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Bioactive compounds against neglected diseases isolated from macroalgae: a review

Miriam Falkenberg[1] · Eliana Nakano[2] · Leonardo Zambotti-Villela[3] · Gabriele A. Zatelli[1] · Ana Claudia Philippus[1] · Kely Braga Imamura[4] · Angela Maria Arenas Velasquez[4] · Rafaela Paula Freitas[2] · Lenita de Freitas Tallarico[2] · Pio Colepicolo[3] · Marcia A. S. Graminha[4]

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Abstract

To survive in a very competitive environment, marine macroalgae had to evolve defense strategies, resulting in an enormous diversity of compounds from different metabolic pathways. These secondary metabolites have been explored by the pharmaceutical industries in order to generate new drugs to treat several diseases. Recent publications in drug research from natural sources have indicated algae as an interesting choice to provide novel drugs to fulfill this gap. This review highlights algal metabolites that showed bioactivities suggesting their potential against neglected diseases. Drug discovery for neglected diseases has been overlooked by the Big Pharmas, mainly because they affect poor people, most of them living in developing countries. Moreover, this review shows the commercial application of the most explored chemicals from algae such as terpenes, phenols, quinones, macrolides, alkaloids, lipids, chromones, and other related metabolites and an overview regarding the status of green extraction technologies for seaweeds and their concepts.

Keywords Algae · Green extraction · Pharmaceutical application · Natural products · Pharmacology · Antibacterial · Antifungal · Antileishmanial · Antiplasmodial · Antiprotozoal

Introduction

This review describes natural products (NPs) obtained from macroalgae through activity-driven approach or semisynthetic synthesis and available in the public literature or in the database of patents, PATENTSCOPE (World Intellectual Property Organization), encompassing the period from 1998 to 2018. The search criterion adopted was the evaluation of bioactivities of chemically defined compounds against human pathogenic bacteria, fungi, protozoa, and helminthes. Bioactive compounds against model organisms were included, even those not directly related to neglected diseases (NDs) due to the low number of articles approaching their etiologic agents. Finally, articles reporting evaluation of extracts/fractions or compounds without bioactivity or positive controls were excluded.

Human actions and their consequences on neglected diseases

The world's population has increased exponentially and reached nearly 7.6 billion people in 2017 and projected to reach 8.6 billion people by 2030 (United Nations, 2017). Furthermore, growth in human population is causing unplanned and poorly managed urbanization, mainly in developing countries, putting millions of people to live in areas with poor infrastructure. It is estimated that the percentage of people living in urban areas will increase from 54% in 2015 to 66% by 2050 (WHO 2014), contributing to the worsening infrastructure problems, climate changes, and emergence of vector-borne diseases (i.e., leishmaniasis/malaria), soil-transmitted helminthic infections (i.e., ascaridiasis/strongyloidiasis), and food-

✉ Marcia A. S. Graminha
graminha@fcfar.unesp.br

[1] Postgraduate Program in Pharmacy, Health Sciences Center, Federal University of Santa Catarina (UFSC), Florianópolis, Brazil

[2] Parasitology Laboratory, Butantan Institute (IB), São Paulo, SP, Brazil

[3] University of São Paulo (USP), Institute of Chemistry (USP), São Paulo, SP, Brazil

[4] School of Pharmaceutical Sciences, São Paulo State University (UNESP), Araraquara, Brazil

and water-borne illness (i.e., amoebiasis/giardiasis), among other NDs caused by bacteria and fungi (yaws/mycetoma) (Foley et al. 2005; Pinto et al. 2005, 2011; Oryan and Akbari, 2016) (Fig. 1). According to the World Health Organization, NDs are endemic in 149 countries and affect more than one billion people worldwide (http://www.who.int/neglected_diseases/diseases/en/) by (WHO 2018). Chemotherapy is the main approach used to control and overcome the deleterious effect of these NDs; however, its lack of efficacy and several side effects contribute to the elevated index of mortality and morbidity among people in the developing countries.

