




# Biological properties and potential of compounds extracted from red seaweeds

M. Carpena · P. Garcia-Perez · P. Garcia-Oliveira · F. Chamorro · Paz Otero · C. Lourenço-Lopes · Hui Cao · J. Simal-Gandara · M. A. Prieto 



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**Abstract** Macroalgae have been recently used for different applications in the food, cosmetic and pharmaceutical industry since they do not compete for land and freshwater against other resources. Moreover, they have been highlighted as a potential source of bioactive compounds. Red algae (Rhodophyta) are the largest group of seaweeds, including around 6000 different species, thus it can be hypothesized that they are a potential source of bioactive compounds. Sulfated polysaccharides, mainly agar and carrageenans, are the most relevant and exploited compounds of red algae. Other potential molecules are essential fatty acids, phycobiliproteins, vitamins, minerals, and other secondary metabolites. All these compounds have been demonstrated to exert several biological activities, among which antioxidant, anti-inflammatory, antitumor, and antimicrobial properties

can be highlighted. Nevertheless, these properties need to be further tested on in vivo experiments and go in-depth in the study of the mechanism of action of the specific molecules and the understanding of the structure–activity relation. At last, the extraction technologies are essential for the correct isolation of the molecules, in a cost-effective way, to facilitate the scale-up of the processes and their further application by the industry. This manuscript is aimed at describing the fundamental composition of red algae and their most studied biological properties to pave the way to the utilization of this underused resource.

**Keywords** Red algae · Sulfated polysaccharides · Bioactive compounds · Biological properties · Extraction techniques

## Abbreviations

### Generic

FAO Food and Agriculture Organization  
GRAS Generally Recognized As Safe  
CO<sub>2</sub> Carbon dioxide

### Chemical composition

PUFAs Poly-unsaturated fatty acids  
ω-3 Omega-3 fatty acids  
ω-6 Omega-6 fatty acids  
TC Total cholesterol  
LDL-C Low-density lipoprotein cholesterol  
TAG Triacylglycerols

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M. Carpena · P. Garcia-Perez · P. Garcia-Oliveira · F. Chamorro · P. Otero · C. Lourenço-Lopes · H. Cao · J. Simal-Gandara (✉) · M. A. Prieto (✉)  
Nutrition and Bromatology Group, Department of Analytical Chemistry and Food Science, Faculty of Science, Universidade de Vigo, E-32004 Ourense, Spain  
e-mail: jsimal@uvigo.es

M. A. Prieto  
e-mail: mprieto@uvigo.es

P. Garcia-Oliveira · M. A. Prieto  
Centro de Investigação de Montanha (CIMO), Instituto Politécnico de Bragança, Campus de Santa Apolonia, 5300-253 Bragança, Portugal

HDL-C	High-density lipoprotein cholesterol
MAA	Mycosporine-like amino acids

### Biological properties and molecular markers

RSA	Free-radical scavenging activity
ROS	Reactive oxygen species
DPPH	2,2-Diphenyl-picryl-hydrazyl
ABTS	Hydrogen peroxide-mediated 2,2-azinobis-(3-ethylbenzothiazoline-6-sulfonate)
FRAP	Ferric reduction antioxidant power assay
ORAC	Oxygen Radical Absorbance Capacity
TBARS	Thiobarbituric acid reactive substances assay
CKs	Cytokines
LPS	Lipopolysaccharide
COX-1	Cyclooxygenase-1
COX-2	Cyclooxygenase-2
5-LOX	Lipoxygenase
TNF- $\alpha$	Tumor necrosis factor alpha
ILs	Interleukins
NO	Nitric oxide
PTP1B	Protein tyrosine phosphatase 1B
DPP4	Dipeptidyl peptidase-4
TVR	Tumor volume reduction
HSV-1	Herpes simplex virus-1
HIV	Human immunodeficiency virus
AChE	Acetylcholinesterase
BuChE	Butyrylcholinesterase

### Extraction technologies

SLE	Solid-liquid extraction
PLE	Pressurized liquid-assisted extraction
SFE	Supercritical fluid extraction
MAE	Microwave assisted extraction
EAE	Enzymatic assisted extraction

### Introduction

Marine biotechnology (also called blue biotechnology) consists of the application of biological resources from the sea for industrial, medical or environmental purposes (Thompson et al. 2017), which constitutes a precious economical sector presenting a yearly turnover of 3.93 \$ together with great expectations, including many different subjects and organisms which could report benefits to the industry (Bloch and Tardieu-Guigues 2014; Thompson et al. 2017). Among them, micro- and macro-algae have gained

much attention as natural sources of bioactive compounds that exhibit a great applicability as dietary ingredients and other industrial processes (Bloch and Tardieu-Guigues 2014; Sudhakar et al. 2018). On these bases, seaweeds have been consumed for many years in Asian countries, since they constitute a rich source of fiber, vitamins, minerals and antioxidants, thus prompting an increase in their consumption and, consequently, promoting intense efforts on the characterization of their health-enhancing properties (Cardozo et al. 2007; Gómez-Ordóñez et al. 2012; Cian et al. 2015; Rudtanatip et al. 2018; Gurpilhares et al. 2019).

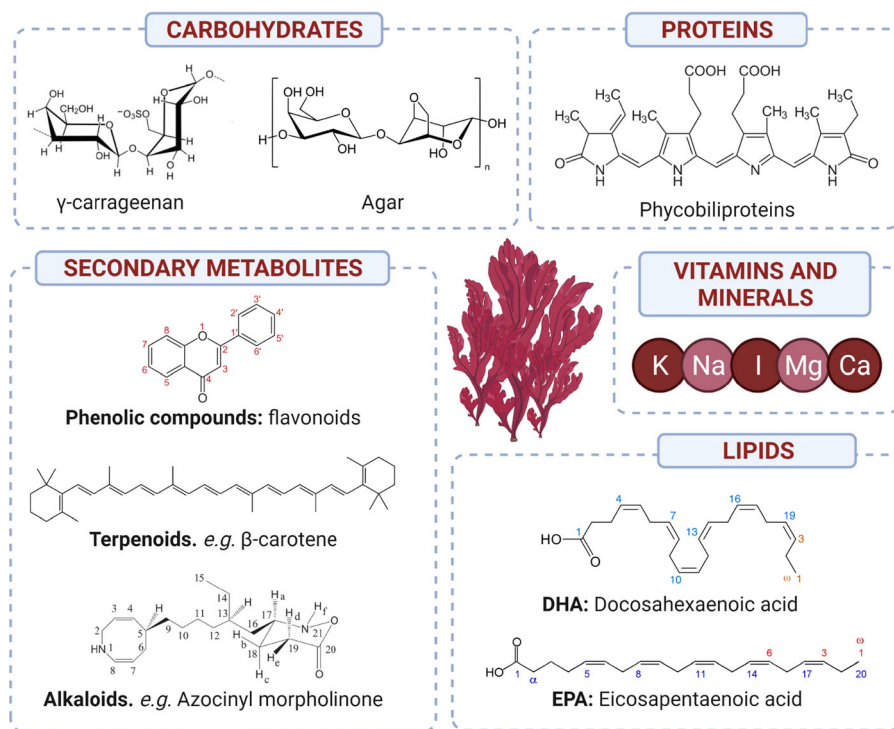
Macroalgae are becoming of great importance within the aquaculture industry, as they are a potential feeding for marine organisms, including corals (Gurgel and Lopez-Bautista 2007), and they do not compete against other resources proceeding from the land and freshwater. Moreover, macroalgae are remarkable for their rapid growth rate and high polysaccharides content, becoming great candidates for biofuel production (Sudhakar et al. 2018). In addition, their associated positive effects on health and biological activities must be highlighted as of great importance on food, pharmaceutical and cosmetic fields (Gurpilhares et al. 2019). Concerning their classification, marine macroalgae are classified into three groups, according to their main pigments as green (Chlorophyta), red (Rhodophyta) and brown algae (Phaeophyta) (Mohamed et al. 2012; Belghit et al. 2017; Davies et al. 2019). Regarding their chemical composition, macroalgae exhibit a high content of water, carbohydrates and proteins and a low lipid percentage (Sudhakar et al. 2018). Considering their differential composition, the phylum Rhodophyta presents the highest proportion of bioactive compounds, accounting for more than 1600 individual compounds, representing the 53% of bioactive compounds reported in algae (Leal et al. 2013).

Additionally, red algae form the largest group of seaweeds, including around 6,000 different species. With respect of biological aspects, red seaweeds are smaller than green and brown algae, being usually found in equatorial regions along intertidal areas and beyond. Due to their color-based classification, red algae contain a specific combination of pigments, *i.e.*: chlorophyll *a* and *d*, carotenoids and phycobiliproteins (Gurgel and Lopez-Bautista 2007; Cian et al. 2015).

Considering their nutritional composition, red algae have been proposed to be incorporated to the human diet because they present the highest levels of proteins among algae, and huge amounts of carbohydrates and minerals (Belghit et al. 2017; Øverland et al. 2019; Torres et al. 2019), as depicted in Fig. 1. In particular, the families *Gelidiaceae* and *Gracilariaceae* have been revealed as economically interesting, as they are the major sources of agar and carrageenans, reaching worldwide production yields of 10,000 tons and 25,000 tons, respectively, valued at 200 \$ million each (Cardozo et al. 2007). Consequently, the cultivation of red seaweeds is mainly aimed at the production of carrageenans, traditionally extracted from *Chondrus crispus* wild populations in Canada, Ireland, Portugal, Spain and France and from *Gigartina* collected in South America and Southern Europe. However, the growing demands of carrageenans motivated the establishment of macroalgae farming systems with *Eucheuma* sp. in Philippines (Valderrama et al. 2013; Hedberg et al. 2018), becoming the major producer worldwide and spreading macroalgae cultivation along other Asian countries, promoting the production of *Porphyra* sp. (nori),

*Kappaphycus alvarezii* and *Eucheuma denticulatum* (Valderrama et al. 2013). According to the Food and Agriculture Organization (FAO), in the last decade red macroalgae production reached almost 9 million wet tons, representing the 47% of the total production of cultivated seaweeds (Valderrama et al. 2013).

On these bases, due to the positive nutritional and economic impact attributed to red algae, greater efforts are required to promote their exploitation and diffusion along Western countries. Thus, this review is aimed at describing the chemical composition of red algae, with a special focus on compounds with health-enhancing properties. Consequently, a deep description of the biological properties associated with red algae extracts is provided, focusing on their antioxidant, antimicrobial, anticancer, anti-inflammatory, antidiabetic, and metabolic regulator activities. Furthermore, a detailed insight on the extraction methodologies applied to the isolation and production of bioactive compounds is also described, with the aim of providing evidence on the beneficial properties of these marine organisms to be incorporated into different food, cosmetic, and pharmaceutical formulations.



**Fig. 1** Main bioactive compounds of red algae

## Chemical composition of red algae

Marine algae are great candidates for being included in dietary regimes due to their nutritional and chemical composition. Over 3000 marine natural products extracted from them have been largely identified (Leal et al. 2013; Belghit et al. 2017). However, seaweeds have not been commonly exploited with pharmaceutical and/or nutraceutical purposes, but a growing interest, led by the traditional consumption in Asian countries, has promoted the research of chemical constituents from algae (Sangha et al. 2013). Consequently, a structural and functional characterization of red seaweed constituents, which are responsible for the biological properties associated with these organisms, should be performed to assess their incorporation into the diet. Taken all together, the chemical composition of red seaweeds is composed of carbohydrates, lipids, proteins, peptides, vitamins, minerals and secondary metabolites (Barbalace et al. 2019; Torres et al. 2019). Figure 1 summarized the most relevant constituents found in red seaweeds. In Table 1, main applications of these constituents have been compiled.

### Carbohydrates

Although monosaccharides have been reported in red algae, little attention has been paid to these molecules, being poorly characterized. In this sense, several free sugars have been found in red algae including fucose, xylose, mannose, galactose, and glucose (Gómez-Ordóñez et al. 2010, 2014). On the contrary, polysaccharides constitute the major constituents in marine algae, including the red ones, which enables the enhancement of the commercial value of red algae, thanks to their potential applications in the food industry, where they are usually exploited as an efficient source of dietary fiber, but also in both the pharmaceutical and biomedical industries. According to their prevalence in algal sources, agar and carrageenan, both sulfated polysaccharides known as phycocolloids, are the most relevant carbohydrates in red seaweeds, accounting for up to 40–50% of the dry weight (Torres et al. 2019), followed by other polysaccharides found in significantly lower amounts, such as xylans, sulphated galactans and porphyrans (Øverland et al. 2019).

