BJPS
Brazilian Journal of Pharmaceutical Sciences
http://dx.doi.org/10.1590/s2175-97902022e201046
Article

Algae Metabolites as an Alternative in Prevention and Treatment of Skin Problems Associated with Solar Radiation and Conventional Photo-protection

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The histological structure and biochemistry of the skin is affected by solar radiation having adverse effects ranging from sunburns, premature aging that includes wrinkles, spots, dryness, and loss of collagen to cancer development. The skin has defense mechanisms to prevent damage caused by radiation, but when radiation exposure is excessive these mechanisms are not strong enough to protect the skin. The use of sunscreen is the most common practice of photo-protection. The active ingredients of these cosmetic protective formulations are generally from synthetic origin and have presented several drawbacks at the level of photo-stability, systemic absorption and can generate contact and photo-contact dermatitis. This review illustrates skin solar radiation problems, common sunscreen ingredients limitation and mentions how algae can be an alternative according to studies that have evaluated the photo-protective potential of extracts and compounds isolated by different techniques.

Keywords: Caroteniods. Mycosporin like Amino Acids. Phlorotannins. Photoprotection. Solar radiation.

SKIN AND THE EFFECTS OF SOLAR RADIATION

Skin functions and structure

Skin is the largest and heaviest organ in the human body also one of the most important and act as a barrier that separates our organism from the environment. The nature of this cover is physical, chemical, and immunological. It controls the flow of substances between the environment and the body. Skin pH between 5-7 works as a chemical barrier that helps to maintain its integrity and natural microbiota (Dragicevic, Maibach, 2015). Langerhans cells, dermal dendritic cells and macrophages are specialized skin cells that make the skin an immune-competent organ (Dragicevic, Maibach, 2015; Wiznia, Elbuluk, 2017). The skin carries out metabolic functions like vitamin D synthesis. Furthermore, thermo-regulation, excretion, endocrine and sensitivity are other functions performed by the skin. (Dragicevic, Maibach 2015)

The histological structure of the skin consists of a complex architecture that has three fundamental layers: epidermis, dermis and hypodermis (Figure 1A). The epidermis is the outermost layer. (Wiznia, Elbuluk, 2017) The main constituent cells of this layer are keratinocytes corresponding to 95 %, the remaining 5 % of the cells are melanocytes, Langerhans cells and dermal dendritic cells (Dragicevic, Maibach, 2015; Wiznia, Elbuluk, 2017) Melanocytes fulfill the production of melanin, which is the main endogenous defense of the skin to protect us against UV-radiation (UVR) (Norman, Menendez, 2008). The dermis is the second layer of the skin and is thicker

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than the epidermis. This layer gives the skin elasticity and mechanical strength (Dragicevic, Maibach, 2015; Norman, Menendez, 2008). In this layer structures like sebaceous glands, hair follicles and blood vessels are held in place thanks to the presence of several protein-like fibers, mainly collagen, elastin and proteoglycans (Dragicevic, Maibach, 2015; Graham *et al.* 2019). Collagen, which is the major compound of this skin layer, is synthesized by specialized cells called fibroblasts. Elastin is the second major compound in the extracellular matrix and is most responsible for contributing to skin elasticity (Jesumani *et al.*, 2019). The set of these fibrous compounds are called the extracellular matrix and they are responsible for the structural and mechanical skin´s properties (Dragicevic, Maibach, 2015; Norman, Menendez, 2008).

The deepest layer is the hypodermis, it is mainly formed by fat cells and loose connective tissue, providing mechanical protection to the body (Dragicevic, Maibach, 2015).

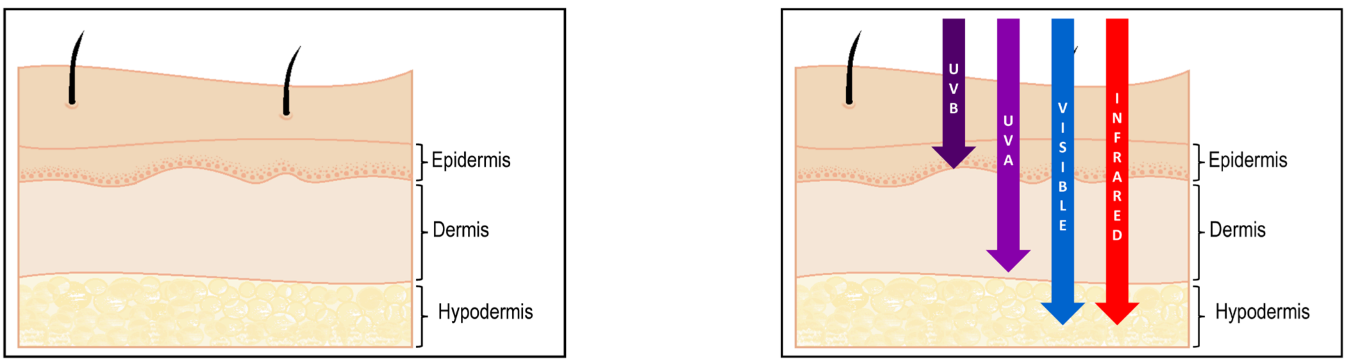

FIGURE 1 - Skin's main layers: Epidermis, dermis and hypodermis, **1A**. Electromagnetic radiation emitted by the sun and its ability to penetrate the skin layers, **1B.**

Solar radiation effects

Sunlight provides several benefits which contribute to man`s well-being. For example, promoting the regeneration of cells, stimulating the production of some hormones, and allowing the conversion of 7-deoxycholesterol to vitamin D (Giraldo, Atehortúa, Mejía, 2014). However, it also induces various adverse effects which are classified as either acute or chronic. Among the acute effects, there are erithema (or sunburn), pigmentation, suppression of acquired immunity, improvement of innate immunity and reduction of blood pressure; and as chronic effects, there is photo-aging and photo-carcinogenesis (Jansen *et al.*, 2013a; Mejía, Atehortúa, Puertas, 2014; Young, Claveau, Rossi, 2017).

Erythema is an inflammatory response to solar radiation and is the most obvious effect (Maslin, 2014). Pigmentation is usually harmless and occurs due to melanogenesis which happens when melanocytes are stimulated by sunlight. Two different types of melanin are synthesized eumelanin and pheomelanin (Jesumani *et al.*, 2019; Lim, Arellano-Mendoza, Stengel, 2017). These chemical structures differ in color, size, shape and distribution. Eumelanin has a brown to black color; it is the one normally found in people with a darker complexion. Pheomelanin has a reddish or orange color and is common to people with light complexions and blond hair. Photoaging is considered premature aging cause for overexposure to sunlight. Photoaging is characterized mainly by the appearance of wrinkles in a severe, deep and thick way, pigmentary changes and loss of elasticity (Addor, 2018; Tobin, 2017).