In 2012, global health partners from public, private, and nonprofit sectors signed "The London Declaration on Neglected Tropical Diseases", a document containing their commitment to control, eliminate, or eradicate NDs by 2020 and improve the quality of life of billions of people (http://unitingtocombatntds.org/london-declaration-neglected-tropical-diseases/). However, despite all the efforts, new therapies for NDs are still far from the ideal, as depicted in Fig. 2, which shows the limited number of new chemical entities approved by regulatory agencies for NDs in a period of 30 years encompassing 1984–2014 (Newman and Cragg, 2016).

Another point to be considered that impacts even more the drug discovery process for NDs refers to the shift of strategy adopted by the pharmaceutical companies in the 80s that emphasized high throughput screening (HTS) of synthetic libraries, which present limited structure diversity when compared to the chemical space presented by the NPs (Baker, 1984; Li and Vederas, 2009). Historically, NPs from different sources have made important contributions to the therapeutical arsenal to treat diverse diseases, including antibiotics (e.g., penicillin, tetracycline, erythromycin) and antiparasitics (e.g., avermectin, quinine, artemisinin), as well as contributed to the development of many analogs synthesized inspired on NPs such as the antimalarial mefloquine and the candidate artefenomel, currently in phase II clinical trial for malaria treatment (Mccarthy et al. 2016; Macintyre et al. 2017). According to Newman and Cragg (2016), 26% of analogs derived from NPs have been approved by the American regulatory agency FDA from 1984 to 2014; together, NPs or those molecules derived by semi-synthesis or inspired on NPs correspond to 51% of the total approved drugs (Newman and Cragg, 2016). Until the decade of 1990, these numbers were around 80%, dropping dramatically to nearly 50% from the moment that the pharmaceutical companies have shifted their strategy from NPs to medicinal chemistry approach (Li and Vederas, 2009).

Macroalgae as a renewable source of high-value compounds

Macroalgae NPs have been widely explored and afforded many chemicals and products with high aggregated value including fibers, minerals, antioxidants, vitamins, pigments, steroids, lectins, halogenated compounds, polyketides, polysaccharides, mycosporine-like amino acids, proteins, polyunsaturated fatty acids, and other lipids (Cardozo et al. 2007). Furthermore, isolated compounds obtained through activity-

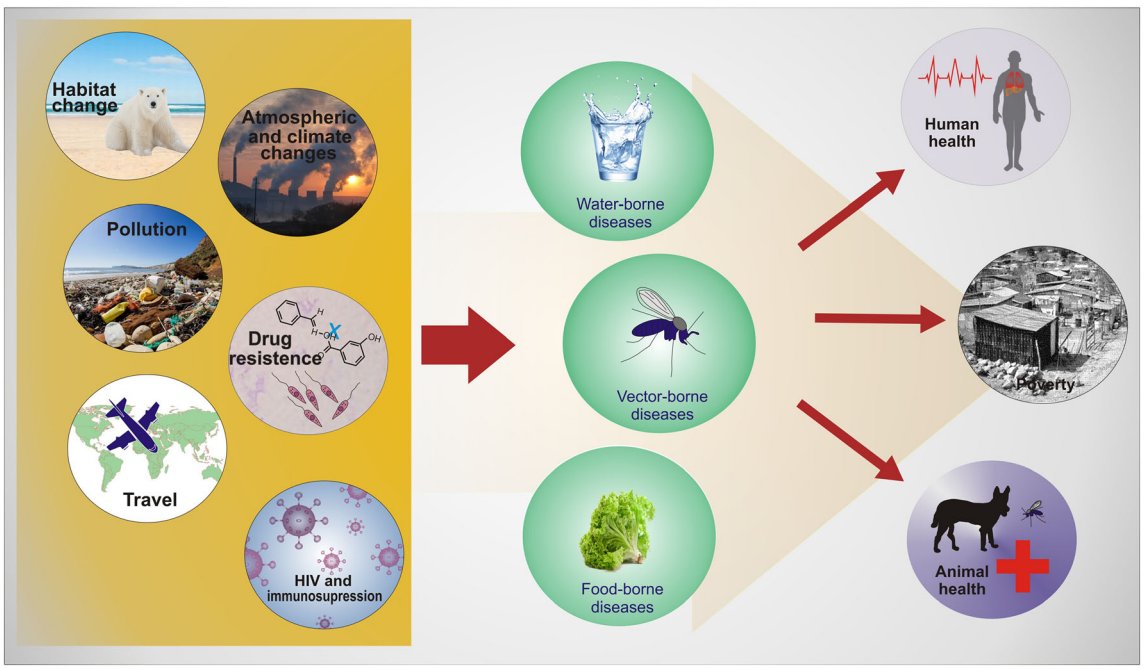


Fig. 1 Major forces that drive the emergence, re-emergence, and spread of insect-, water-, and food-borne diseases and their impacts

