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**Figure 1.** Percentage of penetration of the UV radiation into the skin and its biological effects.



**Figure 2.** Factors that trigger skin aging.

On the other hand, one of the physiological states that is becoming increasingly important is skin aging, which is the result of the synergistic action of intrinsic and extrinsic effects on the structure and functionality of the skin (Fig. 2) (Farage *et al.*, 2008). This has led in recent years to an increase in research of natural sources of photoprotective and antiaging bioactive compounds, to be used in the cosmetics industry to replace conventional sunscreens, as adjuvants to the same or other cosmetic products with the antiaging claim (Saewan and Jimtaisong, 2015).

This article reviews the interaction between UVR and molecules present in the skin, the biological effects that result from such interaction, the current state of sunscreens, and factors and mechanisms that trigger aging and also shows the potential cosmetic use of the bioactives present in marine macroalgae.

### Interaction of UVR with biomolecules

UVR reaching the earth's surface is capable of generating biological skin effects through its interaction with skin biomolecules. This interaction is based on the fact that UVR can be absorbed by chromophores, defined as molecules that are characterized by the presence of  $\pi$ -conjugated bonds. When a molecule absorbs UVR, it experiences changes in its electrons, because one of them is excited, going from a lower energy state to a higher energy state, but due to its instability in this new state, the molecule releases the energy either by the emission of fluorescence, phosphorescence, or heat, to return to the

basal state (Gidolquim, 2016; Gilbertz *et al.*, 2018). However, the recovery of the basal state in the molecule can also occur through chemical processes, where the molecule can undergo a chemical transformation involving radical dissociation, ion dissociation, and molecular reorganization. Besides, another mechanism called cross-systems may occur; in this case, the molecule transfers the absorbed energy to an unexcited molecule (Gidolquim, 2016).

In the skin, there are several important chromophores, such as DNA and intracellular and extracellular proteins, that undergo different functional and structural changes when absorbing UVR directly. However, these molecules can also be changed by the formation of reactive oxygen species (ROS), such as the hydroxyl radical ( $\text{OH}\cdot$ ), hydroperoxide radical ( $\text{HO}_2\cdot$ ), superoxide radical ( $\cdot\text{O}_2^-$ ), and singlet oxygen ( $^1\text{O}_2$ ) (Pattison *et al.*, 2012). ROS can be formed either in the process of direct absorption of UVR by biomolecules or through type I and type II photoreactions, involving endogenous molecules such as cytochromes, flavins, heme, and porphyrins, among others, known as sensitizers, by absorbing UVR transfer excitation energy to an intermediate molecule through the transfer of electrons or hydrogen atoms (type I) or directly to molecular oxygen in a triplet state (type II). In this sense, ROS are considered second messengers of UVR, due to the fact that they can cause harmful biological effects through their action on skin biomolecules (Cadet *et al.*, 2015; Da *et al.*, 2017).

### Action spectrum

It is important to mention that the biological effects triggered by UVR on the skin are wavelength-dependent; i.e., not all wavelengths are harmful or beneficial to the same extent since there are some of them where the biological effect obtained is maximum (Bais *et al.*, 2015). The biological action spectra are graphs wavelength versus reciprocal of radiation that allows knowing the effectiveness of different wavelengths of radiation to generate a biological effect, thus allowing to determine the incident wavelength that is capable of producing a specific response, defined as effective biological UV irradiance ( $UV_{eff}$ ) and obtained by multiplying the spectrum of solar radiation with the action spectrum for the biological effect under study. Due to the effects of UVR on the skin, the spectra of erythematous action, DNA absorption of UVR, and non-melanoma skin cancer are considered the most important and used in the evaluation of the biological effects produced by UVR (Bais *et al.*, 2015; De Argila *et al.*, 2014; De Fabo, 2006; De Grujil, 2000; Matts, 2006). One of the concepts derived from the erythematous action spectrum is the minimum erythema dose minimal erythema dose (MED), which refers to the minimum amount of UVR capable of producing the first noticeable and unambiguous erythema (redness of the skin), with defined edges, without previous exposure, and is determined 16–24 hours after exposure to UVR; it can also be defined as the amount of energy required per unit area ( $J/cm^2$ ) for the appearance of minimum erythema (International Organization for Standardization, 2010).

### Skin structure

The skin is the most extensive organ of the body. It is composed of three layers: epidermis, dermis, and hypodermis. The epidermis is the most external layer; it is metabolically active because it periodically has a renewal process; its main cells are the keratinocytes, which after being submitted to different biochemical and morphological changes give rise to the formation of the stratum corneum which is considered the fundamental physical barrier of the skin. There are also the melanocytes in charge of producing melanin, the Langerhans cells that participate in the immune function of the skin, and the Merkel cells that act as sensory receptors (James *et al.*, 2020). The dermis is the underlying layer of the epidermis; the fibroblasts are the main cells, but they also contain a large extracellular matrix (ECM) which is composed of molecular structures such as structural proteins, including collagen and elastin, as well as macromolecules that participate in different biological processes of the skin such as hyaluronic acid, a polysaccharide that provides hydration (D'Orazio *et al.*, 2013; Gu *et al.*, 2020; James *et al.*, 2020). The molecular structures present in the epidermis and dermis of the skin are those that interact with the UVR, thus generating the different biological effects. It is important to mention that UVA radiation can penetrate the dermis, while UVB radiation is mostly absorbed in the epidermis (Fig. 1) (Samaniego Rascón *et al.*, 2017).

