

Algal nutraceuticals: A perspective on metabolic diversity, current food applications, and prospects in the field of metabolomics

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ABSTRACT

The current consumers' demand for food naturalness is urging the search for new functional foods of natural origin with enhanced health-promoting properties. In this sense, algae constitute an underexplored biological source of nutraceuticals that can be used to fortify food products. Both marine macroalgae (or seaweeds) and microalgae exhibit a myriad of chemical constituents with associated features as a result of their primary and secondary metabolism. Thus, primary metabolites, especially polysaccharides and phycobiliproteins, present interesting properties to improve the rheological and nutritional properties of food matrices, whereas secondary metabolites, such as polyphenols and xanthophylls, may provide interesting bioactivities, including antioxidant or cytotoxic effects. Due to the interest in algae as a source of nutraceuticals by the food and related industries, novel strategies should be undertaken to add value to their derived functional components. As a result, metabolomics is considered a high throughput technology to get insight into the full metabolic profile of biological samples, and it opens a wide perspective in the study of algae metabolism, whose knowledge is still little explored. This review focuses on algae metabolism and its applications in the food industry, paying attention to the promising metabolomic approaches to be developed aiming at the functional characterization of these organisms.

1. Introduction

In the last years, the worldwide population has been reflecting a changing paradigm in which an increasing consumer awareness is driven by skepticism towards synthetic chemical additives, together with an emerging preference for the consumption of natural-based products. On these bases, the food industry has been forced to explore new natural sources with a dual aim: i) replacing the classically applied synthetic ingredients with natural compounds; and ii) providing an additional value to the associated biological properties of such natural compounds, commonly known as nutraceuticals, with a special focus on both food quality and human health. Thus, plants have been traditionally exploited as a natural source of bioactive compounds to be used as nutraceuticals to design functional foods. However, additional resources from marine ecosystems are still receiving little attention as promising

sources of nutraceuticals, as in the case of algae.

In Eastern countries, algae have been used since ancient times to treat several diseases, ranging from wound healing and infections to chronic diseases, as well as a common ingredient in their gastronomy. In contrast, their exploitation in Western countries has been restricted to specific coastal areas. For that reason, Asia represents the 97.4 % share of worldwide seaweed production, reaching ~35 tonnes in 2019, being China and Indonesia the major producers, followed in the distance by South America (<1.5 %) and Europe (<1%), according to the latest report by the Food and Agriculture Organization (FAO, 2021). Consequently, there is an urgent need for the valorization of algae in Western countries, where their production is still considered as an emerging sector belonging to the so-called blue bioeconomy. The promising perspectives on the large-scale exploitation of algae involve their incorporation into economically relevant activities, including not only those

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related to the food industry but also the cosmetic and pharmaceutical industries (Araújo et al., 2021).

Thousands of algal species are found all over the marine surface of the planet, classified into two essential groups according to the complexity of their biological organization degree: macroalgae, also known as seaweeds, and microalgae. Macroalgae are macroscopic, multicellular organisms commonly found around the seabed, which are classified into three different groups or phyla according to the principal pigmentation, with more than 40,000 species described to date: green algae (Chlorophyta), including ~1200 species; red algae (Rhodophyta), with up to 6,000 species; and brown algae (Ochrophyta, class Phaeophyceae), accounting for ~1750 species (Aryee et al., 2018). In contrast, microalgae are microscopic, unicellular organisms distributed equally between freshwater and marine ecosystems, accounting for up to 800,000 species from which only 50,000 have been described, including cyanobacteria (Suganya et al., 2016). Among them, seaweeds present a higher prevalence in the industry, covering two thirds of the companies belonging to the European algae sector (Araújo et al., 2021). The most relevant seaweed species commercially exploited are the brown *Laminaria* and the red *Euchema* species, with more than 10 million tonnes produced yearly, followed by the red *Gracilaria* and *Porphyra* species and the brown *Undaria* species (FAO, 2021). In the case of microalgae, *Spirulina* spp. stands out as the most prevalent microalgal species used industrially, being followed to a much lesser extent by other species, such as those from *Arthrospira*, *Chlorella* and *Nannochloropsis* genera (Araújo et al., 2021).

The consideration of algae as natural sources of nutraceuticals for the food industry is a consequence of the biosynthesis of a wide range of chemicals resulting from their versatile metabolism. Since they are considered the phylogenetic ancestors of land plants, algae present a dual metabolism. Primary metabolism is devoted to life maintenance, cell structure and integrity, survival, nutrition, and reproduction. Thus, primary metabolites are represented by different macromolecules: carbohydrates; especially polysaccharides; proteins and derived peptides and amino acids; lipids; and pigments. In parallel, secondary metabolism aims to defend against external threats and adapt to environmental conditions, such as light intensity, CO₂ concentration, salinity, or heat. Consequently, secondary metabolites are considered as organic low-molecular weight compounds of different biosynthetic origins, mostly represented by phenolic compounds, alkaloids, and terpenoids. Due to their role in defense and adaptation, these compounds present a plethora of associated biological activities, acting as antioxidant, antimicrobial, anti-inflammatory, anticancer, antidiabetic, anti-obesity, cardioprotective, neuroprotectant, hepatoprotective, and anti-ageing agents (Tanna & Mishra, 2018). On these bases, algae are recognized as promising sources of nutraceuticals, promoting the transference of value-added properties to food matrices, thus contributing to the design of functional foods with enhanced organoleptic and/or health-promoting profiles.

The existence of countless algal species and their great chemical diversity make searching for novel bioactive compounds difficult and time-consuming. In response to this paradigm, the application of novel high throughput technologies, especially metabolomics, opens a wide perspective on the fingerprinting and characterization of algal metabolites facing their industrial application. In this work, a systematic characterization of the chemical composition of algae is reviewed, as well as different applications developed in the food industry, together with a deep insight into the potential application of metabolomics as a powerful tool to identify and characterize novel nutraceuticals of natural origin.

2. Algae as a natural source of nutraceuticals

Algae constitute a rich and heterogeneous source of both primary and secondary metabolites, exhibiting various associated properties and biological activities. Both primary and secondary metabolites are found

in a phylum and even species-dependent manner in seaweeds, but their production is also highly dependent on external factors, including harvesting location and season, as well as multiple environmental stimuli, due to their central role in adaptation and defensive responses. Indeed, the production of metabolites by macro- and microalgae has prompted their large-scale exploitation as biofactories of biologically active compounds in different sectors, such as the food, pharmaceutical, bio-energy and cosmetic industries (Fig. 1). Fig. 2 includes an overview of the most relevant metabolites biosynthesized from algal sources.

2.1. Primary metabolites

Concerning primary metabolism, the composition of algae is basically composed of carbohydrates, mainly represented by polysaccharides; proteins, bioactive peptides and mycosporine-like amino acids; and lipids, together with other compounds, such as minerals and vitamins, considered as micronutrients found in very scarce concentrations. The chemical composition of algae shows a species-dependent occurrence. However, general trends are found as a function of different seaweeds families, showing that carbohydrates are the most prevalent compounds in all cases, especially in red algae with carbohydrate proportions of >71 %, whereas green seaweeds present higher protein concentrations (>30 %), and brown algae show the highest rates of minerals up to 15 %; on the contrary, the lipid content of seaweeds is found to be similar for all families, ranging from 3.8 % to 4.5 % (Salehi et al., 2019). Table 1 shows the chemical composition of relevant edible seaweeds and microalgae, commercially exploited in the food industry.

2.1.1. Carbohydrates

Carbohydrates constitute the most important family of primary metabolites from algal sources, achieving the highest concentrations of chemical components. The properties attributed to algal polysaccharides depend on a series of factors related to their structural characteristics that present complex interactions, i.e.: sulfatation degree, the position of sulfated residues, monosaccharidic composition, and molecular weight (Berthon et al., 2017). In particular, sulfated polysaccharides represent the highest proportion of this family as they are the major constituents of algal cell walls, found to a greater extent in the genera *Ascophyllum*, *Porphyra*, and *Palmaria* (Biris-Dorhoi et al., 2020), being alginate, agar and carrageenan the major compounds of marine seaweeds (Ścieszka & Klewicka, 2019). Nevertheless, a differential composition of polysaccharides as part of cell walls is found according to different phyla.

Ulvans are the major constituents of green algae cell walls, reaching an 8 – 29 % of total dry weight (Vera et al., 2011), together with other polysaccharides reported to a lesser extent, as is the case of rhamnans and galactans (Zollmann et al., 2019). Ulvans are soluble sulfated polysaccharides formed by the polymerization of heterogeneous disaccharidic units containing sulfated rhamnose bound to other residues, such as uronic acid, guluronic acid, or xylose, mostly found in the cell walls of algae belonging to *Ulva* sp. (Olatunji, 2020). On the other hand, rhamnans, essentially isolated from *Monostroma* sp., include dimers of L-rhamnose as their common scaffold subunits. In contrast, galactans are particularly found in the cell walls of *Codium* sp., presenting high proportions of galactose subunits within their structure (Cho & You, 2015). Concerning their functionality as bioactive compounds, sulfated polysaccharides from green algae have been found to exert a multifaceted mechanism of action, acting as antioxidant, immunomodulatory, anti-coagulant, antihyperlipidemic, anticancer, and antiviral agents (Cho & You, 2015).

In the case of red seaweeds, galactans are the most prevalent polysaccharides, mainly represented by carrageenans that suppose the 30 – 75 % of total dry weight, followed by agarans and porphyrans (Vera et al., 2011; Yermak et al., 2017). Several families of red seaweeds are considered major sources of these compounds, including species from *Euchema*, *Gigartina*, *Condrus* and *Hypnea* genera. Carrageenans are linear

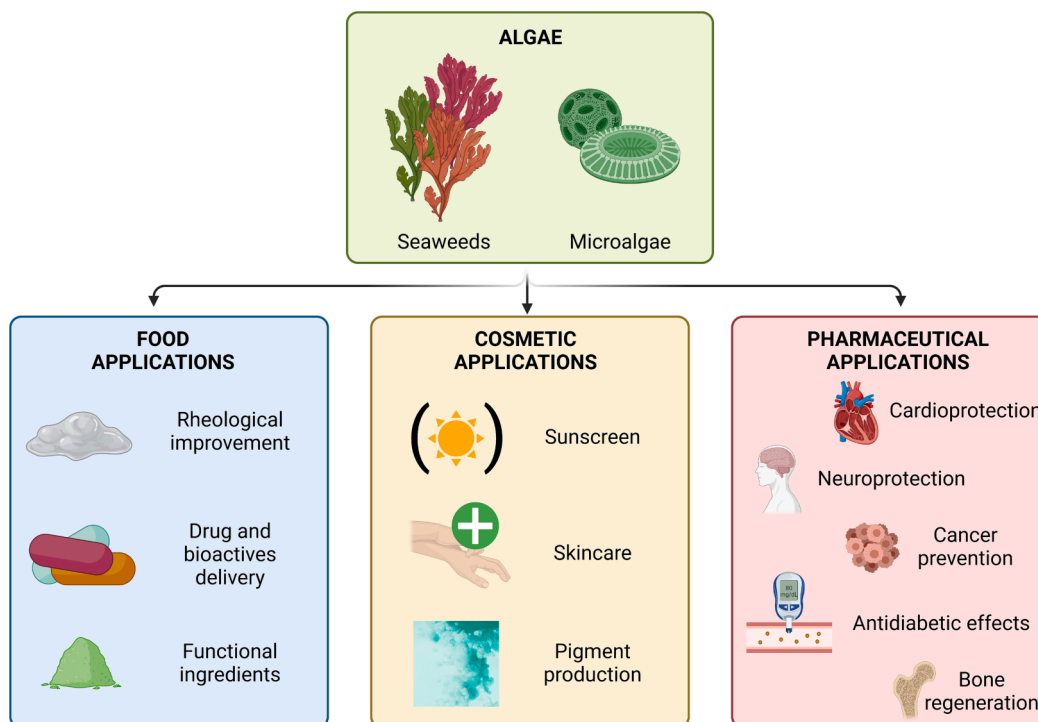


Fig. 1. Current industrial applications of seaweeds and microalgae in different sectors.

