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Review article

A comprehensive review of traditional uses, bioactivity potential, and chemical diversity of the genus *Gracilaria* (Gracilariales, Rhodophyta)

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ABSTRACT

The genus *Gracilaria* is an important marine bio-resource since some members are a source of about 80% of the global production of agar. Moreover, species of *Gracilaria* are used in traditional medicine and human diet in many parts of the world. In this review, it was possible to verify that the number of publications concerning bioactivities for the genus has highly increased, and several promising results in the agriculture and aquaculture fields, as well as antimicrobial, cytotoxic, antioxidant, antinociceptive, anti-ulcer, antidiarrheal, anti-hyperlipidemic, antiacetylcholinesterase, and anti-inflammatory activities, have been reported. However, many bioactivity results are obtained only for the crude extracts and fractions. Phytochemical approaches are uncommon, and the chemical knowledge related to the genus is only available from nutrition, ecology, or physiology fields. The genus contains a wide variety of metabolites, such as mycosporine-like amino acids (MAAs), agarans, lipids, steroids, diterpenes, phenolic acids, bromophenols, sulfonic acids, oxylipins, heterosides, and pigments. Several of these metabolites are bioactives and of particular interest for industrial and medical applications. In general, the genus *Gracilaria* has a high potential as a source of high-value compounds and extracts for several applications. However, only agar is commercially exploited. A better use of the biomass from commercial cultivation may be an important alternative for exploiting the other bioactive components. Further studies on the chemical composition and isolation of bioactives in the genus are also required.

1. Introduction

Macroalgae are important natural resources of the oceans and represent 27% of the global production from aquaculture [1]. They are traditionally used as human food, source of hydrocolloids, fertilizers, and animal feed [2]. The medicinal properties of macroalgae have been described in the ancient text of the traditional Chinese medicine and Ayurveda [3]. However, only in recent years, there has been a considerable increase in the study of bioactivities and bioprospecting of these organisms [4]. An extensive range of compounds are found in macroalgae, such as pigments (e.g., phycobiliproteins and carotenoids), phenolic compounds (e.g., phlorotannins and bromophenols), nitrogen compounds (e.g., alkaloids), polysaccharides (e.g., agarans, carrageenans, and alginate), and terpenoids (e.g., diterpenes and sesquiterpenes) [5]. Several biological properties have been assigned to these compounds including antioxidant, antibacterial, antiviral, anti-aging, anti-inflammatory, and anticancer [6]. Macroalgae have increasingly gained importance in the development of dietary supplements, functional foods, pharmaceuticals, cosmetics, and other industrial applications, due to the presence of these bioactive components [7,8]. In the nutraceutical industry, for example, it has been well reported that macroalgae–rich diets may provide significant health benefits including the reduction of disease risk and promotion of well-being [9–12], and in the cosmetic industry, bioactives and extracts from macroalgae are known mainly for their benefits to skin [7].

Species of *Gracilaria* Greville are an important source of valuable products for industry and exhibit significant pharmacological activities [13,14]. This review aims to provide information concerning the biology, traditional uses, biological activities, and chemical diversity of species of this genus in order to summarize our current state of knowledge and attempt to identify and promote new research opportunities.

2. General biology

The genus *Gracilaria* belongs to the phylum Rhodophyta (or red algae), class Florideophyceae, order Gracilariales, and family Gracilariaceae [15]. This genus was described by Greville in 1830 [16].

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Gracilaria is the largest genus in Gracilariales encompassing 190 species and, together with *Ceramium* Roth (209 species; Ceramiales) and *Polysiphonia* Greville (209 species; Ceramiales), encompass the major genera of Rhodophyta [15].

Members of the genus *Gracilaria* are found from tropical to temperate latitudes, with higher species richness in tropical regions mainly in the Indo-Pacific and Western Atlantic [15,17,18]. However, many species are still poorly known and have a very limited distribution globally [15]. Among the most studied algae, *Gracilaria edulis* (S.G.Gmelin) P.C.Silva and *Gracilaria salicornia* (C.Agardh) E.Y.Dawson are widely reported in the Indo-Pacific region, while *Gracilaria corticata* (J.Agardh) J.Agardh is present in the Western Indo-Pacific region and *Gracilaria changii* (B.M.Xia & I.A.Abbott) I.A.Abbott, J.Zhang & B.M.Xia in the Central Indo-Pacific region [15]. On the other hand, *Gracilaria caudata* J.Agardh and *Gracilaria cornea* J.Agardh are reported in the Western Atlantic region, while *Gracilaria gracilis* (Stackhouse) M.Steentoft, L.M.Irvine & W.F.Farnham is present in several regions of the world [15].

Gracilaria species are common and conspicuous members of the benthic flora and generally inhabit the intertidal and subtidal zones between 0.5 and 10 m deep [19,20], but some species are restricted to deep-water, such as *Gracilaria abyssalis* Gurgel & Yoneshigue-Valentin found between 18 and 54 m depth [21]. The members of this genus grow anchored in a sandy or sandy-muddy substratum or attached on a solid substratum (e.g., rocky), with parts of the thallus often covered by sand. Some species can also be free-living, being able to form large dense mats in calm waters [22]. Although *Gracilaria* species occupy a wide range of marine habitats, they are found mainly in sheltered areas, like estuaries, bays, mangroves, reefs, and mudflats.

A diverse range of growth forms is observed for the species of the genus. For example, the shape of the thallus may be completely cylindrical (or terete) (e.g., *G. gracilis*) to broadly flattened (e.g., *Gracilaria domingensis* (Kützing) Sonder ex Dickie). Individuals of the same species may also present morphological variation in the color, length, branching order, and shape of the thallus. Individuals from the same population of *Gracilaria tikvahiae* McLachlan, for example, may present thallus morphology from cylindrical to flat [23]. The life history for the genus *Gracilaria* is recognized as triphasic and has been revealed as *Polysiphonia*-type, with two free-living isomorphic generations (gametophyte and tetrasporophyte phases) and a third generation (carposporophyte phase), which develops dependent on female gametophyte [24]. Phenological studies suggest a predominance of the tetrasporophyte or about an equal rate of both generations (gametophyte and tetrasporophyte) in the natural populations of many species of the genus [24–28]. The chemical composition and physiological performance may vary between the generations [29–33].

A wide range of environmental tolerances have been reported for *Gracilaria* species. Several species, for example, are euryhaline, such as *G. gracilis* found in oligohaline (0.5 to 5 ppt) to euhaline (30 to 40 ppt) lagoons within Europe [34]. Eurythermal species are also reported for the genus. *Gracilaria tikvahiae*, for example, tolerates temperatures between 0 and 34 °C [35]. *Gracilaria vermiculophylla* (Ohmi) Papenfuss, an invasive macroalga, has its environmental tolerances well reported in the literature [36]. This species can grow at practically undetectable levels of light ($< 1\ \mu mol\ photon{\cdot}m^{-2}{\cdot}s^{-1}$) [37], survive under salinity of 60 ppt for up to 8 weeks [38], and survive 175 days out of the water in environments with dehydration of up to 19% under complete darkness at 8 °C [39].

In general, changes in the morphology, anatomy, physiology, growth, reproduction, and chemical composition in response to environmental (e.g., water temperature, salinity, type of substrate, light intensity, and nutrients) and biotic (e.g., epiphytism) factors are often reported in the literature for *Gracilaria* species, thus suggesting a considerable phenotypic plasticity for the genus. This high level of phenotypic plasticity and large number of species in the genus make their identification quite complex when based only on morphological characteristics [18]. Recently, the widespread use of molecular analyses based on DNA sequence data has made the knowledge related to taxonomy, biogeography, and phylogenetic relationships in this genus more consistent [40–44]. In this review, we chose to adopt the genus *Gracilaria* as proposed recently by Iha et al. [40].

3. Traditional uses and economic importance

Gracilaria species are widely exploited by humans and have great economic importance. The earliest use as food or medicine goes back to prehistory (~14,000 years ago) by the first inhabitants of Monte Verde in Chile [45]. In China, the exploitation of *Gracilaria* species is quite old. These algae were utilized as food and as a binder material to improve the fixation of lime in wall paintings [46]. It is believed that the use of these algae has spread out from China to other eastern countries. Some *Gracilaria* species are edible macroalgae (or sea vegetables) being consumed mainly in Japan, Southeast Asia, Hawaii, and the Caribbean. In Hawaii, for example, these algae are used as a garnish for the fish salad known as “Poke” [47]. In Japan, they are known as ogonori (or ogo) and are consumed mainly in salads or as a garnish in dishes such as sashimi. In Jamaica, they are known as “Irish moss” and are utilized to prepare a typical drink, which has the same name (in the world at large, Irish moss is the popular name of the red macroalga *Chondrus crispus* Stackhouse) [48].

Gracilaria species are better known as raw material exploited for the extraction of agar, one of the typical phycocolloids found in some species of red algae. Agar was discovered in the mid-seventeenth century by the Japanese, and it is one of the oldest gelling agent [49]. Initially, the red algae *Gelidium amansii* (J.V.Lamouroux) J.V.Lamouroux, also known as “Tengusa”, was the main source for the exploitation of agar. However, due to excessive exploitation, some species of *Gracilaria* started being employed as substitutes or mixed to “Tengusa”, yielding a poor quality agar [50]. Only after the discovery of alkaline hydrolysis, a process applied for reduction of the sulfate content of the polysaccharides, there was an improvement in the quality of the agar obtained from these species [50], enabling the widespread use of *Gracilaria* for this purpose.