### Biological effects of UVR

Low-dose UVR induces the conversion of 7-dehydrocholesterol to vitamin D, which is important in calcium binding in the bone system (Fioletov *et al.*, 2009; Sarkany, 2019).

However, excessive exposure to UVR is a health risk, due to the generation of acute and chronic effects (D'Orazio *et al.*, 2013). Acute effects include sunburn (erythema), which can be mild or severe; epidermal thickening (hyperkeratosis), mainly of the stratum corneum; immunosuppression and skin pigmentation (tanning) that involve immediate darkening of the pigment immediate pigment darkening (IPD), persistent darkening of the pigment, permanent pigment darkening (PPD), and late tanning or delayed tanning (DT), which appears according to the amount of radiation received; furthermore, they differ in that the IPD usually appears seconds after exposure, the PPD appears 2–24 hours later, and the DT can be observed 72 hours after exposure. On the other hand, the chronic effects of UVR are photoaging (dry, wrinkled, and inelastic skin) and skin cancer, which is divided according to the type of cell affected into melanoma and nonmelanoma, the latter being subdivided into both basal cell and squamous cell carcinoma (Matsumura and Ananthaswamy, 2004; Poon *et al.*, 2014; Samaniego Rascón *et al.*, 2017; Sarkany, 2019). UVR can also cause eye diseases such as cataract, photokeratitis, and tumor formation, among others, through interaction with molecules present in the structure of the eye (Yam and Kwok, 2014). Figure 1 shows the percentage of penetration of UVR into the skin and its biological effects.

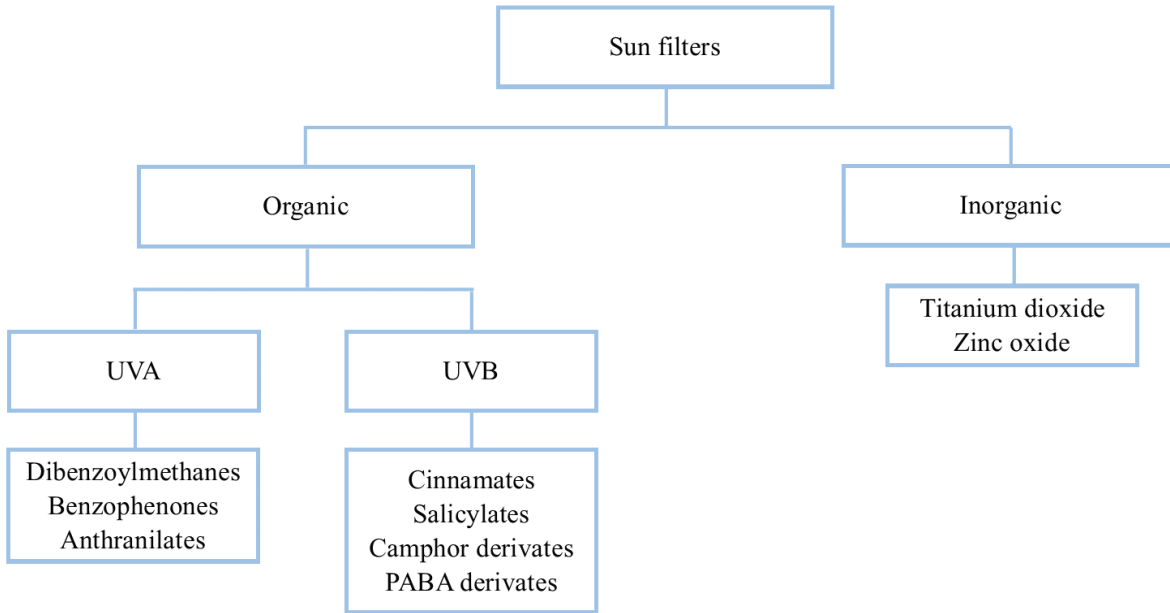
To protect against the effects of UVR, the skin contains several photoprotective molecules capable of absorbing radiation, including urocanic acid, melanin, bilirubin, reduced hemoglobin, and aromatic amino acids, such as tryptophan and tyrosine (Jansen *et al.*, 2013; Juzeniene *et al.*, 2009; Young *et al.*, 2017). Also, the skin has an enzymatic and nonenzymatic defense system against ROS caused by UVR. The first group includes the enzymes catalase, glutathione peroxidase, and superoxide dismutase, while the second group includes antioxidants such as glutathione (Kullavanijaya and Lim, 2005). However, with prolonged exposure to UVR, these mechanisms can be exhausted and because of this, the use of sunscreens is necessary to counteract the effects of UVR on the skin.