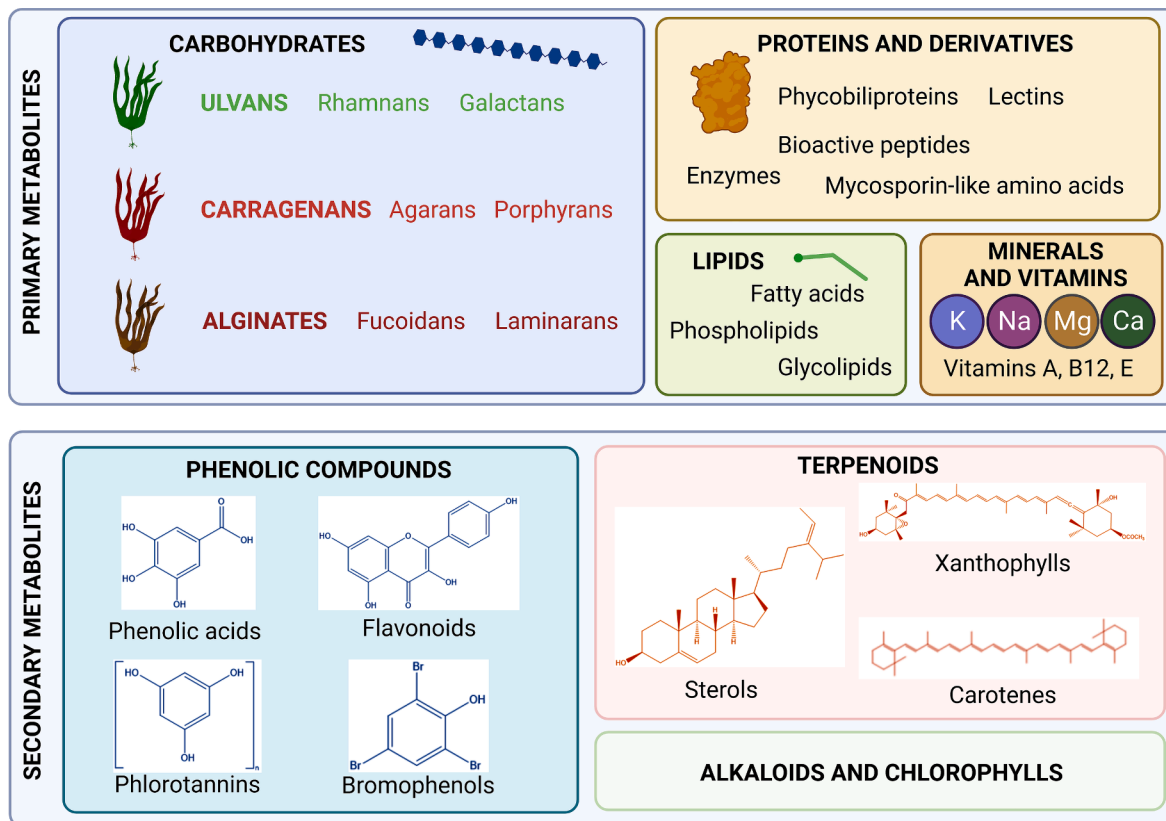


Fig. 2. Overview of the metabolic diversity of chemical constituents of marine seaweeds and microalgae.

sulfated polysaccharides formed by the condensation of different sub-units of carrabiose disaccharides and, among them, κ -, ι -, and λ -carrageenans have gained much attention in different industrial sectors, mostly food industry, due to their high molecular weight that confers

their associated high viscosity and gelling properties (Yermak et al., 2017). Concerning their structure, carrageenans are characterized by two specific features: they present differential monomer constituents, as is the case of 3,6-anhydro-D-galactose, a characteristic residue of κ - and

Table 1
Chemical composition of commercially important edible seaweeds and microalgae.¹

Family	Species	Carb	Proteins	Lipids	Mins	Ref.	
Chlorophyta	<i>Caulerpa lentillifera</i>	38.7	10.4	1.1	13.0	(Matanjun et al., 2009)	
	<i>Codium tomentosum</i>	32.8	18.8	3.6	5.3	(Rodrigues et al., 2015)	
	<i>Enteromorpha compressa</i>	47.0	17.5	3.6	11.8	(Ganesan et al., 2014)	
	<i>Ulva lactuca</i>	55.5	8.5	7.9	7.9	(Yaich et al., 2011)	
	<i>Ulva rigida</i>	42.6	17.8	0.9	0.03	(Taboada et al., 2010)	
Rhodophyta	<i>Chondracanthus teedei</i>	56.0	11.4	1.4	3.4	(Pacheco, Cotas, et al., 2021)	
	<i>Chondrus crispus</i>	53.3	26.4	1.0	25.1	(Parjikolaei et al., 2016)	
	<i>Euchema cottonii</i>	26.5	9.8	1.1	16.3	(Matanjun et al., 2009)	
	<i>Gracilaria gracilis</i>	46.6	20.2	0.6	0.7	(Rodrigues et al., 2015)	
	<i>Grateloupia turuturu</i>	43.2	22.5	2.2	0.3	(Rodrigues et al., 2015)	
	<i>Hypnea musciformis</i>	20.6	18.6	1.3	–	(Siddique, 2013)	
	<i>Kappaphycus alvarezii</i>	25.9	19.3	0.6	14.3	(Suresh Kumar et al., 2015)	
	<i>Osmundea pinnatifida</i>	32.4	23.8	0.9	–	(Rodrigues et al., 2015)	
	<i>Palmaria palmata</i>	71.0	26.4	1.2	11.9	(Parjikolaei et al., 2016)	
	<i>Porphyra</i> spp.	36.8	43.0	0.5	2.5	(Admassu et al., 2018)	
	<i>Pterocladia capillacea</i>	9.6	22.6	2.2	8.6	(Wassef et al., 2013)	
	Ochrophyta	<i>Bifurcaria bifurcata</i>	9.7	8.9	6.5	12.8	(Lorenzo et al., 2017)
		<i>Ecklonia radiata</i>	66.9	9.6	1.8	0.2	(Smith et al., 2010)
<i>Fucus spiralis</i>		17.0	4.1	11.5	–	(Paiva & Lima, 2018)	
<i>Himanthalia elongata</i>		58.4	11.8	0.63	12.2	(Cofrades et al., 2010)	
<i>Laminaria ochroleuca</i>		56.7	12.8	0.5	3.4	(Pacheco, Miranda, et al., 2021)	
<i>Saccharina latissima</i>		46.1	10.6	–	10.1	(Stévant et al., 2017)	
<i>Saccorhiza polyschides</i>		6.3	7.3	8.2	14.8	(Garcia et al., 2016)	
<i>Sargassum</i> sp.		14.2	9.9	2.5	23.9	(Vázquez-Delfín et al., 2021)	
<i>Undaria pinnatifida</i>		50.4	19.7	3.3	9.2	(Smith et al., 2010)	
<i>Arthrospira platensis</i>		6.5	76.7	2.5	–	(Seghiri et al., 2019)	
<i>Chlorella protothecoides</i>		24.9	40.0	16.2	–	(Kent et al., 2015)	
<i>Dunaliella</i> sp.		14.6	34.2	14.4	–	(Kent et al., 2015)	
<i>Euglena gracilis</i>		16.0	50.0	30.0	–	(Koyande et al., 2019)	
Microalgae	<i>Microchloropsis gaditana</i>	25.7	47.0	16.5	10.1	(Zanella & Vianello, 2020)	
	<i>Nannochloropsis</i> sp.	9.6	30.3	21.8	–	(Kent et al., 2015)	
	<i>Scenedesmus</i> sp.	27.7	31.0	15.1	–	(Kent et al., 2015)	

¹ Values are displayed as g of component per 100 g of dry matter. Carb.: Carbohydrates; Mins: Minerals.

-carrageenans, which is absent in the structure of λ -carrageenans. Furthermore, they also differ by the presence of sulfate groups, exhibiting one, two or three groups within the structure of κ -, ι -, and λ -carrageenans, respectively (Lipinska et al., 2020). Regarding their role as bioactive compounds, multiple bioactivities are attributed to carrageenans, including antioxidant, antimicrobial, antiviral, and anticoagulant properties (Yermak et al., 2017).

Besides carrageenans, agarans and porphyrans are secondary polysaccharides also found in red seaweeds. Structurally, agarans are sulfated galactans formed by the condensation of 3-linked β -D-galactose and 4-linked α -L-galactose subunits, although they may present different degrees of complexity and substitution patterns (Ciancia et al., 2020). Among them, the most common representative is agar, commonly extracted from a plethora of sources, including species from Gelidiales, Gracilariales, and Ahnfeltiales orders (Ciancia et al., 2020). On the other hand, porphyrans constitute another relevant family of sulfated galactans from red algae, especially *Porphyra* species. These polysaccharides are characterized by the presence of intermittent 1,4-linked α -L-galactose-6-sulfate and 1,3-linked β -D-galactose. They have gained much attention because of their biological functions as antioxidants, anticancer, anti-allergic, and anti-aging agents (Qiu et al., 2021).

Considering brown seaweeds, these organisms present a heterogeneous polysaccharide composition, presenting alginates, fucoidans and laminarans as major constituents of their cell walls, where they represent 17–45 %, 5–20 %, and < 35 % of the total dry weight, respectively (Vera et al., 2011). Alginates form the most abundant family of marine biopolymers, predominantly isolated from *Ascophyllum*, *Laminaria*, *Lessonia*, and *Macrocystis* genera (Leandro et al., 2020). They contain two structural residues: α -L-guluronic and β -D-mannuronic acid, exhibiting a mode of action similar to that of dietary fibers, including the enhancement of digestibility and anti-obesity effects (Gabbia & Martin, 2020). Fucoidans are another specific family of polysaccharides from brown seaweeds, whose structure is essentially based on L-fucose as the major

monomer (ranging from 40 % to 80 % of total monosaccharide subunits), together with other residues found to a much lesser extent. Among species, *Saccharina* sp. and *Fucus* sp. have been recently identified as the most prevalent sources, showing significant antioxidant, immunomodulatory and anticoagulant activities (Bittkau et al., 2020). Finally, laminarans exhibit lower molecular weights compared to other sulfated polysaccharides, also known as ramified β -1,3-glucans, due to their monomeric organization and the presence of different oligomeric branches (Otero et al., 2021). Among them, laminarin stands out as the most prevalent storage polysaccharide from brown seaweeds due to the ramified nature of this molecule that facilitates the formation of molecular webs, being found in *Laminaria* species, mainly (Vera et al., 2011).