Thus, carrageenan has been reported as the major representative of red marine algae, representing the most relevant constituent of algal cell walls. This

polysaccharide is a sulfated polygalactan mainly formed by  $\alpha$ - and  $\beta$ -D-galactopyranose subunits linked by two different types of glycosidic bonds:  $\alpha$  (1  $\rightarrow$  3) and  $\beta$  (1  $\rightarrow$  4). According to the configuration and proportion of such bonds, different kind of carrageenans have been identified, accounting for more than 15 types with industrial relevance currently described (Prado-Fernández et al. 2003; Hilliou et al. 2006; Cunha and Grenha 2016), being divided into three groups, as a general rule: kappa, iota and lambda,  $\kappa$ ,  $\iota$ ,  $\lambda$  carrageenans, respectively. Such carrageenan classification mostly owes to structural purposes and the heterogeneous existence of chemical substitutions, which lead to specific physicochemical properties that contribute to the differential features and applicability associated with their derivative products (Cunha and Grenha 2016). Furthermore, specific distributions of carrageenans have been attributed to individual algal species. For instance, *C. crispus* presents a mixture of both  $\kappa$ - and  $\lambda$ -carrageenans that cannot be separated during their large-scale extraction procedure. Indeed, for the production of individual compounds, different algal sources are employed, since  $\kappa$ -carrageenan is usually extracted from *Kappaphycus alvarezii*, whereas  $\lambda$ -carrageenan is isolated from different species from the genus *Gigartina* (Cunha and Grenha 2016; Torres et al. 2019). Considering its food application, carrageenans have been identified as Generally Recognized As Safe (GRAS), so they have been collectively approved for their use on human consumption. Due to their chemical nature as complex polysaccharides, carrageenans cannot be digested by human digestive tract, although they can be fermented by the colonic microbiota (Gómez-Ordóñez et al. 2012). On these bases, to date, these substances are not known for their potential to be added to human diet (Necas and Bartosikova 2013; Torres et al. 2019). Instead, carrageenans are well-known for their additional properties that guide their industrial applications as gelling, stabilizing and emulsifying agents (Cunha and Grenha 2016; Sudhakar et al. 2018). Besides such food-related properties, a number of reports have also listed several bioactivities attributed to carrageenans, including anticoagulant, antiviral, antioxidant and antitumoral effects, together with immunomodulatory and cholesterol-lowering properties (Pangestuti and Kim 2014; Cunha and Grenha 2016).

**Table 1** Applications related to the main compounds found in red algae

Compound	Application	Reference
Carrageenan	Jellifying, stabilizing and emulsifying properties	Cunha and Grenha (2016)
	Antioxidant activity	Silva et al. (2012), Gómez-Ordóñez et al. (2014), Cian et al. (2015)
	Antithrombotic, anti-inflammatory and antidiabetic activities	Holdt and Kraan (2011), Gómez-Ordóñez et al. (2012), Cian et al. (2015)
	Oil binding properties and emulsifier	Suleria et al. (2016)
	Antitumor, antiviral, anticoagulant and immunomodulation activities	Cardozo et al. (2007), Gómez-Ordóñez et al. (2012), Mohamed et al. (2012), Silva et al. (2012), Cunha and Grenha (2016), Davies et al. (2019), Torres et al. (2019)
Agar	Cholesterol and lipid-lowering effects	Mohamed et al. (2012)
	Serum cholesterol and triglyceride levels reduction	Silva et al. (2012)
	Gelling and stabilizing properties	Davies et al. (2019)
	Texture improvement and stabilizing properties	Suleria et al. (2016)
Polar lipids, PUFAs and sulfolipids	Viscosifying and emulsifying properties	Maciel et al. (2016)
	Anticoagulant	Holdt and Kraan (2011)
	Antitumor, anti-aggregation, antioxidant, UV rays' absorption	Maciel et al. (2016), Belghit et al. (2017), Gурpilhares et al. (2019)
Lectins	Anti-inflammatory, immunomodulatory, anti-angiogenic, and neuroprotective, antimicrobial, antifungal properties	Mohamed et al. (2012)
	Reducing coronary diseases, diabetes, and osteoarthritis	Holdt and Kraan (2011), Singh and Walia (2018)
Phycobiliprotein	Carcinoma inhibition. Anti-HIV, anti-influenza, anti-coronavirus, anti-hepatitis, anti-herpes simplex virus, miscellaneous, anti-cancer, anti-nociceptive, anti-inflammatory, anti-microbial, anti-encephalitis	Suleria et al. (2016)
	Natural food colorant	Sudhakar et al. (2018)
	Fluorescent pigments: medical reagents	Mohamed et al. (2012)
	Antioxidant properties, prevention of neurodegenerative diseases, cancer and gastric ulcers	Holdt and Kraan (2011)
Sulfated polysaccharides	Anti-inflammatory, antioxidant, antiviral, antitumor, serum lipid reducing, neuroprotective, hypercholesterolemic, liver protecting, hepatoprotective	Rudtanatip et al. (2018)
	Immune stimulant effect	Mohamed et al. (2012)
Porphyran	LDL cholesterol reduction and HDL increase	Mohamed et al. (2012), Davies et al. (2019), Øverland et al. (2019)
	Anti-allergic activity, scavenging free radical activity, antitumor activities	Mohamed et al. (2012)
	Elevation of primary antibody response, macrophages stimulation and Th-2 type immune system suppression without affecting Th-1 type immune system	Holdt and Kraan (2011)
	Anticoagulant, anti-hypercholesterolemic, antitumor	Mohamed et al. (2012)
	Hepatoprotective properties	

**Table 1** continued

Compound	Application	Reference
Fatty acids	Antifungal activity	De Corato et al. (2017)
Pigments and MAA	Photo-protective compounds. Antioxidant properties	Cardozo et al. (2007), Lalegerie et al. (2019)
	Anticancer, anti-proliferative and antitumor effects	Mohamed et al. (2012)
Phloroglucinol	Anti-allergic, antifungal, antimicrobial and anti-feeding	Gómez-Ordóñez et al. (2012)
Soluble dietary fiber	Retard digestion and glucose absorption	Mohamed et al. (2012)
	Prebiotic	Cian et al. (2015)
Iodine	Antioxidant, anti-goiter and anticancer	Mohamed et al. (2012)
Glycolipids	Antimicrobial, antifungal, antitumor, antiviral, anti-inflammatory activities	Maciel et al. (2016)

In addition to carrageenans, agar constitutes another relevant polysaccharide from algae. Concerning its chemical structure, agar is a type of phycocolloid belonging to galactan family composed by  $\alpha$  (1  $\rightarrow$  4)-3,6-anhydro-L-galactose and  $\beta$  (1  $\rightarrow$  3)-D-galactose residues, accompanied by a slight sulfate content. The agar proportions with respect to total algal weight vary among the species and its abundance and quality are also highly dependent of environmental factors and seasonal variations, together with the physicochemical composition of each alga (Cardozo et al. 2007). With respect to its applicability, agar has been identified as GRAS, being already assessed as a safe additive to be incorporated into different food matrices. Thus, regarding its possible incorporation to diet, and keeping in mind its polysaccharidic nature, it cannot be digested by the human gastrointestinal tract, as it occurred with carrageenans, although it can be metabolized by intestinal bacteria to give rise to D-galactose (Sudhakar et al. 2018). Hence, both polysaccharides have been suggested to promote prebiotic effects, improving the performance of human digestion (Mohamed et al. 2012; Cian et al. 2015). Concerning its physicochemical properties as food additives, agar is mainly used as a gelling and stabilizing agent, as currently found for many food matrices, but it has also been exploited as cryoprotectants and solidifying agents, incorporated as ingredients of growth media for the *in vitro* culture of different organisms, including plants and microorganisms (Sudhakar et al. 2018; Torres et al. 2019).

## Lipids

In general, marine algae present a low content of lipids, which ranges between 1 and 5% of total dry weight. However, they do possess a high proportion of poly-unsaturated fatty acids (PUFAs) (Belghit et al. 2017; Praveen et al. 2019) and other lipids like sterols but also make part of different heterogeneous compounds, such as glycolipids and phospholipids (Torres et al. 2019). Among fatty acids, marine algae are rich in essential fatty acids, especially omega-3 fatty acids ( $\omega$ -3). In particular, red macroalgae contain C-20  $\omega$ -3 PUFAs, including eicosapentaenoic acid,  $\alpha$ -linolenic acid, and docosahexaenoic acid (Maciel et al. 2016; Torres et al. 2019). Furthermore, besides  $\omega$ -3 PUFAs, omega-6 fatty acids ( $\omega$ -6) have been found in red algae in a much lesser extent, being mostly represented by arachidonic acid. As a result, they show a very low  $\omega$ -6/ $\omega$ -3 rate, suggesting a healthy lipid profile in which the prevalence of  $\omega$ -3 PUFAs over  $\omega$ -6 indicates an efficient profile with beneficial properties on the prevention of cardiovascular diseases, osteoarthritis and diabetes, together with enhanced anti-inflammatory and anti-thrombotic properties (Macartain et al. 2007; Maciel et al. 2016). Moreover, besides such bioactivities, additional biological properties have been associated with those essential fatty acids derived from marine sources, including red algae, acting as antifungal, antibacterial, antiviral and antitumor agents (Pereira 2011; Torres et al. 2019).

## Proteins and peptides

Among the different algae classes found in marine ecosystems, red seaweeds exhibit the highest content of proteins, followed by green and, finally, brown algae (Belghit et al. 2017; Øverland et al. 2019). As a general rule, the protein content of algae usually ranges between 5 and 20%, although red algae may achieve greater proportions, with maximum values reaching 47% of total dry weight (Cian et al. 2015; Rudtanatip et al. 2018; Praveen et al. 2019). Nevertheless, proteins depict a species-dependent occurrence, considering that some species, such as those from *Gracilaria* genus present a low protein content below 5%, whereas others like *Pyropia tenera* shows a protein content of 37% of dry weight. Moreover, it should be noted that protein content also shows a significant influence on several experimental, environmental and geographical factors, such as the extraction and purification procedures, seasonal variations and the collection area (Holdt and Kraan 2011).

Concerning the amino acidic composition of red algae proteins, a high content of essential amino acids has been reported, being aspartic acid and glutamic acid the most prevalent residues, accounting for up to 22–44% of total amino acids making part of red algae proteins (Cian et al. 2015). Thus, such elevated proportion of acidic amino acids has been identified as a specific trait of red seaweeds, being responsible for their organoleptic characteristics, such as flavor and taste (Cian et al. 2015). Moreover, with respect of total proteins, phycobiliproteins constitute the most prevalent proteins in red seaweeds achieving values up to 50% of total protein content, and causing the reddish coloration attributed to these species (Niu et al. 2007). Among phycobiliproteins, phycoerythrin and phycocyanin, together with their combination, have been reported as the major constituents of this family of biomolecules (Cian et al. 2015). Deriving from proteins, bioactive peptides have been isolated in different red algal sources, mostly in *Palmaria* spp. and *Porphyra* spp., although a limited application of these molecules was observed, being only exploited as food additives in a number of functional foods commercialized in Asian countries (Lafarga et al. 2020). In a lesser extent, lectins have been also identified as versatile proteins widely distributed in red algae, acting as cell signaling mediators and antimicrobial compounds (Liao et al. 2003).

## Vitamins and minerals

In addition to the above-mentioned macronutrients associated with red seaweeds, these organisms also contain several nutrients found in very scarce concentrations but developing a significant beneficial effect on human health. Among these nutrients, vitamins play a major role, as great variety of these compounds have been isolated from red algae, including both water-soluble vitamins, B1, B2, B12, and C) and lipid-soluble vitamins, such as pro-vitamin A ( $\beta$ -carotene) and vitamin E (Škrovánková 2011). Indeed, vitamins from marine sources have been already used for the enrichment of functional foods (Figure 1).

