

Review

Mycosporine-Like Amino Acids from Red Macroalgae: UV-Photoprotectors with Potential Cosmeceutical Applications

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Abstract: Macroalgae belong to a diverse group of organisms that could be exploited for biomolecule application. Among the biocompounds found in this group, mycosporine-like amino acids (MAAs) are highlighted mainly due to their photoprotection, antioxidant properties, and high photo and thermo-stability, which are attractive characteristics for the development of cosmeceutical products. Therefore, here we revise published data about MAAs, including their biosynthesis, biomass production, extraction, characterization, identification, purification, and bioactivities. MAAs can be found in many algae species, but the highest concentrations are found in red macroalgae, mainly in the order Bangiales, as *Porphyra* spp. In addition to the species, the content of MAAs can vary depending on environmental factors, of which solar radiation and nitrogen availability are the most influential. MAAs can confer photoprotection due to their capacity to absorb ultraviolet radiation or reduce the impact of free radicals on cells, among other properties. To extract these compounds, different approaches can be used. The efficiency of these methods can be evaluated with characterization and identification using high performance liquid chromatography (HPLC), associated with other apparatus such as mass spectrometry (MS) and nuclear magnetic resonance (NMR). Therefore, the data presented in this review allow a broad comprehension of MAAs and show perspectives for their inclusion in cosmeceutical products.

Keywords: antioxidants; cosmeceutic; extractions; integrated multitrophic aquaculture (IMTA); mycosporine-like amino acids (MAAs); purification; red macroalgae



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1. Introduction

In recent decades, macroalgae have attracted significant biotechnological interest due to their wide biochemical composition (e.g., polysaccharides, fatty acids, carotenoids, phycobiliproteins, or mycosporine-like amino acids) with diverse potential bioactivities (e.g., antioxidant, anti-inflammatory, or photoprotective activities) [1]. Algae biomass can be used for different applications: (1) human consumption or feed due to its high nutritional value; (2) food additives due to its phycocolloid content; (3) biostimulants for plants due to algal growth-stimulating compounds; (4) cosmeceutical, nutraceutical, or pharmaceutical products due to its antioxidant, anti-inflammatory, or photoprotective properties [2,3]. This review is focused on the cosmeceutical applications of marine red macroalgae (Rhodophyta), and particularly on their use as natural ultraviolet (UV) filters due to their antioxidant and photoprotective capacity. The cosmetic industry is growing at a global scale and it is seeking innovations such as natural active principles. In recent decades, consumers have also tended to prefer natural products rather than synthetic

ones, because the former look better, are safer, and are more beneficial for health and the environment.

UV radiation (UVR) that reaches the Earth's surface (<10% of the total received) is composed mainly of UV-A (320–400 nm) and a small portion of UV-B (290–320 nm). UV-B is the most dangerous, causing DNA mutations such as cyclobutane pyrimidine dimers (CPDs) or 6-4 photoproducts (6-4PP), which can be associated with cancer cell development. UV-A is considered less harmful, but can produce reactive oxygen species (ROS), altering the expression of certain genes related to premature skin aging [4–6]. Sunscreens are composed by different UV filters that protect the skin from exposure to UVR. UV filters are normally classified as: (1) synthetic or organic, based on the capacity to absorb UVR (e.g., octocrylene, butyl methoxydibenzoylmethane, oxybenzone); and (2) physical or inorganic, which can reflect the UVR (e.g., titanium dioxide). These filters have been found in different aquatic environments [7–9] associated with marine organisms such as mussels, fish or mammals [10,11]. Their presence can provoke negative effects such as inhibition of growth in phytoplankton [12], endocrine disruptions in fish [13,14] or stimulus of coral bleaching [15–17]. Different studies have also reported their negative effects in humans, such as in photoallergies or hormone disorders [18,19]. Thus, it is necessary to develop natural atoxic and biodegradable photoprotectors.

Mycosporine-like amino acids (MAAs) are secondary metabolites, mainly implicated in photoprotection, and produced by various organisms (algae or corals), of which red macroalgae are one of the main producers [20,21]. MAAs are a diverse group of nitrogenous compounds with low molecular weight (<400 Da), and are colorless, uncharged, and water soluble. More than 30 types have been identified. All MAAs share the same central structure, a cyclohexenone or cyclohexenimine ring, responsible for the UV absorption. The different types of MAAs vary according to their nitrogen substituent (amino acid or its imino alcohol) in the chromophore, which determines their specific absorption spectra [22,23] (Figure 1). Different pathways have been proposed for its synthesis: (1) Firstly, the shikimate pathway was suggested [24–26]. The production of MAAs was inhibited in the coral *Stylophora pistillata* using glyphosate, an inhibitor of the shikimate pathway [25]. (2) More recently, the pentose-phosphate pathway was also demonstrated to be implicated in MAA biosynthesis [27–30]. Balskus and Walsh [27] found that a four-gene cluster linked to the pentose-phosphate pathway in *Trichormus variabilis* (previously known as *Anabaena variabilis*) was able to produce the MAA shinorine when inserted into *Escherichia coli*. However, Spence et al. [31] showed that this is not the major route of MAA synthesis. *T. variabilis*, with a deletion of the gene that encodes EVS (a key gene in the pentose phosphate pathway), still produces shinorine at levels of UV exposure. In recent years, some authors proposed that both pathways can be linked [32,33]. A deletion of the OMT gene (linked to the pentose phosphate pathway) in *T. variabilis* completely prevented shinorine synthesis, revealing that this gene product is essential to both pathways [32]. This evidence suggested that the shikimate pathway can be predominant for UV-induced MAA biosynthesis, whereas the pentose phosphate pathway can be used for the conservative production of MAAs.

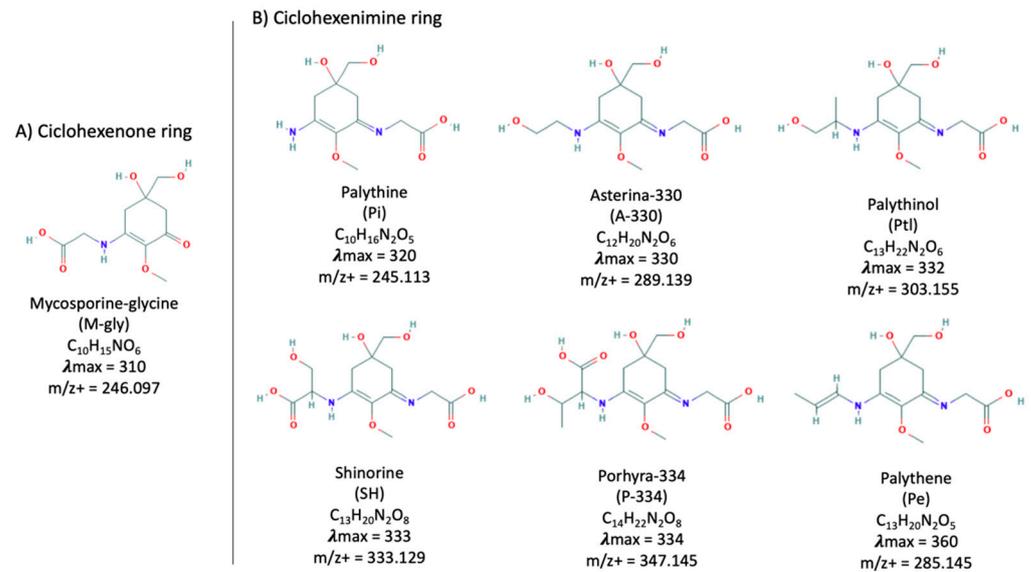


Figure 1. Chemical structure of the most common MAAs found in red macroalgae [20,21,34–40].