According to the FAO (Food and Agriculture Organization of the United Nations), > 80% of the global production of agar is obtained from *Gracilaria* species [51,52]. The main producers are China (70% of annual production) and Indonesia (28%) [53]. Commercial cultivation is mainly carried out in sheltered areas (ponds and bays), using native algae of each region. However, the agar yield and gelling properties vary among species and are affected by abiotic (e.g., light intensity, temperature, and nutrients) and biotic (e.g., epiphytism) factors [54]. According to the review by Lee et al. [54], extreme salinities (> 40 ppt and < 10 ppt) and light deprivation, in contrast to higher epiphyte abundance and nitrogen availability, generally increase the agar yield. A seasonal effect was also observed, since higher yields were obtained in summer (temperate regions) and rainy seasons (tropical regions).

Agar from *Gracilaria* is a food-grade agar utilized as thickening, stabilizing or gelling agent for the baking and confectionery industry in the production of desserts, such as pies, icings, and jelly candies [55]. In Western cuisine, agar has been widespread in diets for weight loss and as an alternative to gelatin, a product of animal origin. In Eastern countries, the agar is traditionally used in desserts, such as “Anmitsu” (China), “Yōkan” (Japan), and “Halo-halo” (Philippines), and is present in soups, snacks, and typical dishes such as “Tokoroten” (Japan).

Gracilaria species are used in folk medicine for several treatments (Table 1). In China, for example, some species of *Gracilaria* are indicated in the treatment of intestinal constipation, enteritis, dysentery, urinary disorders, thyroid diseases, and respiratory disease [56]. In India, *Gracilaria edulis* (= *Gracilaria lichenoides*) is used as an emollient and demulcent in treatments of respiratory diseases, diarrhea, and dysentery [57–59]. In some Central American countries, *Gracilaria* species are known to have aphrodisiac properties [60]. The most

Table 1
Uses in traditional medicine of *Gracilaria* species.

	Folk medicinal uses	References
Cardiovascular system	- Antihypotensive properties	[57]
Digestive system	- Diarrhea - Dysentery - Enteritis - Hemorrhoids - Intestinal constipation - Jaundice	[56,58,61–65]
Endocrine system	- Thyroid goiter - Thyroid tumor	[56,62,63]
Reproductive system	- Aphrodisiacs properties - Leucorrhea - Menorrhagia	[60,65]
Respiratory system	- Bronchitis - Cough - Irritation of throat - Pulmonary complications	[56,58,59,62,64,65]
Urinary system	- Bladder complications - Difficult urination - Diuretic properties	[56,62]
Others	- Beriberi - Diabetes - Obesity - Sores - Swelling or edemas (e.g. swollen knee)	[56,64,65]

reported use for the genus was the treatment of intestinal constipation or as a laxative. Powdered *Gracilaria* or direct agar are sold in some countries, promoting a good digestive health and as appetite moderator.

In aquaculture, the genus *Gracilaria* has also been successfully used in feeds mainly for abalone and as a biofilter in integrated multi-trophic aquaculture (IMTA) systems in combination with shrimps, fishes, and abalones in different regions especially in Asia [66–69]. *Gracilaria* species are particularly interesting for use in IMTA systems since they have high bioremediation efficiency in the removal of inorganic nutrients and added value due to the agar [70–73]. Other uses of *Gracilaria* species include the use in cosmetics, such as shampoos (e.g., shampoo *Gracilaria* by Thermalabs®), soaps (e.g., hydrogel soap by Sea Laria®), hydrating creams (e.g., day cream by Thalasso®), facial mask (e.g., detox facial mask by Balinique®), lotions (e.g., *Gracilaria* hydrogel by Sea Laria®), and deodorants (e.g., natural deodorant by Bali secrets®). The applications of *Gracilaria* in cosmetics are mainly due to thickening, stabilizing or gelling properties of agar [74].

4. Bioactivities from species of *Gracilaria*

The genus *Gracilaria* has been extensively evaluated in terms of its bioactivity. The latest review of the genus was performed by Almeida et al. [14], and the database was built with 31 articles. In the present review, a wider database research was built for the period of 1980 to 2017, using the Google Scholar platform, reaching 417 published papers concerning bioactivities related to species of *Gracilaria* (see the database in the supplementary data – Appendix A). The number of annual publications increased significantly from 2003 (two publications), reaching a peak in 2017 (51 publications) (Fig. 1). These results suggest a recent interest in the investigation of the bioactive potential of species of *Gracilaria*.

In general, two broad areas of research can be distinguished from the database. On the one hand, several studies were focused on human health, which includes antimicrobial (bacteria, fungi, protozoa, and viruses), anti-inflammatory, antinociceptive, and cytotoxicity activities, as well as activities against various diseases, such as neurological, gastrointestinal, cardiovascular, and diabetes. On the other hand, the second broad field, not human-health related, included studies

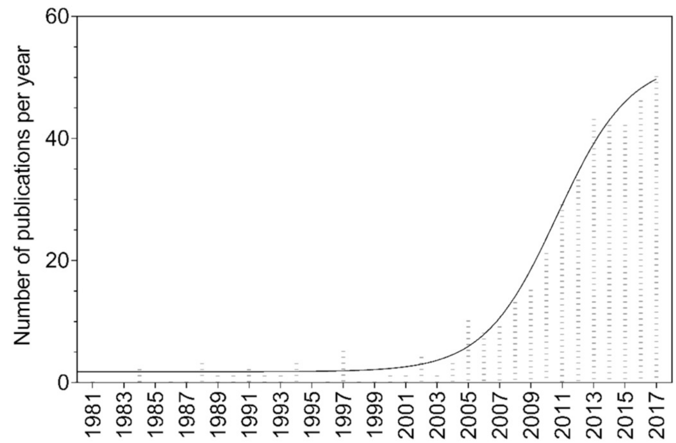

Fig. 1. Number of published papers concerning bioactivities of species of *Gracilaria* based on Google Scholar. Database obtained for the period of 1980 to 2017. See online Supplementary data: Appendix A. Small traces on the x axis represent the papers. The continuous line represents the sigmoidal tendency line (R^2 = 0.98).

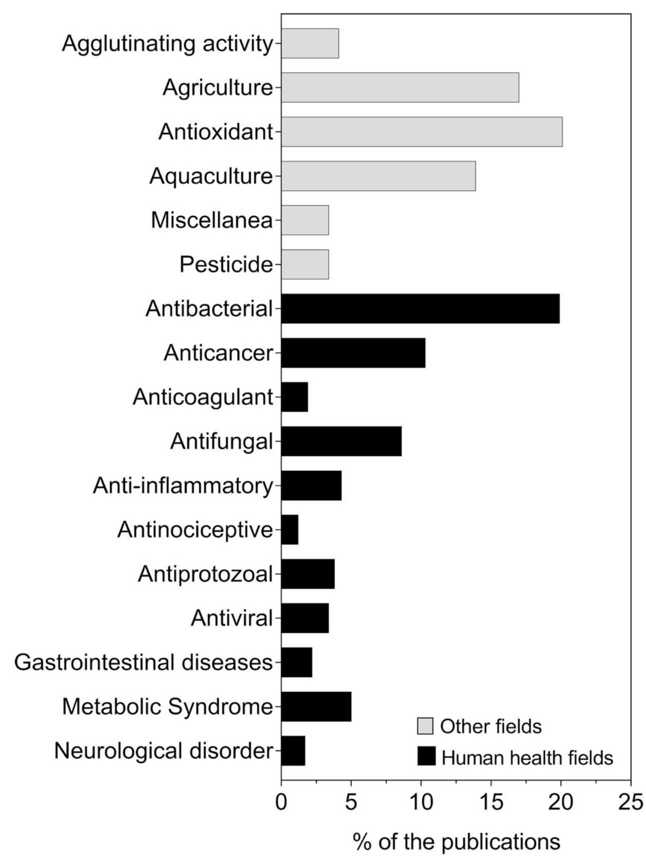

Fig. 2. Percentage of total published papers (417 articles) concerning specific bioactivities of species of *Gracilaria* based on Google Scholar. Database obtained in the period of 1980 to 2017.See online Supplementary data: Appendix A.

concerning antioxidant assays, applications in agriculture and aquaculture, agglutinating activity, and pesticides (Fig. 2). Antioxidant (20.1%) and antibacterial (19.9%) activities are the most evaluated properties.