Due to solar radiation, reactive oxygen and nitrogen species are generated excessively (Amatu, Imberti, 2012; Kozina *et al.*, 2012). These chemical species are an important mediator in aging since they can influence this process by direct damage of cellular and extracellular structures or they can trigger signaling chains that eventually lead to the expression of degenerative enzymes, an example of a metal and protein matrix that degrades compounds of the extracellular matrix-like collagen (Berthon *et al.*, 2017; Jesumani *et al.*, 2019).

Skin cancer is the most serious consequence of sun exposure and is the most recurrent. Skin cancer is classified into two types: melanoma and non-melanoma. Non-melanoma cases alone generate an incidence between 30-40% of the total reported cancers (Maslin, 2014; Seebode, Lehmann, Emmert, 2016). Melanoma represents only about 3% of total reported cases of skin cancer, but this type of cancer is attributed to about 75% of mortality associated with the pathology. This is due to the ability of this cancer to metastasize (Seebode, Lehmann, Emmert, 2016). There are two main subtypes of non-melanoma skin cancer, squamous cell carcinoma (SCC) and basal cell carcinoma (BCC). BCC occurs at a 4:1 ratio over SCC according to the World Health Organization (Seebode, Lehmann, Emmert, 2016; Watson, Holman, Maguire-Eisen, 2016).

To protect against solar radiation some aspects have to be taken into account, one of them is that there are several environmental factors that can change the intensity of solar radiation, such as the quality of the ozone layer, latitude, altitude, time of day, cloudiness, humidity, pollutants and season of the year (Tobin, 2017; Yeager, Lim, 2019). Another important implication is the skin type. Fitzpatrick classified the skin into six groups, according to the type and content of melanin. Types I, II and III belong to groups of lighter complexion that are more likely to suffer damage from the sun than groups IV, V and VI. (Addor, 2018; Han, Chien, Kang, 2014; Watson, Holman, Maguire-Eisen, 2016) For a long time, the adverse effects mentioned above were attributed to ultraviolet radiation, while visible and IR rays were considered harmless. However, recent research has proven that the latter forms of light on the skin have unwanted effects and greater penetration (Tobin, 2017; Yeager, Lim, 2019).

Ultraviolet Radiation

UVR has a great impact on the skin interacting with structures including DNA, RNA, proteins and cell lipids. UVR has been classified into three ranges: UVC (200-290 nm), UVB (290-320 nm) and UVA (320-400 nm), the latter is divided into UVA I (340-400 nm) and UVA II(320-340 nm) (Lim, Arellano-Mendoza, Stengel, 2017; Maslin, 2014; Yeager, Lim, 2019). UVC rays are the most energetic rays emitted by the sun, it can kill unicellular organisms and produce severe effects on the skin. Thankfully, UVC does not reach the earth's surface since it is easily filtered by the ozone layer (Figure 2) (Addor, 2018).

UVB radiation is partially filtered by the ozone layer. It penetrates the epidermis layer (Figure 1B) (Young, Claveau, Rossi, 2017). There, this radiation interacts with different chromophores: melanin, urocanic acid and DNA, which are the most important ones (Dupont, Gomez, Bilodeau, 2013; Jansen *et al.*, 2013a; Young, Claveau, Rossi, 2017). Melanin fulfills a photoprotective function. This compound is usually distributed over the nucleus in order to protect it from UVB radiation (Addor, 2018). The result of the interaction between UVB radiation and urocanic acid is the isomerization of *trans* to *cis*, for the latter its role in suppressing skin immunity is well documented (Berthon *et al.*, 2017). When UV radiation interacts with DNA, it causes lesions such as the formation of cyclobutane pyrimidine dimers (CPDs) and photoproducts of 6-4 pyrimidine pyrimidone. This damage to the DNA structure inhibits DNA replication and transcription, which can lead to mutations (Dupont, Gomez, Bilodeau, 2013; Young, Claveau, Rossi, 2017). Research has shown CPDs promote cytokine-mediated inflammation leading to erythema, immunosuppression and transition mutations. The accumulation of epithelial cell mutations, coupled with the suppression of skin immunity, makes this radiation have an important participation in tumor initiation, for this reason, UVB-radiation is attributed as the main cause in the onset of cancer (Addor, 2018; Dupont, Gomez, Bilodeau, 2013; Young, Claveau, Rossi, 2017).

UVA radiation is less energetic than UVB, but has greater penetration capacity, reaching the dermis (Figure 1B) (Giraldo, Atehortúa, Mejía, 2014). For a long time, UVA was considered harmless since the damage it generates is not as obvious as the erythema produced by UVB. Even the most noticeable effect it produces, which is tanning, is desired by many people. Today, however, the different adverse effects it contains are well researched (Giraldo, Atehortúa, Mejía, 2014). UVA radiation is the greatest contributor to oxidative stress since it has the capacity to produce more reactive species than UVB radiation. UVA radiation in conjunction with the process of cellular respiration generates reactive oxygen species (ROS) such as the reactive oxygen singlet, hydrogen peroxide and hydroxyl free radicals (Giraldo, Atehortúa, Mejía, 2014). In addition, other classes of radical species in UVA such as reactive nitrogen species (RNS) and even recent studies have shown that UVA-radiation has the ability to interact with melanin to form superoxide anion and nitric oxide. Both of which contribute to more oxidative stress. ROS can cause damage to proteins, lipids and cell saccharides. They are also a factor that triggers the overproduction of the matrix metalloproteinase (MMP), enzymes that are responsible for degrading components of the extracellular matrix. For these reasons, it is the largest contributor of photo-aging. UVA wavelengths are attributed to participation in the promotion of carcinoma. This is confirmed by studies that find a relationship between exposure to tanning beds and the risk of skin cancer, mainly melanoma (Young, Claveau, Rossi, 2017).