Concerning microalgae, sulfated polysaccharides are also the most prevalent polysaccharides with largely described applications in the food, feed, and pharmaceutical industries, thanks to their associated bioactivities (Saide et al., 2021). Indeed, polysaccharides represent an average of <30 % of total microalgal biomass, showing a heterogeneous monosaccharidic composition and playing fundamental roles in microalgal physiology, such as energy storage and cell wall formation (Bernaerts et al., 2018). Among species, *Porphyridium* and *Chlorella* are considered two major sources of polysaccharides, like the exopolysaccharides from *Porphyridium cruentum*, reflecting a potent antiviral activity and, secondarily, other important bioactivities, such as antioxidant, anti-inflammatory, and anticancer activity (Saide et al., 2021).

2.1.2. Proteins and derivatives

Algae constitute a relevant source of proteins, being red algae those exhibiting the highest proportion (31–55 %) concerning the total dry weight, reaching a maximum of 71 % in the case of *Palmaria palmata* (Parjikolaei et al., 2016) (Table 1). Nevertheless, microalgae exhibit a higher proportion of proteins, reaching up to 77 % for *Arthrospira* sp. (Vuppaladadiyam et al., 2018). On these bases, seaweeds and

microalgae have been used to produce value-added proteins, such as phycobiliproteins and lectins, together with derived products, including bioactive peptides, mycosporine-like amino acids, essential amino acids, and enzymes.

There are two major proteins mostly isolated from algal sources: lectins and phycobiliproteins. Lectins are carbohydrate-binding proteins, mostly isolated from red seaweeds, with multiple properties that have been widely exploited in the field of biotechnology (Holanda et al., 2012). Structurally, they are classified as complex *N*-glycan-specific lectins, high-mannose *N*-glycan-specific lectins, and mixed lectins, depending on their glycoprotein-binding properties (Tanna & Mishra, 2018). Griffithsin, a high-mannose glycan-specific lectin from the red alga *Griffithsia* sp., constitutes one of the most prevalent lectins commercially exploited (Pliego-Cortés et al., 2020). Due to their role in intercellular communication, lectins have been revealed as effective antimicrobial, antiviral, antitumor, and drug-targeting agents (Holanda et al., 2012), being promising nutraceuticals to be incorporated into food products. On the other hand, phycobiliproteins are considered the major light-harvesting complex in both cyanobacteria and red seaweeds and have been equally exploited at an industrial level by different sectors, including the food industry (Li et al., 2019). Phycobiliproteins are formed of macromolecular complexes, known as phycobilins, with a core of opened tetrapyrroles, which can be classified according to their spectral features into: phycoerythrin, phycocyanin, allophycocyanin, and phycoerythrocyanins (Li et al., 2019). Due to their coloration and high-water solubility, these proteins are considered an important family of algal pigments, together with chlorophylls and carotenoids, and they are normally used as natural colorants in the food industry, as demonstrated by the phycobiliprotein-enriched extracts from the red alga *Gracilaria gracilaris* (Pereira et al., 2020). In addition, protein-enriched extracts from the microalga *Tetraselmis suecica* were found to promote interesting gelling properties to food matrices (Suarez García et al., 2018), thus opening a wide range of applications to algae-derived proteins as ingredients of functional foods.

In parallel, different functional enzymes can also be isolated from seaweeds, as in the case of the alkaline phosphatase from *Ulva pertusa*, alternative oxidases from *Caulerpa cylindrea*, and fibrinolytic enzymes from *Codium* sp. (Pliego-Cortés et al., 2020). In a lower level of structural complexity, bioactive peptides have also been isolated from different algal sources, generated by either the fermentation or enzymatic hydrolysis of algal proteins. *U. pinnatifida* was shown to be a rich source of bioactive peptides, exhibiting 10 dipeptides with potent multifaceted bioactivities (Suetsuna et al., 2004), as well as *P. palmata*, *U. lactuca*, *Saccharina longicruris* (Bondu et al., 2015), and *Enteromorpha clathrata* (Pan et al., 2016), whose enzyme-mediated protein hydrolysis conferred a great variety of peptides with associated biological activities.

Concerning amino acid composition, all of them are found in algae, including great amounts of essential amino acids in red algae, with high proportions of Gly, Arg, Ala, and Glu (Pangestuti & Kim, 2015). Thus, the red *Chondrus crispus* and *Porphyra tenera* are considered a valuable source of Arg, which represents the 33.6 % and 16.4 % of total protein composition, while *Palmaria palmata* contains high proportions of Asp (18.5 %) and Gly (13.3 %) (Fleurence et al., 2018). In parallel, microalgae also contain a valuable amount of essential amino acids, being Leu and Lys the most prevalent amino acids in *Nannochloropsis* sp., *Scenedesmus* sp., and *Dunaliella* sp., therefore accounting for high essential amino acid index values in comparison with other microalgae, such as *Spirulina* (Kent et al., 2015). Similar essential amino acid contents have been found in *Chlorella vulgaris* and *Haematococcus pluvialis*, whose amino acidic composition contains ~50 % of essential amino acids (Kusmayadi et al., 2021). Besides these, seaweeds and microalgae also contain mycosporine-like amino acids (MAAs), water-soluble low-molecular weight compounds devoted to the prevention of oxidative stress and resistance against intense light and UV radiation. Thus, MAAs are found to a greater extent as part of red seaweeds, being shinorine, palythine, porphyra-334, and asterina-330, the most prevalent

compounds (Y. Sun et al., 2020). Up to now, 74 different MAAs have been described in marine sources, showing a significant efficiency to be exploited as cosmetic ingredients for the design of UV protectants (Geraldés & Pinto, 2021), and also as nutraceutical ingredients for food matrices thanks to their antioxidant and anti-inflammatory properties (Nishida et al., 2020). Moreover, other non-conventional amino acids, like taurine, have also been reported in significant amounts in red algae with an associated hypocholesterolemic activity, reaching a total content of >1 % in *Porphyra* sp. (Wells et al., 2017).

2.1.3. Lipids

Algae present a limited content of lipids compared to other primary metabolites, with higher contents in the case of microalgae and, secondarily, brown seaweeds (Table 1). Thus, the lipid content of *Chlorella vulgaris* reached 50 %, followed by *Scenedesmus dimorphus* (47 %), *Selenastrum minutum* (40 %), and *Euglena gracilis* (30 %) (Koyande et al., 2019; Ramesh Kumar et al., 2019), whereas this content is <5 % for most brown seaweeds and it is normally <3 % for both red and green algae (Cherry et al., 2019). Within this family of chemical constituents, fatty acids and membrane-associated lipids have been described to a greater extent. Indeed, lipids represent up to 90 % of algal cell walls (Rico et al., 2017). Considering fatty acids (FAs), all kinds of compounds are found in algae, including saturated FAs (SFAs), mono-unsaturated fatty acids (MUFAs), and polyunsaturated fatty acids (PUFAs), considering both ω 3 and ω 6 PUFAs. Among them, PUFAs show a predominant proportion in algal organisms, reaching values of 70 % out of the total FAs, with a phylum-dependent occurrence; thus, green seaweeds present a high C18 PUFA content (for instance, α -linolenic acid and stearidonic acid), red seaweeds exhibit a high C20 PUFA proportion, mainly represented by arachidonic acid and eicosapentaenoic acid together with the MUFA oleic acid, and brown algae show enhanced concentrations of C20 PUFAs, oleic acid and the SFA myristic acid, whereas microalgae exhibit a wider variety of FAs (Kumari et al., 2013; Ramesh Kumar et al., 2019). Furthermore, Harwood indicated that algae may constitute a promising source of very long-chain PUFAs with 20 – 22 carbon atoms, closely related to the synthesis of essential PUFAs (Harwood, 2019). Additionally, in general terms, algae contain a low ω 6: ω 3 ratio, indicating the healthy profile of PUFAs isolated from these organisms, whose additional health-promoting benefits have been largely reported (Imchen, 2021).

Besides free FAs, these compounds may also make part of membrane-associated seaweed lipids, essentially phospholipids, glycolipids, and sterols. Indeed, phospholipids represent 10 – 20 % of total seaweed lipids, being phosphatidylglycerol and phosphatidylcholine the most prevalent examples (Kumari et al., 2013). In contrast, glycolipids are shown to a lesser extent, as they are strictly found in the thylakoid membranes of photosynthetic tissues (Kumari et al., 2013). Fucosterol and cholesterol are the most prevalent sterols found in brown red and seaweeds, respectively (Kumari et al., 2013). Considering the biological properties associated with PUFAs (some of them considered essential for humans) and sterols, the major application of lipid seaweeds can be summarized in the bioactive enrichment of functional foods to take advantage of their attributed antidiabetic and anticancer properties, among others (Kumari et al., 2013).

2.1.4. Minerals and vitamins

Inorganic minerals and vitamins are considered the main micro-nutrients in algal species. Thus, macroalgae constitute an important source of vitamins A, B, and E, especially vitamin B12 making algae a significant alternative to be incorporated into vegan diets, whereas potassium, sodium, magnesium, and calcium represent 97 % of total seaweed minerals (Biris-Dorhoi et al., 2020). Thus, the red seaweed *Chondrus crispus* exhibits a great mineral content of 25 % (Parjikelaei et al., 2016), followed by *Euchema cottonii* and *Kappaphycus alvarezii* (16 % and 14 %, respectively) (Matanjan et al., 2010; Suresh Kumar et al., 2015), the brown *Saccorhiza polyschides* (14 %) and *B. bifurcata*

(13 %) (Garcia et al., 2016; Lorenzo et al., 2017), and the green alga *Caulerpa lentillifera* (13 %) (Matanjun et al., 2010). It is noteworthy that, although seaweeds tend to accumulate heavy metals, toxicological studies of commercially exploited algae belonging to *Gracilaria*, *Ulva* and *Enteromorpha* genera have demonstrated that these elements are found in lower levels with respect to the tolerable limit (Ganesan, Subramani, Balasubramanian, et al., 2020; Ganesan, Subramani, Shanmugam, et al., 2020). Considering microalgae, significant differences are shown between species and derived from other external factors. In this sense, commercial products derived from *Aphanizomenon* and *Chlorella* species were reported to be rich sources of calcium, iron, magnesium, and zinc, together with vitamins D and E (Sandgruber et al., 2021).

2.2. Secondary metabolites

Secondary metabolites are mainly produced by plants, microorganisms, and algae due to the defensive and/or adaptive responses against environmental stimuli. As a result, these compounds possess a series of associated bioactive properties, being essentially exploited in the fortification of different food matrices to incorporate their associated health-promoting properties (Ścieszka & Klewicka, 2019). More than 3,000 different compounds have been isolated from macroalgae, particularly those living in subtropical and tropical waters (Leal et al., 2013), including species from all phyla. As a general rule, red seaweeds have been traditionally considered as potent sources of anticoagulants, anti-parasitic, and gastroprotective agents, meanwhile green seaweeds are traditionally employed in the treatment of parasitosis and gout, and brown seaweeds were usually used for the treatment of several chronic diseases, such as rheumatism, hypertension, arteriosclerosis, etc. (Barzkar et al., 2019). Interestingly, due to their lower complexity and higher metabolic plasticity, microalgae present a highly inducible secondary metabolism, being widely exploited to produce stress-mediated bioactive compounds at an industrial level (Sun et al., 2018). Owing to the biosynthetic origin, three major families of secondary metabolites are usually found in algae, namely phenolic compounds, alkaloids, and terpenoids. Fig. 2 illustrates an overall composition of seaweeds and microalgae secondary metabolites.