Different characteristics and bioactivities have been attributed to MAAs that make them good candidates for cosmeceutical applications such as biological photoprotectors. These molecules are good UV-absorbing compounds with low toxicity, and high stability and antioxidant activity, among others (potential bioactivities are reviewed in Section 7) [2,23,41].

This review describes the possible use of MAAs as biological photoprotectors for cosmeceutical applications, covering the different steps of the process: the screening of species with relevant bioactive compounds; the factors involved in the MAA productivity; the harvesting/culture of the biomass; the extraction, quantification, characterization, and purification of MAAs; and their different bioactivities (Figure 2). The information/data used in this review was obtained from different search engines (mainly Google Scholar) using keywords such as: UV-screen, antioxidant, macroalgae, photoprotection or culture. The most reliable information was obtained from research undertaken during the past 20 years (2000–2020).

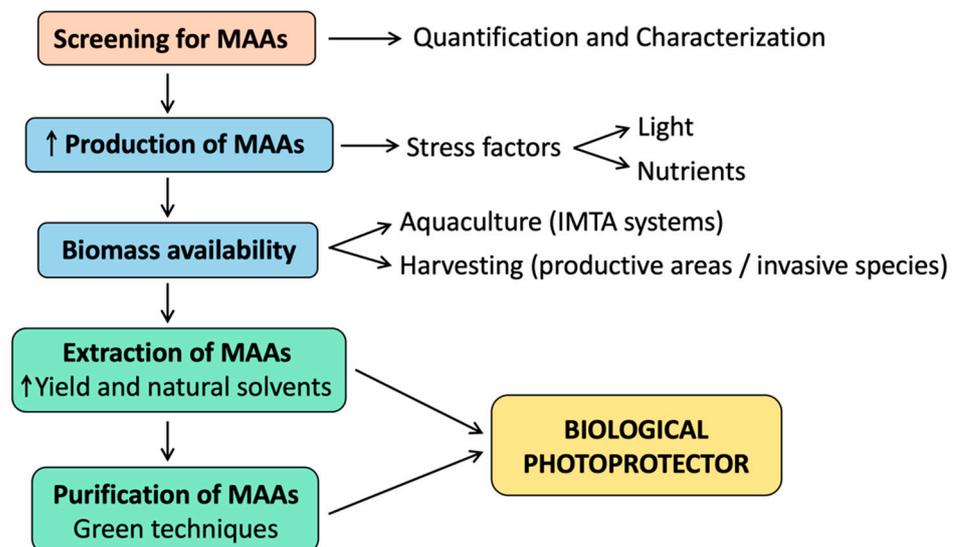


Figure 2. Scheme of the different steps of the process described in this review, involving screening, production, extraction, and purification.

2. Screening of MAAs

Several authors studied the presence/concentration of MAAs in different red algae species and its geographical or seasonal variations. Navarro et al. [2] summarized in a book chapter the MAA content of different species from different geographic locations: Huovinen et al. [42] studied the MAA concentration in macroalgae from southern Chile, obtaining the highest content in *Pyropia columbina* (previously, *Porphyra columbina*) (7.2–10.6 mg g⁻¹ DW), followed by *Bostrychia* sp. (4.7 mg g⁻¹ DW), *Gelidium* sp. (2.2–6.8 mg g⁻¹ DW), and *Mazzaella laminarioides* (2.1–4.8 mg g⁻¹ DW). Briani et al. [43] studied macroalgae from the Brazilian coast and also obtained the highest MAA content in the genus *Porphyra* (*Pyropia acanthophora*, 5.2–6.6 mg g⁻¹ DW), followed by *Laurencia caraibica* (2.2–3.6 mg g⁻¹ DW). Karsten et al. [44] studied different species found in tropical mangroves and observed a high content in species from the genus *Bostrychia* (3–12 mg g⁻¹ DW) and *Stictosiphonia* (6 mg g⁻¹ DW). More recently, Lalegerie et al. [45] analyzed the photoprotective compounds in several red algae species from Brittany (France), obtaining the highest concentrations in *Bostrychia scorpioides*, *Porphyra dioica*, *Agarophyton vermiculophyllum* (as *Gracilaria vermiculophylla*) and *Vertebrata lanosa*. The MAA content of species from southern Spain was also analyzed, obtaining high values in *Porphyra umbilicalis* (2.6–10 mg g⁻¹ DW) and *Bangia atropurpurea* (5 mg g⁻¹ DW), followed by *Feldmannophycus rayssiae*, *Chondracanthus acicularis*, *Gelidium* sp. and *Osmundea pinnatifida* (1.5–3 mg g⁻¹ DW) [46–48].

Seasonal variation of MAAs has been reported in red macroalgae. *A. vermiculophyllum* from “Ria de Aveiro” (Portugal) showed a high MAA content in spring, due to the nitrogen (N)-enriched waters [49]. Guihéneuf et al. [50] observed an increase in the MAA content of different red algae (*Palmaria palmata*, *Chondrus crispus*, and *P. dioica*) in spring, induced by the increasing daily light and irradiance. Lalegerie et al. [51] also observed a high seasonal variability in *P. palmata*, with a higher content of MAAs in April and May, due to the light increase. In addition, short-term variation has been also reported (hourly and daily variations) [52–54]. For example, under days with ozone depletions in Patagonian, a rapid increase in myc-glycine was detected in *P. columbina* [53].

Korbee-Peinado [55] analyzed species from different orders and observed some patterns in the MAA content: the highest values were observed in Bangiales (*Porphyra* spp. and *Bangia* sp.), followed by Bonnemaisoniales (*Asparagopsis* spp.) and Gelidiales (*Gelidium* sp.), whereas the lowest content was observed in Corallinales. Rhodophyta algae can be classified into three groups according to the concentration of MAAs: (1) species without the capacity to synthesize MAAs or with very low content of MAAs (<1 mg g⁻¹ DW) (e.g., Corallinales or Plocamiales); (2) species with low content of MAAs (1–2 mg g⁻¹ DW) (e.g., Rhodymeniales or Ceramiales); and (3) species with a high content of MAAs (>2 mg g⁻¹ DW) (e.g., Bangiales, Gelidiales, Gracilariales) [21,56]. In most cases, the quantity and quality of MAAs can vary depending on the environmental factors [57–60]. Within these orders, some species stand out, such as *Porphyra* spp., *B. atropurpurea* (Bangiales), and *Gelidium pusillum* (Gelidiales) [55].