### Photoprotection: sun filters

A sunscreen or UV filter is defined by the Food and Drug Administration (FDA) as an active ingredient that absorbs, reflects, or scatters UVR at wavelengths of 290–400 nm (Food and Drug Administration, 2011). However, a sunscreen must also be stable, safe, preferably broad spectrum, and possess acceptable sensory characteristics (Geoffrey *et al.*, 2019; Jansen *et al.*, 2013). The UV filters available in the market and therefore in commercial sunscreens are classified into two groups: organic or chemical filters and inorganic or physical filters, which differ basically in their chemical structure and mechanism of action; the former are aromatic compounds that absorb UVR and the latter are minerals that reflect, disperse, and/or absorb UVR (Mancebo *et al.*, 2014). Figure 3 shows the classification of sun filters.

Furthermore, it is possible to classify them according to the UV range in which they absorb as UVB filters, UVA filters, or broad-spectrum filters, which absorb both UVB and UVA radiation (Osterwalder *et al.*, 2014).

Organic filters are molecules that are characterized by having in their structure one or more aromatic rings (conjugated electrons  $\pi$ ), with substitutions in position para or ortho of electron



**Figure 3.** Classification of sun filters. It is adapted from Geoffrey *et al.* (2019).

donor groups, besides, they have hydrophobic groups that improve their properties, such as their substantivity to the skin (Cadena-Aizaga *et al.*, 2020; Jansen *et al.*, 2013; Osterwalder *et al.*, 2014). According to their UVR absorption range and the chemical group they are divided into UVA filters (dibenzoylmethanes, benzophenones and anthranilates) and UVB filters (cinnamates, salicylates, camphor derivatives and Para Aminobezoic Acid (PABA) derivatives) (Cadena-Aizaga *et al.*, 2020; Osterwalder *et al.*, 2014; Wong and Orton, 2011). Organic UV filters exert their photoprotective action by absorbing UVR, which causes that one electron in the molecule jump into an excited state and when it returns to its fundamental state, it releases the absorbed energy through different mechanisms such as heat or at longer wavelengths (fluorescence; phosphorescence) (Mancebo *et al.*, 2014). It is important to mention that each organic UV filter has an absorption spectrum limited to a range of wavelengths, which is why sunscreen formulations contain an association (Cadena-Aizaga *et al.*, 2020; Kockler *et al.*, 2012).

Inorganic UV filters are chemically inert minerals that act as a barrier by absorbing, scattering and reflecting UVR in the range of 290-400nm, and therefore they are considered as broad-spectrum filters. Among this group, the two filters approved for use in sunscreens are titanium dioxide (TiO<sub>2</sub>) and zinc oxide (ZnO) (Kockler *et al.*, 2012). The reflection and scattering capacity of these filters depend largely on particle size, so large particle sizes (larger than nanometers scale) with high light reflection index leave a white film on the skin surface. For this reason, the cosmetic industry has opted for reducing particle size to nanometers or micrometers, in order to decrease light reflection and improve not only consumer acceptability but also UVR absorption, reflection, and scattering. These filters in comparison with the chemical filters have a lesser instability by the UVR; however, being semiconductor materials, they can generate ROS; nevertheless, this effect has been improved using its nanoencapsulation with

aluminum oxide or silica mainly, which avoids the adhesion of the filter to the skin and, therefore, the passage of ROS to the same one (Kockler *et al.*, 2012; Mancebo *et al.*, 2014; Osterwalder *et al.*, 2014).

Nevertheless, in the mechanism of action of organic UV filters, there are some photoreactions derived from their interaction with UVR, which lead to structural changes in the molecule, for example, *trans-cis* isomerization in ethylhexyl methoxycinnamate (Hojerová *et al.*, 2011; Mancebo *et al.*, 2014), and several studies have shown that butyl methoxydibenzoylmethane is one of the most photounstable filters due to its keto-enol tautomerism and fragmentation with the formation of photolysis products (Chatelain and Gabard, 2001; Gaspar and Maia Campos, 2006; Karlsson and Hillerström, 2009). These phenomena cause the loss of effectiveness and safety of these molecules. For these reasons, the photostability of sunscreens is an important parameter to evaluate in their development, since it allows establishing the stability of the filters by interacting with the UVR, a factor that in turn determines their effectiveness and safety (Berkey *et al.*, 2019). Nowadays, sunscreens are the most common cause of contact, photocontact, phototoxic, and photoallergic dermatitis around the world (Bryden *et al.*, 2006; Kockler *et al.*, 2012; Victor *et al.*, 2010; Wong and Orton, 2011). In the 1990s, benzophenone-3 was the most common photoallergic sunscreen and isopropyl-dibenzoylmethane was withdrawn from the market in 1993, after being identified as the most common cause of photoallergic contact dermatitis in the 1980s–1990s (Wong and Orton, 2011). Therefore, it is necessary to improve the effectiveness of sunscreens through new sources of photoprotective compounds that can replace or reduce the concentrations of traditionally used filters. Thus, various studies have been carried out on groups of secondary metabolites and extracts from seaweed, in order to evaluate their possible photoprotective properties and obtain new sources of raw materials of natural origin.