2.2.1. Phenolic compounds

Phenolic compounds constitute the largest family of secondary metabolites, with tenths of thousands of individual compounds isolated from natural sources. Although they have been ubiquitously determined throughout the Plant Kingdom, algae are also recognized as potential sources of phenolics. Particularly, four families of phenolic compounds are found in algae: two of them (phenolic acids and flavonoids) are widely found in other organisms, while the other two (bromophenols and phlorotannins) are considered more specific (Cotas et al., 2020).

Concerning phenolic acids, Sabeena Farvin and Jacobsen (2013) identified up to 13 different compounds in hydroethanolic extracts of seaweeds from the three phyla, being gallic acid, protocatechuic acid, gentisic acid, and chlorogenic acid present in all species analyzed. In contrast, others like hydroxybenzoic acid, vanillic acid, caffeic acid, salicylic acid were more restrictedly identified depending on the alga. Among them, gentisic acid was the compound found at the highest concentrations, with 130 – 170 mg per gram of extract of the green species *Ulva lactuca* and the red *Mastocarpus stellatus*, *Porphyra purpurea* and *Chondrus crispus*, the latter showing the highest concentration (Sabeena Farvin & Jacobsen, 2013). In the same way, the phenolic profile of different South African seaweeds indicated that *p*-hydroxybenzoic acid was the most prevalent phenolic acid throughout all the analyzed species, the red *Laurencia complanata* showing the highest concentrations (13.5 µg/g of dry weight, dw), followed by protocatechuic acid, found at the greatest concentration in the green alga *Halimeda cuneata*, ~2 µg/g dw (Rengasamy et al., 2015). In the case of brown seaweeds, *Undaria pinnatifida* and *Laminaria digitata* were

revealed to present 2,5-dihydroxybenzoic acid as the major compound, with contents in methanolic extracts of 17.4 and 13.9 mg/g extract, respectively (Zaharudin et al., 2018). In the case of microalgae, a similar composition of phenolic acid has been determined. As recently reviewed by Del Mondo et al. (2021), gallic acid, ferulic acid, caffeic acid, chlorogenic acid, synapic acid, coumaric acid, vanillic acid and protocatechuic acid are the most prevalent compounds in microalgae, being *Nostoc*, *Arthrospira*, and *Scenedesmus* the genera containing the species with the highest concentrations. As bioactive compounds, algal phenolic acids have been assessed as potent antioxidants through different mechanisms of action, and antidiabetic agents, as reported both *in vitro* and *in vivo* (Rengasamy et al., 2015; Zaharudin et al., 2018).

Flavonoids are usually found in algae in glycosylated forms, as it occurs in plants. Despite being less exploited than phlorotannins, a great diversity of flavonoids is found in algal sources. Thus, flavones are reported in high concentrations in the green seaweeds *Ulva intestinalis* (~230 mg/g of fresh weight, fw) and *Cladophora vagabunda* (~61 mg/g fw) (Sava & Sirbu, 2010). Equally, the red alga *Phaeocystis globosa* was a great source of flavone compounds, like luteolin, apigenin, chrysin and baicalein, and flavonols, such as myricetin, kaempferol, and quercetin, and the isoflavone formononetin (Xiao et al., 2019). Furthermore, catechins have also been detected in the methanolic extracts of brown seaweeds, as in the case of *U. pinnatifida*, with a content of 6–7 mg/g of extract for both epicatechin and epigallocatechin (Zaharudin et al., 2018). The same flavonoid richness is observed in microalgae, where flavonoid distribution is highly dependent on their evolutionary lineages; for instance, *Haematococcus pluvialis* contains a heterogeneous flavonoid composition, including flavones, isoflavones, and flavonols, with apigenin showing the highest concentrations throughout different microalgae (6.0 – 13.6 ng/g dw) (Goiris et al., 2014). In this way, thanks to the easily inducible secondary metabolism of microalgae, species from *Chlorella* genus were exploited as a biotechnological resource to produce flavonoids, especially quercetin and catechins, under the presence of L-phenylalanine, considered the metabolic precursor of this family of compounds (Yadavalli et al., 2020). Several bioactivities have been assessed to algal flavonoids, reporting their effectiveness as bioactive compounds. In particular, flavonoids from the green algae *Enteromorpha prolifera* exert a potent antidiabetic activity in diabetes-induced mice models (Yan et al., 2019), whereas Ferdous & Balia Yusuf (2021) recently indicated that algal flavonoids exhibit a multifaceted mode of action in terms of anticancer activity, developing a plethora of biochemical and molecular mechanisms on the inhibition of carcinogenesis. In parallel, it is important to note that several studies have proven that flavonoids from algal sources are excellent antioxidant and antibiotic compounds, showing promising exploitation of red seaweeds to that end (Mohy El-Din & El-Ahwany, 2016).

Phlorotannins are the most studied phenolic compounds in both seaweeds and microalgae. Structurally, phlorotannins are polymers of phloroglucinol (1,3,5-trihydroxybenzene) that, depending on the condensation and linkage patterns, make almost 150 compounds divided into four subfamilies: i) fucols, containing C—C linkages; ii) phlorethols, containing C—O—C linkages; iii) fucophlorethols, containing a C—C and C—O—C combination of linkages; and iv) eckols, which are heterocyclic phlorotannins presenting a 1,4-dibenzodioxin moiety (Fernando et al., 2021). Brown algae are regarded as the exclusive source of phlorotannins, whose contents are especially high for the members of the Laminariaceae family, such as *Ecklonia cava* and *Eisenia bicyclis* (Thomas et al., 2020). However, they are commonly isolated from other species, i.e.: *Sargassum muticum*, *Ascophyllum nodosum*, or *Saccharina japonica* (Cassani et al., 2020). Indeed, in the case of *E. cava*, phlorotannin contents reach >10 % of the whole chemical composition of this alga, depending on the harvesting season (Sugiura et al., 2021). Comparing the occurrence of these compounds in different algae, eckols, like eckol, 7-phloroeckol, dieckol, or 6,6'-bieckol are the most prominent compounds throughout the whole Phaeophyceae phylum (Negara et al., 2021). Thanks to the combination of their water

solubility and their defensive roles in brown seaweeds, phlorotannins are recognized as promising health-promoting agents of marine origin to be incorporated in both food and pharmacological matrices. For instance, phlorotannin-enriched extracts exhibit significant associated bioactivities, playing a protective role on important diseases like diabetes, inflammatory, immune, metabolic, cardiovascular, or neurodegenerative diseases (Thomas et al., 2020).

Finally, bromophenols are the fourth family of phenolic compounds with high existence in algae. Bromophenols are formed after the action of vanadium peroxidases, in charge of catalyzing the bromination of phenolic rings in algae (Francezon et al., 2021). After being first identified in the red alga *Neorhodomela larix*, where they stand out as the major source, these compounds have been extensively found in all seaweed phyla, including green and brown seaweeds as well as microalgae (Cotas et al., 2020). Such ubiquitous presence in these organisms can also be demonstrated by the aromatic properties of these compounds, as they are responsible for the marine seafood aromas of algae, attributed to 2-bromophenol, 2,6-bromophenol, and 2,4,6-tribromophenol (Francezon et al., 2021). In addition, bromophenols have also been reported as multifaceted bioactive compounds, acting as antioxidant, anticancer, antibiotic, antidiabetic and antithrombic agents (Liu et al., 2011), and more importantly, they are the molecular scaffolds for the synthesis of analogues with proven enhanced efficiency in the field of pharmacology (Dong et al., 2020).

2.2.2. Alkaloids

Alkaloids constitute an important family of compounds characterized by the presence of nitrogen-containing heterocycles in their structures, presenting a high structural diversity. They are found in macro- and microalgae, although their occurrence is limited compared to terrestrial plants. More than 40 alkaloids have been isolated from macroalgal sources, especially red algae, with indole alkaloids representing the highest proportion, including some halogenated alkaloids specific to marine algae, followed by phenylethylamine and naphthyridine derivatives (Güven et al., 2013). Indeed, halogenated alkaloids are mostly found in Chlorophyta and depict a wide range of associated bioactivities, acting as hormonal agents, stimulants, hallucinogens, bronchodilators, and antidepressants (Vidhyananandan et al., 2020).

Considering macroalgal species, phenylethylamine is mostly detected in brown algae from *Desmarestia* genus and several families of red algae, reaching a maximum value of ~30 µg per gram in the case of *Gelidium crinale* (Percot et al., 2009). In parallel, indole alkaloids are mostly described as bioactive constituents of red algae, highlighting the species from *Martensia* spp. as the richest sources, presenting several compounds, for instance: fragilamide, denticin, martefragin A, and martensins (Güven et al., 2013). Equally, green algae belonging to *Caulerpa* genus were also revealed as a source of indole alkaloids, such as caulerpin and caulersin (Güven et al., 2013). On the other hand, concerning microalgae, *Arthrospira platensis* has been applied as a biofactory to produce several alkaloids throughout the salicylic acid-mediated elicitation, suggesting their large-scale production with pharmacological associated activities (Hadizadeh et al., 2019). Nevertheless, to the best of our knowledge, the knowledge on algal alkaloids is currently limited, and further research is required.

2.2.3. Terpenoids

Terpenoids are highly diverse compounds formed after the condensation of isoprenoid C₅-subunits, giving rise to several subfamilies with different structural complexity. Although sesquiterpenoids, monoterpenoids, diterpenoids and triterpenoids have been isolated from several macro- and microalgal sources, most attention has been paid to more complex compounds from a structural point of view, i.e.: steroids, carotenoids and xanthophylls (Ferdous & Yusof, 2021).

In the case of steroids, algal sterols have gained much attention in the last decades, as they contain similar compounds to those detected in terrestrial plants, including fucosterol, β-sitosterol, stigmasterol, and

ergosterol, among others (Fagundes & Wagner, 2021). As it occurs with other compounds, seaweed sterols present a phylum-dependent occurrence, reaching the highest maximal contents in both green and red seaweeds, representing around 25 % of chemical constituents, reaching only a 15 % content in brown seaweeds (Andrade et al., 2013). Thus, green algae present a high species-dependent sterol composition. For example, β-sitosterol was the major sterol of *Codium* species with concentrations reaching almost 100 µg/g (Milović et al., 2019), whereas cholesterol was found to be the most relevant sterol in *U. lactuca*, as well as in other related species (Kapetanović et al., 2005). In the case of red algae, cholesterol was the most prevalent sterol, especially in the species *Soliera chordalis*, where it represents the 43 % of all sterols (Kendel et al., 2015), meanwhile it has also been detected to a great extent in several *Gracilaria* species (Hannan et al., 2020). Finally, concerning brown algae, fucosterol is the major sterol isolated from *F. vesiculosus*, as it represents the ~90 % of sterols in relevant species, such as *H. elongata*, *U. pinnatifida*, and *L. ochroleuca* (Sánchez-Machado et al., 2004).