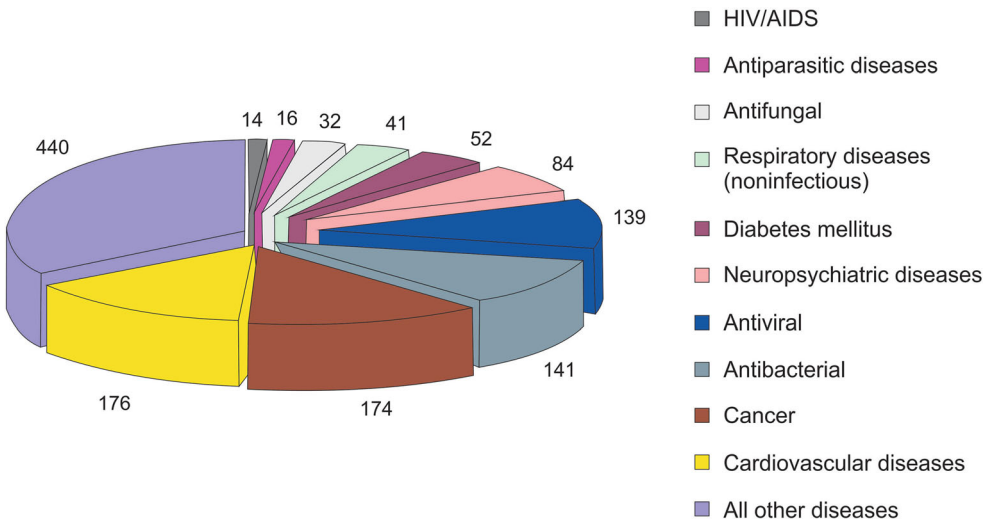


Fig. 2 Disease burden and number of developed New Chemical Entities (NCEs) for major diseases from 1984 to 2014, adapted from Newman and Cragg (2016)

guided isolation process have shown sophisticated chemical structures and great potential in the pharmaceutical areas including drugs for NDs (Tanaka et al. 1975; Cardozo et al. 2007; Gressler et al. 2011a, 2011b; Torres et al. 2014). Due to the different uses and wide availability of these photosynthetic organisms, the interest has turned from wild harvest to farming and controlled cultivation.

In order to obtain algae in large scale cultivation in open ponds, photobioreactors, or tanks applying integrated multi-trophic aquaculture (IMTA) has been adopted (Rorrer et al. 1995; Huang and Rorrer, 2002; Fernandes et al. 2017). Although advantages and disadvantages in each of these cultivation methods exist, they definitely have changed the concept from the wild harvesting to the sustainable production of algae. The great advantage of any cultivation technique is to avoid overexploitation of natural algae resources. Additionally, cultivation can also promote the selection of germplasm of the desired algae in the laboratory and therefore their use as seed stock (Tomazela et al. 2000). Thus, algae producing secondary metabolites important for human being can be generated as seeds in laboratory and then transferred to cultivation areas (Fernandes et al. 2017).

Additionally to the presence of the aforementioned high-value products, macroalgae are little affected by seasonality and have both high productivity (biomass production) and capacity to capture CO_2 (Martins et al. 2016). These features are pivotal when one looks for a feedstock inserted in a sustainable supply chain. Nowadays, considering the concept of "bioeconomy" and its strategies, not only the biomass production has to be environmentally friendly but also the entire bioprocess must be sustainable, maximizing the valorization of raw material. The development of new technologies (breakthrough or disruptive innovation) or improvement of existing ones (incremental innovation) and the design of extractions processes that efficiently recover not just the target compound but also co-products and by-products are mandatory (Prieto-Sandoval et al. 2018).