## Efficacy test on sunscreens

Sunscreens are considered as medicine in the United States of America and the United Kingdom, while in the European Union, they are part of cosmetics. Based on this, the efficacy tests for these products are carried out using *in vitro* and *in vivo* methodologies according to the protocols of each regulatory entity. For example, in the USA, the protocols established by the FDA are applied, but in the United Kingdom, the Boot's star system is used and in the countries of Europe, the protocols given by COLIPA (The European Cosmetic, Toiletry and Perfumery Association) and International Organization for Standardization (ISO) are used (Geoffrey *et al.*, 2019; Kaimal and Abraham, 2011; Osterwalder *et al.*, 2014).

### Tests *in vivo*

One of the *in vivo* methods to evaluate the efficacy of sunscreens is the determination of the sun protection factor (SPF). SPF is considered the universal indicator of the effectiveness of a sunscreen to protect from UVB radiation because it is calculated by dividing the MED dose of the skin protected with the test product by the MED dose of the unprotected skin (European Commission, 2006). This method that is carried out by exposing human subjects to a source of artificial UVR does not therefore indicate that the evaluated sunscreen protects against UVA radiation, since erythema (redness) or sunburns are a biological effect caused mainly by wavelengths of 290–320 nm, with maximum absorption at 308 nm, which corresponds to the UVB range (European Commission, 2006; FDA, 2011; International Organization for Standardization, 2010).

Therefore, the PPD method is a method that allows evaluating the ability of a sunscreen to protect against UVA radiation. Like SPF, it is carried out on human subjects exposed to UVR from an artificial source and allows calculating the UVA protection factor (UVA-PF) by dividing the minimum pigmentation dose or minimal pigmentation dose (MPD) on the skin protected by MPD on unprotected skin. MPD is the smallest dose of UVA energy that causes minimal unambiguous pigmentation with bounded edges after 2–4 hours of radiation exposure as a result of melanin photooxidation reactions. However, it is necessary to mention that, due to human exposure to UVA radiation in carrying out this method, in addition to factors such as cost and time, there are alternative *in vitro* methods that allow obtaining results equivalent to those obtained with *in vivo* methodologies alive (European Commission, 2006; FDA, 2011).

### Tests *in vitro*

For the evaluation of the *in vitro* protective capacity of a sunscreen against UVA radiation, there are three proposed methodologies: one from the USA through the FDA, one from Europe available in ISO 24443 in 2012, and another from the United Kingdom known as the Boot's star system, which preferably uses the transmittance technique.

The FDA proposes the critical wavelength ( $\lambda_c$ ) method, defined as the wavelength where the area under the curve of the absorbance spectrum for the irradiated product (obtained by FDA methodology) from 290 nm corresponds to 90% of the total area of the absorbance spectrum of 290–400 nm. The FDA establishes

a critical wavelength greater than or equal to 370 nm as a criterion for the declaration of a broad spectrum in the sunscreens under study (FDA, 2011, 2012).

Meanwhile, the European Union not only considers the critical wave methodology to measure the UVA protection capacity of the product under study but also proposes the determination of the UVA protection factor *in vitro*, since it has been shown to correlate with the obtained *in vivo* tests in the PPD method. Therefore, the European Union establishes two parameters for the broad spectrum declaration:  $\lambda_c \geq 370$  nm and UVA-PF  $\geq 1/3$  of the SPF value obtained for the product in *in vivo* test (European Commission, 2006; International Organization for Standardization, 2012). Lastly, the method proposed in the United Kingdom known as the Boot's star system is based on the calculation of the relationship between the absorbances obtained in the UVA and UVB regions, measured before and after the application of the photoprotector under study. This system allows a star rating, ranging from zero to five, where the higher the ratio, the greater the number of stars and the greater the protection of the product against UVA radiation (Kaimal and Abraham, 2011; Padera, 2011).

Regarding the determination of the SPF *in vitro*, several methodologies have been developed, which are sometimes used and supported by *in silico* measurements in the process of developing sunscreens; however, there is no standardized or harmonized methodology by regulatory entities for the *in vitro* determination of this parameter (Osterwalder and Herzog, 2009; Stanfield *et al.*, 2010). Table 1 describes the main characteristics of protocols for evaluating the effectiveness of sunscreens.