Besides seaweeds, a wide range of microalgae has been exploited as a potent source of sterols, reaching great productivity values at an industrial level up to 6000 kg/ha of total phytosterols yearly, including those observed in both terrestrial plants and macroalgae (Randhir et al., 2020). In this sense, *Navicula* sp. produced 76 % w/w of β-sitosterol, *Tretaxelmis* sp. reached up to 99 % w/w of campesterol (Randhir et al., 2020), *P. cruentum* achieved a 92.2 % w/w of cholesterol (Durmaz et al., 2007), whereas *Rhodomonas salina* and *Phaeodactylum tricornutum* produced the same rate of brassicasterol, 99 % w/w (Chen et al., 2011; Fabris et al., 2014).

Beyond sterols, terpenoids have gained much attention in nutraceutical research of algae since carotenoids and xanthophylls are the major pigments of brown algae. Among them, brown algae are characterized by the prominent content of xanthophylls, which form a heterogeneous group of pigments found as paramount constituents of the Phaeophyceae family that includes fucoxanthin, violaxanthin, neoxanthins, zeaxanthin, lutein, and auroxanthin as the most relevant compounds (Park & Lee, 2021). In addition to their role as pigments, the economic interest of seaweed carotenoids also relies on their associated properties as bioactive compounds to be used in the design of functional foods, since they have been largely shown to play a preventive role in chronic diseases, such as cancer, inflammatory and neurodegenerative diseases, and diabetes (Aryee et al., 2018). On these bases, intense efforts are currently underway to achieve the revalorization of brown algae as significant sources of carotenoids. In this sense, nine brown algae from the Atlantic coastline were recently subjected to their evaluation as biological producers of carotenoids, indicating that fucoxanthin was reported as the most concentrated pigment among all species, with *L. saccharina* and *U. pinnatifida* achieving the highest contents, up to ~5 mg/g dw, whereas the ethanolic extracts of *H. elongata* exhibited the highest xanthophyll content, reaching 12 mg/g dw (García-Perez et al., 2022).

Among these pigments, fucoxanthin has focused the major research on brown algae bioactive constituents due to their well-known associated properties involved in the treatment of neurological disorders (Yang et al., 2021), and consequently, novel reports have claimed the benefits of the establishment of a fucoxanthin-based value chain to maximize its commercial exploitation, also considering the valorization of their degradation products (Yusof et al., 2022). In parallel, several strategies are currently being designed from a biotechnological point of view for the sustained production of fucoxanthin using microalgae cultures as biofactories to facilitate not only the production of this valuable compound but also enable the performance of downstream applications to improve and further optimize its extraction, purification, and stabilization (Sun et al., 2022). Thus, a number of microalgal strains were used to that aim, achieving the highest production rates by *Tysochrysis lutea* and *Phaeodactylum tricornutum* (Wang et al., 2021). Indeed, fucoxanthin produced by *P. tricornutum* received the approval of the Food and Drug Administration (FDA), being recognized as a new dietary

ingredient, thus enabling its use as a functional food constituent and leading to its incorporation into several food matrices (Novoveská et al., 2019).

3. Current applications of algae metabolites in the food industry and related sectors

The global seaweed market is continuously expanding with an annual growth rate of 8.9 % (Cotas et al., 2020). The vast majority of seaweed production is cultivated and takes place in Asian countries (China, Indonesia, Korea and Philippines) (Lähteenmäki-Uutela et al., 2021). More than 200 algae species are currently used for food and phycocolloid production. Among cultivated algae, *Saccharina* spp., *Kappaphycus* spp., *Eucheuma* spp., *Gracilaria* spp., *Porphyra* spp. *Undaria*

spp. *Monostroma* spp. and *Enteromorpha* spp. are the most commercially exploited genera representing 90 % of global seaweed production (Lähteenmäki-Uutela et al., 2021). Despite being a billionaire industry, most global seaweed production is destined to the phycocolloids industry. Carrageenan, agar, and alginate are the most exploited and industrially used hydrocolloids in the current market. Although agar possesses the highest retail price per kg (18 USD/kg), carrageenan leads the total commercial production (60,000 tons/year), accounting for USD 626 million per year (Rhein-Knudsen et al., 2015). On the other hand, the global market of fucoidan is continuously growing as it reached USD 33 million in 2020 and is estimated to achieve USD 42 million by 2027 with a compound annual growth rate (CARG) of 3.4 % during 2021–2027 (Expresswire, 2022). In the same line, the fucoxanthin global market is in continuous expansion with a CARG of 3.8 % during

Table 2
Functional properties and main applications of algae metabolites in the food industry.

Metabolites	Species/genera	Functional properties	Food application and related sectors	Ref.	
Polysaccharides	Agar	<i>Gelidium</i> and <i>Gracilaria</i> genera	Stabilizing, thickening, gelling, flocculating, clarifying agent. Water holding capacity.	<i>Food additive</i> in bakery products, dairy products, canned meat and fish products, candy, beverages, dessert, jellies, etc. <i>Edible film</i> of fish products, spinach, etc.	(Mostafavi & Zaeim, 2020; Qin, 2018; Rioux & Turgeon, 2015; Şahin, 2021)
	Alginate	<i>Ascophyllum nodosum</i> , <i>Laminaria hyperborea</i> , <i>L. saccharina</i> , <i>L. japonica</i> , <i>Durvillaea antarctica</i> , <i>D. apotatorum</i> , <i>L. digitata</i> , <i>Ecklonia maxima</i> , <i>Macrocystis pyrifera</i> , <i>Lessonia nigrescens</i> , and <i>L. trabeculata</i>	Stabilizing, emulsifying, gelling, and thickening agent.	<i>Food additive</i> in ice creams, ready-to-eat soups, ketchup, mayonnaise, juices, dessert, jam, pudding, dairy products. <i>Edible films and coating</i> of fresh-cut fruits and vegetables; meat, poultry, and seafood products; cheese, etc. <i>Encapsulating material</i> of probiotics, vitamin C, anthocyanin, astaxanthin, β-carotene, curcumin, etc. <i>Sustained delivery system</i> of drugs and bioactive molecules.	(Alvarez et al., 2021; Parreidt et al., 2018; Rioux & Turgeon, 2015; Şahin, 2021)
	Carrageenan	<i>Kappaphycus alvarezii</i> , <i>Eucheuma denticulatum</i> , <i>Ahnfeltia</i> , <i>Anatheca</i> , <i>Furcellaria</i> , <i>Gigartina</i> , <i>Gymnogongrus</i> , <i>Hypnea</i> , <i>Iridaea</i> , <i>Meristotheca</i> , and <i>Phyllophora</i>	Gelling, stabilizing, and thickening agent.	<i>Food additive</i> in dairy products (e.g., flan, pudding, and mousse), cake frosting, meat products, etc. <i>Edible films and coating</i> of chicken meat, fish products, etc. <i>Encapsulating material</i> of glycomacropeptide, β-galactosidase, etc. <i>Sustained delivery system</i> of drugs and bioactive molecules.	(Rioux & Turgeon, 2015; Zhang et al., 2018)
	Fucoidan	<i>Fucus vesiculosus</i> , <i>A. nodosum</i> , <i>F. evanescens</i> , <i>F. serratus</i> , <i>Chorda filum</i> , <i>E. kurome</i> , and <i>L. brasiliensis</i>	Pseudoplastic or shear-thinning behavior in dilute water solutions. Biological activities (antioxidant, antimicrobial, anticancer, anti-inflammatory, anticoagulation, antidiabetic, neuroprotective).	<i>Food additive</i> in surimi products, fruit and vegetable beverages, etc. Food supplement and nutraceutical industry. <i>Sustained delivery system</i> of drugs and bioactive molecules.	(Chen et al., 2021; Rioux & Turgeon, 2015; Zheng et al., 2021)
	Laminaran	<i>L. digitata</i> , <i>Eisenia bicyclis</i> , <i>Sargassum fusiforme</i> and <i>Sargassum trichophyllum</i>	Low viscosity and high solubility in organic and aqueous solvents. Biological activities (antitumor, anti-inflammatory, enhancement of immunity system, antimicrobial, antioxidant activity)	Nutraceutical industry.	(Custódio et al., 2016)
	Ulvan	<i>Ulva lactuca</i>	Gelling capacity. Biological activities (antioxidant, antihyperlipidemic activity)	Nutraceutical industry. Food supplement in some countries.	(Rioux & Turgeon, 2015)
Proteins	C-phycoyanin	<i>Spirulina platensis</i>	Natural blue dye. Biological activities (antioxidant, anti-inflammatory, anticancer, improvement of immune system).	<i>Food additive</i> used in chewing gum, dairy products and jellies. Food supplement. Nutraceutical industry.	(Galetović et al., 2020); (Bannu et al., 2020)
Terpenoids	Astaxanthin	<i>Haematococcus pluvialis</i> , <i>Chlorella zofingiensis</i> , <i>Chlorococcum</i> , <i>Neochloris wimmeri</i>	Natural red colorant. Biological activities (antioxidant, anti-diabetic, enhancement of immune system, anticancer)	<i>Food additive</i> in animal and fish feed (e.g., salmon, trout and shrimp). Food supplement. Nutraceutical industry.	(Ambati et al., 2014)
	Fucoxanthin	<i>Undaria</i> , <i>Sargassum</i> , <i>Laminaria</i> , <i>Eisenia</i> , <i>Alaria</i> , <i>Cystoseira</i> , and <i>Hijikia</i> genera	Natural colorant. Biological activities (anti-diabetic, anticancer, anti-inflammatory, antioxidant, anti-angiogenic, antihypertensive, photoprotective).	Nutraceutical industry.	(Lourenço-Lopes et al., 2021)
Phenolics	Phlorotannin	<i>Ecklonia cava</i> , <i>Eisenia bicyclis</i> , <i>Sargassum muticum</i> , <i>Ascophyllum nodosum</i> , <i>Saccharina japonica</i> , <i>Fucus vesiculosus</i> , <i>Himanthalia elongata</i>	Biological activities (antioxidant, anticancer, anti-inflammatory, antimicrobial, anti-diabetic, antiviral, anti-allergic).	Food supplement. Nutraceutical industry.	(Cassani et al., 2020)

2021–2027. In this context, polysaccharides lead the total commercial production of algae-derived compounds, although there is an increasing demand for other poorly exploited algal metabolites in the food, nutraceutical, cosmeceutical and pharmaceutical industries. This growing demand is related to the beneficial health effects beyond basic nutrition ascribed to such compounds. This section presents the most extended applications for algal metabolites in the food industry.