Despite the large number of traditional uses pointed out for species of *Gracilaria* (Table 1), it is worthy to mention that few studies have been conducted to validate the traditional uses of these macroalgae. For example, the use of *Gracilaria* for treatment of gastrointestinal diseases is widespread in traditional medicine [56,61–65]. However, only two

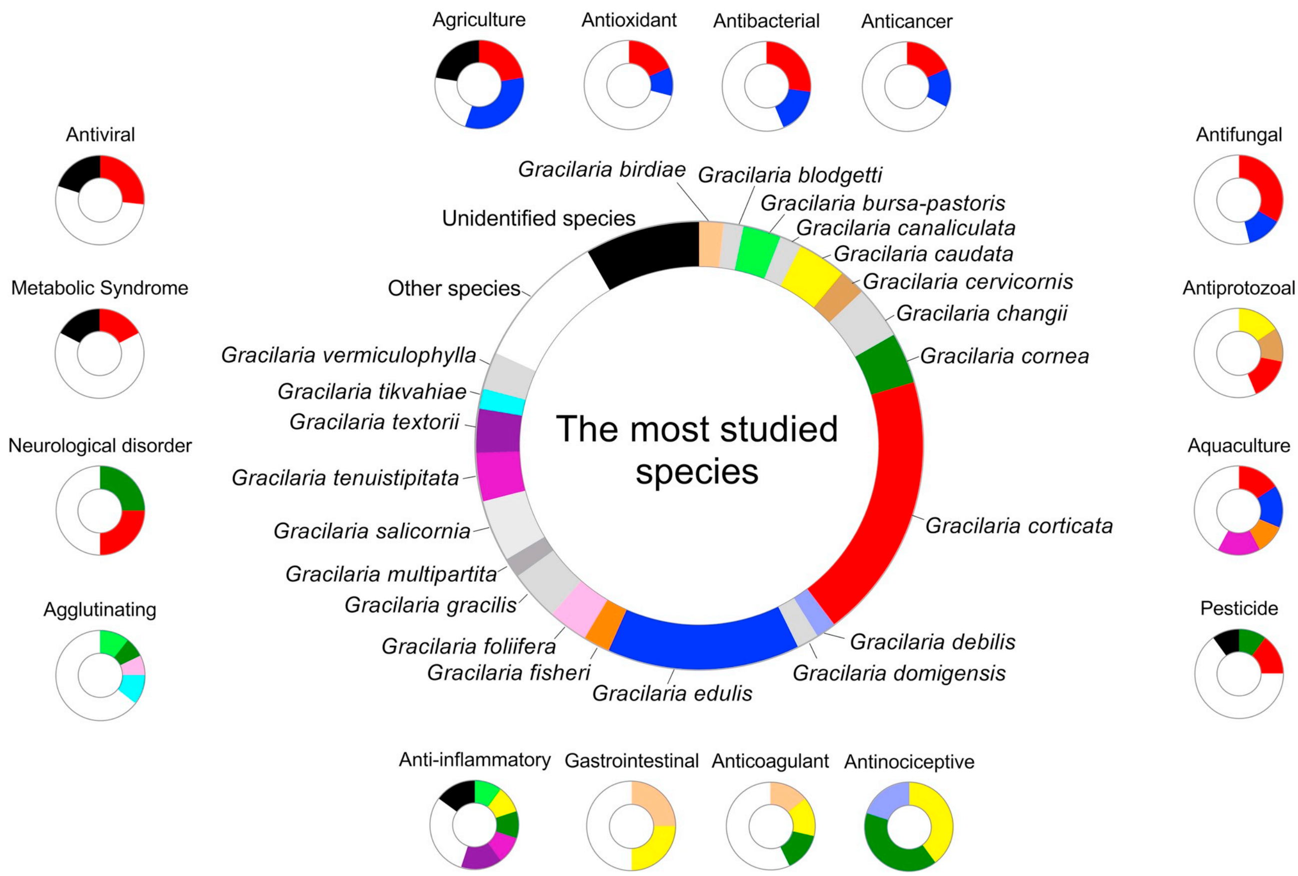

Fig. 3. Percentage distribution of species of *Gracilaria* analyzed for biological activities. Central large pie shows the percentage distribution of species of *Gracilaria* within all assays. Small pies show percentage distribution of species of *Gracilaria* within a specific assay. Different color fragments represent distinct species of *Gracilaria* as marked in the central pie. Database obtained for the period of 1980 to 2017. See online Supplementary data: Appendix A.

papers have reported the effects of species of *Gracilaria* against diarrhea [75,76]. Important areas of traditional uses, such as respiratory disorders have never been evaluated. Therefore, the search for scientific evidence for traditional uses may provide a good perspective for future research.

Among the 190 species of *Gracilaria*, only 49 species (25.7%) have been evaluated for biological activity. Papers with misidentified species, for example "*Gracilaria verrucosa*" and "*Gracilaria lemaneiformis*", now *Gracilariopsis longissima* and *Gracilariopsis lemaneiformis*, respectively [15], were not included in this review. *G. corticata* (19.2% of studies) is the most frequently studied species, followed by *G. edulis* (13.8%), *G. salicornia* (4.5%), *G. changii* (3.8%), *G. cornea* (3.8%), and *G. gracilis* (3.7%) (Fig. 3). However, it was not possible to point out from the database the most active *Gracilaria* species, since comparisons between the species were rare.

Except for antinociceptive, agglutinating, anticoagulant, anti-gastrointestinal, and anti-inflammatory assays, *G. corticata* appeared as the main algae in all specific studies (Fig. 3). Among the 49 species investigated, 21 of them appear in 82% of the studies. The other 28 species, pooled together as 'other species' correspond only to 10% of all bioactivity investigations with *Gracilaria*. This observation indicates that many species have been sporadically evaluated, suggesting another important point to be explored in future studies with the genus. Unidentified species (*Gracilaria* sp.) were frequent in studies of agriculture (22%), metabolic syndrome (17.0%), antiviral (15%), and anti-inflammatory (15%) activities (Fig. 3).

The present review brings out that most of the publications evaluating bioactivities of species of *Gracilaria* used crude extracts or fractions. Few publications identified bioactive compounds or worked on the isolation of the compounds responsible for the activities. One of the few examples is the paper of Sakthivel et al. [77] in which the authors isolated phytol through bioassay-guided fractionation of extracts of *G. edulis*, using cytotoxic assays against pulmonary adenocarcinoma cells (A549). Similar results were found by Sheeja et al. [78] studying the same alga but using breast cancer cells (MCF-7). Contrary, identification of sulfated polysaccharides of the agaran group from aqueous extracts of several species of *Gracilaria* is common. These compounds account for 10.6% of total publications on bioactivities for the genus. Examples include antinociceptive and anti-inflammatory activities reported by Chaves et al. [79] studying *G. caudata*, antioxidant activities reported by Souza et al. [80] studying *Gracilaria birdiae* E.M.Plastino & E.C.Oliveira, and antiviral activities reported by Mazumder et al. [81] studying *G. corticata* against herpes simplex virus (HSV) types 1 and 2. The best results with *Gracilaria* species for the anti-inflammatory, antinociceptive, gastrointestinal, neurological, and antiviral activities were obtained from aqueous extracts or agarans.

Below we will briefly present the main bioactivity assays performed with species of the genus *Gracilaria*, arranged in the two broad groups of research mentioned before.

4.1. Human health fields

4.1.1. Anticancer activities

According to the World Health Organization – WHO (2018), cancer is one of the leading causes of mortality worldwide, killing > 8 million people a year. Chemotherapy is one of the main cancer treatments; however, side effects are common, and cases of drug resistance have become more frequent [82]. It is not surprising, therefore, that there is an intense and justifiable search for new anticancer drugs. Extracts of *Gracilaria* were evaluated mainly in cell viability assays based on metabolic activity (79% of studies) by reduction of tetrazolium salts (67%) or resazurin dye (10%). Many of these studies were flawed by the lack of a positive control, which was only reported in 21% of studies. In general, instead of a positive control, cell inhibition higher than 50% at $100\,\mu g{\cdot}mL^{-1}$ (or IC50 $< 100\,\mu g{\cdot}mL^{-1}$) were considered active. Using this criterion, only 29% of studies with *Gracilaria* for anticancer activities were promising. One of the best results was obtained by Costa et al. [83] studying lipid extracts of an unidentified species of *Gracilaria*. These authors found IC50 values of $12.2\,\mu g{\cdot}mL^{-1}$ and $12.9\,\mu g{\cdot}mL^{-1}$ against a human breast cancer cell line (T-47D) and human bladder carcinoma cell line (5637), respectively. In general, the most studied and active extracts were obtained from organic solvents. As seen previously, Sakthivel et al. [77] and Sheeja et al. [78] identified phytol as one of the components responsible by the anticancer activities of ethyl acetate extracts from *G. edulis*.

Other studies, such as anti-migration and cytotoxicity effects, were rarely evaluated in *Gracilaria* species. Cytotoxicity assays, such as necrosis and apoptosis detection, were reported in 29% of studies. For example, Patra and Muthuraman [84] studying ethanolic extracts from *G. edulis* found that the cell inhibition against Ehrlich ascites tumor was due to apoptosis. Anti-migration effects were reported only by Sae-Lao et al. [85]. These authors found that sulphated agaran from *Gracilaria fisheri* (B.M.Xia & I.A.Abbott) I.A.Abbott, J.Zhang & B.M.Xia act against the migration of two lines of cholangiocarcinoma cells showing IC50 values of $7\,\mu g{\cdot}mL^{-1}$ and $8\,\mu g{\cdot}mL^{-1}$ for HuCCA-1 and RMCCA-1, respectively.

4.1.2. Anticoagulant activities

Anticoagulants prevent or reduce the formation of blood clots [86]. The use of anticoagulants is widespread in laboratory analysis and for prevention of diseases such as thrombosis [86]. Aqueous extracts or sulfated agarans [87–94] from *Gracilaria* were evaluated against this activity; however, the results were not promising as compared to heparin activity (reference standard) or other algae.