### Skin aging

Skin aging is a degenerative biological process that results from the action of intrinsic and extrinsic factors on skin tissue. Figure 2 shows the factors that trigger skin aging. Among the intrinsic factors are mainly age and genetics, while extrinsic factors include environmental pollution (smog, particulate matter, smoke, etc.) and UVR, which is considered as the extrinsic factor that mostly induces aging. These factors exert a synergistic effect on each other that produces a loss of the integrity and functionality of the skin that is reflected through a series of clinical manifestations. However, there are differences between these, when aging corresponds to the natural physiological process and when it is due to external factors (Farage *et al.*, 2008; Fussell and Kelly, 2020).

Intrinsic aging is characterized by a thinning of the epidermis due to a decrease in the ability of keratinocytes to proliferate and renew, in addition to reduction not only of

**Table 1.** Summary of the main characteristics of protocols for evaluating the effectiveness of sunscreens.

Protocolo	FDA		ISO		
	<i>In vivo</i>	<i>In vitro</i>	<i>In vivo</i>	<i>In vitro</i>	
Methodology	SPF	$\lambda_c$	SPF	$\lambda_c$	UVA-PF
Parameter	MED	$\lambda_c \geq 370$ nm	MED	$\lambda_c \geq 370$ nm	$\geq 1/3$ SPF
Measurement	UVB	UVA	UVB	UVA	UVA
UV protection range					

epidermal stem cells but also of the lipid synthesis of the stratum corneum; as for the thickness of the dermis, it also decreases because the number of fibroblasts decreases and with it the synthesis of collagen and elastin decreases; these alterations lead to dry, smooth skin with fine wrinkles, less elastic and sometimes benign neoplasms (Strnadova *et al.*, 2019). On the other hand, extrinsic aging is characterized by an increase in the thickness of the epidermis; in the dermis, the number of fibroblasts is less, the synthesis of the components of the ECM decreases, and there is an accumulation of disorganized amorphous collagen and elastin fibers as a consequence of an increase in their degradation. Unlike intrinsic aging, extrinsic aging results in roughly textured, unevenly pigmented skin, with a yellowish color, thick and deep wrinkles, and very little elasticity, with telangiectasias (dilation of small blood vessels) and benign and malignant neoplasms can occur (Gruber *et al.*, 2020; Landau, 2007; Strnadova *et al.*, 2019).

Despite the differences between the clinical manifestations of intrinsic and extrinsic aging, both are the result of alterations at the cellular and molecular level caused by the aforementioned factors. Among these alterations, one of the most important alterations involves the components of the dermal ECM, especially the organized fibers of collagen and elastin, which play an important role in the mechanical resistance and elasticity of the skin. In the aging process of the skin, there is a decrease in these proteins through two mechanisms, the first is by the inhibition of the synthesis pathways and the second by stimulating the expression of matrix metalloproteinases (MMPs), a family of zinc-containing proteolytic enzymes whose function is to degrade the molecular structures present in the ECM; their overproduction leads to an increase in disorganized fragments of collagen and elastin in the connective tissue, resulting in elastosis, characterized by the skin with wrinkles and thick, as well as other clinical manifestations of aging (Quan *et al.*, 2004, 2009). The main MMPs involved in this mechanism are MMP-1 (collagenase) which acts on type I collagens (majority collagen in ECM) of types II, III, VII, and X; MMP-3 (stromelysin-1) whose substrates are elastin and collagens of types IV, V, IX, and X. Furthermore, MMP-9 (gelatinase) is also involved, which degrades mainly elastin and types I, IV, and V collagens (Pérez-García, 2004; Quan *et al.*, 2004).

On the other hand, there are also ROS that have an important role in skin aging, both intrinsic and extrinsic. ROS can be the result of normal endogenous biological processes and the action of exogenous factors; in the first case, they are generated in the electron transport chain in the aerobic metabolic process of the skin; an example of this is the formation of the superoxide radical in the oxidation of NADPH to NADP<sup>+</sup> by the enzyme NADPH oxidase; however, this and other ROS are also mainly generated by the action of UVR through the aforementioned mechanisms (Fisher *et al.*, 2009; Gu *et al.*, 2020). ROS participates in aging through different mechanisms: they can alter gene expression and signaling pathways, activate matrix metalloproteinase transcription, and expression by activating the AP-1 nuclear transcription complex and inactivating MMP tissue inhibitors. They cause cellular lipids oxidation, damage to proteins through the oxidation of amino acids, and damage to cellular and mitochondrial DNA, through the oxidation of guanine to 8-oxoguanin, which can, in turn, cause damage to the telomeres that participate in cell proliferation and whose decrease is considered a marker of aging (Fussell and Kelly, 2020; Gu *et al.*, 2020; Kosmadaki and Gilchrest, 2004; Tobin, 2017).