3.1. Food additives

Seaweed polysaccharides have been traditionally used in the food industry for their rheological behavior. Carrageenan, agar and alginate are water-soluble polymers that can produce high viscous solutions when dissolved in water (Qin, 2018). These polysaccharides have been extensively employed as food ingredients for their unique functional properties as gelling, stabilizing, emulsifying, and thickening that allowed the development of numerous food products (Rioux & Turgeon, 2015). Carrageenan, agar and alginate are considered “generally regarded as safe (GRAS) substances” for human consumption by the European Food Safety Authority (EFSA) and Food and Drug Administration (FDA, USA) under the following European codes: E-407 for carrageenan, E-406 for agar, and E-400 – 404 for alginic acid and its salts (Younes et al., 2018). Table 2 shows the functional properties of seaweed polysaccharides and their direct food application. About 90 % of the total produced agar is destined to the food industry. Agar may act at low concentrations and a wide range of pH. It is soluble in hot water and forms a gel after cooling that remains stable at 85 °C (Rioux & Turgeon, 2015). This property encouraged its incorporation into many food products, such as meat and dairy products (Şahin, 2021). Additionally, agar can be mixed with high amounts of sugar avoiding crystallization, opacity, or even losing adhesive characteristics and thus, this polysaccharide is suitable for bakery glazes, toppings, icing, etc. (Qin, 2018). Carrageenan is used during hot filling in food processing as this polysaccharide remains soluble at 70 °C or higher and can form a continuous and sliceable gel while cooling (Qin, 2018). This feature makes carrageenan suitable for incorporation into dairy products such as flan, pudding, and mousses (Rioux & Turgeon, 2015). In water-based products, such as gelled desserts and cake frosting, κ -carrageenan allows forming a brittle and strong gel. The carrageenan blend (κ - and ι -carrageenan) is suitable for developing vegetarian food products because of its similar texture to gelatin, but stable at room temperature (Rioux & Turgeon, 2015). Carrageenan is widely used in meat products to enhance water retention, mouthfeel and texture (Rioux & Turgeon, 2015). Another interesting advantage of carrageenan is the ability to form a gel with low amounts of sugar, resulting in a suitable additive for the production of low-calorie dessert gels (Qin, 2018). On the other hand, alginate is used as a thickening agent in desserts and savory sauces (Qin, 2018). Alginate can form stable gels in a wide range of temperatures and at low pH, resulting suitable for stabilizing bakery creams and avoiding syneresis (Qin, 2018). Propylene glycol alginate is used to retain the foam stability of mousses and desserts and is also employed to stabilize the frothing head of beers and thus, ensuring a safe pouring (Qin et al., 2018).

Regarding poorly exploited polysaccharides, fucoidan from *F. vesiculosus* and *U. pinnatifida* have been authorized by the European Commission (Regulation 2017/2470) as novel ingredients in foods and food supplements with an allowed intake of 250 mg/day (Lähteenmäki-Uutela et al., 2021). Many efforts have been made to show the potential of fucoidan as a food additive. For example, Zheng et al. (2021) found the addition of crude fucoidan (0.125 % w/w) in surimi products significantly improved their water holding capacity and gel strength without affecting textural properties (Table 2). In addition, fucoidan-containing surimi products also showed strong antioxidant activities and antimicrobial effects against *Escherichia coli* and *Staphylococcus aureus* (Zheng et al., 2021). Chen et al. (2021) developed a beverage containing vegetables, spelled wheatgrass and mulberry juices with

fucoidan extract (5 %), as a functional beverage to be used as an alternative to mitigate oral cancer since that beverage effectively reduced cancer cells proliferation. In contrast, despite their associated biological and physicochemical properties, ulvans and laminarin have not been authorized as food additives yet (Rioux & Turgeon, 2015). Besides these technological and rheological features associated with algal polysaccharides, they present a wide range of bioactivities, being also exploited as health-enhancing compounds. Among their bioactivities, it is important to note that these polysaccharides promote a promising prebiotic effect, due to their structural analogism with other dietary fibers, acting as enhancers of the gut performance and playing a beneficial role in the human microbiota, as shown for galactan, porphyran, fucoidan, and ulvan (Zheng et al., 2020).

Among seaweed proteins, phycobiliproteins are water-soluble proteins used as natural colorants in food products (Galetović et al., 2020). *Spirulina* extracts containing phycobiliproteins are currently authorized by FDA for their use in human foods, especially as color additives for candy, chewing gums, frosting, ice cream, beverages, yogurts, etc. (Table 2) (FDA, 2015; Galetović et al., 2020). In particular, the bright blue characteristic of phycocyanin makes this pigment suitable for confectionery products instead of using gardenia blue and indigo (Galetović et al., 2020).

Regarding secondary metabolites, phlorotannins have been widely explored for their therapeutic properties, encouraging their incorporation into functional foods (Cassani et al., 2020). Despite not being authorized for food applications yet, some attempts have reported their potential as an antimicrobial and antioxidant agent, extending the shelf-life of chicken meat (Surendhiran et al., 2019), and as natural melanosis inhibitors in Pacific white shrimp (Sharifian et al., 2019). On the other hand, the FDA has approved astaxanthin for specific uses in animal food, for example, as a colorant added to the fish feed (Table 2) (Ambati et al., 2014). Fucoxanthin was added to goat whole and skimmed milk and its thermal and storage stability were assessed by (Nuñez de González et al., 2021), reporting high recovery yields either after pasteurization (64 °C, 30 min) or after four weeks of refrigerated storage. However, the incorporation of fucoxanthin significantly affected milk's color, turning it into yellowness. In this regard, fucoxanthin encapsulation could extend its scope of application to foods resulting in a functional ingredient with many advantages, such as water-solubility, stability, and bioaccessibility improvement, without affecting the food sensory quality (Wang et al., 2020).

3.2. Food packaging

Since carrageenan, agar and alginate are non-toxic, biodegradable, and biocompatible polymers with gelling ability, they have been widely used to produce edible films and coating as packaging biomaterials for food products. They have shown to provide a good barrier to oxygen, fats, and oils while offering many advantages, such as the extension of the product's shelf life, food quality enhancement, reduction of microbial growth, and protection against lipid oxidation and moisture loss (Table 2) (Zhang et al., 2018). Alginate and carrageenan are the most employed hydrocolloids for such applications (Zhang et al., 2018). In this respect, alginate and carrageenan-based coating and films have been used to retain firmness, improve appearance, reduce microbial growth and delay senescence, thus extending the shelf life of fresh-cut fruits and vegetables (Parreidt et al., 2018). In addition, these coating and films were also employed to inhibit lipid oxidation and improve barriers against moisture loss and volatile flavor loss in meat, poultry and seafood products (Parreidt et al., 2018; Zhou et al., 2021). Edible films and coating based on the above-mentioned polysaccharides can be mixed with other biopolymers, such as chitosan (Reyes-Avalos et al., 2019), carboxymethyl cellulose (Salama et al., 2019), and pectin (Fan et al., 2021) to enhance mechanical properties (tensile strength and elongation) of different food matrices, widening the scope of applications. In this way, Gomaa et al. (2018) developed alginate-fucoidan-

based films with improved thickness, increased water vapor permeability and oxygen permeability, conferring protection against UV light, and delaying the oxidative reaction of packaged foods (Gomaa et al., 2018). In addition, seaweed polysaccharides-based edible films and coating have also been employed as carriers for probiotic bacteria, ensuring their viability during storage and gastrointestinal digestion (Alvarez et al., 2021).

Another interesting approach is the addition of antimicrobial and antioxidant compounds (plant essential oils, nanoparticles, phenolics-rich extracts), plasticizers (glycerol), and anti-browning agents (ascorbic acid and citric acid) to films and coating formulations to improve their physicochemical, mechanical and biological properties (Mostafavi & Zaeim, 2020). In this respect, Wu et al. (2021) developed bio-nanocomposite films by adding phlorotannins extracted from *Sargassum* spp. to Konjac glucomannan (KG) and cotton cellulose nanocrystals (CN) composites to improve mechanical properties and water vapor resistance. Besides, phlorotannins provided additional antioxidant and antibacterial activities, suggesting KG/CN films as promising active packaging in the food industry (Wu et al., 2021). On the other hand, Cian et al. (2014) obtained two aqueous fractions of phycobiliproteins and phycocolloids from *Porphyra columbina* and developed phycobiliproteins–phycocolloids-based films, acting as plasticizing agents with enhanced antioxidant activity.

3.3. Food supplementation and drug delivery systems

Several biological activities have been attributed to algal metabolites that promote their use as food supplements and components of drug delivery systems. For example, among seaweed polysaccharides, fucoidan has been added to many supplements available in the current market in different formats such as capsules, beverages and gels (Fitton et al., 2019).

Regarding secondary metabolites, phlorotannins and fucoxanthin have mostly shown to play a key role in human nutrition and health because of their bioactivities mentioned above, becoming great candidates to be used as food supplements (Lourenço-Lopes et al., 2021). In addition, phlorotannin-enriched extracts from *Ecklonia cava* have been approved for their use as food supplements (Commission Regulation (EU) 2017/2470), with a recommended daily intake of 263 mg for adults (Lähteenmäki-Uutela et al., 2021), being mostly commercialized as capsules. Equally, because of the biological activities ascribed to astaxanthin (antioxidant, anti-inflammatory, antidiabetic, anticancer, immune modulation, cardiovascular disease prevention), there are an increasing number of supplements containing this pigment currently commercialized in different formats, such as powder, capsules, tablet, soft gel, and cream (Ambati et al., 2014).

Given the abundance, biodegradability, biocompatibility, and bioactivities of algal metabolites, application in drug and bioactive molecules delivery systems has promoted the development of micro and nanoparticles for the controlled and sustained release of target compounds (Sorathiyakarn et al., 2022). In addition, obtaining particles at the micro and nanoscale provides additional advantages, such as the physicochemical and thermal stability enhancement during long-term storage and water-solubility improvement, which results in increased bioaccessibility, bioavailability, and retention of biological activities (Wang et al., 2020) (Table 2). In this respect, κ-carrageenan-based nanoemulsions were developed to encapsulate fucoxanthin-rich seaweed oils, with improved oxidative stability during storage, enhanced bioaccessibility and inhibitory effect on different cancer cells lines (Saravana et al., 2019). Similarly, Kaushalya & Gunathilake (2022) obtained phlorotannin-loaded, 12-μm microparticles from *Sargassum ilicifolium* using chitosan, with loading capacity (62.6 %) and encapsulation efficiency (85.1 %). In addition, phlorotannins encapsulation positively affected the sensory attributes of fortified gels by masking undesirable attributes associated with these molecules (e.g., bitter taste, dark brown color, astringency, and unfavorable odor), facilitating its use

by the food industry. On the other hand, fucoidan has been attracting attention in the field of cancer research since can be used as a nano-carrier of anticancer drugs with a slow-release effect (Ouyang et al., 2021). In this respect, in breast cancer, pH-responsive and enzymatically responsive fucoidan-based nanocarriers allowed the slow release of doxorubicin (an anticancer drug) from the nanoparticles in the acidic intracellular microenvironment, leading to the enzymatic digestion of cancer cells (Lu et al., 2017). In this context, the development of encapsulating techniques opens new perspectives on the enhancement of algal metabolites as functional agents, thus contributing to preventing and mitigating chronic diseases, in which innovation plays a key role.

4. Metabolomics: A next-generation tool for the search and characterization of algal nutraceuticals

Metabolomics constitutes a high throughput technology, defined as the qualitative and quantitative study of all or a determined group of metabolites present in a biological sample at a given time, which are mainly governed by gene and protein expression and environmental factors, whose interaction determines the composition of the metabolome. Metabolomics has many practical applications in analytical chemistry, biochemistry, biostatistics and clinical science (Fraga-Corral et al., 2020; Tanna & Mishra, 2018), and it has been proven a powerful tool in the research of nutraceutical compounds in different matrices, including algae. Metabolomic approaches can be categorized into three types, depending on the study's objective. Firstly, untargeted metabolomics is employed to identify and relatively quantify a high coverage of the metabolome in a biological sample, including previously unknown compounds, providing wide metabolic profiling through advanced bioinformatics and data processing tools (Fraga-Corral et al., 2020). Secondly, targeted metabolomics (sometimes defined profiling) is focused on quantifying particular compounds or groups of compounds (e.g. phenolic compounds, lipids, amino acids, etc.), involving a high-sensitivity approach, while the complexity of the data analysis is usually low (Fraga-Corral et al., 2020). Finally, metabolic fingerprinting is usually applied to classify samples according to their metabolomic patterns under specific conditions, such as those related to the environment and other external stimuli, without identifying or quantifying particular metabolites with a high confidence level of identification (Kumar et al., 2018).