Some authors published databases of MAAs. Sinha et al. [20] summarized the MAA data obtained in fungi, cyanobacteria, phytoplankton, macroalgae, and animals. More recently, Sun et al. [21] collected the MAA values observed in marine macroalgae over the past 30 years (1990–2019), and confirmed that 572 species of marine macroalgae contained MAAs (45 species of Chlorophyta, 41 species of Phaeophyceans, and 486 species of Rhodophyta). In this review, we analyzed the MAA values of the different red algae species obtained in previous articles [2,42,43,45,47] and observed the pattern shown in Figure 3, in which the order Bangiales presented the highest MAA content, followed by Gracilariales and Ceramiales; the lowest MAA content was observed in the orders Corallinales, Rhodymeniales, Nemaliales, and Plocamiales.

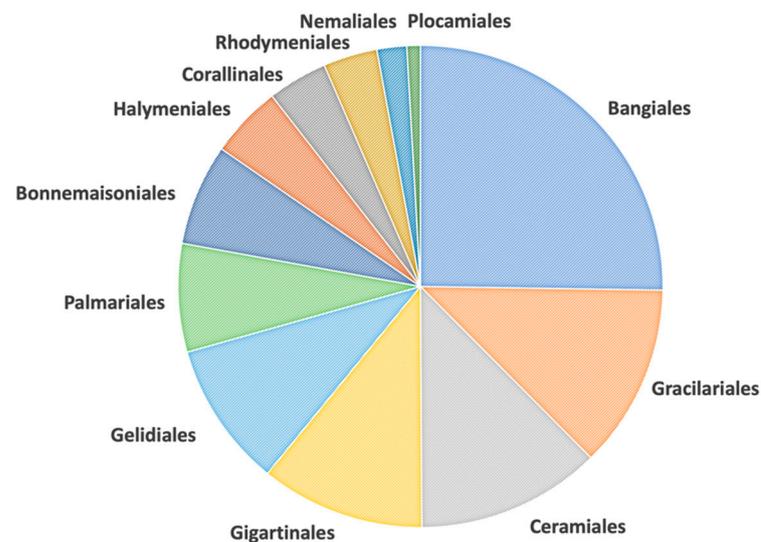


Figure 3. Distribution of MAAs in different orders of red macroalgae, according to the values obtained in previous studies [2,42,43,45,47].

3. Regulation of MAA Biosynthesis

It is well known that the diversity and concentration of MAAs can vary, depending on environmental factors or culture conditions, such as radiation (PAR and UV), temperature, salinity, nutrients, pH, or desiccation. The main factors involved in MAA biosynthesis are radiation (PAR and UV) and inorganic N availability [51,61–67].

PAR and mainly UVR are key factors in the induction of MAA production. Karsten et al. [68] observed that algae exposed to sunlight had 2.5-fold more MAA content than shaded species. Different authors studied the effect of quality and intensity of PAR and UVR in the synthesis of the different MAAs [67,69]. In *C. crispus*, the MAA palythine was synthesized under blue and white light. In the same study, pre-exposure to blue light followed by growth in UV-A increased the synthesis of shinorine seven-fold compared to treatments without previous exposure to blue light [70]. MAA accumulation (porphyra-334, palythine and asterina-330) under blue light also occurred in *Neopyropia leucosticta* (previously *Porphyra leucosticta*), whereas white, yellow, green, and red lights favored an increase in shinorine content [57]. In *C. crispus*, UV-B radiation induced the synthesis of asterina-330, palythanol, and palythene, whereas UV-A radiation induced the synthesis of shinorine and palythine [71]. MAA palythanol content increased under a high level of PAR in *Gracilariopsis tenuifrons* [72]. MAAs were stimulated in *Agarophyton tenuistipitatum* (ex-*Gracilaria tenuistipitata*) by UV radiation, including UV-A and UV-B [73]. The gametophytes of *M. laminarioides* showed a reduction in asterina-330 and palythine in different radiation treatments, including PAR, PAR + UV-A, and PAR + UV-A + UV-B, whereas tetrasporophytes showed an increase in these MAAs, mainly under PAR + UV-A [59].

Availability of nutrients, particularly inorganic N, is another important factor that positively affects MAA biosynthesis. The N can be quickly mobilized to MAAs, which act as N reservoirs [74]. Navarro et al. [75] verified the effects of nitrate (NO_3^-) on *M. laminarioides* grown under solar radiation. The authors observed an increase in mycosporine-glycine that occurred according to the increase in nitrate concentration, reaching saturation at 0.18 mM. The interaction between UVR and nutrients was investigated in *Gracilariopsis longissima*. The experiment showed a 65% increase in the MAA content under PAR + UV-A + UV-B and high N availability (300 μM NH_4Cl and 30 μM HNa_2PO_4) compared to the other treatments with low nutrients (10 μM NH_4Cl and 1 μM HNa_2PO_4) and without UVR radiation [76]. The MAAs amount also increased 50% in *Gracilaria cornea* (previously, *Hydropuntia cornea*), 40% in *G. longissima*, and 30% in *Halopithys incurva* when grown under high nutrient concentration (150 μM of ammonium NH_4^+ and 15 μM of phosphate PO_4^{3-}) and PAR + UV-A + UV-B radiation, compared with PAR only [54]. *A. tenuistipitatum* showed an increase in

MAAs, reaching constant maximum values at concentrations greater than 0.5 mM nitrate (NO_3^-) [64]. The same species increased MAAs up to eight-fold in the presence of UVR and 0.5 mM NO_3^- [63]. *N. leucosticta* and *P. umbilicalis* increased MAA content when grown under 300 μM ammonium and PAR + UV-A + UV-B radiation [58]. *P. columbina* also increased the concentration of MAAs under 300 μM ammonium, although the increase was greater in PAR + UV-A than in PAR + UV-A + UV-B [77]. *P. columbina* was also grown under different radiation treatments (PAR and UVR) and different concentrations of nitrate. Samples of this algae were collected during the light and dark (recovery) periods. The highest concentration of MAAs was achieved in samples under PAR + UV-A + UV-B and 0.38 mmol L^{-1} of NO_3^- , whereas in the dark the MAAs were higher in PAR and PAR + UV-A + UV-B, without addition of nitrate [53].

4. Biomass Availability for MAA Production

The potential application of algae as a source of commercial bioactive compounds requires high biomass availability (Figure 4). The global production of macroalgae has tripled during the past 20 years, reaching 32.4 million tons per year. The most cultivated red algae in the world are *Eucheuma* spp., *Gracilaria* spp. (for phycocolloid extraction), and *Porphyra* spp. (for human consumption), cultured mainly in China and Indonesia [78,79]. Algae can be cultured in combination with fish and other aquatic organisms, under integrated multitrophic aquaculture (IMTA) systems, in which the inorganic nutrients (mainly nitrogen and phosphorous) from the fish pond effluents can be used for algae to grow and produce high-value biocompounds.