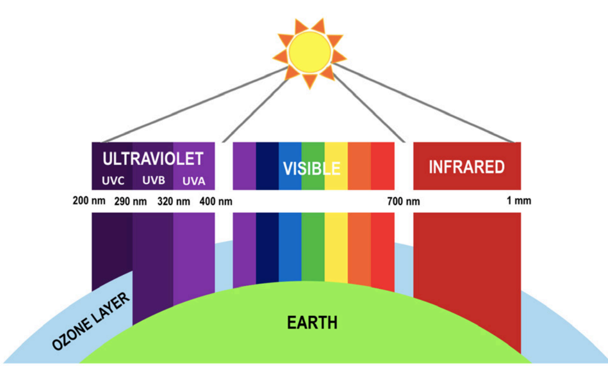

FIGURE 2 - Different electromagnetic ranges from the sun ability to penetrate the ozone layer (UVB, UVA Visible and Infrared).

Visible Light

Visible light radiation contributes between 40 and 45 % of the total electromagnetic radiation that reaches the earth's surface (Figure 2). It penetrates deeper into the skin even reaching the hypodermis. (Figure 1B) Visible light affects the physiology of the skin, and although there are few studies in this regard, it has been proven that this radiation induces changes in pigmentation, which has an important role in the production of ROS. Visible light induces the activation of inflammatory photosensitizers and cytokinins and increases the expression of the MMP (Lim, Arellano-Mendoza, Stengel, 2017; Yeager Lim, 2019).

Infrared Light

It is the least energetic range of total solar radiation but contributes to about 45% of total radiation. This range is divided into three main regions IRA (700-1400 nm), IRB (1400-3000 nm) and IRC (3000 nm - 1mm). Although the latter two do not penetrate very deep into the skin, IRA does. IRA radiation contributes to about 30% of the total infrared radiation that reaches the earth's surface. 65% of this radiation reaches the dermis and 10% reaches the hypodermis (Figure 1B) (Addor, 2018; Lim, Arellano-Mendoza, Stengel, 2017). IRA affects mitochondrial integrity, which results in inadequate energy production but also translates into an increase in the generation of ROS, which is about a quarter of those produced by ultraviolet radiation (Addor, 2018; Singer, Karrer, Berneburg, 2019). It has also been found that they produce an imbalance between the genetic expression of the MMP and a decrease in the expression of collagen, making it considered to be an important contributor in photo-aging (Berthon *et al.*, 2017; Lim, Arellano-Mendoza, Stengel, 2017).

Conventional photo-protection

Photoprotection can be defined as a variety of protective strategies that seek to prevent or mitigate radiation damage on a substrate, and in the case of skin, these strategies can be endogenous or exogenous. The skin has several photo-protection endogenous mechanisms like thickening of the stratum corneum and synthesis of compounds with high UVR absorption capacity including urocanic acid, tryptophan and the main melanin (Berthon *et al.*, 2017; Giraldo, Atehortúa, Mejía, 2014). The skin also synthesizes antioxidant enzymes and low molecular weight compounds that have the ability to neutralize ROS produced by radiation and lipid peroxidation. Glutathione peroxidase and reductase, catalase, Cu-Zn-superoxide dismutase and Mn-superoxide dismutase are some of these enzymes (Addor, 2018; Berthon *et al*., 2017). L-ascorbic acid, glutathione, vitamin E and ubiquinol are some of the low molecular weight substances that fulfill the antioxidant function in the skin (Addor, 2018; Giraldo, Atehortúa, Mejía, 2014; Young, Claveau, Rossi, 2017).

Physical barriers include clothing, umbrellas, hats, UV-protected lenses and any other environmental shade avoiding sunlight exposure but the use of sunscreen is the most common practice to protect against it (Giraldo, Atehortúa, Mejía, 2014). Sunscreen is a cosmetic formulation for topical use with the purpose of protecting the skin from solar radiation, especially UV (Jansen *et al*., 2013b; Mancebo, Hu, Wang, 2014). Currently, sunscreens of mainly synthetic origin are available on the market to which different adverse effects have been attributed, in addition to a number of disadvantages such as low photo-stability and absorption in a narrow range of UVR. So far there are only 16 filters approved by the FDA (Table I) (Mancebo, Hu, Wang, 2014; U.S. Food and Drug Administration, 2018). These filters are broadly classified into organic or chemical filters, and inorganic or physical filters according to nature and way of action.

Table 1. Allowed Ultraviolet filters listed in the US Food and Drug Administration.

Type of filters	Name INCI	UV range	Maximum allowed concentration (percentage)
Organic	Aminobenzoic acid (PABA)	UVB	15
	Padimate O	UVB	8
	Cinoxate	UVB	3
	Octinoxate	UVB	7.5
	Trolamine salicylate	UVB	12
	Homosalate	UVB	15
	Octocrylene	UVB	10
	Octisalate	UVB, UVA2	5
	Ensulizole	UVB	4
	Oxybenzone	UVB, UVA2	6
	Dioxybenzone	UVB, UVA2	3
	Sulisobenzone	UVB, UVA2	10
	Avobenzone	UVA1	3
	Meradimate	UVA2	5
Inorganic	Zinc oxide	UVB, UVA	25
	Titanium dioxide	UVB, UVA	25

U.S. accepted compounds for use as active ingredients in sunscreens, their UV absorption range and maximum allowed concentrations in percent. Data from U.S. Food and Drug Administration. Code of Federal Regulation, Title 21, Volume 5 Revised as of April 1, 2019. 39,44

Organic filters are aromatic compounds that absorb ultraviolet radiation, and also provide a more pleasant formulation for the user, since they are transparent. In most cases, they are used in combination with other filters including inorganic ones, since these alone do not provide a broad spectrum of absorption over the entire UV range (Gilbert *et al.*, 2013). The photo-degradation, induction of contact and photo-contact dermatitis, systemic absorption, generation of reactive oxygen species with or without stimulation of light are the drawback of filters (U.S. Food and Drug Administration, 2018; Wong, Orton, 2011). Sunscreen degradation can compromise the photoprotective properties and safety of photo-protectors (Kockler *et al.*, 2012). Avobenzone is a better example. It degrades after one hour of UV irradiation and is the only organic filter approved in the United States of America that provides protection throughout the UVA range. On the other hand, it can affect the stability of other organic filters. FDA statement is that avobenzone cannot be treated with aminobenzoic acid (PABA), ensulizole meradimate (methyl anthranilate), padimate O, titanium dioxide, or zinc oxide (U.S. Food and Drug Administration, 2018).