Among others, metabolomics has been used to characterize algae and algae-derived products. Table 3 contains a detailed overview of featured metabolomic analyses performed on algal species. From an operational perspective, metabolomics is a hypothesis-free approach whose general workflow involves three fundamental steps. Initially, sample preparation is essential to perform an adequate extraction of metabolites, avoiding contamination and preserving their chemical integrity, to comply with the requirements of the downstream analytical approach performed. Different strategies have been applied to that aim in the case of algal matrices. Sample extraction can be performed from fresh or dried matrices, using solvents with a wide range of polarities, such as methanol and perchloric acid, at different temperatures (Arumugam et al., 2021; Nazarudin et al., 2020; Yan et al., 2019). To favor the release and solubility of metabolites, several techniques are usually employed to disrupt the rigid algal cell wall, ranging from mechanical methods (e.g. automatic grinders or mortar) to efficient extraction techniques like maceration, microwave-assisted extraction, pressurized-liquid extraction, pulsed electric fields, supercritical fluid extraction, or ultrasound-assisted extraction. The advantages and disadvantages of using different emerging techniques for the extraction of algal metabolites have been extensively reviewed in the literature (Azizan et al., 2020; Feline et al., 2019; Hamid et al., 2019). The design of optimized protocols is highly important on the extraction and further production of algal metabolites, as they also influence the operational outcomes involving the industrial application of these compounds.

Afterwards, the obtained extracts are subjected to their analytical

Table 3
Overview of the metabolomic studies performed on both macro- and microalgae.

Algae	Sample extraction	Analytical approach	Metabolites	Main results	Ref.
Macroalgae					
<i>Sargassum micracanthum</i> , <i>Sphaerotrichia firma</i> , <i>Papenfussiella kuromo</i> , <i>Saccharina japonica</i> , <i>Pyropia pseudolinearis</i> , <i>Gelidium elegans</i> , <i>Neodilsea yendoana</i> , <i>Dasya sessilis</i> , <i>Botryocladia wrightii</i> , <i>Ulva australis</i> , <i>Chaetomorpha moniligera</i>	Maceration, 1) MeOH/W, 2) MeOH/W/Chl, 4 °C, 10 min	CE-MS LC-Q-MS/MS	Amino acids, organic acids Sugars	The metabolite concentration profiles varied depending on species and taxonomic groups, regardless the extraction method.	(Hamid et al., 2019)
<i>Ulva</i> sp., <i>Caulerpa</i> sp., <i>Codium</i> sp., <i>Dasya</i> sp., <i>Grateloupia</i> sp., <i>Centroceras</i> sp., <i>Ecklonia</i> sp., <i>Sargassum</i> sp.	Maceration, 80 % EtOH, 4 °C, 16 h	LC-QTOF-MS/MS	Phenolic compounds	Fifty-four compounds were identified, mostly phenolic acids, flavonoids, and lignans. The selected species were a source of phenolic compounds with antioxidant properties.	(Zhong et al., 2020)
<i>Ascophyllum nodosum</i> , <i>Bifurcaria bifurcata</i> , <i>Fucus vesiculosus</i>	Maceration, W, RT, 5 min	LC-ESI-MS/MS	Phenolic compounds	Main compounds identified were phlorotannins followed by phenolic acids, and flavonoids. All species could be a source of antioxidant phenolic compounds.	(Agregán et al., 2017)
<i>Durvillaea antarctica</i> , <i>Lessonia spicata</i> , <i>Macrocystis integrifolia</i>	Maceration, EtOH:W (1:1), RT, 24 h	LC-ESI-MS/MS	Phenolic compounds	Different phlorotannins were identified in <i>D. antarctica</i> and <i>L. spicata</i> . <i>M. integrifolia</i> and <i>L. spicata</i> showed a great variety of flavonoid compounds.	(Olate-Gallegos et al., 2019)
<i>Enteromorpha prolifera</i>	UAE, W, 60 °C, 1 h + 95 % EtOH	LC-QTOF-MS/MS	3-kDa compounds	In the 3 kDa fraction, six flavonoids were identified: eriodyctiol, and kaempferol glycosides and other unknown metabolites.	(Yan et al., 2019)
<i>Ulva fasciata</i> , <i>Pterocladia capillacea</i> , <i>Sargassum hornschurchii</i>	UAE, 70 % EtOH, 35 °C, 1 h, 3 times	LC-QQQ-MS	Untargeted	Eighty-five compounds were identified, belonging to different phytochemical classes (fatty acids, flavonoids, phlorotannins, carotenoids, amino acids, etc.), were differentially present in a phyla-dependent manner.	(Ghallab et al., 2022)
<i>Lobophora rosacea</i> , <i>Lobophora obscura</i> , <i>Lobophora monticola</i> , <i>Lobophora sonderii</i>	UAE, MeOH/DCM, RT, 5 min	LC-QTOF-MS	Untargeted	Significant metabolic variations were observed between species, but also caused by spatio-temporal conditions, attributed to the changes in the profile of fatty acids derivatives and polyolefins.	(Gaubert et al., 2019)
<i>Dictyota dichotoma</i>	UAE, liquid N ₂ -70 % MeOH, 25 °C, 1 h	LC-QTOF-MS	Untargeted	The metabolic fingerprinting revealed sixteen metabolites, belonging to fatty acid glycosides, mono and diterpenoids, flavonoids and coumarin derivatives, among others.	(Dixit et al., 2020)
<i>Sargassum fusiforme</i> , <i>Sargassum pallidum</i>	Maceration, W, RT, 15 min; DCM/MeOH (1:2 v/v), RT, 2 min; MeOH, RT, 2 min	NMR	Phytosterols	<i>S. fusiforme</i> presented the highest content of phytosterols, being fucosterol the most discriminant compound between species	(Zhang et al., 2016)
<i>Dictyota menstrualis</i>	Maceration: DCM, RT, 72 h	GC-MS/ NMR	Diterpenes	Eleven diterpenoids were accumulated under long-term incubation in seawater at laboratory scale.	(Obando et al., 2022)
<i>Agarophyton chilense</i> , <i>Pyropia plicata</i> , <i>Champia novae-zelandiae</i>	UAE, DCM, 15 min. Dry material: UAE, MeOH, 15 min; MeOH, 15 min.	LC-ESI-MS/ NMR	MAAs	Eleven metabolites were identified in the samples, some of them reported for the first time. Shinorine, palythine, asterina-330 and porphyra-334 were revealed as predominant MAAs in red algae.	(Orfanoudaki et al., 2019)
<i>Fucus virsoides</i>	Maceration, D ₂ O: d-MeOH (80:20)	NMR	Untargeted	Amino acids and organic acids drove the algal response against glyphosate contamination.	(Felline et al., 2019)
<i>Sargassum polycystum</i>	UAE, d-MeOH-PPB, RT, 20 min	NMR	Untargeted	Twelve low-molecular-weight metabolites were identified, showing a metabolite profile highly dependent on sample processing.	(Nazarudin et al., 2020)
<i>Padina gymnospora</i>	UAE, 1) Hx, 2) Chl, 3) 70 % EtOH, 4) MeOH, RT	NMR	Untargeted	Thirteen compounds were identified, and the metabolic profiling showed that amino acid composition strongly varied according to the solvent employed.	(Nazarudin et al., 2022)
Microalgae					
<i>Nannochloropsis oceanica</i>	Maceration, MeOH, W (80:20)	GC-MS LC-ESI-MS	Lipids, omega-3 fatty acids and metabolites from citric acid cycle, glycolysis, and pentose phosphate pathway	Plant growth regulators increased ATP, NADPH, NADP, and NADH concentrations, which led to an increase in lipid production, especially that of omega-3 fatty acids.	(Arumugam et al., 2021)
<i>Haematococcus pluvialis</i>	UAE, ACN-MeOH-W, 4 min	LC-Orbitrap-MS	Astaxanthin and lipids	Under melatonin-mediated stress conditions, astaxanthin and lipids were	(Zhao et al., 2021)

(continued on next page)

Table 3 (continued)

Algae	Sample extraction	Analytical approach	Metabolites	Main results	Ref.
<i>Bathycoccus</i> sp., <i>Micromonas</i> sp., <i>Ostreococcus</i> sp.	Maceration, EtAc, 19 °C, overnight	LC-Orbitrap-MS/MS	Untargeted	accumulated via proline and succinate induction. The metabolic fingerprinting provided a series of chemotaxonomical markers, represented by polar galactolipids and pigments.	(Marcellin-Gros et al., 2020)
<i>Scenedesmus quadricauda</i>	MAE, 65 % HNO ₃ -30 % H ₂ O ₂ , 140 °C, 40 min	LC-QQQ-MS/MS	Phenolic acids	The presence of heavy metals influences the concentrations of phenolic acids, which can be involved in antioxidative response.	(Strejckova et al., 2019)
<i>Euglena gracilis</i>	Maceration, cold 10:3:1 (MeOH/Chl/H ₂ O (1:1:1), frozen in liquid N ₂ - thawed	GC-MS	Untargeted	Eighty-six metabolites were identified, being dioctyl phthalate and putrescine the markers involved in the response to differential culture conditions, together with a significant change in fatty acid composition.	(Zeng et al., 2016)
<i>Chaetoceros calcitrans</i>	UAE, 1) Chl, 2) AcO, 3) MeOH, 4) 70 % EtOH, 5) Hx, RT, 30 min	LC-Orbitrap-MS	Lipids and pigments	Lipid metabolites were mainly identified: 16 glycolipids, 13 fatty acids, and 13 pigments. Fucoxanthinol, chlorophyll c2 and 3-hexadecenoic acid were correlated with biological properties.	(Azizan et al., 2020)
Genetically modified <i>Phaeodactylum tricorutum</i>	UAE, cold MeOH, 30 min	LC-QTOF-MS/MS	Untargeted	Glucose-6-phosphate dehydrogenase overexpression led to high lipid accumulation by concentrating metabolic intermediates involved in pentose phosphate pathway and NADPH consuming pathways.	(Xue et al., 2017)
<i>Aurantiochytrium</i> sp.	UAE. ice-cold MeOH/EtOH/Chl (2:6:2), 15 min	GC-MS/MS	Untargeted	A total of 34 metabolites, including fatty acids, sugars, and organic acids, amino acids, and sterols were reported. Metabolic adaptations, involving glucose metabolism were observed depending on the carbon substrate, which impacted the biosynthesis of docosahexaenoic acid.	(Mariam et al., 2021)
<i>Chaetoceros calcitrans</i>	UAE, 1) MeOH, 2) 70 % EtOH, 3) AcO, 4) Chl, 5) Hx, RT, 30 min	NMR	Untargeted	Twenty-nine compounds were identified in the extracts, including amino acids, pigments, fatty acids, organic acids and sugars. The metabolites extracted varied according to the polarity of the solvent.	(Azizan et al., 2018)
<i>Isochrysis galbana</i>	UAE, 1) d-MeOH/phosphate D ₂ O buffer (1:1), 2) d-MeOH/d-Chl (1:4), 20 min	NMR	Untargeted	In aqueous extracts, 39 compounds were identified, whereas 18 lipidic and sterol compounds and 2 pigments were found in lipophilic extracts. Irradiance and temperature caused a decrease in pigments, polyunsaturated fatty acids, and the conversion of polar fatty acids to neutral fatty acids.	(Aguilera-Sáez et al., 2019)
<i>Amphidinium carterae</i>	UAE, 1) d-MeOH/phosphate D ₂ O buffer (1:1), 2) d-MeOH/d-Chl (1:4), 20 min	NMR	Untargeted	Growing bioreactor conditions motivated a metabolite regulation, involving amphidinols, fatty acids, and carotenoids. In general, high irradiance led to an inhibition of fatty acids, whereas high-nutrient conditions caused the accumulation of sugars, amino acids, omega-3 fatty acids and pigments.	(Abreu et al., 2019)
<i>Chlorella vulgaris</i>	UAE, 1) HX, 2) Ch, 3) EtAc, 4) EtOH, 5) EtOH 50 %, 6) W, 33 °C, 30 min	NMR	Untargeted	Altogether, 35 compounds were identified among solvents with different polarities: fatty acids, amino acids, carotenoids, and vitamins were reported as discriminant markers. EtOH and EtAc showed the most enriched extracts.	(Pantami et al., 2020)
<i>Dunaliella</i> sp., <i>D. salina</i> , <i>Chaetoceros calcitrans</i> , <i>C. gracilis</i> <i>Tisochrysis lutea</i>	UAE, Hx, 10 min; centrifugation; EtAc, 10 min; centrifugation; MeOH, 10 min	NMR	Untargeted	Lipids, pigments, amino acids and carbohydrates were characterized in the samples. Such metabolites were involved in a chemotaxonomic discrimination, as well as differentially determined in solvents with a wide range of polarity.	(Iglesias et al., 2019)