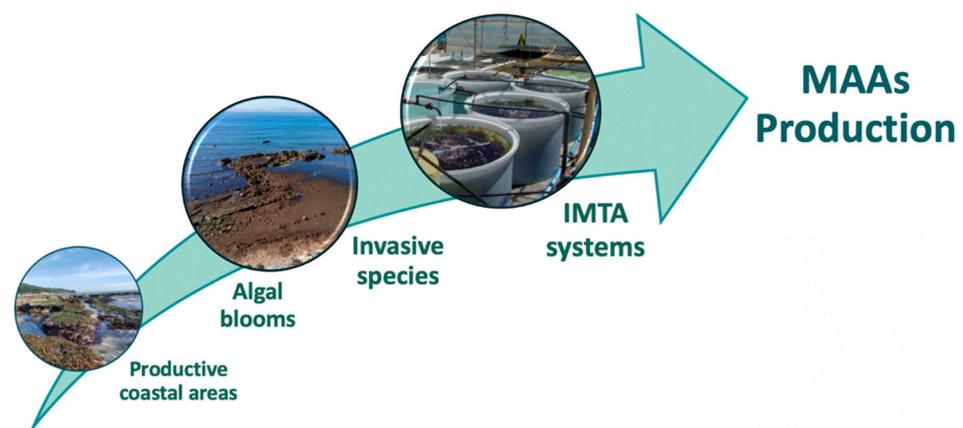


Figure 4. Scheme of the most important source of biomass for MAA production.

High production of MAAs has been reported in algae grown in IMTA using fishpond effluents [49,65,80,81]. *A. vermiculophyllum* and *G. cornea* were grown under different concentrations of nutrients obtained from fishpond effluents and high concentration of nitrogenous compounds, such as chlorophyll and phycobiliproteins, was observed. The highest yield of MAAs was obtained when *G. cornea* was grown in fishpond effluents under natural light (sunlight) [81]. Pliego-Cortés et al. [65] cultivated *Rhodymenia pseudopalmeta* under high concentrations of ammonium (around 78.2 to 99.5 μM) using fishpond effluent in IMTA cultivation. The MAA content was five-fold higher compared to wild populations (grown in the natural environment under concentrations around 0.17 μM ammonium). Based on the data obtained, the authors presented an estimation of production for 100 m^2 of surface, totaling 941 g DW in 100 $\text{m}^{-2} \text{d}^{-1}$ of biomass and 1167 mg of MAAs (yield of 1.24 mg MAAs g^{-1} DW). In another study, *A. vermiculophyllum* was grown for one year in tanks under natural light and addition of fishpond effluents. The MAA content varied seasonally; the highest values were observed in April (about 3.13 mg g^{-1} DW). According to the results of this study, a total amount of 71.33 g MAA year^{-1} could be produced in 100 m^2 [49].

Alternatively, algae biomass can be obtained from very productive coastal areas, e.g., algae from nutrient-enriched areas due to upwellings, as reported in Brazilian or Southern Iberian Peninsula coasts [35,47]. Haroun et al. [82] also reviewed the potential biotechnological use of Macaronesian seaweeds, either wild-collected or cultivated. In this way, algal blooms and invasive species can be a natural source of MAAs. Some authors studied the possible use of these species as source of bioactive compounds, such as *A. armata*, *Sargassum muticum*, *Caulerpa cylindracea*, *A. vermiculophyllum*, or *Grateulopia turuturu* [83–87]. The utilization of these species presents two opportunities: (1) high availability of biomass and (2) mitigation of their negative effects, through biomass collection, contributing to ecosystem restoration and sustainability. In relation to red algae, Pinteus et al. [85] reviewed different bioactivities of *A. armata* for possible applications, including MAAs, and Felix et al. [86] analyzed the extraction of UV-absorbing and antioxidant compounds from *G. turuturu*. Recently, an extensive guide was published on the biotechnological uses of *Sargassum* spp. accumulated biomass in the Caribbean coast [88].

5. Extraction Methods

To date, little information exists about the optimization of MAA extraction in macroalgae at a significant scale. Most authors extracted MAAs by maceration or sonication in distilled water, ethanol, methanol, or different percentages of methanol/ethanol:water and incubation at low temperature. Some authors compared different solvents and obtained a higher extraction with combinations of methanol/ethanol:water, in comparison with only methanol or ethanol extractions [48,72,77,89,90].

Conventional extraction methods included different cell disruption techniques: (1) mechanical (e.g., mortar and pestle or blender type instrument); (2) thermal (e.g., water bath or oven); and (3) chemical (e.g., acid or alkaline solution). The combination of these methods can increase the yield of the extraction. The type of extraction and the solvent used will be selected depending on the physico-chemical characteristics of the molecule of interest and the purpose for its extraction. For cosmeceutical applications, MAA extraction should be undertaken with so-called green solvents, such as water and ethanol, with low or no toxicity [91,92].

In recent years, novel extraction methods have been developed in an attempt to minimize or eliminate the use of non-renewable and polluting solvents in the extraction process of bioactive compounds. As a result, the use of green solvents has increased, leading to higher quality products, decreasing the formation of by-products, improving the separation of products, and avoiding toxicity [93]. Some authors reviewed the different existing novel extraction techniques that can increase the yield and reduce the time of extraction [94–96]; some of these could be used for MAA extraction due to the application of polar and non-toxic solvents:

Enzyme-assisted extraction (EAE): This method is based on the high specificity and selectivity of enzymes in aqueous solutions. Enzymes (such as carragenases, agarases, or proteases) can degrade the cell wall, releasing the inside bioactive compounds. This technique works under moderate conditions, protecting the molecules of interest from high temperature or acidic/alkaline pH. A disadvantage is the cost of the enzymes, which makes it to scale up the process. EAE has been used in marine organisms to obtain different bioactive compounds, such as polyphenols, fucoidans, carotenoids, and phycobiliproteins [97–102].

Ultrasound-assisted extraction (UAE): This technique uses acoustic waves (20–100 kHz) that travel through the solvent producing cavitation bubbles that can cause cell disruptions. It can be used with a wide variety of solvents, and the temperature during the extraction is relatively low (ice can be used to reduce the temperature). The equipment needed for this extraction is not very expensive, meaning it can be used for large-scale applications. Some studies have indicated that the combination of EAE and UAE generated a synergistic effect, increasing the extraction percentage from 74% to 91%. UAE has been used by

different authors to extract polyphenols, polysaccharides, or phycobiliproteins, among others [99,103,104].

Microwave-assisted extraction (MAE): Microwaves (non-ionizing electromagnetic radiation; 300 MHz–300 GHz) induce vibration of water molecules inside the cell by interacting with the dipole structure of the water molecule. MAE is a cost-effective technique that can use lower solvent amounts and can be combined with other techniques such as UAE. A disadvantage is that MAE is not suitable for heat-sensitive biocompounds. MAE has been used mainly for polyphenol and fucoidan extraction [105,106].