4.1.3. Anti-inflammatory and antinociceptive activities

Anti-inflammatory compounds act in reducing certain signs of inflammation, such as pain, fever, and swelling. Half of the studies on anti-inflammatory activities in *Gracilaria* species were performed with aqueous extracts or sulfated agarans [79,95–101]. In general, these studies showed a good anti-inflammatory potential. In contrast, the results with organic extracts showed moderate to no activity [102–106]. The aqueous extracts and sulfated agarans caused a reduction in edema and migration of leukocytes, and suppressed the expression of important compounds for inflammation. There is strong evidence that the aqueous extracts and sulfated agarans act on different inflammatory mechanisms, such as inhibition of the NF-κB (factor nuclear kappa B) and MAPK (mitogen-activated protein kinase) pathways [98] and act on mast cells, preventing the release of their content [99]. In addition, the heme oxygenase-1 pathway appears to be important in the anti-inflammatory mechanism of these extracts and fractions [96,99].

Antinociceptive activity reduces sensitivity to stimuli that cause pain. This activity was described for sulfated agarans of *Gracilaria* [79,101,107,108]. In these studies, the pain was a consequence of the inflammatory process. In general, the sulfated agarans promoted an analgesic effect. However, Chaves et al. [79] pointed out that this analgesic effect was due to the mitigation of inflammatory effects by the agarans and not by the direct action on the pain receptors.

4.1.4. Antimicrobial activities

Antimicrobials kill microorganisms or slow down their growth [109]. Side effects and the emergence of drug-resistant strains of microorganisms show the need to search for new antimicrobial agents for combating infectious diseases, such as pneumonia, tuberculosis, herpes, malaria, and AIDS (acquired immunodeficiency syndrome) [110]. Only microorganisms of importance to human health will be treated in this topic. Bacteria followed by fungi, protozoa, and viruses were the most frequently evaluated microorganisms in studies with *Gracilaria* species.

The assays against bacterial and fungal pathogens were performed mainly by disk or well diffusion assay (> 89%). As well as for anticancer assays, the main problems with these studies were poor descriptions of methods. For example, ~40% of publications did not provide information concerning mass (or concentration and volume) of the tested sample (extract and/or fraction), and ~75% of publications did not describe the results for reference standards. Screening of macroalgae was the focus of > 70% of articles. Among them, 49% using bacterial pathogens and 20% with fungal pathogens reported *Gracilaria* species among the most active algae against at least one bacterium or fungus. A promising result was obtained with the methanolic extract from *G. changii* [111]. This extract was reported among the most active against the antibiotic-resistant *Staphylococcus aureus*, a pathogenic bacterium responsible for many hospital-acquired infections.

The most studied virus was herpes simplex virus types 1 (HSV 1) and 2 (HSV 2) (57.8% of total publications). In general, the organic extracts were inactive against different viruses and the aqueous extracts (or sulfated agaran) presented promising results. Mazumder et al. [81] found a sulfated agaran fraction of *G. corticata* more active against HSV 1 and HSV 2 than the positive control (Heparin). Publications that reported antiprotozoal activities in *Gracilaria* screened several algae genera. The most frequent were anti-leishmanial activity, followed by Chagas diseases and malaria. In general, activities against Chagas disease [112–116] and malaria [115,117–120] were not promising, and the results for anti-leishmanial activities [114,115,121–126] indicated intermediate or no activity, as compared to other algae genera.

4.1.5. Gastrointestinal diseases

Gastrointestinal diseases are those that affect the digestive system and accessory organs. Crude extracts and mainly sulfated agarans from *Gracilaria* species showed a protective function against intestinal damage, such as ulcers induced in rats by pylorus ligation [127], ethanol [102,128] or naproxen [129]. Antidiarrheal activity assays were performed on the sulfated agarans extracted from *G. caudata* [75] and *Gracilaria intermedia* J.Agardh [76]. The antidiarrheal effects of these polysaccharides involved anti-secretory activity and reduction in intestinal motility by anticholinergic mechanisms. In contrast, species of the genus are also used to relieve intestinal constipation in folk medicine (Table 1). In this case, agarans act as bulk-forming laxatives and promote improvement in peristaltic movement [130].

4.1.6. Metabolic syndrome

Metabolic syndrome refers to a set of factors, such as hyperglycemia, hypocholesterolemia, hypertension, hypertriglyceridemia, and obesity, which increase the risk of heart disease and diabetes mellitus type 2 [131]. These risk factors were objects of research in studies with *Gracilaria* species. Antihyperglycemic or anti-diabetic activities were mainly performed in vitro, evaluating the inhibition of α-glucosidase and α-amylase enzymes. In general, anti-diabetic activity was weak, as compared to that of other macroalgae (red, brown, and green) or positive controls. One of the exceptions was Xiancui et al. [132] who reported *G. textorii* among the most active algae.

Activities against hyperlipidemia (high levels of lipids or lipoproteins in the blood) were evaluated in rats fed with diets rich in cholesterol and fat. In general, diets supplemented with algae promoted a reduction in the plasma levels of triglycerides, total cholesterol, and LDL (Low Density Lipoprotein) [133–135]. Moreover, Chan et al. [136] reported from histopathological studies that diets supplemented with *G. changii* promoted protective effects on livers of hyperlipidemic rats and no toxic effects on cardiac muscle and kidney. An increase in the activities of antioxidant enzymes was also observed on these organs, suggesting that one of the likely protective effects exerted by the diets supplemented with *G. changii* was due to the reduction of oxidative stress [137].

4.1.7. Neurological disorders

Neurological disorders are diseases of the nervous system, such as brain tumors, epilepsy, Parkinson's disease, stroke, and Alzheimer's disease [138]. Sulfated agarans of *G. cornea* presented neuroprotective effects in rats used for study of Parkinson's disease [139] and anxiolytic properties [140]. Other studies evaluated activity against the enzyme acetylcholinesterase. Inhibitors of this enzyme are used to alleviate neurological symptoms in Alzheimer's disease. Some authors, such as Natarajan et al. [141], obtained promising results. These authors verified good potential for methanolic extracts of *G. gracilis* and *G. edulis*, with lower IC50 than donepezil (reference standard). Similar results were found by Suganthy et al. [142] for methanolic extracts of *G. edulis*. However, species of *Gracilaria* showed moderate [143] and weak [120] activities, as compared to other algae genera.

4.2. Other fields

4.2.1. Agglutinating activities

Agglutinins are compounds that cause agglutination of cells or organic particles [144]. Lectins and antibodies are well-known examples of these compounds [144,145]. In general, agglutinins are used for blood typing and present numerous other bioactivities, such as antimicrobial and cytotoxic [144,145]. In the context, > 80% of the published papers concerning agglutinating properties of extracts from species of *Gracilaria* evaluate the capacity of agglutination of red blood cells. The agglutinating activities were variable, as compared to other groups of macroalgae (red, brown, and green). An example of a promising result was found by Dinh et al. [146] evaluating 44 species of algae. These authors found that crude extracts of *Gracilaria eucheumatoides* Harvey and *G. salicornia* were among the most active, agglutinating erythrocytes of rabbits, chicken, and sheep.

4.2.2. Agriculture

Macroalgae have long been used in agriculture because of their beneficial effects on the plant crops, such as higher productivity and resistance to biotic and abiotic stresses [147]. Brown algae are the most commonly used for this purpose, mainly *Ascophyllum nodosum* (Linnaeus) Le Jolis and *Ecklonia maxima* (Osbeck) Papenfuss. Recently, species of *Gracilaria* have also shown positive effects on land plants. For example, Chitra et al. [148] found that the use of the aqueous extract from *G. corticata* on mung bean (*Vigna radiata* (L.) R. Wilczek) promoted an increase in the number of leaves and length of roots and stems. More recently, Torres et al. [149] studying extracts of *G. caudata* and *G. domingensis* reported sulfated agarans, palmitic acid, and phenylacetic acid (auxin) as biostimulants for lettuce. *Gracilaria* extracts have been also evaluated against pathogens of agricultural importance, mainly fungi. However, the results, in general, were not promising, as compared to other groups of macroalgae (red, brown, and green) or positive controls. An example of positive results is the study by Jiménez et al. [150] who found that aqueous and ethanolic extracts of *G. chilensis* inhibited the root-rot fungus (*Phytophthora cinnamomi*).

4.2.3. Antioxidant activities

Antioxidants are compounds that delay or inhibit the oxidation of organic material or organisms under oxidative stress [151]. These compounds can be used to prevent a wide range of diseases and as preservatives in food and cosmetics [151]. The evaluation of antioxidant activities of species of *Gracilaria* was mostly made by in vitro assays, mainly against the DPPH (2,2-diphenyl-1-picrylhydrazyl) radical (79.0%), the Folin-Ciocalteu reagent (67.1%), and applying the ferric reducing antioxidant power assay (FRAP) using potassium ferricyanide (28.2%) or TPTZ (tripyridyltriazine) (17.6%).

About half of the publications were focused on comparisons between different groups of macroalgae (red, brown, and green). In these articles, species of *Gracilaria* generally showed of moderate to weak antioxidant potential. Some examples include Zhang et al. [152] studying Chinese algae, Farvin and Jacobsen [153] studying Danish algae, and Zubia et al. [154] studying Mexican algae. Sulfated agarans have rarely been studied but promising results have been reported, such as by Seedevi et al. [155] studying sulfated agarans from *G. corticata*. These authors found similar results to those of reference standards (ascorbic acid and butylated hydroxytoluene - BHT). In vivo antioxidant studies were rare but presented a good antioxidative potential [135,137,156–158]. For example, Murakami et al. [158] reported that the chloroform extract of *Gracilaria blodgettii* Harvey was one of the most effective, among several land plants and algae, to attenuate the oxidative and nitrosative stress induced in leucocytes.