Green extraction technologies applied to macroalgae processing

Green extraction is based on principles that contemplate (i) the use of renewable plant resources (e.g., seaweeds), (ii) the use of alternative solvents replacing petrochemicals ones, (iii) the reduction of both energy consumption, (iv) business unit operations, and (v) the transformation of waste residue into co-products and by-products via processes that (vi) do not degrade nor contaminate the raw material (Gorka and Wieczorek, 2017; Ospina et al. 2017). These features are in complete agreement with the concept of circular economy, which demands eco-friendly innovations and sustainable feedstock as macroalgae to close the loop of the products lifecycle (Prieto-Sandoval et al. 2018) (Fig. 3).

In this context, supercritical fluid extraction (SFE), microwave-assisted extraction (MAE), ultrasound-assisted extraction (UAE), and pressurized liquid extraction (PLE) are examples of green technologies that have been used in seaweed NPs research (Table 1).

Supercritical fluids are among the best green alternatives to substitute organic solvents for seaweed processing (Table 1). To be considered in its critical state, a solvent has to surpass its critical temperature (T_c) and pressure (P_c) (Chemat et al. 2017). Different combinations of these physical properties can be used to modulate the selectivity of the extraction. Although any solvent, including the petrochemical ones, can be used as a supercritical fluid, CO_2 is the most used because of its

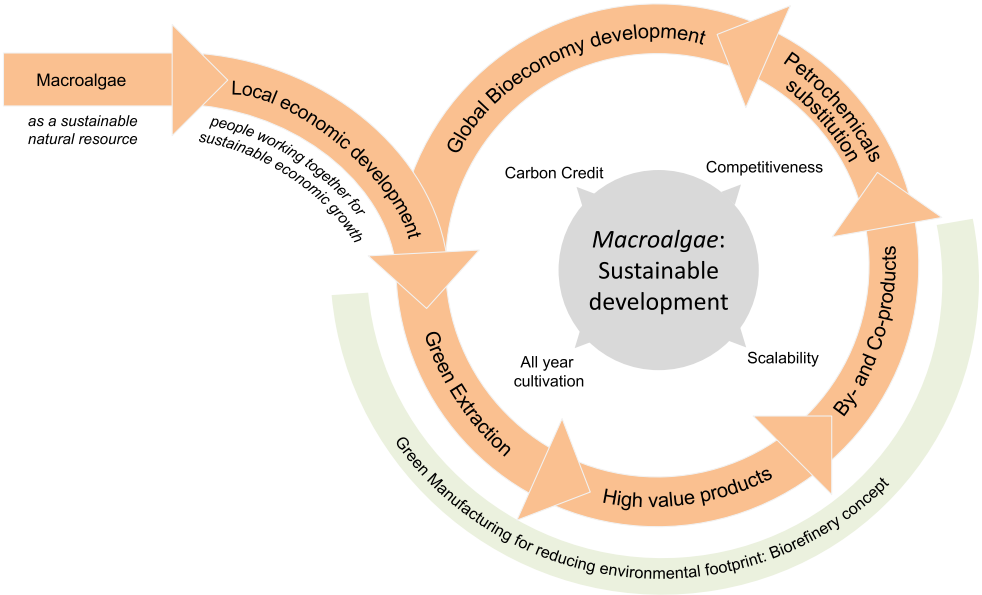


Fig. 3 Macroalgae integrated into the circular economy concept

safeness (does not interact with the matrix nor remain on the extraction residue), high availability, and reasonable costs (Pereira and Meireles, 2010). CO_2 in the supercritical state ($T_c = 304.1$ K and $P_c = 7.37$ MPa) might present a non-polar feature similar to hexane, which means that it can be a natural substitute. In addition to the temperature and pressure parameters, green co-solvents such as ethanol or water have been used to enhance the fluid's polarity and by this manner extend the range of added value compounds that can be extracted from seaweeds (Anaelle et al. 2013; Becerra et al. 2015; Sivagnanam et al. 2015; Ospina et al. 2017).

Recently, it has been demonstrated that the use of SFE in a biorefinery concept at a first step of processing has a positive effect on downstream technologies during annatto seed valorization (Albarelli et al. 2016). It is tempting to consider the same scenario for the seaweeds. After the extraction of non- and semi-polar added value bioactive compounds such as essential oils, carotenoids, antioxidants, antiparasitic, antibacterial, and others (Table 1), the remaining residue is a by-product that contains valuable polar compounds, e.g., phycobiliproteins and carrageenan (Boulho et al. 2017; Mittal et al. 2017) and others (antioxidants, biopolymers, antibacterial, antiparasitic, and antiviral compounds) (Table 1) that could be complementarily extracted by MAE, UAE, and PLE as downstream technologies.