Pressurized liquid extraction (PLE): This technique is performed at high temperature (50–200 °C) and high pressures (10–15 MPa). The main consequences of PLE utilization are increasing mass transfer, and decreasing the surface tension of solvents and viscosity. This technique allows selective extraction, significantly reducing the extraction times and the amounts of solvents used, with water the most used. PLE has been used by several authors to extract polysaccharides, polyphenols, carotenoids, fucoxanthin, fatty acids, and fucosterol [94,107].

Subcritical Water Extraction (SWE): In this extraction method, water remains in a subcritical state (high pressure and temperature conditions), between the boiling point (100 °C at 1 bar) and the critical point (374 °C at 221 bar). It is a simple process, in which the extraction time and the amount of solvent are reduced, and the yield of bioactive substances increases. However, it has an elevated cost for scaling and needs relatively high temperatures. SWE has been used by authors to extract flavanones, fatty acids, carotenoids, phenolic compounds, and sulfated polysaccharides [108–111].

These methods can increase the yield of extraction and reduce time, energy consumption, and waste. The goal of their combination is to determine the optimization of extraction procedures for an industrial application.

6. Characterization, Identification, and Purification of MAAs

Chromatography, mainly high performance liquid chromatography (HPLC) with a photodiode array detector (DAD), is the analytical technique commonly used for the analysis and identification of MAAs. The methodology used can vary depending on the polarity of the MAA (e.g., shinorine, porphyra-334, and myc-2-glycine are MAAs with high polarity, whereas asterina-330, palythine, and usurjirine present a low polarity) [25,112–115]. The most recent methodologies try to evaluate a wide variety of MAAs in different species [72,90,116,117]. However, HPLC methods are not considered sufficient for safe identification due to the lack of commercial MAA standards. Thus, other procedures such as ESI-MS, NMR, or MALDI-TOF/MS, are required [113,118]. The most recently used methods for identification and characterization of MAAs are summarized in Table 1.

Table 1. Summary of the most recently used methodologies for identification and characterization of MAAs. Asterina 330 (A-330); aplysiapalythine A (APA); aplysiapalythine-B (APB); catenelline (CLL); E-palythenic acid (EPA); mycosporine-glycine (M-gly); mycosporine-glycine-alanine (M-gly:a); mycosporine-2-glycine (M-2-gly); mycosporine-methylamine-serine (M-MA:ser); mycosporine methylamine threonine (MM-thr); mycosporine sulfate ester (MSE); mycosporine-serinol (M-ser(OH)); mycosporine taurine (M-tau); porphyra 334 (P-334); palythene (Pe); palythine (Pi); palythine serine (P-ser); palythine-serine sulfate (PSS); palythanol (Ptl); shinorine (SH); shinorine methyl ester (SME); usujirene (Ue); Z-palythenic acid (ZPA). Matrix assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF/MS); Liquid chromatography-tandem mass spectrometry (LC-MS/MS); Nuclear Magnetic Resonance (RMN 1D (one dimension) and 2D (two dimensions)); Quadrupole time-of-flight mass spectrometry (QTOFMS); Electrospray ionization-mass spectrometry (ESI-MS); Liquid chromatography-mass spectrometry (LC-MS); Homonuclear Correlation Spectroscopy (COSY); Hydrophilic interaction liquid chromatography (HILIC); Photodiode-array (PDA); Heteronuclear multiple quantum correlation (HMQC); Hydrogen/Deuterium (H/D).

Species	Type of MAAs	Extraction	HPLC Methodology	Purification	Identification	Ref.
<i>Palmaria palmata</i>	SH, Pi, A-330, P-334, Ue, Pe	<ul style="list-style-type: none"> Extraction in water (6 h, use of methanol to remove impurities) Re-dissolve in 0.1% trifluoro acetic acid (TFA) 	<ul style="list-style-type: none"> Mightysil RP-18GP column (5 μm, 250 \times 10 mm) Eluent A: 0.1% TFA in water, Eluent B: 0.1% TFA in acetonitrile Gradient flow (4.73 mL min⁻¹) 	NO	MALDI-TOF/MS	[119]
Several cyanobacteria: <i>Microcystis panniformis</i> , <i>Nostoc</i> sp., <i>Calothrix</i> sp. or <i>Nodularia spumigena</i> , among others.	SH, P-334, M-glya	<ul style="list-style-type: none"> Extraction in 0.1% formic acid in water + 0.2 mM ammonium formate 	<ul style="list-style-type: none"> Luna C18 column (2) (5 μm, 250 \times 10 mm) Eluent A: 0.2% formic acid in water + ammonium hydroxide (pH 3.15), Eluent B: Milli-Q water/acetonitrile/methanol (8:1:1) + formic acid (pH 2.2), Eluent C: Acetonitrile/methanol (1:1) + 0.1% formic acid Gradient flow (0.5 mL min⁻¹) 	YES	LC-MS/MS	[120]
<i>Agarophyton vermiculophyllum</i> , <i>Gracilaria cornea</i> , <i>Gracilariopsis longissima</i> , <i>Pyropia leucosticta</i>	Pi, A-330, Ptl, SH, P-334, P-ser	Different extraction and re-dissolutions methods: <ul style="list-style-type: none"> Extraction in water:methanol (80:20) and water. Redissolution in methanol, 1.5% methanol and 0.15% acetic acid in water or water 	<ul style="list-style-type: none"> Luna C8 column (5 μm, 250 \times 4.06 mm) Eluent: 1.5% methanol and 0.15% acetic acid in water Isocratic flow (0.5 mL min⁻¹) 	NO	HPLC-ESI-MS	[121]
Several red algae: <i>Asparagopsis armata</i> , <i>Bostrychia scorpioides</i> or <i>Porphyra dioica</i> , among others	SH, Pi, A-300, P-334, Ue, Pe, unknown	<ul style="list-style-type: none"> Extraction in water:ethanol (30:70) (2 h, 45 °C) Redissolve in 2.5% methanol and 0.1% acetic acid in water 	<ul style="list-style-type: none"> Zorbax eclipse XDB C18 column (5 μm, 250 \times 4.6 mm) Eluent: 0.1% acetic acid in water Isocratic flow (1 mL min⁻¹) 	NO	LC-ESI-Q-TOF-MS	[45]

Table 1. Cont.