On the other hand, in 2011 sunscreens were the most common cause of photoallergic contact dermatitis in the UK (Wong, Orton, 2011). It is due to conventional sunscreen ingredients like Octyl-triazone, Octyl salicylate, octocrylene, oxybenzone, 4-aminobenzoic acid, oxybenzone and avobenzone have the ability to generate contact allergy and photo-contact (Gilbert *et al.*, 2013; Mancebo, Hu, Wang, 2014; Wong, Orton, 2011). The photo-allergy produced by this compound can be intensified if this organic filter is combined with TiO_2 (Gilbert *et al.*, 2013; Mancebo, Hu, Wang, 2014). Organic filter lipophilicity is the main characteristic that allows passing the skin barrier. At the systemic level, these compounds can undergo biotransformation processes in the organism (González, 2014; Hiller *et al.*, 2019). Compounds such as 4-aminobenzoic acid, homosalate, oxybenzone, octinoxate, octyl salicylate and camphor-derived filters have been attributed to systemic absorption and estrogenic activity (Gilbert *et al.*, 2013; Kockler *et al.*, 2012; Mancebo, Hu, Wang, 2014; Siller *et al.*, 2018).

In general terms, inorganic filters are considered safer than organic ones. Titanium dioxide (TiO_2) and Zinc oxide (ZnO) have a great ability to reflect, disperse and filter UVR. The most notable disadvantage is presented at the aesthetic level since the formulations containing these filters have a thick texture and leave white marks on the skin that are not pleasing to the user (Gilbert *et al.*, 2013; Mancebo, Hu, Wang, 2014; Yeager, Lim, 2019). To solve the problem of appearance, products containing TiO_2 and ZnO nanoparticles have been developed, allowing more transparent, lightweight and easy to spread formulations (Gilbert *et al.*, 2013). Although nanoparticles of inorganic filters were a cosmetic solution in aesthetic, titanium dioxide nanoparticles (nano-TiO_2) present several problems. nano-TiO_2 was tested on pig ears skin like this way particle´s penetration through the stratum was found and they exhibit increases its toxicity in the presence of UVA causing effects like cell apoptosis, changes in glycosylation levels and arresting cell cycle (Geng *et al.*, 2020). The ROS generation is the mechanism through cell toxicity that occur since these inorganic articles in UVR generate these reactive species which have the ability to alter cell homeostasis by oxidizing molecules like lipid, protein, nucleic acid, or other biomolecules (Geng *et al.*, 2020). These oxides have been widely used in catalysis because they are semiconductors and when the particles are exposed to UVR allow the electron flow helping to generate radicals at the epithelial level including ROS. Additionally, these chemical species can cause comedogenesis (Yeager, Lim, 2019). Another alternative used to solve the problems associated with inorganic UV filters is the exploration of new materials that can replace TiO_2 and ZnO. Cerium dioxide (CeO_2), hydrotalcite and hydroxyapatite are some of the explored compounds. Although they showed promising results, the time and the research necessary to attain the regulatory criteria can be a great challenge for new UV filters (Nery *et al.*, 2021).

All the aforementioned problems have directed the attention of the cosmetic industry to use bioactive compounds of natural origin as an alternative to synthetic filters since they exhibit wide ranges of UV absorption and additional properties such as antioxidant, anti-aging, anti-inflammatory, antimutagenic, anticarcinogenic and low toxicity which are clear advantages. These have been extracted from different biological materials such as plants, fungi, cyanobacteria and algae (macro and micro) (Berthon *et al*., 2017; Giraldo, Atehortúa, Mejía, 2014; Morocho-Jácome *et al*., 2021). In the case of sunscreen, the market has tried to include antioxidant compounds and natural extracts due to the benefits that these have for the skin such as increased protection against UVR, helping prevent cancer and improving the conditions of aging skin (Mercurio *et al*., 2015). Polyphenols, mycosporine-like amino acids and carotenoids compounds are used as a natural alternative to synthetic filters. Polyphenols are one of the many natural compounds studies in photoprotection, they have been found in several organisms. Various plants have been used for this aim. *Polypodium leucotomos* extract is a very popular polyphenols source. This leaves extract show properties like antioxidant, anti-inflammatory, immunomodulatory, tumor-suppressive, and anti-aging properties. *p*-coumaric acid, chlorogenic acid, vanillic acid, caffeic acid, and ferulic acid are the main constituents. These last two are the most powerful antioxidants of the set. *Camellia sinensis* extract is another important polyphenol source. This plant is known as green tea and exhibits antioxidant, anti-inflammatory, immunomodulatory, and chemopreventive properties. *Punica granatum* (pomegranate), Grapeseed, grape peel and even red wine (Resveratrol), *Curcuma longa* (Curcumin), *Silybum marianum* (Silymarin) and other plant extracts have been shown photoprotective activity (Torres, Luk, Lim, 2020). On the other hand**,** mycosporine-like amino acids show antioxidant, anti-age and photoprotective activities, they are produced by fungi, algae and cyanobacteria (Lawrence, Long, Young, 2017). Carotenoids ate are called oral photo-protectors due their activity is mediated by their antioxidant properties. (Jansen *et al*., 2013b; Jesumani *et al*., 2019). These types of compounds are bio-generated by different organisms such as plants, bacteria, fungi, some invertebrates and protists like algae (Berthon *et al*., 2017; Morocho-Jácome *et al*., 2020).

ALGAE AND ITS' USE IN PHOTO-PROTECTION

Algae are a group of polyphyletic heterogeneous organisms, ranging from small cells to giant seaweeds. This collection of eukaryotic organisms belongs to the kingdom of protists. They are mostly photosynthetic species that produce oxygen and develop mainly in aquatic environments (Ariede *et al*., 2017; Kumar, Baweja, Sahoo, 2015; Radulovich, Umanzor, 2013). William Henry Harvey classified macroalgae into three groups according to their majority pigment. The *Chlorospermae* group, commonly referred to as green algae, is the closest to terrestrial plants at a chemical level and its majority pigment is chlorophyll, *Rhodospermae* corresponds to red algae and its' photosynthetic pigments are phycoerythrin and phycocyanin and the third group called *Phaeophyta* consists of brown algae that owe their color to the fucoxanthin pigment (Kumar, Baweja, Sahoo, 2015; Radulovich, Umanzor, 2013).