Besides such organic micronutrients, minerals have been also reported in red seaweeds as inorganic micronutrients. Due to their marine habitats, red algae are able to accumulate great mineral concentrations, proceeding from seawater (Rosemary et al. 2019). In this sense, Na, K, Ca, and Mg, have been identified in high concentrations, ranging 0.4–4 g per 100 g of red seaweeds, such as *Chondrus* spp. and Nori, whereas trace elements, such as Fe, Zn, Mn, and Cu have been reported, as well, in concentrations up to 10 mg per 100 g (Rupérez 2002). Moreover, special attention has been paid to iodine, since this essential mineral has been also reported in significant amounts in *Gracilaria lemaneiformis*, contributing to the promotion of thyroid function (Wen et al. 2006).

## Secondary metabolites

Besides the previously described compounds from red algae, as part of their primary metabolism, these seaweeds also biosynthesize different compounds with associated biological activities as a result of their secondary metabolism, committed to the development of defensive and adaptative responses against environmental stresses. In the particular case of red seaweeds, multiple reports have indicated the presence of phenolic compounds, terpenoids, and alkaloids as the most prevalent secondary metabolites (Aziz et al. 2020).

Among phenolic compounds, ubiquitously found natural phenolics, mostly phenolic acids and flavonoids are present in red seaweeds, together with other phenolic compounds characteristic of marine sources, such as phlorotannins and bromophenols, all characterized by their potent antioxidant associated activity.

Thus, phenolic acids reported in red algae are *p*-coumaric acid, caffeic acid, salicylic acid, hypogallic acid, and chlorogenic acid (Kazłowska et al. 2010; Onofrejová et al. 2010). In the same way, multiple flavonoids have been also identified, mostly flavonols and flavan-3-ols, like rutin and catechin from *Porphyra dentata* (Kazłowska et al. 2010), and quercetin, rutin and catechin from *Euchema cottonii* (Namvar et al. 2012). Despite being reported as exclusive of brown algae, phlorotannins have been also recently associated with red algae (Aziz et al. 2020). These polymers of phloroglucinol have caught the attention of many researchers due to their function as bioactive compounds restricted to marine sources. On the contrary, little is known about bromophenols, which contribute to seaweed flavor but have been also reported as secondary metabolites, thus requiring further studies aiming at their characterization as bioactive compounds (Cotas et al. 2020). Besides phenolics, another compounds proceeding from the polyketide biosynthetic pathway are furanones, which have been largely determined in different red algae combining their involvement in settlement and their effectiveness as bioactive compounds (Dworjany et al. 2006).

In the case of terpenoids, several compounds with different isoprene polymerization degree have been found in red seaweeds, ranging from sesquiterpenoids to tetraterpenoids. Thus, in the case of red algae, most terpenoids are biosynthesized in response to the attack of herbivores and pathogenic microorganisms (Philippus et al. 2018). Nevertheless, on top of these compounds, carotenoids are considered one of the major terpenoids found in red algae, also contributing to their special pigmentation, being mainly represented by  $\alpha$ - and  $\beta$ -carotene, lutein, and zeaxanthin. Among them,  $\beta$ -carotene gained much interest in the field of food industry because of its behavior as a natural colorant and antioxidant, being suggested as a promising candidate for its addition to food matrices (Holdt and Kraan 2011).

With respect to alkaloids, limited information is available in seaweed sources from the literature. However, previous evidence has pointed at these nitrogen-containing compounds as excellent anti-inflammatory compounds of marine origin, which prompted the research on their isolation and characterization (Souza et al. 2020). In this sense, red algae from *Gracilaria* genus have been identified as

excellent sources of these marine alkaloids, together with those from *Laurencia* genus in a lesser extent, whose anti-inflammatory and antimicrobial mechanisms of action have been widely characterized, being azocinyl morpholinone the major compound (de Almeida et al. 2011).

## Biological properties

### Antioxidant activity

Several reports have indicated that extracts derived from different red algae species promote a potent antioxidant activity throughout different mechanisms, including free-radical and reactive oxygen species (ROS) scavenging activity, inhibition of lipid oxidation, and metal chelation. It is important to highlight that this activity has been proved by different assays, showing a strong dependence on the species and the experimental procedure employed for the performance of plant extracts (Rodrigues et al. 2015c). Moreover, among the different compounds isolated from red seaweeds, phenolic compounds, especially phenolic acids and flavonoids, and sulphated polysaccharides, mostly carrageenans, have been identified as the major responsible of the antioxidant activity associated with these species. Table 2 shows an overview of the antioxidant activity determined in different red algal extracts. Thus, the phenolic compounds-enriched extracts from different Rhodophyta species were assessed in terms of free-radical scavenging activity (RSA), as determined by 2,2-diphenylpicryl-hydrazyl (DPPH), and hydrogen peroxide-mediated 2,2-azinobis-(3-ethylbenzothiazoline-6-sulfonate) (ABTS) oxidation of the extracts from *Porphyra tenera* (Onofrejová et al. 2010), *Gracilaria verrucosa* (de Almeida et al. 2011), *Gracilaria arcuata* (Agatonovic-Kustrin and Morton 2017), and *Palmaria palmata* (Wang et al. 2010; Hardouin et al. 2014). In the same way, polysaccharides from red algae have been revealed as potent antioxidant compounds, according to the results found for the extracts from *Mastocarpus stellatus* (Gómez-Ordóñez et al. 2014) and *Pterocladia capillacea* (Fleita et al. 2015), by means of DPPH scavenging. On the other hand, the antioxidant properties of red algal extracts in terms of metal chelation and reducing power were assessed via the determination of ferric reduction antioxidant



**Table 2** Antioxidant and anti-inflammatory properties of red algae

Species	Extraction (solvent)	Compound	Activity	References
<b>Antioxidant</b>				
<i>Porphyra tenera</i>	PLE (50% MeOH)	PA	TEAC = 20–25 $\mu\text{mol/g}$	Onofrejová et al. (2010)
<i>Gracilaria birdiae</i>	UAE (0.1 M NaOH)	SP	Total antioxidant capacity = 41.6–75.9 mg/g AAE	Fidelis et al. (2014)
<i>Porphyra yezoensis</i>	UAE (W)	PF	Scavenging activity on hydroxyl (0.065 mg/mL) and superoxide radical (0.182 mg/mL)	Zhou et al. (2012)
<i>Mastocarpus stellatus</i>	SLE (W)	Carrageenans	FRAP (44.9 $\mu\text{mol TE/g}$ )	Gómez-Ordóñez et al. (2014)
<i>Gigartina</i> spp.	EAE (alkaline protease)	Fucoidan	Inhibition of superoxide radical ( $\text{IC}_{50}$ = 0.058 mg/mL). Peroxidation ( $\text{IC}_{50}$ = 1.250 mg/mL)	Rocha De Souza et al. (2007)
<i>Gracilaria arcuata</i>	SLE (EtOH)	PC, sterols	DPPH (27.3 GAE mg/100 g)	Agatonovic-Kustrin and Morton (2017)
<i>Palmaria palmata</i>	EAE (proteases & cellulases, W)	TPC	DPPH ( $\text{EC}_{50}$ = 0.6–1.9 mg/mL) ORAC (35.8 mmol TE/g extract)	Wang et al. (2010)
<i>Pterocladia capillacea</i>	EAE (glucanase & galactosidase)	PF	DPPH (Top value = 91.5% at 1000 mg/mL)	Fleita et al. (2015)
<i>Palmaria palmata</i>	HHPE + EAE (polysaccharidases)	TPC	ORAC (4–12 $\mu\text{g TE/g}$ )	Suwal et al. (2019)
<i>Solieria chordalis</i>		PF, Proteins	ORAC (15–20 $\mu\text{g TE/g}$ )	
<b>Anti-inflammatory</b>				
<i>Gracilaria caudata</i>	HAE (W)	SP	MPO activity, CKs levels reduction	Chaves et al. (2013)
<i>Solieria filiformis</i>	SLE (0.1 M NaCOOH buffer, papain digestion)	SP	Inhibition of nociceptive effects	De Araújo et al. (2011)
<i>Chondrus verrucosus</i>	HAE (0.17 M HCl)	SP	Inhibition of RBL-2H3 cell line	He et al. (2019)
<i>Gelidium pacificum</i>	HAE, (W, 95% EtOH)	SP	Inhibition of NO production from LPS-induced THP-1 cell line	Cui et al. (2019)
<i>Gracilaria salicornia</i>	SLE (EtOAc:MeOH, 1:1)	Chromenyl compounds	Inhibition of anti-inflammatory enzymes: COX-2, 5-LOX	Antony and Chakraborty (2019)
<i>Gracilaria birdiae</i>	SLE (0.1 M NaCOOH buffer, papain digestion)	SP	Inhibition of HO-1 pathway	De Sousa Oliveira Vanderlei et al. (2011)
<i>Gracilaria cornea</i>	SLE (0.1 M NaCOOH buffer, papain digestion)	SP	Inhibition of nociceptive effects, neutrophil migration, and oedema	Coura et al. (2012)
<i>Gracilaria opuntia</i>	HAE (W)	SP	Inhibition of anti-inflammatory enzymes: COX-1, 5-LOX	Makkar and Chakraborty (2017)
<i>Kappaphycus alvarezii</i>	SLE (MeOH:EtOAc, 1:1)	Terpenoids	Inhibition of inflammatory enzymes: COX, LOX	Chatter et al. (2011), Makkar and Chakraborty (2018)
<i>Laurencia glandulifera</i>	n.d	Neorogioltriol (diterpenoid)	Inhibition of edema in vivo, activity against LPS-induced macrophages, inhibition of NF- $\kappa$ B activation, TNF- $\alpha$ and NO levels and COX-2	Chatter et al. (2011), Makkar and Chakraborty (2018)

**Table 2** continued

Species	Extraction (solvent)	Compound	Activity	References
<i>Palmaria palmata</i>	SLE (MeOH/CHCl <sub>3</sub> )	Phospholipids	Inhibition of NO production by LPS-induced macrophages	Banskota et al. (2014)
<i>Laurencia snackeyi</i>	SLE (MeOH)	Halogenated monoterpenes	CKs, TNF- $\alpha$ , IL-1 $\beta$ , and IL-6 levels reduction	Wijesinghe et al. (2014)
<i>Porphyra columbina</i>	SLE (W)	PB	Upregulation of CKs: IL-10	Cian et al. (2012)

PLE, Pressurized liquid extraction; UAE, Ultrasound assisted extraction; SLE, Solid–liquid extraction; EAE, Enzyme assisted extraction, High hydrostatic pressure extraction; HAE, Heat assisted extraction; W, Water; TPC, Total phenolic compounds; PA, Phenolic acids; PC, Phenolic compounds; PB, Phycobiliproteins; SP, Sulfated polysaccharides; PF, Polysaccharide fraction; AAE, Ascorbic acid equivalent; TE, Trolox equivalents; GAE, Gallic acid equivalent; DPPH, 2-diphenyl-1-picrylhydrazyl; ORAC, Oxygen Radical Absorbance Capacity; TEAC, Trolox equivalent antioxidant capacity; MPO, Myeloperoxidase; NO, Nitric oxide; HO-1, Hemoxygenase-1; LPS, Lipopolysaccharide; COX-2, Cyclooxygenase-2; 5-LOX, 5-lipoxygenase; CKs, Cytokines; TNF- $\alpha$ , Tumor necrosis factor; NF-kB, nuclear factor kappa-light-chain-enhancer of activated B cells; IL, Interleukin

power assay (FRAP) and the ferrous chelating ability determination, being reported in extracts derived from *Gracilaria birdiae* (Fidelis et al. 2014), *M. stellatus* (Gómez-Ordóñez et al. 2014), and *P. palmata* (Yuan et al. 2005; Wang et al. 2010; Hardouin et al. 2014). Once again, both phenolic compounds and carrageenans have been suggested as responsible for the development of such bioactivity (Table 2). Furthermore, both compounds were reported to scavenge ROS, shown by the Oxygen Radical Absorbance Capacity (ORAC) determination, and inhibit lipid peroxidation through the thiobarbituric acid reactive substances assay (TBARS), as recorded in extracts from different species, such as *G. birdiae* (Fidelis et al. 2014), *Porphyra yezoensis* (Zhou et al. 2012), *Gigartina* spp. (Rocha De Souza et al. 2007), *P. palmata* (Yuan et al. 2005; Wang et al. 2010; Hardouin et al. 2014) and *Soliera chordalis* (Suwal et al. 2019).