Species	Type of MAAs	Extraction	HPLC Methodology	Purification	Identification	Ref.
Several red algae: <i>Pyropia columbina</i> , <i>Ceramium</i> sp., <i>Pterocladia</i> sp., or <i>Agarophyton chilense</i> , among others.	SH, Pi, A-330, P-334, M-gly, Ue, Pe, APA, APB, MM-thr, M-gly:a	· Extraction with methanol, followed by three-fold extractions with water:methanol · Redissolve in water	· YMC-Pack ODS column (5µm, 250 × 4.6 mm) · Eluent A: 20 mM ammonium formate and 0.6% formic acid in water. Eluent B: Methanol · Gradient flow (0.65 mL min ⁻¹)	YES	ESI-MS	[122]
<i>Gracilariopsis tenuifrons</i>	A-330, Ptl, Pe, Ue	· Extraction in water:ethanol (30:70) (50 °C, 1 h)	· Zorbax C18 column (250 × 4.5 mm) · Eluent: 0.1 acetic acid in water:acetonitrile (9:1) · Isocratic flow (0.3 mL min ⁻¹)	NO	HPLC-ESI-MS	[72]
Cyanobacteria (<i>Calothrix</i> sp. or <i>Nostoc commune</i> , among others) and <i>Catenella repens</i>	P-334, SH, M-ser (OH), Pi, A-330, CLL	· Extraction in water:methanol (25:75) (45 °C, 2 h)	· HILIC Columns type (3.5 µM, 150 × 4.6 mm) · Eluent A: water:acetonitrile (9:1). Eluent B: 5 mM Ammonium Acetate (pH = 6.6) · Gradient flow (50 µL min ⁻¹)	YES	HPLC, HILIC, LC-MS, RMN, ESI-MS	[118]
<i>Porphyra yezoensis</i>	P-334	· Extraction with methanol/water (80:20) (45 °C, 2 h)	· Gemini-NX 5 µ C18 Column (250 × 21.2 mm) · Eluent: 0.1% acetic acid in water · Isocratic flow (30 mL min ⁻¹)	YES	ESI-MS	[123]
<i>Gloeocapsa</i> sp.	SH, M-307	· Extraction with methanol (4 °C, 12 h)	· ODS-3 RP-18 Column (5 µm, 250 × 4 mm). · Eluent: 25% methanol + 0.1% acetic acid. · Isocratic flow (1 mL min ⁻¹)	YES		[124]
<i>Palmaria palmata</i>	Pi, SH, A-330, Ptl, P-334, Ue	· Hydration + extraction in methanol (sonication bath 5 min)	· Inertsil ODS-3 column (5µm, 250 × 4.6 mm) · Eluent A: 0.2% formic acid in water. Eluent B: 0.2% formic acid in acetonitrile · Gradient flow (1 mL min ⁻¹)	NO	ESI-MS	[125]

Table 1. Cont.

Species	Type of MAAs	Extraction	HPLC Methodology	Purification	Identification	Ref.
<i>Prasiola crispa</i> , <i>Porphyra umbilicalis</i>	Pi, SH, P-334	· Extraction with methanol:water (25:75), (45 °C, 2 h) followed by redissolve in 100% methanol, 100% water or (2.5:97.5) Methanol: Water	· Three different columns: Synergi Fusion RP-18 (4 µm, 250 × 3.0 mm I.D.); Sphercclone ODS (RP-8) (5 µm, 250 × 4.6 mm I.D); Luna C8 (5 µm, 250 × 4.6 mm I.D) · Eluent: 2.5% methanol in water + 0.1% acetic acid in water. · Isocratic flow: (0.7 mL min ⁻¹ with Sphercclone) (0.5 mL min ⁻¹ whit Synergi and Luna)	NO		[126]
<i>Neopyropia elongata</i> , <i>Gelidium corneum</i> , <i>Ahnfeltiopsis devoniensis</i> and <i>Lichina pygmaea</i>	P-334, SH, A-330, Pi, M-gly	Extraction with methanol:water (20:80), (45 °C, 2 h) followed by redissolve in 100% methanol.	· C8 column (5 µm, 250 × 4.0 mm) · Eluent: 2.5% methanol in water + 0.1% acetic acid in water. · Isocratic flow (0.5 mL min ⁻¹)	YES		[127]
<i>Aphanizomeno flos-aquae</i>	P-334	Extraction with methanol/water (80:20) followed by Chloroform. Redissolve in 80% Methanol.	· C18 column (7 µm, 300 × 7.8 mm) · Eluent A: (10:90) Methanol:Ethanol; Eluent B: (90:10) Methanol: Ethanol. · Gradient flow	YES	1D/2D NMR, Q-TOF-LC-MS, COSY, HMQC	[128]
<i>Agarophyton tenuistipitatum</i>	Pi, A-330, Ptl, SH	· Extraction in water:methanol (1:1) (30 min sonication/24 h at 4 °C) · Redissolve in 0.2% acetic acid in water	· Phenomenex Luna C18 (5 µm, 250 × 10 mm) · Eluent: 0.2% acetic acid in water · Isocratic flow (4.7 mL min ⁻¹)	NO	ESI-MS/MS, ESI-Q-TOF-MS, HDX-ESI-MS	[129]
Different marine organisms (Red algae: <i>Palmaria decipiens</i> , <i>Porphyra columbina</i> and liophylized <i>Porphyra</i> sp. (Nori))	PSS, SH, M-2-gly-, MSE, P-ser, Pi, A-330, P-334, M-MA:ser, M-gly, Ptl, ZPA, SME, EPA, MM- thr, M-tau, Ue, Pe, M-320, M335/360	· Extraction in water:methanol (75:25) (2 h, 45 °C, 3 times) · Redissolve in 0.2% TFA and ammonium hydroxide (pH 3.15)	· Two C18 columns in tandem: Alltima (5 µm, 150 × 4.6 mm) and CapCell Pak UG (5 µm, 250 × 4.6 mm) · Eluent A: 0.2%TFA and ammonium hydroxide in water (pH 3.15). Eluent B: eluent A (pH 2.2):methanol:acetonitrile (80:10:10) · Gradient flow	NO	LC/MS	[90]

Table 1. Cont.

Species	Type of MAAs	Extraction	HPLC Methodology	Purification	Identification	Ref.
<i>Pyropia columbina</i>	M-gly, SH, P-334, Pi, A-330	· Extraction in water:methanol (80:20) (2 h, 45 °C) · Redissolve in methanol	· Spherclone C8 column (5 µm, 250 × 4.6 mm) · Eluent: 2.5% methanol + 0.1% acetic acid in water · Isocratic flow (0.5 mL min ⁻¹)	NO		[77]
<i>Crassiphycus corneus</i>	SH, P-334	· Extraction in water:methanol (80:20) (2.5 h, 45 °C) · Redissolve in methanol	· LiCrospher RP 18 column (5 µm, 250 × 4 mm) · Eluent: 0.2% acetic acid in water · Isocratic flow (1 mL min ⁻¹)	NO		[130]
<i>Chondrus crispus</i>	Pi, SH, Ptl, Pe	· Extraction in water:methanol (75:25) (2 h, 45 °C) · Redissolve in methanol	· Spherisorb RP 8 column (5 µm, 250 × 4 mm) · Eluent: 25% met + 0.1% acetic acid in water · Isocratic flow (0.7 mL min ⁻¹)	NO		[131]

Chromatography is a general analytical technique used to separate a mixture into its individual components. In relation to the MAA purification process, there are different approaches depending on the chemical characteristics and the aim. In the case of its use for cosmeceutical products, the ideal is an extraction and purification free of hazardous solvents for the environment and health, which increases the biocompatibility and safety of the final product. However, to date, very few methodologies use green solvents for the identification and purification of MAAs. This indicates an opportunity to explore new methodologies and techniques for the identification and purification of these molecules with green solvents [121,132–134]. It is important to note that there are different criteria and legislations for the selection of green solvents, for which some solvents, such as alcohols of methanol or propanol type, are allowed in low amounts depending on the legislation (e.g., European Chemicals Agency, ECHA).