The worldwide multibillion-dollar macroalgae industry has been primarily engaged in the production of biomass for human consumption and obtaining hydrocolloids. In recent years, algae have attracted the attention of pharmaceutical and cosmetic companies for the development of novel natural medicines and cosmetics products (Wijesinghe, Jeon, 2012). This is due to the presence of different compounds in the algae such as vitamins, carotenoids, polyphenols, amino acids, functional polysaccharides such as fucoidans and metals such as iodine, magnesium, manganese, zinc (Bajpai, Prokop, Zappi, 2014; Lena *et al*., 2019; Mobin, Chowdhury, Alam, 2019). This set of compounds have shown a wide range of biological activities such as antiviral, antibiotic, cytotoxicity, antimutagenic, anticancer, anti-tumor, fungicide and anti-inflammatory (Mobin, Chowdhury, Alam, 2019; Wijesinghe, Jeon, 2012). Algae are fast-growing species especially microalgae that is a clear advantage to get metabolites against plants (Morocho-Jácome *et al*., 2020).

Photo-protection, anti-aging, antioxidant, bleaching, anti-acne, antimicrobial, and anti-allergic are the important biological activities that algae have shown in skincare (Kim, Pangestuti, 2011; Mobin, Chowdhury, Alam, 2019; Senevirathne, Kim, 2013). *Chlorella vulgaris*, *Chondrus crispus*, *Corallina officialis*, *Spirulina platensis*, *Fucus vesiculosus*, *Ulva compressa*, *Ulva lactuca* and several species of the genus *Laminaria* like *ochroleuca*, *hyperborea*, *digitata* and *saccharina*, are the most prominent species in cosmetic use (Mobin, Chowdhury, Alam, 2019).These properties have been attributed to the presence of different families of metabolites but photoprotective activity has been attributed mainly to MAAs, phlorotannins y carotenoids (Berthon *et al.*, 2017; Lalegerie *et al.*, 2019; Senevirathne, Kim, 2013). Some metabolites from algae have been used for some commercial cosmetic formulations, including anti-aging and regenerating creams, emollients, sunscreens, and hair care products (Morocho-Jácome *et al.*, 2020).

Seaweed extracts in photo-protection

The use of algae in photoprotective formulations is a growing field of study. Metabolites have been found to have a high capacity to absorb UVR and also have a high antioxidant potential (Ariede *et al.*, 2017). This has been shown in several studies when the inclusion of antioxidant compounds in photo-protective formulations improves the effects of photo-protection (Lorigo, Cairrao, 2019; Souza, Campos, 2017). *Chlorogloeopsis spp* extracts evaluated in keratocytes protect against UVB and UVA radiation prevent radical species production and photo-aging and improves the appearance of wrinkles and skin sagging (Ariede *et al.*, 2017). Algae extracts from *Isochrysis* and *Nannochloropsis* provide photoprotection throughout the UV range and they can enhance formulations with organic and inorganic filters (Ariede *et al.*, 2017). Another study evaluated the photo-protective activity of formulations containing UV filters in conjunction with extracts of *Porphyra umbilicalis* with vitamins and *Ginkgo biloba* through the use of in vivo preclinical studies. These experiments showed that the red algae *P. umbilicalis* extract could be an ingredient to be used in cosmetic formulations. Formulations containing these algae extracts were applied to a mice group and they showed a significant increase in the time required to produce the erythema. For immunohistochemical assays (p53 and caspase-3) where apoptotic markers were considered, it was found that the formulations containing the algae extract caused a reduction in the expression of p53, especially the formulation that only contained the UV filters and the extract of the seaweed (Mercurio *et al.*, 2015). Extracts from the *Phaeodactylum tricornutum* microalgae can protect against the adverse effects of UVR, and in addition, it improves skin elasticity and firmness (Ariede *et al.*, 2017). In the purification and elucidation of secondary metabolites responsible for the photo-protective activity, mycosporin-like amino acids, polyphenols and carotenoids have been widely reported (Schmitz *et al.*, 2018).

ISOLATED ALGAE METABOLITES IN PHOTOPROTECTION

Mycosporin like Amino Acids

These secondary metabolites are hydrophilic and colorless (Rastogi, Sonani, Madamwar, 2017). Its low molecular weight structure (<400 Da) is formed by a cyclohexenone or cycloheximide skeleton with a methoxy group in position two of the ring and conjugation with one or two amino acids (Figure 3) (Hartmann *et al.*, 2016; Lalegerie *et al.*, 2019). They have high molar extinction coefficients (28000–50000 $M^{-1}cm^{-1}$) and wide absorption bands at about 40 nm. The maximum absorption of these types of compounds has a range of 310-360 nm (Cardozo *et al.*, 2007; Hartmann *et al.*, 2016). So far, more than 30 compounds of this type have been elucidated (Conde, Churio, Previtali, 2000). In addition to having photo-protective activity, they also have very good stability, an important antioxidant and anti-aging activity (Cardozo *et al.*, 2007; Lalegerie *et al.*, 2019; Tosato *et al.*, 2016). Stability is one of the most important characteristics of MAAs in cosmetic formulations since it can withstand temperatures, solvents, pH and high exposure to UVR. In terms of stability, MAAs have an advantage over conventional filters. Porphyra-334, shinorine and mycosporine-glycine are the most studied MAAs and it was found that after irradiation these molecules have been shown between 96-98% energy absorbed is released to the medium as heat without the production of ROS (Lawrence, Long, Young, 2017). Furthermore, De la Coba *et al.* (2019) showed that MMAs are stable in a wide range of pH (4.5-8.5) at room temperature, however, they were shown to be unstable at alkaline pH (i.e., 10.5) at temperatures above 50°C. These authors included different MMAs in cosmetic formulations and demonstrated their photoprotective efficacy not only with the evaluation of SPF but also developed a series of in vitro measures to evaluate the efficacy of MMAs against different biological effects such as DNA Damage, photocarcinogenesis, systemic immunosuppression, urocanic acid photoisomerization, formation of singlet oxygen radicals and (de la Coba *et al.*, 2019). Additionally, these authors have generated five (5) patents concerning to the use of algae extracts and various purified MMAs for the prevention of the oxidation of cosmetic and pharmaceutical products and the treatment of actinic erythema, photocarcinogenesis and photoaging (Coba, Aguilera, Figueroa, 2008b, 2008a, 2009a, 2009b; López-Figueroa *et al.*, 2009).

MAAs are attributed to anti-aging activity because can induce cell regeneration and proliferation in fibroblasts, neutralize and prevent the production of ROS, suppress the production of MMPs, and modulate the expression of genes associated with aging such as procollagen C and elastin (Berthon *et al.*, 2017; Ryu *et al.*, 2014).