#### Anti-inflammatory activity

Inflammation constitutes a multifactorial physiological process, developed by the immune system, closely related to oxidative stress, and contributing to cancer onset. Consequently, greater efforts should be directed to alleviate inflammation-related phenomena. In this sense, red algae extracts have been reported to

promote a multifaceted anti-inflammatory activity, as presented in Table 2, by the regulation of several phenomena, including the alleviation of inflammation-associated nociceptive effects, the inhibition of pro-inflammatory enzymes and cytokines (CKs), the inhibition of leukocyte migration, the regulation of cell signaling pathways involved in the onset of inflammation, and the promotion of anti-inflammatory CKs. Once again, sulphated polysaccharides, especially carrageenans, and proteins, such as lectins and phycobiliproteins, were assigned as the major responsible for the anti-inflammatory effects attributed to red algae (Table 2). Indeed, such effects have been demonstrated in both in vitro models, as it is the case of lipopolysaccharide (LPS)-induced RAW 264.7 macrophages, and in vivo, mostly murine models.

Thus, carrageenan-enriched extracts from different Rhodophyta species have been assessed in terms of anti-inflammatory effects, as it was observed by *Gracilaria caudata* (Chaves et al. 2013), *Soliera filiformis* (De Araújo et al. 2011), *Chondrus verrucosus* (He et al. 2019), *Gelidium pacificum* (Cui et al. 2019), different species from *Gracilaria* genus (*Gracilaria salicornia* (Antony and Chakraborty 2019), *G. birdiae* (De Sousa Oliveira Vanderlei et al. 2011), *G. cornea* (Coura et al. 2012), and *Gracilaria opuntia* (Makkar and Chakraborty 2017)). Among the

different effects attributed to these extracts, the most relevant pro-inflammatory enzymes inhibited were cyclooxygenases-1 and -2 (COX) and lipoxygenase (5-LOX) and myeloperoxidase. In addition, lipid-enriched extracts from *Kappaphycus alvarezii* [92], *Laurencia grandulifera* [93], *P. palmata* (Banskota et al. 2014), and *Laurencia snackeyi* (Wijesinghe et al. 2014) enabled the reduction of the expression of pro-inflammatory CKs *i.e.*: tumor necrosis factor alpha (TNF- $\alpha$ ), and interleukins (ILs) 1 $\beta$  and 6, the inhibition of nitric oxide (NO) production. Additionally, the phycobiliprotein-enriched extracts of *Porphyra columbina* were recorded in the basis of the up-regulation of anti-inflammatory CKs, such as IL-10 (Cian et al. 2012).

In general, the combined determination of antioxidant, anticancer, and anti-inflammatory activities from red seaweed extracts could face the further determination of these species as promising natural sources of cancer chemopreventive agents (García-Pérez et al. 2019).

#### Metabolic activity

Nowadays, diabetes and cardiovascular diseases are one of the most important global health problems, since they are the main responsible for premature deaths between 30 and 70 years, together with cancer (World Health Organization 2019). In this context, numerous studies have pointed at red macroalgae as natural sources of compounds devoted to the prevention and treatment of metabolic and chronic diseases, as it is the case of diabetes and obesity. Several authors have highlighted the existence of multiple compounds isolated from red macroalgae with the ability of regulating the hyperglycemia caused by diabetes, as reported by both in vivo and in vitro models, indicating that red algae are interesting candidates for the development of novel drugs for the treatment of this metabolic disorder (Ezzat et al. 2018). Thus, different mechanisms of actions have been proposed for the anti-diabetic effects of red algae extracts, as shown in Table 3. In summary, three major mechanisms have been described for the anti-diabetic activity of red algae extracts, including the inhibition of insulin cell-signaling repressors, such as protein tyrosine phosphatase 1B (PTP1B) (Wang et al. 2015b), reduction of circulating glucose levels, and the inhibition of saccharidases, involved in the

synthesis of free monosaccharides, as it is the case of  $\alpha$ -amylase,  $\alpha$ -glucosidase, aldose reductase or dipeptidyl peptidase-4 (DPP4) (Table 3). Among the different compounds from red algae responsible for such bioactivity, bromophenols play a fundamental role, on top of other molecules, like sulphated polysaccharides and proteins.

Thus, bromophenols have been reported as multifaceted antidiabetic agents, developing different mechanisms which include the inhibition of PTP1B by both in vivo and in vitro models, as found for *Rhodomela confervoides* (Shi et al. 2012), *Odonthalia corymbifera* (Xu et al. 2016), and *Symphyclocladia latiuscula* (Liu et al. 2011), and the enzymatic inhibition of  $\alpha$ -glucosidase by *Polyopes lancifolia* and *Grateloupia elliptica* extracts (Kim et al. 2008, 2010), and aldose reductase by *S. latiuscula* extracts (Wang et al. 2005). Besides bromophenols, the inhibition of enzymes related with type-2 diabetes has been reported to sulphated polysaccharides from *K. alvarezii* and *G. opuntia* extracts, exhibiting a potent inhibition of  $\alpha$ -amylase,  $\alpha$ -glucosidase, and DPP-4 (Makkar and Chakraborty 2017), and the protein hydrolysate from *P. palmata*, acting as inhibitor of DPP-4 (Harnedy and FitzGerald 2013).

Concerning anti-hyperlipidemic effects of red seaweed extracts, strong evidence has been reported on rodent in vivo models, as well as in vitro systems. Therefore, the dietary administration of several species, such as *Gracilaria changii* (Chan et al. 2014), *K. alvarezii* (Matanjan et al. 2010), *Gigartina pistillata* (Villanueva et al. 2014), *P. tenera* (Bocanegra et al. 2008), and *P. umbilicalis* (Moreira et al. 2010) on hypercholesterolemic rodent models have promoted the reduction in the plasmatic levels of total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and triacylglycerols (TAG), as well as the increase in high-density lipoprotein cholesterol (HDL-C). Moreover, red algal extracts were shown to decrease the hepatic accumulation of cholesterol, reduce the atherogenic index, inhibit lipid peroxidation, and alleviate the obesity-related oxidative stress in the same in vivo models (Chan et al. 2015; Patil et al. 2018). With respect to individual compounds, sulphated polysaccharides, especially porphyran, were revealed as the major responsible of the above-mentioned mechanisms, together with the increase on fecal excretion of cholesterol and the reduction of the apolipoprotein B 100 level in vitro, as found for

**Table 3** Antidiabetic and lipid metabolism related activities of red algae

Species	Extraction (solvent)	Compound	Activity	References
<b>Antidiabetic</b>				
<i>Rhodomela confervoides</i>	Synthetic derivation	Bromophenols	Inhibition of PTP1B in vitro and in vivo	Shi et al. (2012)
<i>Odonthalia corymbifera</i>	Isolation of bis(2,3-dibromo-4,5-dihydroxybenzyl) ether	Bromophenols	Inhibition of PTP1B in vitro and in vivo	Xu et al. (2016)
<i>Symphyclocladia latiuscula</i>	SLE (95% EtOH)	Bromophenols	Inhibition of PTP1B in vitro	Liu et al. (2011)
<i>Kappaphycus alvarezii/ Gracilaria opuntia</i>	HAE (W)	SP	Inhibition of $\alpha$ -amylase, $\alpha$ -glucosidase and DPP-4	Makkar and Chakraborty (2017)
<i>Symphyclocladia latiuscula</i>	SLE (95% EtOH)	Bromophenols	Inhibition of aldose reductase	Wang et al. (2005)
<i>Polyopes lancifolia</i>	SLE (80% MeOH)	Bromophenols	Inhibition of $\alpha$ -glucosidase, sucrase and maltase	Kim et al. (2010)
<i>Grateloupia elliptica</i>	SLE (75% MeOH)	Bromophenols	Inhibition of $\alpha$ -glucosidase	Kim et al. (2008)
<i>Palmaria palmata</i>	SLE (W, alkaline hydrolysis 0.12 M NaOH)	Protein hydrolysate	Inhibition of DPP-4	Harnedy and FitzGerald (2013)
<b>Lipid metabolism</b>				
<i>Gracilaria changii</i>	Powdered, directly administered to animals	Whole algae	Reduction of plasma levels of TC, LDL-C, TAG and atherogenic index	Chan et al. (2014)
<i>Kappaphycus alvarezii</i>	Powdered, directly administered to animals	Whole algae	Reduction of plasma levels of TC, LDL-C, TAG, lipid peroxidation, increase of HDL levels	Matanjun et al. (2010)
<i>Gigartina pistillata</i>	Powdered, directly administered to animals	Whole algae	Reduction of plasma levels of TC, LDL-C, TAG, and hepatic TAG levels	Villanueva et al. (2014)
<i>Porphyra tenera</i>	Powdered, directly administered to animals	Whole algae	Reduction of plasma levels of TC	Bocanegra et al. (2008)
<i>Porphyra umbilicalis</i>	Powdered, directly administered to animals	Whole algae	Reduction of plasma level of TC, alleviation of obesity-related oxidative stress	Moreira et al. (2010)
<i>Melanothamnus afaqhusainii</i>	SLE (EtOH)	SP	Reduction of plasma levels of TC, LDL-C, TAG, increase of HDL-C levels	Ruqqia et al. (2014)
<i>Porphyra yezoensis</i>	HAE (W)	SP	Increase of fecal excretion of cholesterol	Tsuge et al. (2004)
<i>Porphyra</i> sp.	Porphyran isolation	SP	Reduction of ApoB100 levels in vitro	Inoue et al. (2009)
<i>Porphyra haitanensis</i>	Oxidative degradation	SP	Reduction of TC, TC and LDL-C, increase of HDL-C	Wang et al. (2017)

SLE, Solid–liquid Extraction; HAE, Heat Assisted Extraction; W, Water; SP, Sulfated polysaccharides; PTP1B, protein-tyrosine phosphatase 1B; DPP4, Dipeptidyl peptidase-4; TC, total cholesterol; LDL-C, low density lipoprotein cholesterol; TAG, triglycerides; HDL-C, high density lipoprotein cholesterol

*Melanothamnus afaqhusainii* (Ruqqa et al. 2014) and several *Porphyra* species (Inoue et al. 2009), such as *P. yezoensis* (Tsuge et al. 2004) and *P. haitanensis* (Wang et al. 2017). On these bases, carrageenans were also reported for their hypocholesterolemic properties (Panlasigui et al. 2003). Keeping all this in mind, the consumption of red seaweeds can be regarded as a beneficial approach to alleviate the physiological complications attributed to chronic metabolic diseases, such as type-2 diabetes and hypercholesterolemia, with positive implications on the development of currently critical diseases, as it is the case of obesity and cardiovascular diseases.

#### Antitumor activity

Seaweed secondary metabolites have been reported to show antitumor activity, thus showing the potential of a novel source of natural pharmaceuticals (Ahmed et al. 2011). This is the case of halogenated metabolites and sulphated polysaccharides, mostly. Such efficiency, as antitumor agents from red seaweeds, has been assessed towards a plethora of cancer cell lines from human neoplastic diseases. Table 4 contains a summary of the different studies committed to the description of anticancer activity of red algae extracts.

Different authors have pointed at brominated compounds from *Callophycus serratus* (Kubanek et al. 2006) *Laurencia obtusa* (Iliopoulou et al. 2003), *Plocamium cartilagineum* (De Inés et al. 2004), *Polysiphonia lanosa* (Shoeib et al. 2004), *Portieria hornemanii* (Fuller et al. 1992), and *Sphaerococcus coronopifolius* (Smyrniotopoulos et al. 2010; Rodrigues et al. 2015a). As a result, a panel of diverse cancer cell lines has been proved to be affected by halogenated compounds-enriched extracts, including leukemia, lung, breast, colon, and cervix cancer cell lines. Accordingly, sulphated polysaccharides, such as carrageenans, have been also reported as efficient anticancer agents, being conducted in different red seaweed species, *i.e.*: *Champia feldmannii* (Lins et al. 2009), *Gelidium amansii* (Chen et al. 2004; Shao et al. 2013), *Gracilaria caudata* (Costa et al. 2010), *Hypnea masciformis* (Souza et al. 2018), and *Jania rubens* (Gheda et al. 2018). In a lesser extent, polyphenols from *E. cottonii* (Namvar et al. 2012) extracts, and lectins from *Euchema serra* (Sugahara et al. 2001; Hayashi et al. 2012) and *S. filiformis* (Chaves et al.