In recent decades, different authors have attempted to purify MAAs. The different strategies vary from simple columns of a resin that are not automated to highly complex systems as UHPLC coupled to a fraction-collection device or liquid-liquid chromatography. Torres et al. [128] purified the MAA porphyra-334 using a silica gel column. A methanolic extraction was chromatographed on a silica gel column using a gradient of ethanol and methanol as eluent. De la Coba et al. [127] isolated porphyra-334, shinorine, asterine-330, and palythine using adsorption and ionic exchange chromatography. First, the MAA extractions were blended with activated charcoal (adsorption) and eluted with methanol:water (1:1). The fraction obtained was dried, re-dissolved in distilled water, and passed through a Dowex 50 W-X8 (H⁺ form; 50–100 µm mesh) ion exchange column. To separate porphyra-334 and shinorine, distilled water was used as eluent, whereas to separate asterina-330 and palythine, the authors used a gradient of distilled water and 0.35 M HCl. Roullier et al. [135] isolated mycosporine-serinol using centrifugal partition chromatography (CPC). A system composed of n-butanol, acetic acid, and water (4:1:5, *v/v/v*) was used. Ryu et al. [123] also purified the MAA porphyra-344. An aqueous-methanolic extract (water:methanol; 4:1) was dried, redissolved in ultrapure water, and transferred to a separating funnel containing chloroform-methanol-ultrapure water. The water fraction, called the crude MAA fraction, was identified through LC/MS. Hartmann et al. [118] also used a Dowex column (50 WX H⁺ form, 100–200 µm mesh) to obtain a MAA-enriched fraction, as a pre-purification step. The purification was realized by semi-preparative HPLC with a Lichrosorb C18 100 Å column (7 µm, 200 × 10 mm) and a mobile phase containing 0.1% acid acetic in water (A) and acetonitrile (B). Boulhbo et al. [136] also used CPC for fractioning of UV-B absorbing molecules. More recently, Orfanoudaki et al. [122] described the purification of 11 MAAs, using a combination of silica gel column chromatography, flash chromatography, semi-preparative HPLC on diverse stationary phases, and fast centrifugal partition chromatography (FCPC). Geraldès et al. [124] purified porphyra-334, shinorine and mycoposrine-glycine-alanine using a semi-preparative HPLC with a Luna C18 column (5 µm, 250 × 10 mm) and a fraction collector. As mobile phase the authors used a gradient of: (A) 0.2% (*v/v*) formic acid solution + ammonium hydroxide (pH 3.15); (B) Milli-Q water/acetonitrile/methanol (8:1:1) + formic acid (pH 2.20); and (C) acetonitrile/methanol (1:1) + 0.1% (*v/v*) formic acid (phase C). The MAAs were quantified and the method validated by LC-MS/MS.

Semi-preparative and preparative HPLC are the methods associated with scaling up the purification of small molecules. With bigger columns and a higher flow than analytic HPLC, it is possible to obtain a higher amount of these molecules with a high degree of purity. However, the cost of the equipment still limits its widespread use [137]. Alternatively, liquid-liquid chromatography (such CPC) is a very attractive method used for separation of different natural molecules, due to its capacity to be scaled up. This technique presents various advantages in comparison with HPLC, including: (1) no use of columns with solid phase; (2) high loading capacity; (3) total recovery of the injected sample; (4) low risk of sample denaturalization; (5) low solvent consumption [138,139].

7. MAA Bioactivities

Considering the ability of MAAs to absorb light between 310 and 360 nm, which comprises the UV-B and UV-A spectrum, numerous studies have focused on their potential for the development of natural sunscreens. UV radiation also induces high production of reactive oxygen species (ROS) that can promote other effects, such as premature skin aging or immunosuppression. Thus, photoprotection also involves other bioactivities such as antioxidant, immuno-modulatory, or anti-aging properties [41,140,141] (Figure 5).

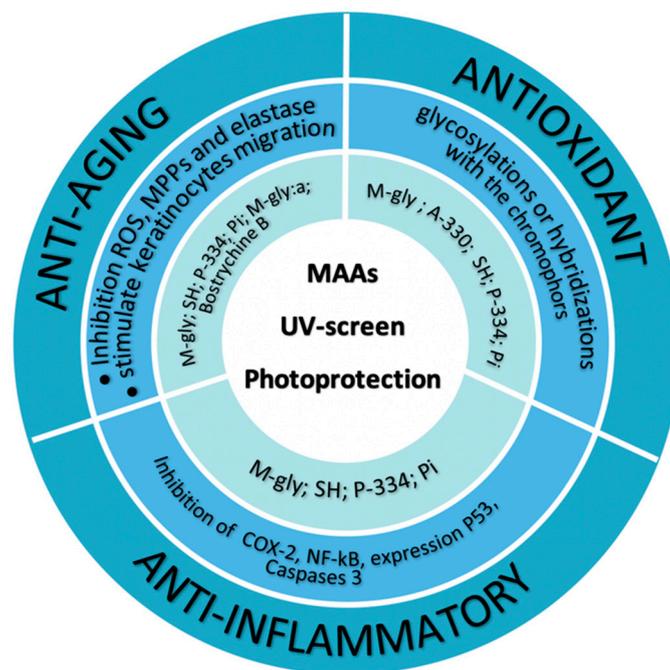


Figure 5. Scheme of the different bioactivities described in MAAs, indicating the relevance of some MAAs [33,41,47,123,127,142–155].

Several authors analyzed the potential antioxidant activity of MAAs *in vitro*. Wada et al. [41] reviewed the molecular diversity of MAAs and their antioxidant activities. De la Coba et al. [127] evaluated, using different methods, the antioxidant potential of different MAAs (mycosporine, asterine-330, shinorine, and porphyra-334). The authors found that the antioxidant activity of all MAAs depended on the dose and pH, with greater activity in alkaline pH. Mycosporine-glycine showed the highest activity in all pH tested. This MAA had previously shown concentration-dependent antioxidant potential [142]. More recently, Torres et al. [143] observed high antioxidant activity in some imino-MAAs (palythine, asterina-330, shinorine, or porphyra-334) under alkaline pH. However, they also found pro-oxidant effects in some of these MAAs. Most of the studies concluded that MAAs can eliminate ROS *in vitro*, although the role of these molecules *in vivo* is not yet fully understood. In addition, the antioxidant activity of MAAs can also increase due to changes in the molecules such as glycosylations or hybridizations with the chromophors [41].