These compounds are not exclusive to algae and have been found in marine organisms from bacteria to fish and in terrestrial organisms such as fungi (Hartmann et al., 2016; Lalegerie et al., 2019; Rastogi, Sonani, Madamwar, 2017). However, it has been demonstrated that red algae show great diversity and percentage of MAAs (Lalegerie et al., 2019). These occur at the intracellular level, Its' biosynthesis occurs along the shikimate route that plays a photo and osmo-protective role in the algae (Lalegerie et al., 2019). In many cases it has been possible to elicit this type of molecules with the use of radiation, controlling the concentrations of nitrogen in the medium and according to its osmo-protective function, some species increase their production of MAAs under conditions of high salinity (Hartmann et al., 2016). Sub- and eulitoral red algae experience a strong response to UVR to synthesize and accumulate MAAs, a good example of the genus *Porphyra* and *Prasiola*. Red algae grown in deeper waters usually cannot synthesize MAAs (Hartmann et al., 2016). Rastogi, Sonani and Madamwar (2017), found that 18 red algae from Antarctica, eight of them, produced several MAAs such as shinorine, porphyra-334, palythine and asterine-330 were the majority, palythinoly and usujirene were also found. The algae were incubated under different conditions of radiation, and it was found that the algae *Kallymenia*, *Gymnogongrus antarcticus*, *Palmaria decipiens* and *Porphyra*, have an increase in the production of MAAs after treatments with UVA and UVB radiation. For some genus of green algae such as *Acrosiphonia*, *Boodle*, *Caulerpa*, *Chaetomorpha*, *Codium* and *Ulva*, the presence of MAAs such as Porphyra-334, shinorine, palythinol, mycosporine-glycine and asterina-330 have been reported (Rastogi, Sonani, Madamwar, 2017).These kind of compounds have been included in a cosmetical formulation like Helioguard 365 and Helionori. Both commercial products containing Porphyra umbilicalis extract but with different compositions, Helioguard 365 has two main active ingredients: porphyra-334 and shinorine and Helionori is composed of three MAAs: porphyra-334, palythine, and shinorine. Although there is a variety of information about the MAAs potential to be used as UV filters and antioxidants, not many products have been developed based on it, since the current bioproduction of these naturally occurring metabolites is an expensive process. Finally, Lawrence *et al.* (2017), conclude that MAAs are photostable compounds with multiple photoprotection properties that act not only as chemical filters but also as biological antioxidants. In addition, evidence suggests that MMAs may offer an eco-friendly photoprotection option for the skin (Lawrence, Long, Young, 2017).

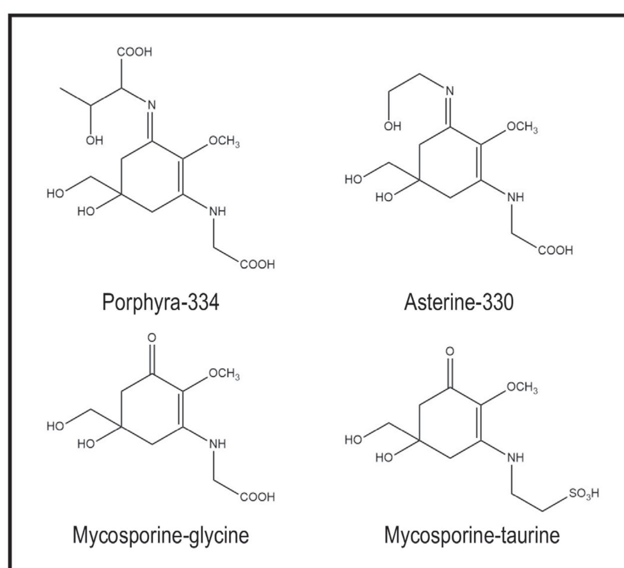

FIGURE 3 - Molecular structure of some common mycosporin like amino acids found in algae.

Polyphenols -Phlorotannin

These secondary phenolic metabolites are an important product of natural origin. These compounds are widely distributed in plants and algae and have a wide range of chemical structures (Łęska, Messyasz, Schroeder, 2018; Mobin, Chowdhury, Alam, 2019). This complex group is characterized by the presence of at least one aromatic ring that contains two or more hydroxyl groups such as gallic acid and pyrocatechol but the most prominent are those that present in its structure two or more aromatic rings such as usnic acid and hypericin (Łęska, Messyasz, Schroeder, 2018). Polyphenolic acids, flavonoids, isoflavonoids, anthocyanins, catechins, coumarins, stilbenes and tannins are different structural groups of this big set of compounds (Łęska, Messyasz, Schroeder, 2018). Tannins make up an extended family that is subdivided into three different chemical classes: hydrolyzable tannins, condensed tannins and phlorotannins (Łęska, Messyasz, Schroeder, 2018; Wijesekara *et al*., 2011). The latter is one of the most important metabolites that occur naturally in algae (Berthon *et al*., 2017; Łęska, Messyasz, Schroeder, 2018; Wijesekara *et al*., 2011). They have several structures characterized by monomeric units of phloroglucinol (Figure 4) that polymerize with each other in different ways through the acetate–malonate pathway. These compounds are highly hydrophilic and have different molecular sizes from 126 to 650 Da (Wijesekara *et al*., 2011).

Mainly brown algae and certain green algae can bio-generate large amounts of fluorotannins including fucoles, phlorethols and fucophlorethols type (Karsten, 2008; Łęska, Messyasz, Schroeder, 2018). These compounds are not involved in primary processes such as photosynthesis, cell division, or reproduction, but they do have a very important role in the protection of the contracting organisms as pathogens or abiotic such as UVR or the presence of heavy metals (Łęska, Messyasz, Schroeder, 2018; Giraldo, Atehortúa, Mejía, 2014). *Fucus vesiculosus*, *Ascophyllum nodosum* and *Eisenia bicyclis* are one of the brown algae that have important polyphenol content (Łęska, Messyasz, Schroeder, 2018). The marked interest of these compounds is focused on the protective effect they have against UVR, although they also have other biological activities that benefit the skin such as antimicrobial, antioxidant, anti-aging, anti-cancer and anti-inflammatory (Ariede *et al*., 2017; Berthon *et al*., 2017; Copia *et al*., 2012; Le Lann *et al*., 2016; Łęska, Messyasz, Schroeder, 2018; Senevirathne, Kim, 2013; Wijesekara *et al*., 2011). The antioxidant property has been strongly correlated with the number of hydroxyl groups in the molecule (Łęska, Messyasz, Schroeder, 2018). The mechanism of action of these molecules is as antioxidants is by the inactivation of reactive oxygen species and prevention of radical species formation (Copia *et al*., 2012; Łęska, Messyasz, Schroeder, 2018).