2018) have been reported in the basis of their antitumor activity.

The anticancer activity reported on red algae extracts have been conducted under in vitro conditions and little information on in vivo models is currently available. However, some studies have proven the activity of certain compounds in tumor volume reduction (TVR) (Campos et al. 2012; Namvar et al. 2012) and in combination with 5-Fluoroacil, a drug used in chemotherapy (Zhou et al. 2005, 2006; Lins et al. 2009). Also, similar percentages of TVR were reported when using elatol extracted from *Laurencia microcladia* (71%) compared to positive control cisplatin (81%) (Campos et al. 2012) (Table 4). Further studies are required, in this sense, to ensure their effectiveness in humans, and molecular insights are equally desired to elucidate the specific mechanism of action of anticancer compounds, to facilitate their consideration as official food and pharmaceutical ingredients.

#### Antimicrobial activity

Antimicrobial activity has been attributed to different compounds derived from red seaweeds, being regarded as effective antibacterial, antifungal, and antiviral compounds, especially glycolipids, lectins, terpenoids and furanones, as well as different halogenated metabolites. Table 5 shows an overview of the effectiveness of red algae extracts as sources of antimicrobial compounds. Concerning antibacterial activity, several red algae species have been shown to promote a relevant effectiveness towards both Gram + and Gram—bacteria, as it is the case of *C. crispus*, *Gelidium latifolium*, *P. palmata*, *Ceramium rubrum*, *Cryptopleura ramosa*, *Laurencia pinnatifida* and *Polysiphonia lanosa* (Hellio et al. 2001).

For instance, halogenated acetogenins of genus *Laurencia* have shown a multifaceted antimicrobial activity against a wide range of bacteria, including those from *Clostridium* and *Salmonella* genera, as well as other pathogenic species, such as *Proteus mirabilis* and *Klebsiella pneumoniae* (Vairappan et al. 2001; Vairappan 2003). Regarding the fractions rich in polar glycolipids from the algae *Chondria armata*, these compounds exhibited not only a potent antimicrobial activity against *Klebsiella* sp., but also a relevant antifungal activity against *Candida albicans* and *Cryptococcus neoformans* (Al-Fadhli et al. 2006).

**Table 4** In vitro and in vivo antitumor activity of red algae

Species	Compound	Cell line/Animal	Solvent	Activity	References
<b>In vitro experiments</b>					
<i>Callophycus serratus</i>	Bromophycolide H	DU4475	A:W	IC <sub>50</sub> = 3.88 µM	Kubanek et al. (2006)
<i>Champia feldmannii</i>	SP	HL-60, MDA-MB-435, SF-295, HCT-8	CPC	IC <sub>50</sub> = > 25 µg/mL	Lins et al. (2009)
<i>Chondria atropurpurea</i>	Chondriamide-A	KB and LOVO cells	E:C	n.d	Palermo et al. (1992), Smit (2004)
<i>Euclidean cottonii</i>	Polyphenols	MCF-7 // MB-MDA-231	M	IC <sub>50</sub> = 20 // 42 µg/mL	Namvar et al. (2012)
<i>Euclidean serra</i>	Agglutinin (lectin)	Colo201, HeLa // OST, LM8	E	IC <sub>50</sub> = -// 50 µg/mL	Sugahara et al. (2001), Hayashi et al. (2012)
<i>Galaxaura cylindrica</i>	Sulfolipids	Hep G2 // MCF-7	C:M	IC <sub>50</sub> = 2.75 // 0.40 µg/mL	El Baz et al. (2013)
<i>Gelidium amansii</i>	SP (agar)	Hepa-1, HL-60, NIH-3T3	M	n.d	Chen et al. (2004)
<i>Gloiopeltis furcate</i>	SP	MKN45 and DLD-1	W	< 25% and 19.07% inhibition	Shao et al. (2013)
<i>Gracilaria caudata</i>	SP	HeLa	Maxataze (protease)	30–40% inhibition	Costa et al. (2010)
<i>Grateloupia elliptica</i>	Pheophorbide A	U87MG // SK-OV-3 // B16-BL6 // SiHa // HeLa	M	IC <sub>50</sub> = 2.8 // 7.0 // 18.3 // 13.2 // 9.5 µg/mL	Cho et al. (2014)
<i>Hypnea musciformis</i>	Kappa-carrageenan	MCF-7, SH-SY5Y	Papain, SA, CPC	50–75% proliferation inhibition	Souza et al. (2018)
<i>Jania rubens</i>	SP	CoCa2 // MCF7	W:E	IC <sub>50</sub> = 20 // 0.3125 mg/mL	Ghedda et al. (2018)
<i>Laurencia microcladia</i>	Elatol	L929 > DU145 > MCF7 > A549 > B16F10	E	IC <sub>50</sub> = Max. 1.1 µM (L929), Min. 10.1 µM (B16F10)	Campos et al. (2012)
<i>Laurencia obtusa</i>	Brominated diterpenes	MCF-7 // PC3 // HeLa // A431 // K562	C:M	IC <sub>50</sub> = 149.5 // 138 // 78.4 // 86.2 // 108.3 µM	Iliopoulou et al. (2003)
<i>Laurencia popillose</i>	Sulfolipids	Hep G2 // MCF-7	C:M	2.21 // 0.67 µg/mL	El Baz et al. (2013)
<i>Polysiphonia lanosa</i>	Major Bromophenols	DLD-1	M	IC <sub>50</sub> = 39.7 ± 1.5 µg/mL	Shoeb et al. (2004)
<i>Solieria filiformis</i>	Mixture of lectins isoforms	MCF-7	PBS	IC <sub>50</sub> = 125 µg/mL	Chaves et al. (2018)

Table 4 continued

Species	Compound	Cell line/Animal	Solvent	Activity	References
<i>Sphaerococcus coronopifolius</i>	Sphaerococconol A (Bromoditerpene) Bromoditerpenes	HepG-2 U373, A549, SKMEL-28, OE21, PC3, LOVO	DCM, DCM:M	IC <sub>50</sub> = 42.87 µg/mL IC <sub>50</sub> = 3–76 µM	Rodrigues et al. (2015a) Smyrniotopoulos et al. (2010)
In vivo experiments					
<i>Champia feldmannii</i>	SP + 5-Fu	Swiss mice (25–30 g) subc. S180	CPC	Dose = 10 + 10 mg/kg. TVR = (48–68%)	Lins et al. (2009)
<i>Chondrus ocellatus</i>	Low MW λ-Carrageenan + 5-Fu	65 ICR mice (20 g) transplanted subc. S180	W:E	Dose = 100 + 25 mg/kg TVR = (63%)	Zhou et al. (2005)
	Low MW λ-Carrageenan + 5-Fu	65 ICR mice (20 g) transplanted with H-22	W:E	Dose = 100 + 25 mg/kg TVR = (52%)	Zhou et al. (2006)
<i>Eucheuma cottonii</i>	Polyphenols	Rats (200–250 g) subc. LA7	M	Dose = 150–300 mg/kg (37%)	Namvar et al. (2012)
<i>Laurencia microcladia</i>	Elatol	C57BL6 mice (18–25 g)	E	Dose = 10 mg/kg TVR = (71%)	(Campos et al. 2012)

B16F10 (Murine melanoma number CR-010), A549 (human lung carcinoma), DU145 (human prostate carcinoma), L929 (murine fibroblast), Hepa-1 (murine hepatoma), HL-60 (human leukemia), NIH-3T3 (murine embryo fibroblast cells), MB-MDA-231 (human breast cancer cell), LA7 (aka, CRL 2283; rat mammary gland tumor cell line), MKN45 (gastric cancer cells), MDA-MB-435 (Melanoma), SF-295 (glioblastoma), HCT-8 (Human colon), DLD-1 (human colon adenocarcinoma), Colo201 (human colon adenocarcinoma), HeLa (human cervix adenocarcinoma), MCF-7 (human breast adenocarcinoma), HB4C5 cells (human hybridoma cell line), OST (Human osteosarcoma Takase cells), LM8 cells (Murine osteosarcoma cell line), DU4475 (breast tumor cell line), PC3 (prostate adenocarcinoma), A431 (derived from epidermoid carcinoma), K562 (chronic myelogenous leukemia cell line), SkMel28 (human malignant melanoma), CHO (Chinese hamster ovary cells), SH-SY5Y (human neuroblastoma), Caco-2 (colon cancer cell line), U87MG (Human glioblastoma cells), B16-BL6 (mouse melanoma cells), SiHa (human cervical cancer cells), SKOV-3 (human ovarian cancer cells), OE21 (oesophageal squamous cell carcinoma), TVR (Tumor volume reduction), A (Acetone), W (Water), CPC (Cetylpyridinium chloride), C (Chloroform), E (Ethanol), SA (Sodium acetate), M (Methanol), PBS (phosphate buffered saline), DCM (Dichloromethane), ip. (intraperitoneal), subc. (subcutaneously), S180 (Sarcoma-180 tumor cells), H-22 (mouse hepatocellular carcinoma), LA7 (rat breast cancer stem cells)

**Table 5** Antimicrobial activity of red algae

Species	Compound	Solvent	Microorganism	References
<i>Ascidium corallinum</i>	ns	M	<i>E. coli</i> , <i>K. pneumoniae</i> , <i>S. aureus</i>	Rhimou et al. (2010)
<i>Amphiroa rigida</i>	ns	M	<i>S. aureus</i>	Val et al. (2001)
<i>Asparagopsis taxiformis</i>	ns	M	<i>B. subtilis</i> , <i>E. faecium</i> , <i>M. smegmatis</i> , <i>P. aeruginosa</i> , <i>S. marcescens</i> , <i>S. aureus</i> , <i>S. cerevisiae</i> , <i>C. albicans</i> , <i>A. fumigatus</i>	Val et al. (2001)
<i>Callophycus serratus</i>	Bromophycolide	W, M, DCM	VREF, MRSA	Lane et al. (2009)
<i>Ceramium rubrum</i>	ns	M	<i>E. coli</i> , <i>E. faecalis</i> , <i>S. aureus</i>	Rhimou et al. (2010)
<i>Ceramium virgatum</i>	Fatty acids	EE:H	<i>B. cereus</i> , <i>E. coli</i> , <i>L. monocytogenes</i> , <i>S. enteritidis</i>	Horinear et al. (2014)
<i>Chondria armata</i>	Glycolipids	M	<i>Klebsiella</i> sp., <i>C. albicans</i> , <i>A. fumigatus</i> , <i>C. neoformans</i>	Al-Fadhli et al. (2006)
<i>Chondrocanthus acicularis</i>	ns	M	<i>E. coli</i> , <i>E. faecalis</i> , <i>K. pneumoniae</i> , <i>S. aureus</i>	Rhimou et al. (2010)
<i>Chondrus crispus</i>	ns	E, EA	<i>B. cereus</i> , <i>C. marina</i> , <i>E. coli</i> , <i>E. faecalis</i> , <i>H. marina</i> , <i>L. brevis</i> , <i>L. innocua</i> , <i>M. hydrocarbonoclasticus</i> , <i>P. aeruginosa</i> , <i>P. erythrorhizus</i> , <i>P. irgensis</i> , <i>S. enteritidis</i> , <i>S. putrefaciens</i> , <i>S. aureus</i> , <i>V. aestuariatus</i> , <i>Candida</i> sp.	Chambers et al. (2011); Mendes et al. (2013); Salta et al. (2013)
<i>Corallina elongata</i>	Lipids	A, M or E	<i>B. subtilis</i> , <i>E. coli</i> , <i>K. pneumoniae</i> , <i>S. typhi</i> , <i>S. aureus</i> , <i>C. albicans</i>	Val et al. (2001), Osman et al. (2010)
<i>Corallina mediterranea</i>	1,2-BDC	M, E	<i>V. fluvialis</i>	Mohy El-Din and El-Ahwany (2016)
<i>Delisea pulchra</i>	Furanes	95% E	<i>E. coli</i> , <i>P. aeruginosa</i>	Maneifield et al. (2001), Ren et al. (2004)
	Furanones, catechins	n.d	<i>C. jejuni</i>	Castillo et al. (2015)
<i>Eucheama serra</i>	Lectins	W:E	<i>V. vulnificus</i>	Liao et al. (2003)
<i>Falkenbergia-phase of A. taxiformis</i>	Volatile compounds	M	<i>B. subtilis</i> , <i>K. pneumoniae</i> , <i>P. aeruginosa</i> , <i>S. aureus</i> , <i>S. epidermidis</i> , <i>V. alcaligenes</i> , <i>V. vulnificus</i>	Manilal et al. (2010)
<i>Galaxaura marginata</i>	Lectins	W/E	<i>V. neresis</i> , <i>V. pelagius</i> , <i>V. vulnificus</i>	Liao et al. (2003)
<i>Galaxaura rugosa</i>	ns	M	<i>B. subtilis</i>	Val et al. (2001)
<i>G. rugosa</i>	ns	M	<i>B. subtilis</i>	Val et al. (2001)
<i>Gelidium arbuscula</i>	ns	M	<i>B. subtilis</i>	Val et al. (2001)
<i>Gelidium attenuatum</i>	ns	M	<i>E. coli</i> , <i>E. faecalis</i> , <i>K. pneumoniae</i> , <i>S. aureus</i>	Rhimou et al. (2010)
<i>Gelidium micropterum</i>	ns	M	<i>V. alcaligenes</i> , <i>V. parahaemolyticus</i>	Manilal et al. (2010)
<i>Gelidium pulchellum</i>	ns	M	<i>E. coli</i> , <i>E. faecalis</i> , <i>S. aureus</i>	Rhimou et al. (2010)
<i>Gelidium pusillum</i>	ns	M	<i>E. coli</i> , <i>E. faecalis</i> , <i>K. pneumoniae</i> , <i>S. aureus</i> , <i>V. alcaligenes</i> , <i>V. vulnificus</i> , <i>V. parahaemolyticus</i> , <i>V. vulnificus</i>	Manilal et al. (2010), Rhimou et al. (2010)
<i>Gelidium spinulosum</i>	ns	M	<i>E. coli</i> , <i>E. faecalis</i> , <i>S. aureus</i>	Rhimou et al. (2010)
<i>Gracilaria corticata</i>	ns	M or DMSO	<i>B. subtilis</i> , <i>E. coli</i> , <i>P. fluorescens</i> , <i>S. aureus</i>	Arulkumar et al. (2018)
<i>Gracilaria dura</i>	Lipids	C:M (2:1)	<i>V. alginolyticus</i> , <i>V. ordalii</i>	Cavallo et al. (2013)