Despite the fact that microalgae and seaweed are considered renewable and valuable feedstock, they have been poorly explored in the biorefinery concept. To overcome it, some efforts have been done regarding microalgae such as *Scenedesmus obliquus* (Gilbert-Lopez et al. 2017) and *Nannochloropsis* sp. (Ferreira et al. 2013) as well as the seaweeds *Ulva lactuca* (Bikker et al. 2016; Postma et al. 2018) and *Saccharina latissima* (Sterner et al. 2016).

Antibacterial, antifungal, and antiparasitic NPs isolated from seaweed: a contribution of marine resources against NDs

This topic discusses antibacterial, antifungal, and antiparasitic bioactive compounds from macroalgae encompassing the period of 1998 to the present and is organized by chemical class and then by their bioactivities. As depicted below, the number of bioactive compounds is higher for antibacterial activity rather than for the other etiologic agents herein approached. It is worth to mention that although most of the articles about antibacterial and antifungal compounds present a bias to *Escherichia coli*/*Staphylococcus aureus* and *Candida albicans*, the value of this information is inestimable, considering the potential of development of new antibacterial, antifungal, and even antiparasitic agents with wide spectra of action based on evolutionary similarities among these microorganisms and their pathogenic counterparts known to cause NDs (Mobegi et al. 2017). Furthermore, other important etiologic agents of NDs are also missing in this review due to the lack of articles on organisms such as *Treponema pallidum*, *Paracoccidioides brasiliensis*, *Trypanosoma brucei*, or *Schistosoma mansoni.* The inclusion of microorganisms other than NDs is important not only to contribute to macroalgal researchers focused on ND, providing what is known regarding bioactive compounds on model microorganisms, but also to point out that it is possible to correlate such information as a short cut in drug discovery to ND, since many metabolic pathways are known to be shared by both parasites and bacteria. Indeed, some antibiotics known to be active against bacteria, for instance, are active against Apicomplexa parasites. This group of parasites, including pathogens like *Plasmodium* spp. and *Toxoplasma gondii*, has a relict non-photosynthetic plastid, the apicoplast that contains a