All these mechanisms contribute to skin aging either intrinsically or extrinsically; however, hydrated, nourished, and protected skin against the effects of UV radiation has a greater resistance to them.

### Potential photoprotective and antiaging molecules

Like humans, marine macroalgae are affected by high exposure to UVR, as well as other extreme environmental conditions of pH, temperature, and high salinity that have led to the development of defense mechanisms against these factors, such as the synthesis of bioactive compounds. Among these compounds are mycosporine-type amino acids (MAAs), polyphenols, and sulfated polysaccharides, among others, which have been shown to have various biological activities, such as photoprotective, antioxidant, and anti-inflammatory capacity, among others, on the skin (Pangestuti *et al.*, 2018; Wang *et al.*, 2015).

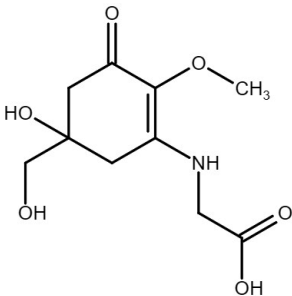
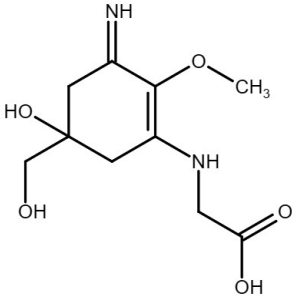
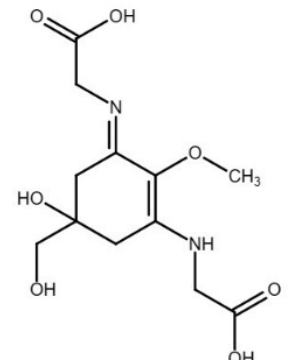
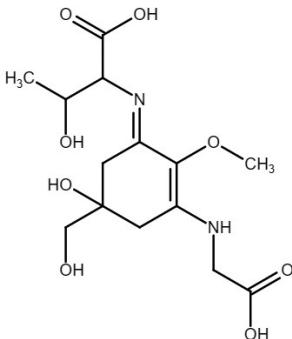
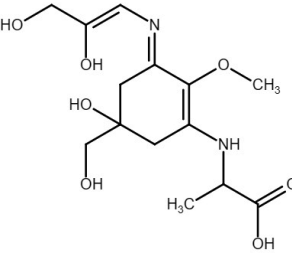
### Mycosporine-type amino acids

Mycosporine type amino acids (MMAs) are secondary metabolites synthesized as a defense mechanism against the effects of solar radiation. It is characterized by having a molecular weight less than 400 Da and a ring of cyclohexenone or cycloheximide (chromophore group) with nitrogenous substituents, mainly amino acid residues and amino alcohols (Bhatia *et al.*, 2011; Kageyama and Waditee-Sirisattha, 2019). The MAAs can be divided according to the number of substitutions in monosubstituted and disubstituted: the former has substitutions in carbon three (C3) and among them is mycosporine-glycine which is considered as an intermediate MAAs from which disubstituted MAAs are found (mainly substituted in C1 and C3). MAAs have absorption in the UVB and UVA radiation range (310–360 nm) with molar absorption coefficients between 28,000 and 50,000 M<sup>-1</sup>cm<sup>-1</sup>; however, their absorption maxima depend on the ring substituents; for example, mycosporine-glycine has a maximum absorbance at 310 nm, while porphyria 334 substituted with threonine and glycine has an absorption maximum at 334 nm. An important feature in MMAs is its photostability, which will then absorb radiation and release energy in the form of heat upon returning to the ground state (Kageyama and Waditee-Sirisattha, 2019; Lalegerie *et al.*, 2019). Table 2 shows different mycosporine amino acids with the chemical structures and absorption maxima.