Table 5 continued

Species	Compound	Solvent	Microorganism	References
<i>Gracilaria edulis</i>	ns	EA, M or DMSO	<i>A. hydrophyla</i> , <i>B. subtilis</i> , <i>E. coli</i> , <i>P. fluorescens</i> , <i>S.aureus</i> , <i>V. fluvialis</i>	Arulkumar et al. (2018), Kasanah et al. (2019)
<i>Gracilaria fisheri</i>	Proteins	25 mM Tris-HCl	<i>V. harveyi</i> , <i>V. parahaemolyticus</i>	Boonsri et al. (2017), Karnjana et al. (2019)
<i>Gracilaria gracilis</i>	Lipids	C:M (2:1)	<i>V. salmonicida</i>	Cavallo et al. (2013)
<i>Gracilaria omata</i>	SP	W	<i>E. coli</i>	dos Santos Amorim et al. (2012)
<i>Gracilaria vermiculophylla</i>	ns	E or EA	<i>B. subtilis</i> , <i>E. coli</i> , <i>E. faecalis</i> , <i>L. brevis</i> , <i>L. innocua</i> , <i>P. aeruginosa</i> , <i>S. enteritidis</i> , <i>S. aureus</i> , <i>Candida</i> sp.	Mendes et al. (2013)
<i>Gracilariopsis longissima</i>	Lipids	C:M (2:1)	<i>V. alginolyticus</i> , <i>V. cholerae non O-1</i> , <i>V. fluvialis</i> , <i>V. ordalii</i> , <i>V. salmonicida</i> , <i>V. vulnificus</i>	Stabili et al. (2012), Cavallo et al. (2013)
<i>Grateloupia livida</i>	ns	E or M	<i>B. subtilis</i> , <i>E. coli</i> , <i>P. aeruginosa</i> , <i>S. aureus</i> , <i>V. alcaligenes</i> , <i>V. alginolyticus</i> , <i>V. harveyi</i> , <i>V. parahaemolyticus</i> , <i>V. vulnificus</i>	Manilal et al. (2010), Jiang et al. (2013), Kavita et al. (2014)
<i>Halipilton virgatum</i>	ns	M	<i>S. aureus</i>	Val et al. (2001)
<i>Haloptys incurvus</i>	ns	M	<i>B. subtilis</i> , <i>E. coli</i> , <i>E. faecalis</i> , <i>K. pneumoniae</i> , <i>S. aureus</i>	Val et al. (2001), Rhimou et al. (2010)
<i>Hypnea musciformis</i>	Agglutinins, kappa carrageenan	M or PBS:W	<i>E. coli</i> , <i>E. faecalis</i> , <i>K. pneumoniae</i> , <i>S. aureus</i> , <i>C. albicans</i> , <i>T. rubrum</i> , <i>C. lindemuthianum</i>	Melo et al. (1997), Rhimou et al. (2010), Souza et al. (2018)
<i>Hypnea pannosa</i>	ns	M	<i>B. subtilis</i> , <i>E. coli</i> , <i>P. aeruginosa</i> , <i>S. aureus</i>	Kavita et al. (2014)
<i>Hypnea valentiae</i>	ns	E	<i>B. subtilis</i> , <i>E. coli</i> , <i>P. aeruginosa</i> , <i>S. aureus</i> , <i>S. pyogenes</i>	Rhimou et al. (2010), Kavita et al. (2014)
<i>Jania rubens</i>	Lipids/1,2-BDC	A, M, E, DCM or C	<i>B. cereus</i> , <i>B. subtilis</i> , <i>E. cloacae</i> , <i>E. coli</i> , <i>E. faecalis</i> , <i>K. pneumoniae</i> , <i>P. aeruginosa</i> , <i>S. typhi</i> , <i>S. typhimurium</i> , <i>S. aureus</i> , <i>S. epidermidis</i> , <i>V. fluvialis</i> , <i>C. albicans</i>	Horzum et al. (2006), Osman et al. (2010), Mohy El-Din and El-Ahwany (2016)
<i>Laurencia majuscula</i>	Halogenated acetogenins	M	<i>E. coli</i> , <i>K. pneumoniae</i> , <i>Pseudomonas</i> sp., <i>S. aureus</i> , <i>S. epidermidis</i>	Vairappan et al. (2001)
<i>Laurencia papillosa</i>	Sulfolipids	M:C (2:1)	<i>B. subtilis</i> , <i>E. coli</i> , <i>K. pneumoniae</i> , <i>P. aeruginosa</i> , <i>S. flexneri</i> , <i>S. aureus</i> . Antiviral against HSV-1	El Baz et al. (2013), Kavita et al. (2014)
<i>Laurencia</i> spp.	Halogenated acetogenins	M	<i>Clostridium</i> spp. and <i>P. mirabilis</i>	Manilal et al. (2010)
<i>Liagora farinosa</i>	ns	M	<i>B. subtilis</i> , <i>S.aureus</i>	Val et al. (2001)
<i>Osmundea hybrida</i>	ns	M	<i>B. subtilis</i> , <i>M. smegmatis</i> , <i>S. aureus</i> , <i>S. cerevisiae</i>	Val et al. (2001)
<i>Palmaria palmata</i>	ns	M	<i>E. faecalis</i> , <i>L. monocytogenes</i> , <i>P. aeruginosa</i> , <i>S. abony</i>	Rudtanatip et al. (2018)
<i>Plocamium cartilagineum</i>	ns	M	<i>E. coli</i> , <i>E. faecalis</i> , <i>S. aureus</i>	Rhimou et al. (2010)
<i>Polysiphonia tuticorinensis</i>	ns	M	<i>B. subtilis</i> , <i>E. coli</i> , <i>P. aeruginosa</i> , <i>S. aureus</i>	Kavita et al. (2014)
<i>Porphyra dioica</i>	ns	E or EA	<i>B. cereus</i> , <i>E. coli</i> , <i>E. faecalis</i> , <i>L. brevis</i> , <i>S. aureus</i> , <i>Candida</i> sp.	Mendes et al. (2013)
<i>Porphyra umbilicalis</i>	Fatty acids	H, W or 80% W:M	<i>P. digitatum</i> , <i>B. cinerea</i> , <i>M. laxa</i>	De Corato et al. (2017)

Table 5 continued

Species	Compound	Solvent	Microorganism	References
<i>Porphyra yezoensis</i>	Peptide	Pepsin digestion	<i>S. aureus</i>	Jiao et al. (2019)
<i>Portieria horemanii</i>	ns	M	<i>V. alginolyticus</i> , <i>V. harveyi</i> , <i>V. vulnificus</i>	Manilal et al. (2010)
<i>Pterocladia capillacea</i>	Lipids/Lectins/ 1,2-BDC	A, M or E	<i>B. cereus</i> , <i>B. subtilis</i> , <i>E. coli</i> , <i>K. pneumoniae</i> , <i>P. fluorescens</i> , <i>S. typhi</i> , <i>S. aureus</i> , <i>S. pyogenes</i> , <i>V. fluvialis</i> , <i>V. pelagius</i> , <i>V. vulnificus</i> , <i>C. albicans</i> , <i>F. oxysporium</i>	Liao et al. (2003), Osman et al. (2010), Abou Zeid et al. (2014), Mohy El-Din and El-Ahway (2016)
<i>Pterosiphonia complanata</i>	ns	M	<i>E. coli</i> , <i>E. faecalis</i> , <i>S. aureus</i>	Rhimou et al. (2010)
<i>Solieria filiformis</i>	Lectins	20 mM Tris-HCl	<i>E. aerogenes</i> , <i>K. pneumoniae</i> , <i>P. aeruginosa</i> , <i>Proteus</i> spp., <i>S. typhi</i> , <i>S. marcescens</i>	Holanda et al. (2005)
<i>Sphaerococcus coronopifolius</i>	Bromoditerpene	M or DCM	<i>E. coli</i> , <i>P. aeruginosa</i> , <i>S. aureus</i>	Snyrniotopoulos et al. (2008); Rodrigues et al. (2015a)
<hr/>				
<i>Escherichia coli</i> ( <i>E. coli</i> ), <i>Klebsiella pneumoniae</i> ( <i>K. pneumoniae</i> ), <i>Staphylococcus aureus</i> ( <i>S. aureus</i> ), <i>Bacillus subtilis</i> ( <i>B. subtilis</i> ), <i>Enterococcus faecium</i> ( <i>E. faecium</i> ), <i>Mycobacterium smegmatis</i> ( <i>M. smegmatis</i> ), <i>Pseudomonas aeruginosa</i> ( <i>P. aeruginosa</i> ), <i>Serratia marcescens</i> ( <i>S. marcescens</i> ), <i>Saccharomyces cerevisiae</i> ( <i>S. cerevisiae</i> ), <i>Candida albicans</i> ( <i>C. albicans</i> ), <i>Aspergillus fumigatus</i> ( <i>A. fumigatus</i> ), <i>Vancomycin-resistant Enterococcus faecium</i> (VREF), <i>Methicillin-resistant Staphylococcus aureus</i> (MRSA), <i>Enterococcus faecalis</i> ( <i>E. faecalis</i> ), <i>Bacillus cereus</i> ( <i>B. cereus</i> ), <i>Listeria monocytogenes</i> ( <i>L. monocytogenes</i> ), <i>Salmonella enteritidis</i> ( <i>S. enteritidis</i> ), <i>Cryptococcus neoformans</i> ( <i>C. neoformans</i> ), <i>Cobetia marina</i> ( <i>C. marina</i> ), <i>Halomonas marina</i> ( <i>H. marina</i> ), <i>Lactobacillus brevis</i> ( <i>L. brevis</i> ), <i>Listeria innocua</i> ( <i>L. innocua</i> ), <i>Marinobacter hydrocarbonoclasticus</i> ( <i>M. hydrocarbonoclasticus</i> ), <i>Pseudoalteromonas elyakovii</i> ( <i>P. elyakovii</i> ), <i>Polaribacter irgensii</i> ( <i>P. irgensii</i> ), <i>Shewanella putrefaciens</i> ( <i>S. putrefaciens</i> ), <i>Vibrio aestuarius</i> ( <i>V. aestuarius</i> ), <i>Salmonella typhi</i> ( <i>S. typhi</i> ), <i>Vibrio fluvialis</i> ( <i>V. fluvialis</i> ), <i>Vibrio pelagius</i> ( <i>V. pelagius</i> ), <i>Vibrio vulnificus</i> ( <i>V. vulnificus</i> ), <i>Staphylococcus epidermidis</i> ( <i>S. epidermidis</i> ), <i>Vibrio alcaligenes</i> ( <i>V. alcaligenes</i> ), <i>Vibrio alginolyticus</i> ( <i>V. alginolyticus</i> ), <i>Vibrio neresis</i> ( <i>V. neresis</i> ), <i>Pseudomonas fluorescens</i> ( <i>P. fluorescens</i> ), <i>Vibrio ordalii</i> ( <i>V. ordalii</i> ), <i>Aeromonas hydrophyla</i> ( <i>A. hydrophyla</i> ), <i>Vibrio salmonicida</i> ( <i>V. salmonicida</i> ), <i>Vibrio cholerae non O-1</i> ( <i>V. cholerae non O-1</i> ), <i>Trichophyton rubrum</i> ( <i>T. rubrum</i> ), <i>Collectotrichum lindemuthianum</i> ( <i>C. lindemuthianum</i> ), <i>Enterobacter cloacae</i> ( <i>E. cloacae</i> ), <i>Salmonella typhimurium</i> ( <i>S. typhimurium</i> ), <i>Shigella flexneri</i> ( <i>S. flexneri</i> ), <i>Mycobacterium smegmatis</i> ( <i>M. smegmatis</i> ), <i>Salmonella abony</i> ( <i>S. abony</i> ), <i>Penicillium digitatum</i> ( <i>P. digitatum</i> ), <i>Botrytis cinerea</i> ( <i>B. cinerea</i> ), <i>Monilinia laxa</i> ( <i>M. laxa</i> ), <i>Fusarium oxysporium</i> ( <i>F. oxysporium</i> ), <i>Enterobacter aerogenes</i> ( <i>E. aerogenes</i> ), <i>Serratia marcescens</i> ( <i>S. marcescens</i> ), 1,2-Benzenedicarboxylic (1,2-BDC), ns: not specified, A (Acetone), W (Water), C (Chloroform), E (Ethanol), M (Methanol), PBS (phosphate buffered saline), DCM (Dichloromethane), EE (Ethyl ether), H (Heptane), EA (Ethyl acetate)				