4.2.4. Aquaculture

Aquaculture is the farming of aquatic organisms, such as fish, macroalgae, and crustaceans. Promising results with species of *Gracilaria* have been reported, mainly with farming of shrimp and fish. Shrimp were mostly evaluated in in vivo assays and represent 37% of the publications in aquaculture. The use of extracts or algae, either by immersion, injection or ingestion, significantly reduced the mortality rates and improved the immune response of shrimp against abiotic stress [159–162] and pathogens, such as the Gram-negative bacterium *Vibrio alginolyticus* [162–165] and the white spot syndrome virus (WSSV) [166–171]. Lin et al. [170] found that whiteleg shrimp (*Litopenaeus vannamei*) infected with WSSV exhibited lower mortality rates when immersed in seawater containing aqueous extract of *G. tenuistipitata*. Similar results with the same type of extract were found by Yeh et al. [163] studying whiteleg shrimp infected with *V. alginolyticus*. According to Chen et al. [172], the aqueous extracts from *G. tenuistipitata* activate the prophenoloxidase system in the whiteleg shrimp, thus increasing immunity in these crustaceans.

In vivo assays in fish were studied only in 14% of the publications in aquaculture, but promising results have been reported. For example, diets supplemented with *Gracilaria* species reduced the mortality rate in gilt-head bream (*Sparus aurata*) under hypoxia [173], increased antiviral activity against infectious salmon anemia virus in Atlantic salmon (*Salmo salar*) [174], and improved immune responses in European seabass (*Dicentrarchus labrax*) [175,176] and rainbow trout (*Oncorhynchus mykiss*) [177]. Díaz-Rosales et al. [178] proposed a mechanism of action against the Gram-negative bacterium *Photobacterium damselae* ssp. *piscicida*, causative agent of fish Pasteurellosis. This study found that ethanolic extract from *G. cornea* (= *Hydropuntia cornea*) trigger an oxidative burst in the phagocytes of sole (*Solea senegalensis*) in the presence of the pathogens.

The incorporation of *Gracilaria* species in aquaculture feed, as substitutes of traditional ingredients, have been well documented in the literature. Many studies reported animal growth performance as good as with the use of commercial (or control) diets [179–185]. However, the effects on the animal beyond basic nutrition of these macroalgae-rich diets are rarely evaluated. Diets supplemented with *G. cornea*, for example, did not change the intestinal morphology of the gilt-head bream juveniles [186] and positively affected the intestinal microbiota, stimulating the presence of a Gram-positive bacterium (*Lactobacillus delbrueckii*), which can act as a probiotic [187]. In general, dietary supplementation results, taken together with bioactivity properties, support the use of *Gracilaria* species as functional feed in aquaculture.

In vitro antimicrobial studies, corresponding to around 38% of the publications in aquaculture, were made mainly against fish pathogenic bacteria. In general, *Gracilaria* species showed low to moderate antibacterial activity, as compared to that of other macroalgae (red, brown, and green). One of the best results was obtained by Bansemir et al. [188] studying 26 macroalgae. These authors reported the dichloromethane extract from *G. cornea* as the most active, inhibiting the growth of the Gram-negative bacterium *Pseudomonas anguilliseptica*, a pathogen in fish. Anti-fouling activities were less studied [189–193].

Rajan et al. [189] evaluated paints containing extracts of *G. edulis* and found that they are anticorrosive and anti-fouling in seawater.

4.2.5. Pesticides

Pesticides are used for attracting, destroying, mitigating, preventing or repelling pests, which include organisms that cause damage to agriculture and are vectors for human or animal diseases [194]. Species of *Gracilaria* were assessed as insecticide [195–202], nematicide [203–205], and acaricide [206,207]. Most articles have screened groups of algae (red, brown, and green). In these studies, the insecticidal activities were focused on mosquito larvae related to the human-disease vectors: *Anopheles stephensi*, *Culex quinquefasciatus*, and mainly *Aedes aegypti*. Unfortunately, the results obtained for *Gracilaria* species were very poor, ranging from inactive or slightly active, when compared to those of other algae. Nematicidal activity against larvae of *Meloidogyne javanica* (root-knot nematode) showed moderate activity [204]. Other relevant results include lectins isolated from *Gracilaria* species. Lectins isolated from *G. cornea* showed acaricidal activity against *Boophilus microplus* (cattle tick) [207], affecting the hatching period and mass of the eggs, while lectins isolated from *Gracilaria ornata* Areschoug showed insecticidal activity against *Callosobruchus maculatus* (cowpea weevil) [195], reducing larval survival and adult emergence.

5. Chemical diversity

Despite the many biological activities described for species of *Gracilaria* are associated with some specific compounds (Fig. 4), for example: photoprotective effects against ultraviolet (UV) radiation due to MAAs (e.g., porphyra-334) [208]; anticancer properties related to phytol [77,78]; pro-inflammatory or anti-inflammatory potentials due to the eicosanoids (e.g., prostaglandin E2) [209]; and antiviral activity due to agarans [81]; there is a large gap in chemical characterization within this genus, and in general most of the chemical studies have been done with polysaccharides.

In the literature survey on chemical constituents of *Gracilaria*, using Google Scholar database, 116 articles were found within the period of 1960 to 2018. Based on these data, 220 compounds from distinct chemical classes have already been identified in species of *Gracilaria*. The major chemical classes identified in the genus were fatty acids, amino acids, oxylipins, and sterols (Fig. 5). In general, the acetate-malonate pathway appears to be predominant in the metabolism of these organisms, accounting for about 45.6% of all the metabolites already identified (alkanes, fatty acids, fatty alcohols, fatty aldehydes, glycerolipids, sphingolipids, and oxylipins). Terpenoids (carotenoids, diterpene, and sterols) represent 18.9% and compounds, derived from the shikimate pathway, represent 5.9% (benzoic acids and bromophenols). Some toxic macrolides were also identified in the genus, such as polycavernoside A [210], aplysiatoxin [211], debromoaplysiatoxin [211], and manauealide A, B and C [212]. However, these toxins are believed to be of cyanobacterial origin and therefore, were not included in this review.

In general, the chemical profile of the genus *Gracilaria* differs from that found in species of the *Laurencia* complex, the group of Rhodophyta with the largest number of phytochemical studies. Although species of *Laurencia* complex present a great diversity of sesquiterpenes and C15 acetogenins, these two chemical classes have never been identified in the genus *Gracilaria*. In addition, while the halogenation degree of compounds from *Laurencia* complex is relatively high, this substitution pattern is uncommon in *Gracilaria*.

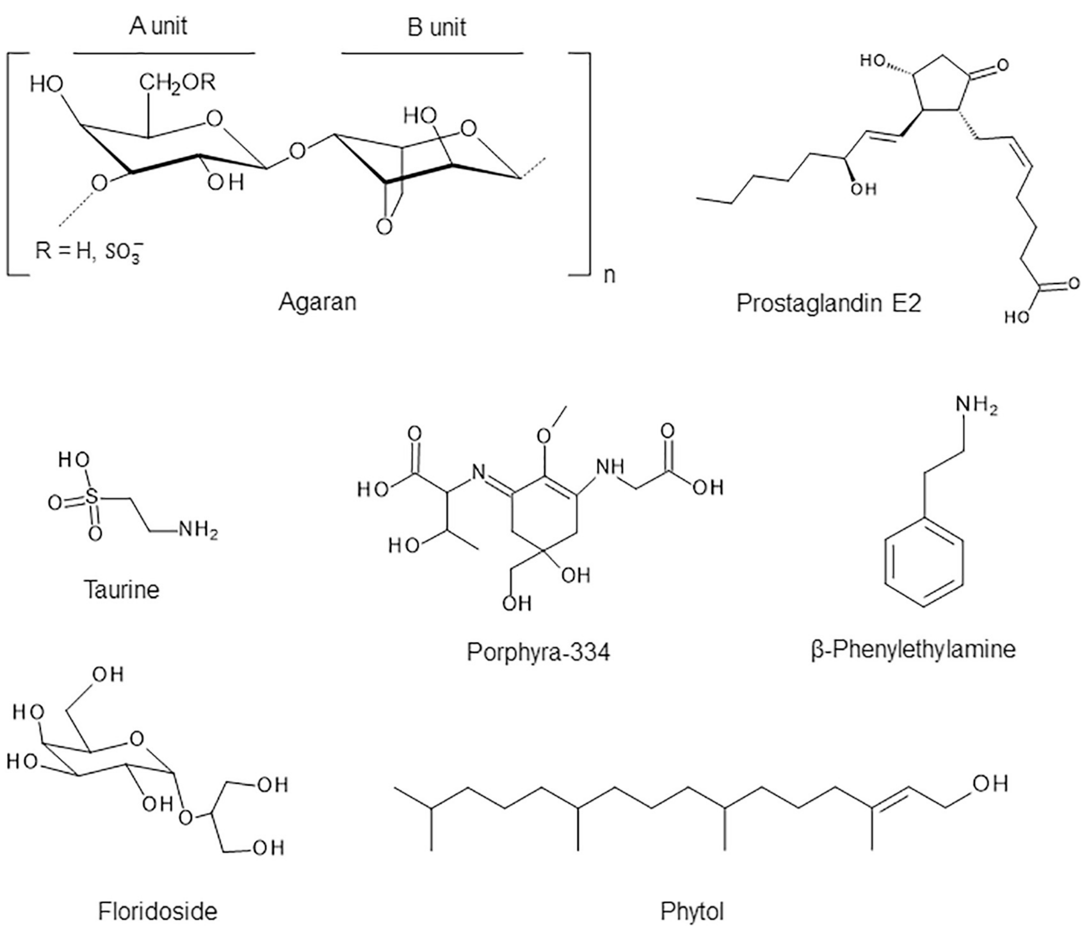

Fig. 4. Some active compounds present in the genus *Gracilaria*.