### Sulfated polysaccharides

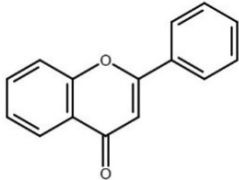
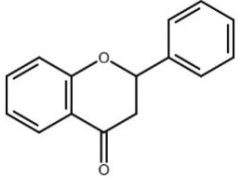
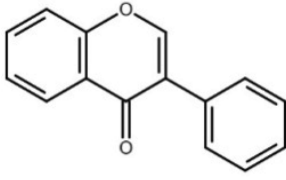
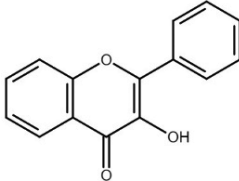
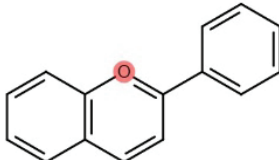
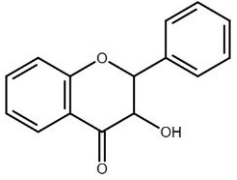
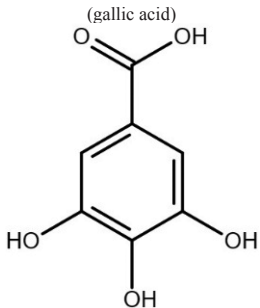
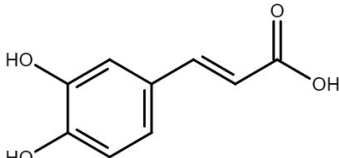
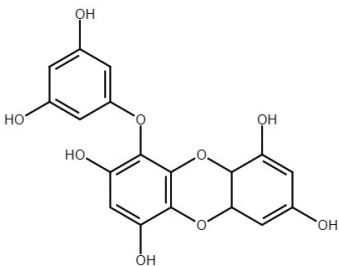
The main sulfated polysaccharides in red macroalgae are carrageenans; meanwhile, fucoidans are present in brown algae (Pangestuti *et al.*, 2018). Carrageenans are composed of galactose and anhydrogalactose units that repeat with alternations of  $\alpha$  (1→4) and  $\beta$  (1→3) type, that is, 3-linked  $\beta$ -D-galactopyranose and 4-linked  $\alpha$ -galactopyranose or 3–6-anhydro- $\alpha$ -galactopyranose. In these molecules, the sulfate group in the galactose unit can be in C4 and C2, while in the 3–6-anhydro- $\alpha$ -galactose unit, it can be in C2, C1, and C6, or it may not be sulfated (Jiao *et al.*, 2011). Fucoidan, on the other hand, is characterized by being polysaccharides with sulfated L-fucose in a greater proportion than other saccharides that can also be found as galactose, uronic acids, mannose, and xylose. In fucoidans, the sulfated portion can be found in C2, C3, or C4 and monosaccharides are associated through  $\alpha$  (1→2),  $\alpha$  (1→3), or  $\alpha$  (1→4) glycosidic bonds; their size can vary from 13 to 950 kDa (Berteau and Mulloy, 2003; Holtkamp *et al.*, 2009).

**Table 2.** Chemical structures of different mycosporine amino acids with absorption maxima (nm).

MAA	Chemical structure	$\lambda$ max (nm)
Mycosporine-glycine		310
Palythine		320
Mycosporine-2-glycine		331
Porphyra-334		334
Euhalotheca-362		362

It is adapted from Bhatia *et al.* (2011).

**Table 3.** Classification of polyphenolic compounds with chemical structures.

Polyphenolic compounds	Chemical structure		
Flavonoids	Flavones	Flavanones	Isoflavones
			
	Flavonols	Anthocyanins	Flavanols
			
Phenolic acids	Hydroxybenzoic acids (gallic acid)	Hydroxycinnamic acids (caffeic acid)	
			
Tannins	Phlorotannins		
			

## Polyphenols

Polyphenolic compounds are a broad group of secondary metabolites that are characterized by having one or more mono- or polysubstituted aromatic rings in their structure by the hydroxyl group which is considered as an electron donor (Pangestuti *et al.*, 2018). Polyphenols include flavonoids, phenolic acids, and tannins. Table 3 shows the classification of polyphenolic compounds with chemical structure.

Flavonoids are characterized by having a C6–C3–C6 configuration for a total of 15 carbons; they have two aromatic rings called A and B, which are united through a chain of three carbons, which is generally found to form a heterocyclic ring (ring C), which according to the substitutions it presents allows obtaining six subgroups: anthocyanins, flavones, isoflavones, flavonols, flavanols, and flavanones. Phenolic acids are characterized by having a carboxyl group; they are subdivided into hydroxycinnamic acids with a C6–C3 configuration and

hydroxybenzoic acids with a C6–C1 configuration (Ignat *et al.*, 2011). Tannins can be divided into hydrolyzable, condensable, and phlorotannins; the latter are mainly associated with brown algae (Balboa *et al.*, 2013; Ignat *et al.*, 2011).

The presence of these compounds in marine macroalgae has drawn attention in research intending to determine the biological activities derived from them. For example, Souza *et al.* (2011) studied two species of red macroalgae on the coasts of Brazil and found that the ethanolic and methanolic extracts showed antioxidant effects due to the presence of polyphenolic compounds, such as gallic acid and apigenin (Souza *et al.*, 2011). On the other hand, Kim *et al.*, 2018, evaluated the anti-photoaging capacity of a fucoidan and concluded that this sulfated polysaccharide had an antioxidant effect and inhibited the expression of MMPs and confirmed several studies on macroalgae extracts (Kim *et al.*, 2018, 2006; Ryu *et al.*, 2009). Also, its photoprotective effect has been evaluated; for example, Bhatia *et al.* (2019) developed



a formulation with MAAs from the macroalgae *Ulva fasciata* with an SPF 7, a value that correlates with that found by Álvarez-Gómez *et al.* (2019), when evaluating the *in vitro* photoprotective capacity (SPF 7.5) of the red macroalgae *Gracilariopsis longissima*.