Concerning other lipidic substances, extracts from *Laurencia papillosa* and *Galaxaura cylindrica* enriched with sulpholipids were effective against *Escherichia coli* and *Bacillus subtilis*, as well as antiviral activity against herpes simplex virus-1 (HSV-1) (El Baz et al. 2013). Moreover, fatty acids from *Gracilaria edulis* extracts promoted an intense effectiveness against marine pathogens, such as those of *Vibrio* sp., thus contributing to the prevention of infectious diseases in the field of aquaculture (Kasannah et al. 2019). In parallel, the combination of *Bacillus amyloliquefaciens* associated with *Laurencia papillosa* has proved to inhibit the growth of some marine vibrios and the bacteria *Aeromonas hydrophilla*, being both typical food pathogens (Chakraborty et al. 2017). Furthermore, protein extracts isolated from red algal sources have been reported as natural antibacterials too. Thus, extracts from *Gracilaria fisheri* promoted an antibacterial activity against *Vibrio parahaemolyticus*, which is considered the etiologic agent of the shrimp acute hepatopancreatic necrosis disease (Boonsri et al. 2017). Among proteins, lectins have emerged as interesting antimicrobials, as those from *Soliera filiformis*, which depict a wide range of effectiveness against different pathogens, including *Serratia marcescens*, *Salmonella typhi*, *K. pneumoniae*, *Enterobacter aerogenes*, *Proteus* sp., and *Pseudomonas aeruginosa* (Holanda et al. 2005). Not only proteins have been detected because of their role as antimicrobial, since algal peptides have also shown the same bioactivity, as reported for *Porphyra yezoensis* inhibiting the growth of *Staphylococcus aureus* (Jiao et al. 2019). At last, furanones have been identified as another relevant family of compounds with associated antimicrobial activity from red algal sources, as demonstrated for *Delisea pulchra* extracts against *Escherichia coli* and *Campylobacter jejuni* (Manefield et al. 2001; Castillo et al. 2015).

In the case of antifungal activity (Table 5), besides the already mentioned activity of glycolipids-enriched *Chondria armata* extracts against human fungal pathogens (Al-Fadhli et al. 2006), the protein extracts from *Hypnea musciformis* showed the same effectiveness against different agricultural pathogens, such as *Trichophyton rubrum* and *Colletotrichum lindemuthianum* (Melo et al. 1997). In the same way, another crop pathogens, like *Botrytis cinerea*, *Monilinia laxa*, and *Penicillium digitatum* were inhibited by the fatty

acids and polysaccharide fractions of *Porphyra umbilicalis* and related species, thus suggesting a promising effect of red seaweed extracts as preventive agents of agricultural diseases (De Corato et al. 2017).

Finally, the antiviral activity of red algal extracts has been widely reported in terms of HSV-1 growth inhibition as stated before. Generally, polysaccharides, mostly carrageenans, and lectins are the major responsible of such bioactivity (Table 5). Thus, extracts from different Rhodophyta species, such as *Gracilaria* sp., *Nothogenia fastigiata*, and *Mastocarpus stellatus* have been assessed in terms of their effectiveness against HSV-1 and HSV-2 (Baba et al. 1988; Damonte et al. 1994; De Clercq 2000; Mazumder et al. 2002; Bouhlal et al. 2010; Soares et al. 2012; Gómez-Ordóñez et al. 2014). Additionally, the same extracts reported a potent activity against cytomegalovirus, vesicular stomatitis virus, and several respiratory viruses, such as respiratory syncytial virus and influenza viruses A and B (Damonte et al. 1994; De Clercq 2000; Bouhlal et al. 2010). Furthermore, the antiviral activity against human immunodeficiency virus (HIV) of red algal extracts has been attributed to the presence of sulphated polysaccharides and lectins, as observed for *Schizymenia pacifica* (Nakashima et al. 1987). Additionally, algal lectins obtained by recombinant production showed a significant activity against hepatitis C virus, as validated in both in vitro and in vivo models (Meuleman et al. 2011; Takebe et al. 2013; Barton et al. 2014).

Overall, the pleiotropic effects of algal extracts as antimicrobial agents may lead to their exploitation as natural ingredients to be incorporated in both food and pharmaceutical preparations for the treatment of multiple infectious diseases. In addition, the widely reported activity against sea and agricultural pathogens open new perspectives in the field of algae valorization for their consideration as natural sources of antibiotics and antivirals.

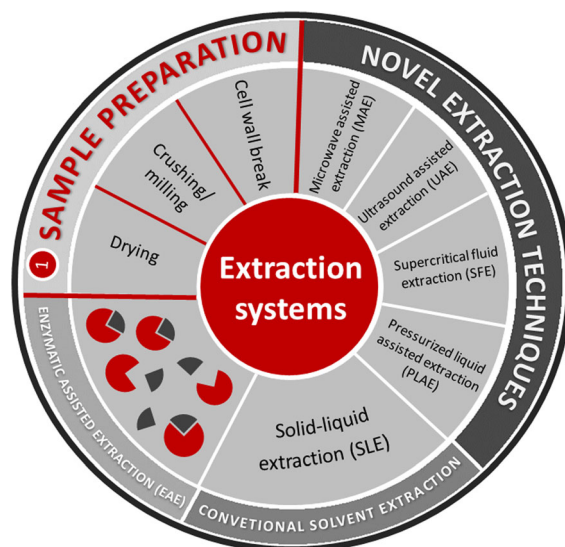
#### Other activities

In addition to the previously described bioactivities associated with red seaweeds, their deriving extracts have been reported in terms of supplementary properties, conferring health-enhancing effects. As a matter of fact, sulphated polysaccharides from *Botryocladia occidentalis* extracts were shown to exert a strong anticoagulant and antithrombotic activity in

low doses (Farias et al. 2000; Fonseca et al. 2008). In the same way, sulphated polysaccharides with anticoagulant activities have been also found in other species, such as *Schizymeria binderi*, *Porphyra haitanensis*, *Gracilaria debilis*, and *Grateloupia indica* (Sen et al. 1994; Zúñiga et al. 2006; Zhang et al. 2010; Sudharsan et al. 2015). Moreover, the photoprotective effects of pigments from red algae, including carotenoids, together with phenolic compounds, and mycosporine-like amino acids (MAA) have prompted the consideration of derived extracts as efficient additives to be used in already commercialized cosmetic preparations, reporting the effectiveness of such compounds isolated from *Hydropuntia cornea*, *Gracilariopsis longissima*, and *Porphyra umbilicalis* (Álvarez-Gómez et al. 2019). In the case of additional health-promoting properties, red seaweed extracts have been identified as natural sources of neuroprotective agents. Hence, neuroprotection of red algae extracts was reported in terms of acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE), two enzymes closely related with Alzheimer's and Parkinson's diseases. For instance, AChE activity has been studied in different compounds extracted from algae which has verified this neuroprotective activity, such as phytol from *Gelidiella acerosa* (tested both in in vitro and in vivo experiments) (Syad et al. 2016) or methanol extracts from *Hypnea valentiae*, *Gracilaria edulis* (Suganthi et al. 2010), *Amphiroa* spp. (Stirk et al. 2007). Finally, the hepatoprotective activity of red algae extracts has been also indicated to be associated with the prevention of oxidative stress. For instance, the oral administration of *Hypnea musciformis* ethanolic extract promoted hepatoprotective activity in liver damage-induced rodent models (Bupesh et al. 2012). Moreover, similar effects were observed by the polyphenol-enriched extracts from *Bryothamnion triquetrum*, (Novoa et al. 2019), the ethanol extract from *Eucheuma cottonii* (Wardani et al. 2017), and the polysaccharide fraction from *Porphyra yezoensis* (Guo et al. 2007).

### Extraction technologies for bioactive compounds

The bioactive compounds of red seaweeds have been extracted using diverse techniques. Usually, the first step of the extraction process involves a pre-treatment stage with the aim of disrupting algal cell walls and



**Fig. 2** Extraction procedure and different systems for red algae

improving the extraction yield (Michalak and Chojnacka 2014). Such pre-treatments can be classified as mechanical, physical, chemical, thermal and enzymatic methods (Fig. 2), and they are highly influenced by the physicochemical nature of target compounds (Michalak and Chojnacka 2014; Jacobsen et al. 2019). A summary of the extraction procedures employed in different studies were included in Table 6.