Table 1 Green extraction technologies for seaweeds and some bioactivities

Technology	Species of seaweed (phylum)	Highlights	Experimental conditions	Reference
Supercritical fluids Keywords: supercrit* AND (seaweed* OR macroalga*)	*Cladophora glomerata*, green	Indoleacetic acid (IAA), indolebutyric acid (IBA), phenyleacetic acid (PAA), naphtyleacetic acid (NAA), *trans*-zeatin (TZ), kinetin (KA), isopentenyladenine (IA), 6-benzylaminopurine (6-BA), and abscisic acid (ABA)	Solvent, CO_2; temp., 40 °C; pres., 500 bar	Górka and Wieczorek (2017)
	Gracilaria mammillaris, red	Carotenoids, phenolic compounds, and antioxidant activity (TBARS)	Solvent, CO_2; temp., 40 to 60 °C; pres., 100 to 300 bar; flow rate, 0.4 kg h^{-1}; co-solvent 2 to 8 wt% EtOH	Ospina et al. (2017)
	Laminaria digitata and *Undaria pinnatifida*, brown; *Porphyra umbilicalis*, *Eucheuma denticulatum*, and *Gelidium pusillum*, red	Extract with antifungal activity against postharvest fungal diseases on fresh fruits	Solvent, CO_2; temp., 50 °C; pres., 379 bar; flow rate, 34 kg h^{-1}	de Corato et al. (2017)
	Saccharina japonica, brown	Total carotenoids and fucoxanthin-rich extracts with antioxidant activities	Solvent, CO_2 plus sunflower oil 2 wt%; temp., 50.62 °C; pres., 300 bar	Saravana et al. (2017)
	Undaria pinnatifida, brown	Essential oil with anti-inflammatory activity	Solvent, CO_2; temp., 40–45 °C; pres., 200–250 bar; flow rate, 250 mL min^{-1}	Kang et al. (2016)
	Saccharina japonica and *Sargassum horneri*, brown	Among the different biological activities tested, the extracts presented antimicrobial activities against *Escherichia coli*, *Listeria monocytogenes*, *Bacillus cereus*, *Staphylococcus aureus*, *Candida albicans*, *Aspergillus brasiliensis*	Solvent, CO_2; temp.,, 45 °C; pres., 250 bar; flow rate, 27 g min^{-1}; co-solvent, EtOH	Sivagnanam et al. (2015)
	Lessonia vadosa, brown	Extract fucosterol-rich with anti-parasitic activity against *Leishmania amazonensis* and *Leishmania infantum*	Solvent, CO_2; temp., 50 °C; pres., 180 bar; flow rate, 6 kg h^{-1}; co-solvent, EtOH at flow rate of 90 g h^{-1}	Becerra et al. (2015)
	Sargassum muticum, brown	Extracts with antioxidant activities	Solvent, CO_2; temp., 60 °C; pres., 152 bar; co-solvent, EtOH	Anaelle et al. (2013)
Microwave-assisted extraction	*Ulva prolifera*, green	Polysaccharides extracted exhibited antioxidant and pancreatic lipase activities	Water plus HCl 0.1 M at 150 °C, 500 W, 15 min	Yuan et al. (2018), Yuan and Macquire (2015)
Keywords: microwave AND (seaweed* OR macroalga*)	*Solieria chordalis*, red	Carrageenan-rich extract presented antiviral activity against *Herpes simplex* virus type 1 (HSV-1)	0.5% KOH at 105 °C for 25 min	Boulho et al. (2017)
	Ecklonia radiata, brown	Antioxidant extract produced by microwave-assisted enzymatic extraction. Carbohydrases (Viscozyme, Celluclast, and Ultraflo) and proteases (Alcalase, Neutrase, and Flavourzyme) were used	Buffers specific for each enzyme tested, 50 °C for 3 h	Charoensiddhi et al. (2015)
	Fucus vesiculosus, brown	Extract with sulfated polysaccharides (fucoidan), known to present anti-leishmania, antiviral, and antibacterial effects besides the antioxidant activities	Pressure, 120 psi; biomass/solvent volume, 1/25 for 1 min	Rodriguez-Jasso et al. (2011)
Ultrasound	*Hormosira banksii*, brown	Polyphenol-rich extract with antioxidant activity	Solvent, EtOH 70% (*v*/*v*); 30 °C, 50 Hz, and 150 W for 60 min	Dang et al. (2017)

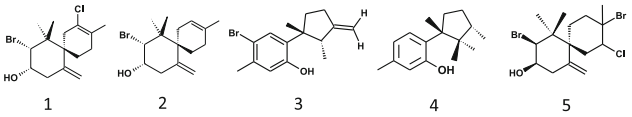
Table 1 (continued)