Based on these results, studies have been carried out on the use of macroalgae extracts in photoprotective and antiaging cosmetic formulations, for which the process of collection and extraction of bioactive compounds, as well as their isolation and purification, has been necessary.

Seaweeds are collected in coastal areas and are subjected to a washing process to eliminate impurities. Then, they are dried in an oven or the air and made to a fine powder by crushing to continue the extraction process (Bhatia *et al.*, 2019; Bittkau *et al.*, 2020; Poulouse *et al.*, 2020). Currently, there are several techniques available for the extraction of bioactive compounds present in macroalgae, among which are conventional solid-liquid extraction (SLE), ultrasound-assisted extraction, microwave-assisted extraction, enzymes assisted extraction, and supercritical fluid extraction; however, due its simplicity and easy scalability, SLE is the most widely used (Pangestuti *et al.*, 2018; Santos *et al.*, 2019).

It is important to mention that the extraction conditions may vary according to the bioactive compounds of interest; for example, for the extraction of MAAs, aqueous binary mixtures with ethanol and methanol are used as solvents (Bhatia *et al.*, 2019; Ryu *et al.*, 2014; Zhaohui *et al.*, 2005); although the proportions may be different, some authors have agreed that the temperature and time of extraction are 45°C for 2 hours (Hartmann *et al.*, 2016; Hoyer *et al.*, 2002). On the other hand, for the extraction of phenolic compounds as in the extraction of MAAs aqueous binary mixtures with ethanol, methanol, acetone, and acetonitrile at different concentrations, times, and temperatures are used (Santos *et al.*, 2019). Vu *et al.* (2017) evaluated the content of phenolic compounds in the macroalgae *Sargassum serratum* at various conditions and concluded that the highest content of polyphenols and antioxidant activity was obtained when extraction was performed with 100% ethanol at 50°C for 32 hours. In the case of sulfated polysaccharides, the extraction can be carried out using hot water or acidified solutions as solvents at room temperature; however, a key process in the extraction of sulfated polysaccharides is the addition of CaCl<sub>2</sub> to avoid the coextraction of alginic acid (Bittkau *et al.*, 2020; Kim *et al.*, 2007). Notwithstanding, the yield obtained in the extraction of macroalgae depends not only on the bioactive compounds of interest, technique used, and extraction conditions, but also on the species of algae evaluated.

After the extraction of bioactive compounds from macroalgae, their purification can be obtained by different techniques; for example, Hartman *et al.* (2016), obtained an extract enriched in MAAs from *Prasiola calophylla* through an adsorption-based separation technique using an ion exchange resin and monitored by preparative high-performance liquid chromatography (HPLC); the purified extract was analyzed by nuclear magnetic resonance, which allowed the identification of MAA N-[5,6 hydroxy5(hydroxymethyl)-2-methoxy-3-oxo-1-cyclohexen-1-yl] glutamic acid (prasiolin) as a new photoprotective compound present in macroalgae (Hartmann *et al.*, 2016). Nevertheless, Bhatia *et al.*, 2019 purified the ethanolic extract from *Ulva fasciata* using a silica gel column and monitoring by Thin Layer Chromatography (TLC), subsequently, the purified fraction was analyzed by HPLC with Photodiode Array (PDA) detector and Liquid Chromatography-Mass Spectrometry (LC-MS). Another

technique used for the purification of extracts obtained from macroalgae is molecular-weight cut-off dialysis (MWCO). Kim *et al.* (2007) purified the extract obtained from *Undaria pinnatifida* by means dialysis (MWCO 14,000) and column chromatography using a cellulose column, from which they obtained a fraction rich in sulfated polysaccharides; then, they analyzed using high performance anion-exchange chromatography with pulsed amperometric detector.

Additionally, studies have been carried out on the use of macroalgae extracts in photoprotective and antiaging cosmetic formulations. For example, Mercurio *et al.* (2015) mixed UV filters together with *Porphyra umbilicalis* (red algae) extract and found that this combination not only improved the photoprotective capacity of the formulation but also had a positive effect on cell proliferation; results indicated that the bioactive compounds in the macroalgae have potential use for the development of photoprotective and antiaging cosmetic formulations (Mercurio *et al.*, 2015).

## CONCLUSION

In recent years, research studies have grown into new natural sources of molecules with potential photoprotective and antiaging activity that is safe and effective. Among these sources, one of the most promising sources is marine macroalgae, due to the environmental conditions in which they are found; they have generated mechanisms of protection against radiation, such as the synthesis of secondary metabolites with photoprotective, antioxidant, anti-inflammatory, and antiaging activity. For this reason, it makes them potential active compounds in the cosmetic industry for the development of products with a photoprotective and antiaging effect, the latter being useful to counteract the action of intrinsic and extrinsic factors on skin aging.

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## CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest among them or with the parent institution.

## AUTHOR CONTRIBUTIONS

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

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