Abbreviations: Acetone (AcO), Acetonitrile (ACN), Capillary electrophoresis (CE), Chloroform (Chl), Deuterated chloroform (d-Chl), Deuterated methanol (d-MeOH), Dichloromethane (DCM), Electrospray ionization (ESI), Ethanol (EtOH), Ethyl acetate (EtAc), Gas chromatography (GC), Hexane (Hx), Liquid chromatography (LC), Mass spectrometry (MS), Methanol (MeOH), Microwave-assisted extraction (MAE), Nuclear magnetic resonance (NMR), Potassium dihydrogen phosphate buffer (PPB), Quadrupole (Q), Quadrupole-time of flight (QTOF), Room temperature (RT), Triple quadrupole (QQQ), Ultrasound-assisted extraction (UAE), Water (W).

characterization, which may vary as a function of the specific aims. As a general rule, analytical workflows on metabolomics include an initial phase of separation of chemical constituents, to resolve complexity, where chromatography is regarded as the most relevant methodology. To this object, either liquid chromatography (LC) or gas chromatography (GC) are used for separating complex mixtures, together with other specific, less common alternatives, like capillary electrophoresis (CE) (Hamid et al., 2019; Tanna & Mishra, 2018). Following the chemical resolution, two major techniques have been mainly employed for detecting metabolic identities: mass spectrometry (MS) and nuclear magnetic resonance (NMR). To our knowledge, compared with MS, fewer studies have employed NMR to discern the metabolites of macroalgae for nutraceutical purposes (Table 3). Finally, the metabolic identification and characterization of algal matrices is achieved by performing bioinformatic and statistical analyses. Whereas in targeted approaches the molecular fingerprint of each detected metabolite should be obtained from the corresponding pure standards and/or retrieved from previous bibliographic references to obtain a specific chemical profile, untargeted metabolomic approaches rely on the putative annotation of chemical identities (features) to cover a wider range of metabolites (Bingol, 2018). Each analytical approach is associated to a certain degree of confidence in annotation, as set out by standards of reporting in metabolomics (Viant et al., 2019). In all cases, the vast amount of information obtained is highly dependent on heterogeneous factors and their interactions, thus urging the application of multivariate statistics (Misra, 2018), as it is the case of the unsupervised hierarchical cluster and principal component analyses, i.e. naïve approaches that can describe patterns amid samples or treatments. Thereafter, supervised approaches such as partial least squares and orthogonal projection to latent structures discriminant analyses are used to model metabolomics profiles and facilitate the identification of differential and discriminant compounds. More recently, artificial intelligence-based tools have also been applied to that aim, facilitating the interpretation of metabolomics data on multifactorial physiological processes in complex organisms like plants (García-Pérez et al., 2021), opening a wide perspective on the metabolic characterization of algae.

Several studies have successfully employed LC-MS combinatorial methodologies to evaluate the metabolic profile of macro- and microalgae, as well as GC-MS and NMR approaches that were conducted in a lesser proportion (Table 3). In general, untargeted approaches in algal species have been developed to achieve four major objectives: a) the optimization of culture conditions at a laboratory scale, especially applied to microalgae, as shown for differential irradiance regimes in *Euglena gracilis* (Zeng et al., 2016); the study of the combination of irradiance and temperature on *Isochrysis galbana* metabolome (Aguilera-Sáez et al., 2019); and the determination of metabolic impact of different irradiation and nutrient dosage on *Amphidinium carterae* bio-reactors (Abreu et al., 2019); b) the optimization of sample treatment and the choice of extraction solvent for maximizing the metabolic richness of algal extracts, as performed for the macroalgae *Sargassum polycystum* (Nazarudin et al., 2020) and *Padina gymnospora* (Nazarudin et al., 2022), and the microalgae *Isochrysis galbana* (Azizan et al., 2018), *C. vulgaris* (Pantami et al., 2020) and different *Dunaliella* sp. and *Chaetoceros* sp. species (Iglesias et al., 2019); c) the characterization of diverse environmental stimuli on algal metabolome, as reported for the spatio-temporal metabolic modulation of the brown seaweeds *Lobophora* sp. (Gaubert et al., 2019) and *Fucus virsoides* (Felline et al., 2019); and d) the determination of intermediate metabolites involved in the modulation of general metabolic pathways, such as pentose phosphate pathway, tricarboxylic acid cycle and glycolysis, influenced by different stimuli, as it was found for many microalgae (Arumugam et al., 2021; Mariam et al., 2021; Xue et al., 2017; Zhao et al., 2021). In parallel, targeted metabolomic approaches in algal research have been mostly focused on the investigation of phenolic compounds biosynthesized by marine seaweeds, providing insight into their composition in terms of phenolic acids, flavonoids, and phlorotannins (Agregán et al., 2017; Olate-

Gallegos et al., 2019; Yan et al., 2019; Zhong et al., 2020). Interestingly, Obando et al. (2022) performed a targeted approach to determine the diterpenoid composition of the brown seaweed *Dictyota menstrualis*, suggesting a novel natural source of these bioactive compounds. Finally, research has also been conducted to achieve the metabolic fingerprinting of a vast number of seaweeds that allowed obtaining important chemotaxonomic markers attributed to different phyla and/or species. Some of those marker metabolites included amino acids, organic acids, and sugars (Hamid et al., 2019); unsaturated fatty acids, terpenoids, and dipeptides (Ghallab et al., 2022); phytosterols, with a special insight into the enhanced species-discriminant behavior of fucosterol among brown seaweeds (X. L. Zhang et al., 2016); mycosporin-like amino acids (Orfanoudaki et al., 2019); and polar galactolipids and pigments on the fingerprinting of *Bathycoccus* sp., *Micromonas* sp., *Ostreococcus* sp. microalgae (Marcellin-Gros et al., 2020). In addition, a lipidomics analysis was performed on the microalga *Chaetoceros calcitrans* to attribute the bioactive properties of extract to different metabolites, featuring particular glycolipids, fatty acids, terpenoids, and carotenoids as responsible compounds (Azizan et al., 2020). Based on the existing literature, metabolomics constitutes a Swiss-army knife for the development of novel insights into the characterization of the unraveled potential of seaweeds and microalgae as a source of economically important natural nutraceuticals.

5. Conclusions and future perspectives

In recent years, the search for natural-based ingredients has exponentially increased in response to consumers' demand for food, nutraceutical, and cosmetics products with no added synthetic additives and additional health benefits. In parallel, more sustainable production and consumption of food products are required to facilitate the transition of the industrial processes towards a more resource-efficient circular economy. In this scenario, algae (seaweed and microalgae) represent an underexploited, highly available and sustainable resource of compounds with associated biological activities due to their primary and secondary metabolism. Among primary metabolites, polysaccharides constitute the most exploited family with industrial purposes, under the form of phycocolloids, exhibiting important features as natural food additives and active ingredients of novel food packaging systems and drug-delivery systems. In a lesser extent, phycobiliproteins, are exploited with a dual objective, acting as colorants and preservative compounds thanks to their associated organoleptic properties and bioactivities. Additionally, algal secondary metabolites are achieving a growing interest, regarding their exploitation as natural supplements with health-promoting attributes, as a consequence of their antioxidant, antimicrobial, anti-inflammatory, and cytotoxic activities. Phlorotannins and xanthophylls, especially astaxanthin and fucoxanthin, represent the major examples of algal bioactive compounds commercially exploited as nutraceuticals. Thus, using algae-based compounds in the design of sustainable food and nutraceutical products offers multiple opportunities: the improvement of food quality, the enrichment of food matrices with health promoters, and a suitable alternative to meet the growing vegetarian and/or vegan food market.

Nevertheless, a precise identification of algae metabolites is of paramount importance to fully unleash these natural matrices' chemical potential through the application of fingerprinting approaches. To fill this gap, metabolomics appears as a powerful tool to obtain a comprehensive metabolic profile of heterogeneous algae extracts scarcely studied, allowing the identification and quantification of algae metabolites. Hence, this work compiled recent advances in metabolomics applied to macro and microalgae that dealt with the functional characterization of these organisms. Thanks to the analytical power and plasticity of metabolomic approaches, several authors have already achieved a detailed insight on the biosynthesis of amino acids, phenolic compounds, phytosterols, terpenoids, lipids, carotenoids, and pigments by a wide range of both seaweeds and microalgae. Moreover, the

combination of metabolomics with other high-throughput technologies, like genomics and proteomics, may open a wide perspective on the field of biotechnology and related sectors to optimize either low-scale or large-scale metabolite production, revealing that algae are potent bio-factories with countless applications in food, nutraceutical, and pharmaceutical fields.

CRedit authorship contribution statement

Pascual Garcia-Perez: Conceptualization, Methodology, Software, Formal analysis, Data curation, Writing – original draft, Writing – review & editing, Visualization, Supervision. **Lucia Cassani:** Methodology, Investigation, Data curation, Writing – original draft, Writing – review & editing, Visualization. **Paula Garcia-Oliveira:** Methodology, Validation, Investigation, Investigation, Writing – original draft, Writing – review & editing, Visualization. **Jianbo Xiao:** Software, Resources, Writing – review & editing, Supervision, Project administration, Funding acquisition. **Jesus Simal-Gandara:** Conceptualization, Formal analysis, Resources, Writing – review & editing, Supervision, Project administration, Funding acquisition. **Miguel A. Prieto:** Conceptualization, Software, Formal analysis, Resources, Writing – review & editing, Visualization, Supervision, Project administration, Funding acquisition. **Luigi Lucini:** Software, Validation, Formal analysis, Resources, Data curation, Writing – original draft, Writing – review & editing, Supervision, Project administration, Funding acquisition.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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