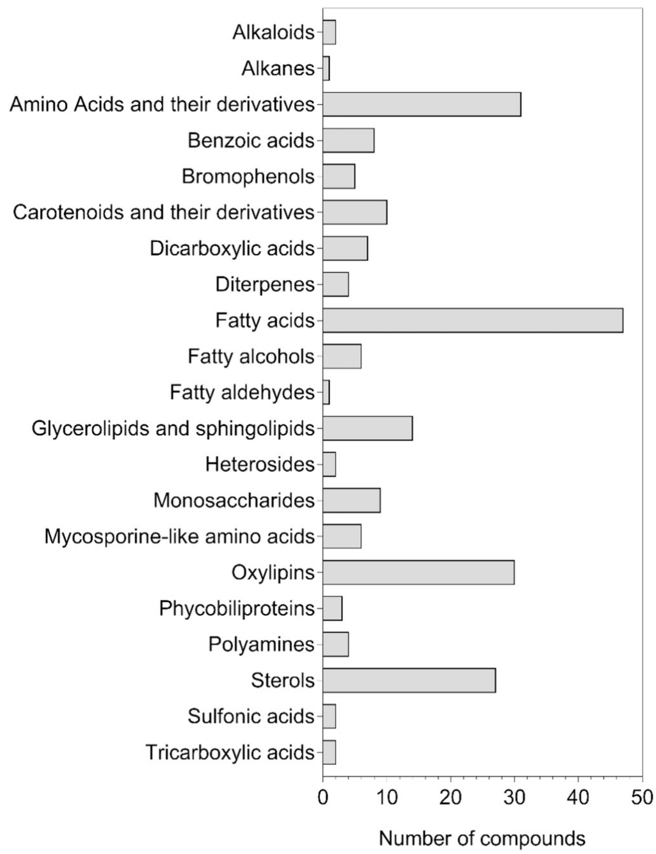

Fig. 5. Number of compounds in each of the main chemical classes already described in species of *Gracilaria* based on Google Scholar database in the period of 1960 to 2018.

5.1. Agarans

The polysaccharides typically found in the genus *Gracilaria* are galactans of the agaran group. These compounds are constituted of residues of 3-linked β-D-galactopyranose (A units) alternating with 4-linked α-L-galactopyranose (B units) arranged in a linear backbone [213]. The B unit is mainly 3,6-anhydro-α-L-galactopyranose residue (as in the example of Fig. 4). Pyruvic acid, sulfate, and methyl group are the main substituents in agaran.

Agar is a complex mixture of different agarans composed of about 70% of agarose and 30% of agaropectin. Agarose is the neutral gelling fraction formed by the agarobiose, which presents alternating residues of D-galactopyranose and 3,6-anhydro-α-L-galactopyranose, while agaropectin is the non-gelling fraction formed by other agarans [214]. The degree and the type of substituents on agarans are important characteristics for the effectiveness of the bioactivities. Generally, higher sulfur content implies higher activity, which explains why active agarans are usually sulfated [215]. Other types of sulfated polysaccharides are also important bioactive products in marine algae, such as fucoidans in brown algae, ulvans in green algae, and carrageenans in red algae. Polysaccharides of macroalgae exhibit promising results including antioxidant, antiviral, anticancer, and anticoagulant activities [216]. As previously commented, the bioactivity of the agarans from *Gracilaria* species includes anti-inflammatory, antinociceptive, gastrointestinal, neurological, and antiviral activities.

5.2. Alkaloids

β-Phenylethylamine has been found in the genus *Gracilaria* [217]. This alkaloid belongs to the class of phenylethylamines, which are characterized by a phenyl group attached to an amine through an ethyl group. This class of alkaloids is one of the most common in marine algae, being found in brown, green, and mainly in red algae [218]. Little is known about the function of these alkaloids for the algae, but their effects are well known to humans. For example, some compounds within of the class of phenylethylamines, such as amphetamine and mescaline, act on the central nervous system [219].

5.3. Alkanes, fatty alcohols, and fatty aldehydes

Alkanes, fatty alcohols, and fatty aldehydes have been described in different organisms, such as bacteria, land plants, micro- and macroalgae. All these compounds present aliphatic-chains, with fatty acids as biosynthetic precursors, at least in land plants [220]. Among the alkanes, *n*-heptadecane is the major compound in the genus *Gracilaria* as well as in other red algae [221–223]. Santos et al. [222] found 1-tetradecanol, 1-hexadecanol, 1-octadecanol, 1-eicosanol, and 1-docosanol in *G. vermiculophylla*. The function of these alkanes and fatty alcohols for algae remains a mystery. Concerning fatty aldehydes, Kajiwara et al. [224] found only pentadecanal in *G. vermiculophylla* (=*Gracilaria asiatica*). Fatty aldehydes are apparently responsible for flavor and chemical defenses against herbivores in some micro- and macroalgae [225,226].

5.4. Amino acids

Amino acids can be classified as proteinogenic amino acids, which are constituents of proteins, and non-proteinogenic amino acids, which are not involved in the formation of proteins. In the genus *Gracilaria*, some proteinogenic amino acids, such as aspartic acid, alanine, glutamic acid, glutamine, glycine, proline, serine, and threonine are accumulated in free forms [227–229]. These compounds can provide the typical flavor in algae [230] and accumulate in response to stress conditions [231]. β-Alanine [232], hydroxyproline [174], lanthionine [174], ornithine [228], and pyroglutamic acid [228] are common non-proteinogenic amino acids found in several organisms, including *Gracilaria* species. Unusual non-proteinogenic amino acids, such as gigartinine [233,234], baikian [229], 1-methylhistidine [229], and 1,3-dimethylhistidine [229], are also reported in the genus.

5.5. Carotenoids and their derivatives

Carotenoids are tetraterpenoids consisting of eight isoprene units. These compounds may act as accessory pigments in photosynthesis and as antioxidants. Alloxanthin, antheraxanthin, β-carotene, canthaxanthin, β-cryptoxanthin, lycopene, lutein, violaxanthin, and zeaxanthin occur in the genus *Gracilaria* [235–237]. More recently, a derivative of β-carotene, dihydroactinidiolide, was also identified in the genus [238]. Carotenoids have several biological properties, such as in the prevention of cancer and cardiovascular diseases [239].

5.6. Dicarboxylic and tricarboxylic acids

Dicarboxylic and tricarboxylic acids are compounds with two and three carboxyl groups, respectively. Citric acid was the only tricarboxylic acid described in the genus *Gracilaria* [228]. In contrast, several dicarboxylic acids have been described in the genus, such as α-hydroxyglutaric acid, adipic acid, azelaic acid, succinic acid, suberic acid, sebacic acid, malic acid, and undecanedioic acid [221,222,228]. Citric acid is a common compound present in all aerobic organisms as part of the citric acid cycle. The use of this compound is widespread in industry, mainly in beverages, food, and cosmetics, as acidulants, flavorings, and preservatives [240]. Several biological activities have been attributed to dicarboxylic acids. For example, azelaic acid presents antibacterial properties against acne bacteria, and it is also used in the treatment of skin hyper-pigmentation [241].

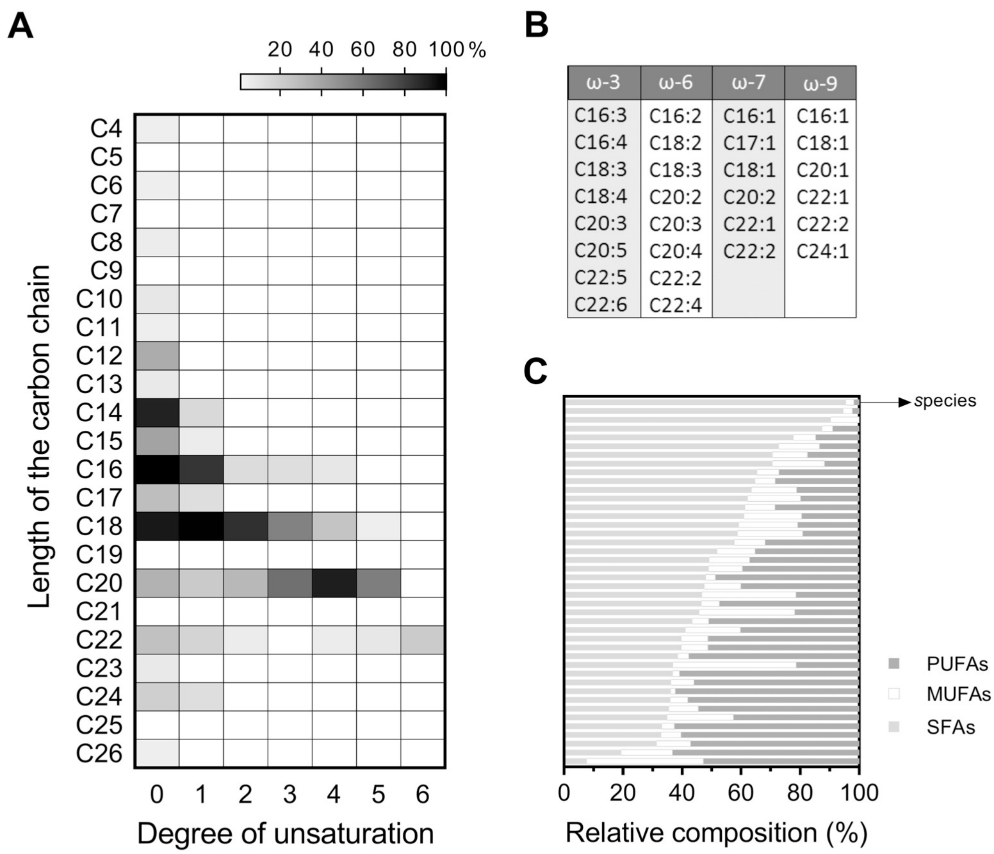

Fig. 6. Frequency (%) of fatty acids (A), types of unsaturated fatty acids (B), and comparisons of fatty acid profiles (C) obtained from *Gracilaria* species. Database obtained in the period of 1960 to 2018. See online supplementary data: Appendix B. SFAs = saturated fatty acids, MUFAs = monounsaturated fatty acids, and PUFAs = polyunsaturated fatty acids.