### Solid–liquid Extraction

Solid–liquid extraction (SLE) is the simplest and most inexpensive method to extract bioactive compounds, thus being considered as the most widely applied methodology on red seaweed extracts. During SLE protocols, solvent penetrates a pulverized tissue, dissolving the soluble compounds without applying other assisting mechanisms. Maceration or percolation are examples of this type of extraction, in which different organic solvents are used, depending on the solubility of the target compounds. Some of the most used solvents are water, methanol, ethanol, ethyl acetate, either alone or mixed in different proportions (Heffernan et al. 2014; Ben Saad et al. 2019). However, this system presents several disadvantages, such as the high amount of pure solvents, high evaporation rates, low selectivity towards compounds, and long extraction times (Jacobsen et al. 2019). Consequently, SLE also generates high amounts of

**Table 6** Extraction methodologies and conditions for bioactive compounds of red algae

Species	Solvent	Compound	Recovery	Bioactivity	References
Solid/liquid extraction <i>Solieria chordalis</i>	C/M	Lipids	ns	Antioxidant	Terme et al. (2018)
<i>Alsidium corallinum</i>	E/W; M/EA	Chlorophyll a, b and $\beta$ -carotene	360.38 and 264.24 mg/100 g DW // 93.45 mg/100 g extract	Antioxidant, Antibacterial	Ben Saad et al. (2019)
<i>Gracilaria</i> sp.	CC (ionic liquid)	PB	46.5%	ns	Martins et al. (2016)
<i>Gracilaria gracilis</i>	Cold water // Hot water // E/W (80:20) // M/W (70:30)	PC	4.76 $\mu$ g GAE// 5.36 // 3.49 // 4.91	Antioxidant	Heffernan et al. (2014)
Pressurized Liquid Assisted Extraction (PLAE)					
<i>Hypnea musciformis</i>	W, 210 °C	PC	39.57 mg GAE/g	Antioxidant	Pangestuti et al. (2019)
<i>Gracilaria gracilis</i>	W// E/W (80:20) // M/W (70:30) // 120 °C, 10.34 MPa	PC	2.79 // 2.44 // 3.50 $\mu$ g GAE	Antioxidant	Heffernan et al. (2014)
<i>Porphyra tenera</i>	M/W, 130 °C, 13 MPa	PC	1911 ng/g	Antioxidant	Onofrejeva et al. (2010)
<i>Kappaphycus alvarezii</i>	W + 1% C4C1im (ionic liquid) 150 °C	Carrageenan	78.75%	Antioxidant	Gerenui et al. (2017)
Supercritical Fluid Extraction (SFE)					
<i>Solieria chordalis</i>	CO <sub>2</sub> + E (8%), 45 °C, 29 MPa	Lipids	ns	Antioxidant	Terme et al. (2018)
<i>Porphyra</i> sp., <i>Hypnea spinella</i> , <i>Chondrus crispus</i> , <i>Halopyxis incurvus</i>	CO <sub>2</sub> + M/W, 35 MPa, 40 °C	Isoflavones	85.11 // 106.75 // 114.44// 200.97 ng/g	ns	Klejdus et al. (2010)
Microwave Assisted Extraction (MAE)					
<i>Porphyridium purpureum</i>	W, 40 °C	PB	73.7 $\mu$ g/mg	ns	Juin et al. (2015)
<i>Solieria chordalis</i>	W/0.5% KOH, 105 °C	Carrageenan	13.5%	Antiherpetic (HSV-1)	Boulho et al. (2017)
<i>Gracilaria vermiculophylla</i>	W/110 °C	Agar	14.8%	ns	Sousa et al. (2010)
<i>Porphyra haitianensis</i>	W, 77.84 W	SP	28.98 mL/g	Antitumor	Chen and Xue (2019)
Ultrasound Assisted Extraction (UAE)					
<i>Porphyra yezoensis</i>	W, 300 V, 41 °C	Taurine	13.0 mg/g	ns	Wang et al. (2015a)

Table 6 continued

Species	Solvent	Compound	Recovery	Bioactivity	References
<i>Gelidium pusillum</i>	Phosphate buffer, 30 °C	R-phycoerythrin and R-phycoyanin	0,16 mg/g and 0,11 mg/g	ns	Mittal et al. (2017)
<i>Osmundea pinnatifida</i>	W, 50 °C, 400 W	PC and sugars	103.7 µg CE/g and 83 mg/g	Antioxidant	Rodrigues et al. (2015b)
<i>Gracilaria birdiae</i>	W + NaOH 0.1 M, 22 °C, 60 W. ED (60 °C, 12 h, pH 8.0)	SP	413 mg	Antioxidant, Anticoagulant	Fidelis et al. (2014)
Enzymatic Assisted Extraction (EAE)					
<i>Chondracanthus chammissoi</i>	Cellulase	Proteins	361 mg/g	Antioxidant	Vásquez et al. (2019)
<i>Palmaria palmata</i>	Umamizyme	PC	57,1 g GAE/kg	Antioxidant	Wang et al. (2010)
<i>Chondrus crispus</i>	Commercial proteases and carbohydrases	ns	40–70% dry matter	Antiviral	Kulshreshtha et al. (2015)
<i>Osmundea pinnatifida</i>	Flavourzyme enzymatic complex // Cellulase	PC and sugars	123.1 µg CE/g // 102.2 mg/g	Antioxidant	Rodrigues et al. (2015b)

A (Acetone), W (Water), C (Chloroform), E (Ethanol), M (Methanol), PBS (phosphate buffered saline), DCM (Dichloromethane), EE (Ethyl ether), H (Heptane), EA (Ethyl acetate), PC (Phenolic compounds), SP (Sulphated polysaccharide), ns (not specified), GAE (Gallic Acid Equivalent), CE (Catechol Equivalent), PB (Phycobiliproteins), DW (Dry Weight), ED (Enzymatic Digestions), CC (Cholinium chloride)

waste that may lead to a negative environmental impact.

As described in Table 6, numerous studies have used SLE to extract biological compounds from red seaweeds, such as pigments, lipids, phenolic compounds, phycobiliproteins and polysaccharides (Martins et al. 2016; Terme et al. 2018; Ben Saad et al. 2019; Jacobsen et al. 2019).

#### Pressurized Liquid Assisted Extraction

Pressurized liquid-assisted extraction (PLE) constitutes an extraction methodology in which solvent preserves the liquid state above its boiling point, by applying high pressure (Michalak and Chojnacka 2014). Different solvents may be used in this extraction, such as water, methanol, and ethanol (Kadam et al. 2015b). Generally, the experimental conditions employed in PLE procedures include a high range of temperatures (120–210 °C), while pressure varies between 10 and 20 MPa (Onofrejová et al. 2010; Heffernan et al. 2014; Pangestuti et al. 2019). This type of extraction is more selective and efficient than SLE and requires significant lower amounts of solvents and shorter extraction times. Nevertheless, due to harsh conditions applied on PLE, this methodology is limited by the thermolabile properties of the compounds subjected to extraction (Kadam et al. 2015a; Jacobsen et al. 2019). Different compounds have been extracted from red algae using this technique, such as phenolic compounds, carbohydrates and proteins (Onofrejová et al. 2010; Heffernan et al. 2014; Gallego et al. 2019; Pangestuti et al. 2019).

#### Supercritical Fluid Extraction

Supercritical fluid extraction (SFE), is a novel extraction methodology in which solvents are subjected to high temperatures and pressures to reach a gas–liquid equilibrium, thus improving the extraction yield (Michalak and Chojnacka 2014). The most used solvent in SFE is carbon dioxide (CO<sub>2</sub>) thanks to its availability, low cost, chemical innocuity, and low critical requirements in terms of temperature and pressure conditions (Michalak and Chojnacka 2014; Jacobsen et al. 2019). Pressure values usually range between 29 and 35 MPa, while temperatures varies between 40 and 50 °C, making SFE a suitable technique for the extraction of thermo-labile compounds

(Jacobsen et al. 2019). On the other hand, the main drawback of this methodology is the expensive equipment required. Concerning red algae, SFE has been employed to extract specially lipophilic substances, such as glycolipids, phospholipids, and  $\omega$ -3 fatty acids (Herrero et al. 2006; Klejdus et al. 2010; Michalak and Chojnacka 2014; Terme et al. 2018).

#### Microwave Assisted Extraction

Microwave assisted extraction (MAE) is based on the application of electromagnetic radiation with a frequency between 300 MHz and 300 GHz to heat intracellular liquids, which exert pressure on the cell walls and leads to their breakdown. Then, the intracellular compounds are released into the solvent, improving the extraction efficiency (Michalak and Chojnacka 2014). In general, the most used solvent on MAE methodology is water (Sousa et al. 2010; Juin et al. 2015; Boulho et al. 2017; Chen and Xue 2019) and temperature may vary between 40 and 110 °C (Sousa et al. 2010; Juin et al. 2015; Boulho et al. 2017). Therefore, MAE is not recommended to extract temperature-sensitive compounds (Kadam et al. 2015b). Nevertheless, this technique reduces the amount of solvent required and wastes produced, is relatively economic, and easy to perform (Kadam et al. 2015b). Several studies have employed MAE to obtain biological compounds from red algae, such as phycobiliproteins and polysaccharides, including agar and carrageenan (Sousa et al. 2010; Juin et al. 2015; Boulho et al. 2017; Chen and Xue 2019).

#### Ultrasound Assisted Extraction

Ultrasound assisted extraction (UAE) is based on the migration of sound waves (whose frequency ranges from 20 to 20,000 Hz), producing micro-bubbles in a liquid medium. These bubbles grow and collapse, disrupting cell walls and, then favoring the penetration of solvents into the matrix (Michalak and Chojnacka 2014; Garcia-Vaquero et al. 2017; Jacobsen et al. 2019). Generally, as it occurs with MAE, water is used as solvent in UAE (Fidelis et al. 2014; Rodrigues et al. 2015b; Wang et al. 2015a). Temperatures usually ranges between 30 and 60 °C, being compatible with the extraction of thermo-labile compounds (Kadam et al. 2015b; Mittal et al. 2017). As a green method, UAE has been reported to improve the extraction yield

and reduce the amount of solvent required and the extraction time. In addition, it has high possibilities to be introduced in industrial processes, due to the high scalability to large-scale applications (Garcia-Vaquero et al. 2017). Different studies have employed UAE in the extraction of carbohydrates, sulphated polysaccharides, proteins, amino acids, and phenolic compounds (Fidelis et al. 2014; Rodrigues et al. 2015b; Wang et al. 2015a; Garcia-Vaquero et al. 2017; Mittal et al. 2017).

### Enzymatic Assisted Extraction

Enzymatic assisted extraction (EAE) is a promising system, based on the use of enzymes to hydrolyze the complex and heterogeneous algal cell walls and extract the intracellular compounds. Some examples of the enzymes used are cellulase,  $\alpha$ -amylase, pepsin, viscozyme, agarase, etc. (Michalak and Chojnacka 2014; Kadam et al. 2015b; Garcia-Vaquero et al. 2017). The optimal extraction conditions depend on the characteristics of the enzyme, including temperature ranges from 40 to 60 °C and pH from 3.8 to 8 (Michalak and Chojnacka 2014; Garcia-Vaquero et al. 2017). Generally, the extraction is conducted on phosphate or acetate buffer to ensure an efficient enzymatic performance (Praveen et al. 2019; Vásquez et al. 2019). This system presents a high efficiency and specificity, reduced time, and allows reaching great extraction yields (Garcia-Vaquero et al. 2017). In addition, EAE is environmentally friendly and non-toxic, thanks to the independence on pollutant solvents. However, its application at industrial scale is limited, due to the expensive cost of the enzymes (Garcia-Vaquero et al. 2017). Different studies have used EAE to extract biological compounds such as proteins or phenolic compounds (Wang et al. 2010; Rodrigues et al. 2015b; Vásquez et al. 2019).

### Conclusions

Red algae are the largest group of seaweeds and a potential source of bioactive compounds. Among their components, agar and carrageenans account for up to 40–50% of their dry weight and although they are mostly known for their technological and industrial applications as gelling, stabilizing and emulsifying agents, they can be also highlighted as bioactive

compounds. The lipid profile of red algae shows a low  $\omega$ -6/ $\omega$ -3 rate which indicates beneficial properties in the prevention of cardiovascular diseases. Red algae show high protein content but also lectins have been proposed as cell signaling mediators and antimicrobial compounds. Moreover, minor components such as vitamins (B1, B2, B12, C,  $\beta$ -carotene), minerals (Na, K, Ca, and Mg) and other secondary metabolites (phenolic compounds, terpenoids or alkaloids) are potential candidates to be explored. Concerning the related biological properties, antioxidant, anti-inflammatory, antitumor, and antimicrobial properties can be highlighted as the most studied but more in vivo experiments need to be performed to further disclose the mechanisms of action behind the activities. On the other hand, regarding the extraction techniques, the optimization and development of new procedures using green extraction technologies are necessary to attach to a circular and sustainable economy. Considering these main findings, further work is directed towards the creation and development of new applications to include bioactive compounds from red algae in the food, cosmetic and pharmaceutical industries.

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