A high production of ROS can also cause elastic fiber dystrophy and secretion of elastases, which activate matrix metalloproteinases (MMPs). MMPs and elastases degrade collagen and elastin fibers, respectively. The reduction of collagen and elastin leads to the formation of wrinkles and accelerated aging [144]. For this reason, MAAs that prevent ROS production and activation of MMPs have high potential to prevent photoaging. Ryu et al. [123] studied the anti-photoaging role of the MAA porphyra-334. This MAA reduces the reactive oxygen species (ROS) production and the levels of matrix metalloproteinases (MMPs) in human fibroblasts exposed to UV-A. Hartmann et al. [145] also demonstrated the inhibition of metalloproteinases by porphyra-334, shinorine, and paly-

thine. Orfanoudaki et al. [146] investigated the collagenase inhibition activity of different isolated MAAs. The authors proved the collagenase inhibition activity for all MAAs, and the inhibition of glycation end products in most of MAAs, which is a property that prevents a decrease in skin elasticity. They also evidenced the ability of shinorine, porphyra-334, mycosporine-glycine-alanine, and bostrychine B to stimulate human keratinocyte migration in vitro, indicating a wound-healing property.

Oxidative stress can also activate various biochemical pathways related to immunomodulatory activities. In UV-induced inflammation, cyclooxygenase-2 (COX-2) mRNA is overexpressed. Some MAAs have the potential to suppress this gene, such as mycosporine-glycine [147]. According to Lawrence et al. [33], the expression of COX-2 appears to be linked to shorter UV wavelengths. Thus, MAAs that absorb shorter wavelengths, such as mycosporine-glycine and shinorine, would be more effective in inhibiting COX-2. Exposure to UV radiation can also activate the nuclear transcription factor- κ B (NF- κ B), which regulates the expression of pro-inflammatory molecules. Tryptophan metabolism is also involved in immunoregulation, and its breakdown and availability depend on an IDO-1 enzyme. NF- κ B and IDO-1 appear to be affected by antioxidant molecules. Becker et al. [148] evaluated the influence of shinorine and porphyra-334 on NF- κ B activation and tryptophan metabolism. In spite of the similar structure of both MAAs, diverse effects were observed, i.e., both MAAs were able to induce NF- κ B activity in unstimulated THP-1-Blue cells, whereby the increase was dose-dependent and more pronounced with shinorine treatment. Although shinorine also slightly superinduced NF- κ B in LPS-stimulated cells, porphyra-334 reduced NF- κ B activity in this inflammatory background.

Different authors analyzed the capacity of algae extracts and creams that contain algae extracts to absorb UV radiation, measuring the in vitro sun protection factor (SPF). De la Coba et al. [149] formulated three different galenic formulations that contain around 5% of different MAAs and measured the SPF, obtaining values that varied from 4.5 to 8.3, depending on the type of MAAs. Because erythema is not the only effect of the UV radiation on the skin, the authors proposed the calculation of protection factors against other biological effects (such immunosuppression, photoaging, or DNA damage), named biological effective protection factors (BEPFs). Other authors studied the SPF of concentrated algae extracts. *Gracilariopsis longissima* extract with a MAA content of 1.6 mg g⁻¹ DW, showed SPF values between 2 and 7.5, depending on the biomass concentration [150], whereas *Porphyra umbilicalis* extract with a much higher MAA content (10 mg g⁻¹ DW) reached an SPF value of 18 in the highest concentration [47]. These authors also proposed another index to measure photoprotection, the effective solar absorbed radiation (ESAR), that measures the percentage of effective solar radiation against any biological effect that can be absorbed by a cream. However, the values obtained from extracts are not applicable in practice due to the dilution needed to be incorporated in the lotions.

The photoprotective capacity has also been demonstrated in vivo, on mouse skin. Studies demonstrated that MAAs can prevent UV-induced skin damage, inhibiting the expression of p53 and caspase-3 (protein indicators of apoptosis), increasing the antioxidant enzymes activities, and inhibiting inflammation [151–153]. Lawrence et al. [154] observed that the MAA palythine (even at low concentration) also reduces the damage caused by UV radiation in human keratinocytes. Rui et al. [155] also observed that MAAs can reduce photoaging induced by UV radiation in mouse skin, by interfering with collagen metabolism. Treatment with MAAs inhibited collagen degradation by the MMPs and promoted collagen synthesis.

8. Commercial Applications

As previously mentioned, numerous studies suggest the use of MAAs as UV screen substances [23,33,41,146]. However, at present, few products based on MAAs and/or red algae extracts are commercially available.

Helioguard™365 is a natural UV-screening active principle based on MAAs from *Porphyra umbilicalis*, commercialized by the Mibelle group. This product has been demon-

strated to exhibit photoprotective properties against UV-A radiation and presents other beneficial effects for the skin, such as inhibition of lipid peroxidation, and improvement of the firmness and smoothness. Helionori[®] is another active ingredient based on a MAA-enriched extract from *Porphyra umbilicalis* commercialized by the Gelyma company. It can act as a natural UV-A photoprotector, prevents the formation of sunburn cells, protects cell metabolism against UVA irradiation, and protects DNA and cell membranes against UV-A. Ronacare[®] RenouMer is also a commercial active principle based on *Polysiphonia elongate* extracts, which can reduce skin roughness, present anti-wrinkle effects, and improve skin hydration.

The sunscreen commercialized with the name ALGA MARIS[®] (Laboratoires Biarritz, Biarritz, France) contains *Gelidium corneum* extracts (Alga-Gorria[®]) enriched in oligoelements and antioxidants such as flavonoids or carotenoids. This sunscreen is a combination of physical filters that protect against UV-B and UV-A radiation, and Alga-Gorria[®], an algal extract that neutralizes the free radicals and protects against premature skin aging.

9. Conclusions and Future Perspectives

In the near future, the use of MAAs in cosmeceutical products is expected to increase due to their excellent properties as natural UV photoprotectors, such as high photo- and thermo-stability, and the lack of oxidant photoproducts after UV absorption. MAAs also present other interesting bioactivities for the skin, such as antioxidant and anti-inflammatory properties, protection of collagen and elastin by the inhibition of collagenase and elastase, and DNA protection by reducing dimer production. The significant diversity of cosmeceutical properties of MAAs has attracted the attention of the scientific community and companies, as observed in the large number of reviews and book chapters published in recent years [1,23,33,41,69,140,156,157].

The limitation of available biomass to extract MAAs can be addressed by culturing macroalgae in N-enriched waters originating from fishpond effluents (IMTA systems) or using invasive species that contain MAAs. In addition, the application of photobiological treatments in algal culture, such as UV-Blue radiation treatments, can substantially increase the MAA content. Finally, it is expected that new advances in extraction and purification techniques will reduce the cost of production of MAAs for use in cosmeceutical products (Figure 1).

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