Dieckol, eckstolonol, eckol, diphlorethohydroxycarmalol, 7-phloroeckol and dioxinodehydroeckol are some fluorotanin compounds that have been isolated (Ariede *et al*., 2017; Kim, Pangestuti, 2011). Fluorotannins isolated from algae *E. cava and E. Stolonifera* have shown to have absorption in the UVB range and antioxidant activity (Jesumani *et al*., 2019). Fluorotannins such as diphlorethohydroxycarmalol as 7-phloroeckol and dioxinodehydroeckol can inhibit the activity of the enzyme tyrosinase, which can help counteract the darkening of the skin that is one of the main effects of radiation (Kim, Pangestuti, 2011). It has also been proven that these compounds inhibit the activity of MMP and hyaluronidase in conventional biological models which indicate their anti-aging activity (Berthon *et al*., 2017). In algae, the production of polyphenols can be induced by UVR, which has confirmed its photoprotective function. There are other reports where it has been found that the availability of nitrates can affect the bio-generation of these compounds (Schmitz *et al*., 2018). This can be used as a tool when scaling production processes (Copia *et al*., 2012). The elicitation of phlorotannins was first described in the brown algae *Ascophyllum nodosum* in 1997 (Karsten, 2008). It has been observed that some algae during the summer season increase their concentration of fluorotaninos such as *Hormosira banksia* (Karsten, 2008).

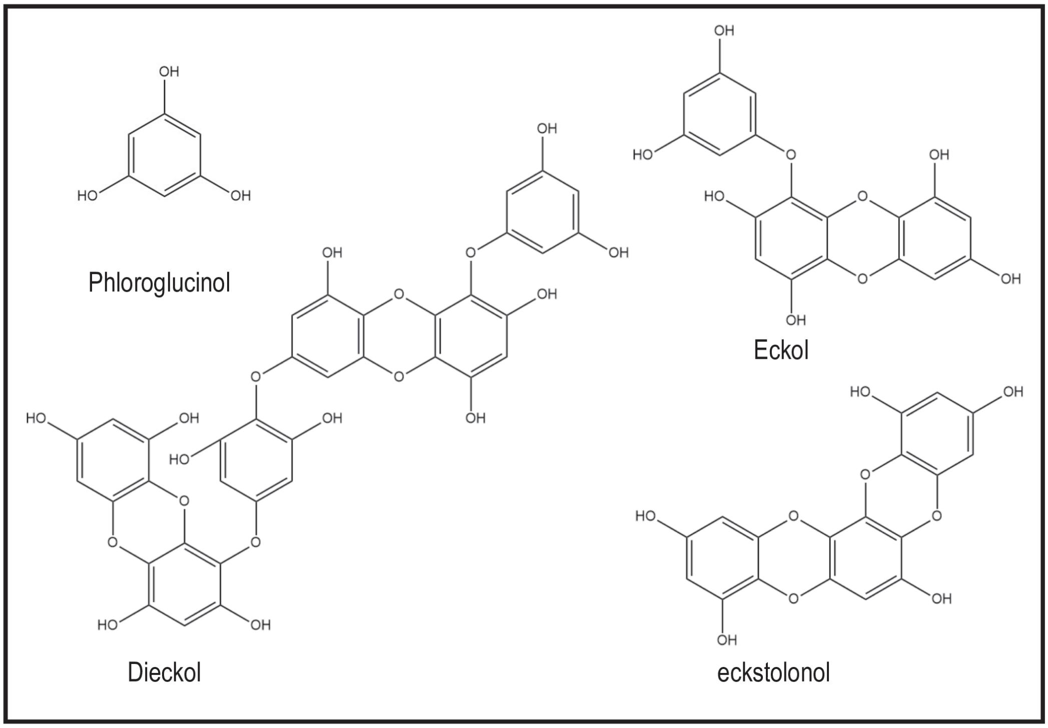

FIGURE 4 - Chemical structure of some common polyphenols phlorotannin type found in algae.

Caroteniods

Carotenoids are tetraterpene-type hydrocarbons (40-carbon atom terpenoids) built of isoprene units containing five carbons (Figure 5). These contain several conjugated unsaturation which can absorb radiation in the visible range. This characteristic makes coloration red or orange, and they are used as lipophilic pigments (Łęska, Messyasz, Schroeder, 2018). These types of compounds are bio-generated by different organisms such as plants, bacteria, fungi, some invertebrates and protists like algae (Berthon et al., 2017; Giraldo, Atehortúa, Mejía, 2014; Morocho-Jácome et al., 2020). Carotenoids are more representative of brown algae, they are found in some red algae and very low amounts in green algae (Łęska, Messyasz, Schroeder, 2018). The main carotenoids found in brown algae are fucoxanthin and β-carotene and in red algae lutein, zeaxanthin, and β-carotene (Bajpai, Prokop, Zappi, 2014; Łęska, Messyasz, Schroeder, 2018; Schmitz et al., 2018). Microalgae are considered the most important producers of carotenoids. In these organisms, carotenoids acquire a classification in primary and secondary according to the function they play in the cell. The primary ones are accumulated in the thylakoid membrane and are associated with photosynthetic functions, while the secondary ones are produced in certain stress conditions (Lena et al., 2019). Carotenoids like astaxanthin, β-carotene and chlorophyll are nontoxic and noncarcinogenic compounds. FDA-regulated and approved. (Morocho-Jácome et al., 2020).

There is a growing interest in the search for new natural sources of carotenoids since these compounds are widely used in the food, feed, nutraceutical and cosmeceutical industry as natural colorants and different biological activities have been reported regarding the prevention of neurodegenerative diseases, cardiovascular and inflammatory (Lena *et al.*, 2019; Łęska, Messyasz, Schroeder, 2018). Around 400 carotenoids are known but only β-carotene, astaxanthin, lutein, zeaxanthin, lycopene and bixin are of commercial importance, the first two being the most commercialized (Mobin, Chowdhury, Alam, 2019). In the cosmetic industry, these compounds have been included in several formulations such as lipsticks, face powders, nail polish, and eyeshadows (Łęska, Messyasz, Schroeder, 2018).