5.7. Diterpenes

Diterpenes are terpenoids composed of four isoprene units. Only phytol and its derivatives phytone and neophytadiene have been identified in the genus *Gracilaria* [222,223,242]. Phytol is a constituent of tocopherols and chlorophylls; however, the role of its derivatives is unknown. Phytol has also an anticancer property as previously described [77,78].

5.8. Fatty acids

Fatty acids are monocarboxylic acids with a saturated or unsaturated aliphatic carbon chain. Usually, they are found in nature in esterified form as major components of lipids. Approximately 45 fatty acids with different carbon chain lengths and degrees of unsaturation have been identified in the genus *Gracilaria* (Fig. 6A and B). Among the identified compounds, long chain fatty acids (LCFAs) (11 to 20 carbons), especially with even-numbered chains (C14, C16, C18, and C20), are frequent, in contrast to short/medium chain fatty acids (< 11 carbons) and very long chain fatty acids (VLCFAs) (> 20 carbons). All the short/medium chain fatty acids are saturated. In contrast, the LCFAs and the VLCFAs are mainly unsaturated. In general, the ω-3 and the ω-6 fatty acids are polyunsaturated (PUFAs), whereas most of the ω-7 and ω-9 fatty acids are monounsaturated (MUFAs) (Fig. 6B). Odd chain fatty acids are present in small amounts.

Most of the studies evaluated only total lipid content (> 90%), using mainly the Bligh-Dyer method [243] for extraction. In general, the total lipid values were not > 2% of the dry weight (DW) ranging from 0.3% DW for *G. changii* [244] to 4.6% DW for *G. vermiculophylla* [245]. These values are in agreement with those found for most macroalgae whose highest values are between 2 and 4.5% DW [12]. In an overview of fatty acid composition of species of *Gracilaria*, the average percentages of saturated fatty acids (SFAs), PUFAs, and MUFAs are 52%, 35%, and 13%, respectively. However, this composition varies considerably in the literature (Fig. 6C). Seasonal [246], environmental [247–249], and methodological [250] influences are reported as important factors responsible for these fluctuations. In the genus *Gracilaria*, palmitic acid (C16:0) is the main SFA and, with rare exceptions, arachidonic acid (C20:4 ω-6) is the main PUFA (see Table 1S in online Supplementary data: Appendix B). MUFA composition is quite variable, nevertheless, oleic acid (C18:1 ω-9) is always present.

5.9. Floridoside and digeneaside

Floridoside and digeneaside are heterosides containing a carbohydrate moiety bound to a polyol. The floridoside molecule is formed by a galactose linked to a glycerol, whereas the digeneaside present mannose as the carbohydrate moiety linked to a glyceric acid. These compounds are important photosynthetic and storage products in red algae [251]. Besides these functions, some studies have also suggested that these metabolites act as compatible solutes [252,253]. There are a few studies related to heterosides in the genus *Gracilaria* [233,254–256]. For example, Collén et al. [256] found that *G. tenuistipitata* accumulates floridoside during nutrient deficiency. Recently, studies concerning the biological activities of these compounds demonstrated that floridoside acts against neuro-inflammatory diseases [257] and appears to have an effect on bone formation by promoting osteogenic differentiation in vitro [258]. In another study, Lin et al. [259] demonstrated the antioxidant capacity of floridoside.

5.10. Glycerolipids and sphingolipids

Glycerolipids and sphingolipids are fatty acid-derived compounds, mainly found as components of biological membranes. The glycerolipids are characterized by a glycerol esterified with fatty acids. The following types of glycerolipids occur in the genus *Gracilaria*:

glycerophospholipids (e.g., phosphatidylcholine), sulfolipids (e.g., sulfoquinovosyldiacylglycerol), galactolipids (e.g., digalactosyldiacylglycerol and monogalactosyldiacylglycerol), monoglycerides (e.g., 1-monoolein, 1-monopalmitin, and 1-monopalmitolein), and triacylglycerols [222,260,261]. The sphingolipids consist of a fatty acid linked to a fatty amine. These compounds are involved in many cellular functions, such as signaling of apoptosis, cell growth, senescence, and differentiation [262]. Among other compounds, three new sphingolipids (gracilarioside, and gracilamides A and B) were isolated from *G. vermiculophylla* (= *Gracilaria asiatica*) and showed moderate anticancer activity in human melanoma cell lines (A375-S2) [263].

5.11. Mycosporine-like amino acids (MAAs)

MAAs are water-soluble nitrogenous compounds with high molar extinction coefficient in the ultraviolet (UV) region. This particular characteristic supports their photoprotective role [264]. Moreover, several other functions have been attributed to MAAs, including antioxidant potential and osmoprotectant property [264–266]. MAAs are found in a myriad of marine organisms including members of *Gracilaria* [267]. The main MAAs found in the genus *Gracilaria* are porphyra-334, shinorine, and palythine (Table 2). Asterina-330 and palythinol are less common, while mycosporine-glycine and palythene are rare (Table 2).

The MAA content and composition vary within and between species (Table 2). In general, the contents are not > 2.5 mg.g^{-1} DW, ranging from 0 to 7.8 mg.g^{-1} DW (Table 2). Several factors may contribute to fluctuations of these compounds, such as UV radiation levels and inorganic nitrogen availability [208,264,268]. Barufi et al. [269], for example, studying *G. tenuistipitata* demonstrated a high positive correlation between the concentrations of MAAs and the nitrate levels in the presence of UV radiation. Besides environmental and intrinsic characteristics, methodological issues may also influence MAA composition. Álvarez-Gómez et al. [270] studying *G. cornea* (= *Hydropuntia cornea*) found a qualitative and quantitative variation in the composition of these compounds, depending on the solvent used in the extraction. The ethanolic extract (0.003 mg.g^{-1} DW) had a MAA content 100 times lower than aqueous extract (0.3 mg.g^{-1} DW). Moreover, palythinol was the major MAA in the aqueous extract, while palythine was the main component in the ethanolic extract.

MAAs isolated from *Gracilaria* species have already been evaluated for antioxidant potential [271], photostability [272], and thermal stability [272]. Since these compounds absorb strongly in the UV region, display excellent photostability, and thermally dissipate the absorbed energy harmlessly [273,274], the biological activities of MAAs are often associated with skin photoprotection. Recent advances in the understanding of the cellular and molecular mechanisms involved in the skin photoprotection conferred by MAAs have also suggested other biological properties for these compounds, such as anti-inflammatory, immunomodulatory, and antioxidant [275,276]. Therefore, MAAs are promising candidates for use in pharmaceutical and cosmetic applications. However, due to the presence of chiral centers [275], these compounds are particularly difficult to synthesize, which means that their commercial use depend on natural sources.

Preparations containing MAAs obtained from red macroalga *Porphyra umbilicalis* Kützing (Helioguard 365® and Helionori®) are available in the global market and used as active ingredients in sunscreens [276]. In the review of Navarro et al. [276], macroalgae considered promising for commercial applications of MAAs showed contents > 3 mg·g^{-1} DW. Based on available data, among *Gracilaria* species, *G. domingensis* from the northeast coast of Brazil presented promising values, with 7.8 mg·g^{-1} DW obtained by Torres et al. [271] and 3.75 mg·g^{-1} DW obtained by Briani et al. [268]. A considerable quantity of MAAs, from this genus, have been obtained under conditions of high nitrogen availability, such as in IMTA system using fishpond effluents [277–279]. Figueroa et al. [278], for example, found that the MAA content more than doubled from 1 to 2.4 mg·g^{-1} DW when *G. cornea* (= *Hydropuntia cornea*) was grown in an IMTA system.

5.12. Oxylipins

Oxylipins are pivotal signaling molecules formed from oxygenation of PUFAs. Octadecanoid (C_{18} PUFAs) and eicosanoid (C_{20} PUFAs) families have been described in red algae [284]. Compounds from the eicosanoid family were first reported in a photosynthetic organism by Gregson et al. [285] studying *G. edulis* (= *Gracilaria lichenoides*). Since then, different types of eicosanoids have been identified in the genus, such as prostaglandins (PGA_2, PGB_2, PGD_2, PGE_2, PGE_3, PGF_2, $PGF_{2\alpha}$, PGJ_2, and 15-keto-PGE_2), hydroxyeicosatetraenoic acids (5-HETE, 8-HETE, 9-HETE, 11-HETE, 12-HETE, 15-HETE, 7,8-di-HETE, and 12,13-di-HETE), and leukotrienes (LTB_4 and derivatives) [228,285–296].

Table 2

Content (mg·g^{-1} dry weight - DW) and relative composition (%) of mycosporine-like amino acids identified in species of *Gracilaria*. Sh = Shinorine; P334 = Porphyra-334; P = Palythine; A330 = Asterina-330; Pl = Palythinol; G = Mycosporine-glycine; Pn = Palythene. tr = trace. Database obtained in the period of 1960 to 2018. The main MAAs for each specie were highlighted in bold.

Species	(%)							mg·g^{-1} DW	Reference
	Sh	P334	P	A330	Pl	G	Pn		
Gracilaria changii	13	37	**39**	9	3	–	tr	0.65	[280]
Gracilaria chilensis	17	**56**	13	10	4	–	–	2.3	[281][a]
	16	**66**	8	8	2	–	–	1.0–2.6	[281][a]
	15	**68**	7	7	2	–	–	0.9–1.8	[282][a]
Gracilaria birdiae	24	**67**	9	–	–	–	–	–	[283]
Gracilaria caudata	12	8	21	**55**	–	4	–	0.01–1.24	[268]
Gracilaria conferta	**95**	5	–	–	–	–	–	0.5–2.4	[279]
Gracilaria cornea	24	21	4	–	**25**	–	–	0.3	[270][b]
	28	15	17	**35**	–	6	–	0.0–1.5	[268]
	50–55	35–48	5–10	–	–	–	–	1.0–2.4	[278]
Gracilaria domingensis	25	**69**	7	–	–	–	–	–	[283]
	22	**70**	6	1	1	–	–	7.8	[271]
	18	10	17	**55**	–	–	–	0.01–3.75	[268]
Gracilaria eucheumatoides	12	29	23	**31**	5	–	–	2.42	[280]
Gracilaria salicornia	15	29	**50**	4	2	–	–	0.85	[280]
Gracilaria tenuistipitata	12	12	24	**41**	12	–	–	–	[283]
	0.5–6	**94–99**	–	–	–	–	–	0.36–2.52	[269]
Gracilaria vermiculophylla	7.5–25	**60–75**	5–25	–	–	–	–	0.4–3.5	[277]

[a] Approximate values.
[b] Water extract.

Eicosanoids are clinically relevant, since they are commonly found also in animals, acting in several physiological processes, such as the immune system, blood pressure, and cell growth [297]. Prostaglandins, for example, are used in glaucoma therapy and in labor induction [298]. Recent studies suggest that eicosanoids, due to their high toxicity in animals, play a role in the chemical defense against herbivores; the rapid synthesis of these compounds after injury to algae supports this hypothesis [228,299]. Cases of intoxications related to *Gracilaria* consumption are usually a consequence of the prostaglandin biosynthesis [300]. Although the food poisoning is rare, it may be severe, leading to death, especially when algae is consumed along with some food source rich in arachidonic acid, the main precursor of the eicosanoids in the genus. In contrast to eicosanoids, compounds from the octadecanoid family are rarely reported in the genus *Gracilaria*. Kumari et al. [296] identified in *Gracilaria dura* (C.Agardh) J.Agardh two derivatives of hydroxyoctadecadienoic acid (9-HODE and 13-HODE) and two derivatives from a hydroxyoctadecatrienoic acid (9-HOTrE and 13-HOTrE).

5.13. Phenolic compounds

Phenolic compounds are a chemical class containing at least one hydroxyl group bonded directly to a benzene ring [301]. The ecological function of phenolics in red algae has been rarely explored, but in other organisms they are known as antioxidants, hormones, cofactors or defense compounds [301]. In general, phenolic compounds are detected at low concentrations in the genus *Gracilaria*. Among the few phenolics already identified are bromophenols and benzoic acids.

Bromophenols are phenolic compounds with bromine substituent in distinct degrees and are present mainly in red algae [302]. The biosynthesis of these compounds has been not completely solved, but tyrosine may be the precursor [303]. Only simple bromophenols with one benzene ring have been identified in the genus *Gracilaria* [303], such as 2-bromophenol, 4-bromophenol, 2,4-dibromophenol, 2,6-dibromophenol, and 2,4,6-tribromophenol. Benzoic acids are C_6–C_1 aromatic carboxylic acids [304] derived from the shikimate pathway. A series of these compounds have already been identified in the genus, such as benzoic acid, *p*-hydroxybenzoic acid, salicylic acid, gentisic acid, protocatechuic acid, vanillic acid, gallic acid, and syringic acid [153,221,305]. Most phenolic compounds possess a broad variety of biological activities. For example, several bromophenols have antidiabetic, antioxidant, and anticancer effects [302].

5.14. Phycobiliproteins

Phycobiliproteins are proteins that function as photosynthetic accessory pigments in cyanobacteria, red algae, glaucophytes, and cryptophytes [306]. These compounds have great economic applications as colorants in food and cosmetics, and as fluorescent probes in diagnostic assays and diverse researches [306]. Phycoerythrin (R-phycoerythrin), phycocyanin (C-phycocyanin), and allophycocyanin occur in species of *Gracilaria* [307–310]. Several bioactivities as antioxidants, anti-inflammatory, and neuroprotective have already been reported for these compounds [311]. Due to commercial interest, some studies have optimized methods of extraction and purification of these pigments from species of the genus [312–315]. An accumulation of phycobiliproteins was found in *G. cornea* grown in IMTA systems [278].

5.15. Sterols

Sterols are a subgroup of steroids containing a hydroxyl group at the C_3 position and a branching side chain at the C_{17} position. The predominant sterols in red algae, including the genus *Gracilaria*, are cholesterol and its derivatives, for example, desmosterol, cholesta-4,6-dien-3-ol, and cholest-5-ene-3,7-diol [221–223,316]. However, Das et al. [317–319] found a series of poriferastane-type sterols (C_{29}), such as clionasterol in *G. edulis*. Other unusual sterols in the genus are fucosterol and isofucosterol (C_{29}), common in brown algae [242], and stigmasterol (C_{29}) [320] and β-sitosterol (C_{29}) [321], common in land plants. Sterols are constituents of membranes and precursors of plant and animal hormones. Several bioactivities have been described for these compounds, such as antioxidant, antiviral, anti-fungal, and antibacterial [322]. For example, Galea and Brown [323] suggest that cholesterol is one of the oldest antioxidant barriers in organisms.

5.16. Sulfonic acids

Taurine and isethionic acid are sulfonic acids commonly found in animals. Taurine occurs also in brown, green, and red macroalgae, including *Gracilaria* species [324]. This compound is essential for animals, but its role in algae remains unclear. Numerous biological roles have been described for taurine, such as antioxidant, anti-hypertensive, anti-diabetic, and anti-cholesterolemic effects [325]. Isethionic acid occurs in different species of red algae. In the genus *Gracilaria*, this compound was identified for the first time by Gupta et al. [326] studying *G. dura*. The role of isethionic acid in algae is still very controversial; however, Hellio et al. [327] found that this compound inhibits settling of larvae of *Balanus amphitrite*, a barnacle, suggesting a role in chemical defense and a potential use in anti-fouling.

6. Conclusions

This review provides a comprehensive compilation of publications regarding the genus *Gracilaria*. This genus is gaining attention due to promising results obtained, especially with the sulfated agarans. Although some traditional uses have been described since ancient times, there are few scientific studies validating this traditional knowledge, which could add value to these biological resources. Undoubtedly, there is a wide field of research to be explored looking for active compounds and new sources, since many species are unexplored.

The genus *Gracilaria* contains a wide variety of metabolites, such as MAAs, carbohydrates, lipids, steroids, diterpenes, phenolic compounds, sulfonic acids, oxylipins, heterosides, amino acids, and pigments. Several of these metabolites are bioactives and of particular interest for industrial and medical applications. Some examples include MAAs as an active ingredient in sunscreens, phycobiliproteins as color additives and fluorescent probes, prostaglandins as medicines for treatment of several diseases and disorders, taurine as a nutrient in animal feed and infant formulas, and carotenoids as an antioxidant, color additive, and provitamin A. However, besides the agarans, only MAAs and phycobiliproteins have been studied with a focus on development for commercial production from the genus.

Two approaches can be proposed to develop the great potential of the genus *Gracilaria* as a source of high-value compounds. Firstly, the efficiency of *Gracilaria* species as biofilters in IMTA systems encourage the search for new uses of the algal biomass under nitrogen-rich conditions. Under these conditions, for example, MAAs and phycobiliproteins have their biosynthesis stimulated. Secondly, since the commercial cultivation of *Gracilaria* species is mainly carried out for agar exploitation, an adaptation of extraction methods of this phycocolloid that avoids the loss of bioactive compounds would enable the exploitation of other bioactive components. In both approaches, the best use of the biomass can improve the exploitation of this natural resource, achieving a higher total economic value and environmental sustainability.

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Author contributions

All the authors have read, approved, and made substantial contributions to the manuscript. PT and DYACS conceived the study; PT built the database; PT and DYACS made the analysis and interpretation of data; PT made the drafting of manuscript; DYACS, FC and JPS made the critical revision.

Conflict of interest

The authors declare no conflict of interest.

Informed consent, human/animal rights

No conflicts, informed consent, human or animal rights applicable. The authors agree to the submission of the manuscript for peer review and publication in Algal research.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.algal.2018.12.009.

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