However, these substances are called oral photoprotectors and although these compounds cannot absorb UVR, their effect is mainly mediated by their antioxidant properties although they also dissipate the heat from the excess radiation (Jansen *et al*., 2013b**;** Jesumani *et al*., 2019). The protective effects against UVR of these compounds result from different mechanisms such as UV and visible light absorption, physical quenching, they also act like as a provitamin A in the skin and it is widely reported they have scavenging ROS property, a good example of this is β-carotene, Astaxanthin and vitamin E. It has been shown that the intake of these compounds decreases the intensity of erythema. This decrease depends on the carotene used, the dose and the duration of treatment (Giraldo, Atehortúa, Mejía, 2014). These also have anti-aging activity being able to stimulate the synthesis of collagen and elastin, reduce the induction of ROS and suppress MMP expression (Jesumani *et al*., 2019). Fucoxanthin obtained from *Sargassum fusiforme* and *Sargassum saliquastrum* exhibited strong antioxidant activity against DPPH and hydrogen peroxide (Jesumani *et al*., 2019). Fucoxanthin isolated from *Laminaria japonica* suppresses tyrosinase activity in UVB-irradiated guinea pigs and avoids melanogenesis in UVB-irradiated mice (Kim, Pangestuti, 2011). Fucoxanthin and astaxanthin inhibit DNA damage and have antioxidant activity (Kim, Pangestuti, 2011). Astaxanthin extracted from *Haematococcus*, shows an improvement in wrinkles and skin appearance providing effective protection against photo-aging (Berthon *et al*., 2017).

Like Mycosporine-like amino acids and polyphenols, the biosynthesis of carotenoids can be influenced by different factors such as temperature, salinity, irradiation and nutrient concentration (Bajpai, Prokop, Zappi, 2014; Lena *et al*., 2019; Mobin, Chowdhury, Alam, 2019). Nitrogen deficiency is one of the conditions used for the stimulation of carotenoid production (Bajpai, Prokop, Zappi, 2014). An example of this is the *Dunaliella* saline alpha which under conditions of high salinity, high irradiation and low nutrient content can accumulate beta carotene up to 14 % of its dry weight (Bajpai, Prokop, Zappi, 2014; Mobin, Chowdhury, Alam, 2019). In the case of *Haematococcus pluvialis*, which is a green microalga under certain conditions, it can accumulate large amounts of astaxanthin, up to 2–3% of its dry weight. (Mobin, Chowdhury, Alam, 2019).

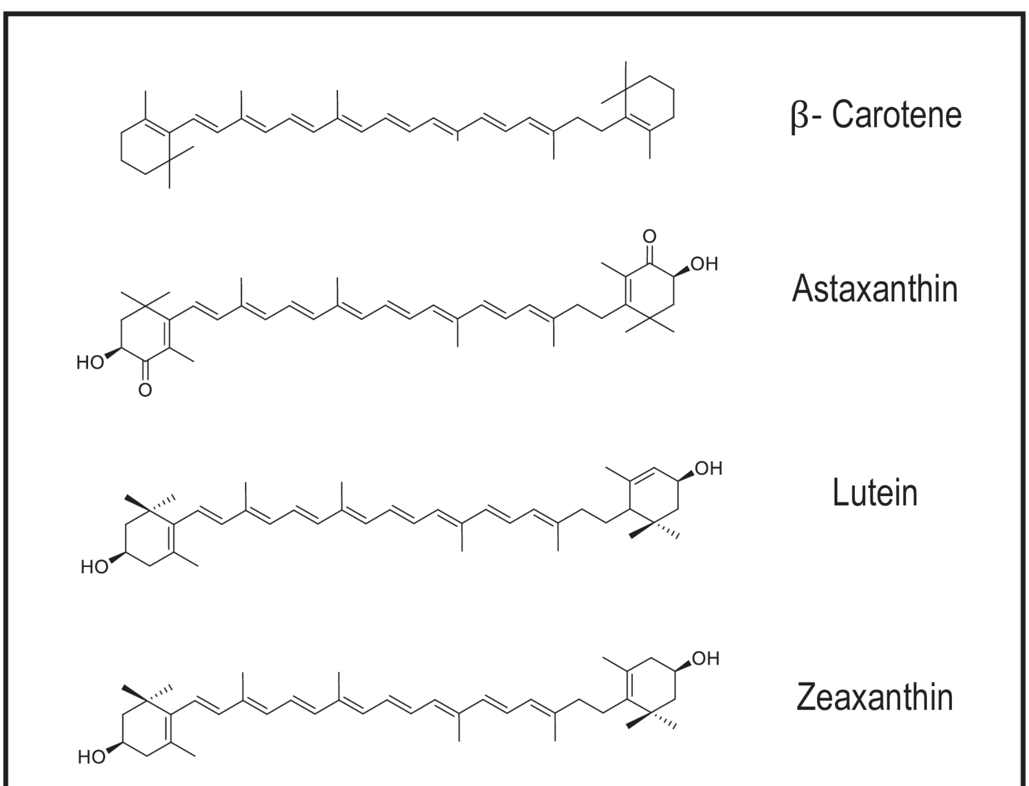

FIGURE 5 - Chemical structure of some common carotenoids.

CONCLUSION

Algae extracts and compounds have a wide range of biological activities that can be used at the cosmetic level. Chemical compounds such as mycosporin-like amino acids, polyphenols and carotenoids report a high potential to be used as naturally photo-protective ingredients to face low stability, contact and photo-contact dermatitis, systemic absorption and estrogenic activity that exhibit the current sunscreen ingredients like avobenzone, oxybenzone, octyl-triazone, octinoxate, octocrylene, etc. Nevertheless, there are not many sunscreen products that include algae functional metabolites in their formulation. The great variety of these organisms means a lot of possibilities. Notwithstanding, many countries still do not take advantage of these extraordinary biomass producers. In the case of Colombia, being one of the most biodiverse countries, including algae, there is no real commercial use of these organisms and in terms of studies that have been mainly focused on taxonomy and obtaining hydrocolloids. According to several reports algal metabolites have good biocompatibility profiles and although this review does not take into account that topic, it is important to consider toxicological studies of the alga extracts and their compounds to corroborate their true commercial potential.

CONFLICT OF INTEREST

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

ACKNOWLEDGMENTS

Stefanie Rincón-Valencia acknowledges the doctoral fellowship granted by Colciencias (727 Doctorados Nacionales). This work was partially supported by CODI-University of Antioquia (Project no. 2019-25210).

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Received for publication on 17th November 2020
Accepted for publication on 04th July 2021