Technology	Species of seaweed (phylum)	Highlights	Experimental conditions	Reference
Keywords: ultrasound AND (seaweed* OR macroalga*)	*Ascophyllum nodosum*, brown	Aqueous extract with polyphenols and carbohydrate and antioxidant activity	Solvent, water, 35 °C, 20 KHz and < 1000 W for 4 min	Moreira et al. (2017)
	Gelidium pusillum, red	Phycobiliprotein-rich extracts wherein part of the extraction process is ultrasonication	Solvent, buffer; ultrasonication amplitude (60 to 120 μm), 30–40 °C for 1 to 10 min	Mittal et al. (2017)
	Sargassum muticum, brown	Fucoidan-rich and phlorotannin-containing extracts with antioxidant activities	Solvent: water, 25 °C, 40 KHz, and 150 W for 5 to 30 min	Flórez-Fernández et al. (2017)
	Laurencia obtusa, red	Extracts with polyphenols and antioxidant activities	Solvent: EtOH 95%, 30–50 °C, 40 KHz, and 250 W for 30 to 60 min	Topuz et al. (2016)
	Ascophyllum nodosum and *Laminaria hyperborean*, brown	Aqueous extract with antioxidant activities and anti-bacterial activities against *Staphylococcus aureus*, *Listeria monocytogenes*, *Escherichia coli*, and *Salmonella typhimurium*	Solvent: water or water plus HCl 0.1 M, 20 KHz, and 750 W for 15 min	Kadam et al. (2015)
Pressurized liquid extraction Keywords: ("pressurized liquid" OR PLE) AND (seaweed* OR macroalga*)	*Saccharina japonica,* brown	Fucoidan-rich extracts with antioxidant activities	Solvents: water, EtOH (25–70%), NaOH (0.1%), or formic acid (0.1%); temp., 80–200 °C; pres., 5–100 bar	Saravana et al. (2016)
	Saccharina longicruris and *Ascophyllum nodosum* a brown; *Ulva lactuca*, green	Aqueous extract with antioxidant activities and anti-bacteria activities against *Escherichia coli*, *Micrococcus luteus*, and *Brochothrix thermosphacta*	Solvent, EtOH; temp., 50 °C; pres., 69 bar for 5 min	Boisvert et al. (2015)
	Fucus serratus and *Laminaria digitata*, brown; *Gracilaria gracilis*, red; and *Codium fragile*, green	Aqueous and ethanolic extracts with antioxidant activities	Solvent, water and EtOH 80%; temp., 100 or 120 °C; pres., 90 or 103 bar for 25 min	Heffernan et al. (2014)
	Ascophyllum nodosum, *Pelvetia canaliculata*, and *Fucus spiralis*, brown; *Ulva intestinalis*, green	Aqueous and ethanolic extracts with antioxidant activities	Solvent, water and EtOH 80%; temp., 100 or 120 °C; pres., 90 or 103 bar for 25 min	Tierney et al. (2013)
	Sargassum muticum, brown	Extracts with antioxidant activities	Solvent, EtOH (25 and 75%); temp., 120 °C; pres., 103 bar for 20 min	Anaelle et al. (2013)
	Himanthalia elongata, brown	Aqueous and ethanolic extracts with antiviral activity against *Herpes simplex* virus type 1 (HSV-1)	Solvent, water or EtOH; temp., 100 °C, pres., 103 bar for 20 min	Santoyo et al. (2011)

few processes that are clearly bacterial in nature and, therefore, potential targets for new (or existing) antibiotics including a set of prokaryotic-/plant-like metabolic pathways for fatty acid, isoprenoid precursors, heme, and Fe/S cluster synthesis among other roles in DNA, RNA, and protein metabolism (Chakraborty 2016). The bioactive compounds presented in the following section were classified as "terpenes", "phenols, quinones, chromones, and other related metabolites", "macrolides", "alkaloids", "polysaccharides", and "lipids" (Table 2).

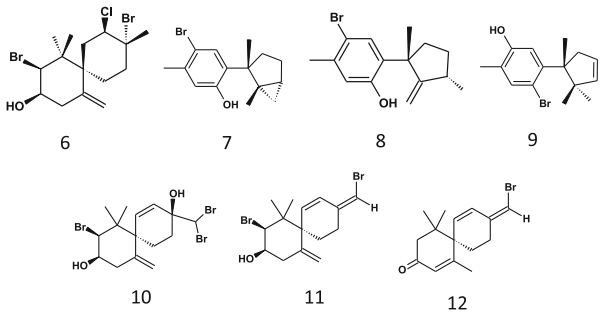
Terpenes

Halogenated sesquiterpenes are among the most interesting antimicrobial compounds reported in the reviewed literature. König et al. (2000) showed that, among 39 marine NPs, 17 were isolated from the genus *Laurencia* (Rhodomelaceae). The compounds elatol (**1**), deschloroelatol (**2**), allolaurinterol (**3**), and debromolaurinterol (**4**) presented anti-*Mycobacterium tuberculosis* and anti-*Mycobacterium avium* activities, with minimum inhibitory concentration (MIC) ranging from 16 to 64 μg mL^{-1}, with **3** the most active compound (MIC = 16 μg mL^{-1}). Ventura et al. (2015) showed that among the halogenated sesquiterpenes isolated from *Laurencia drendoidea* collected in the Southern Eastern of Brazil, obtusol (**5**) was bioactive against *Mycobacterium bovis* (IC_{50} = 31 μg mL^{-1}) and *M. tuberculosis* (IC_{50} = 97 μg mL^{-1}). Interestingly, **5** was less active than the crude extract, which might be due to synergistic interactions with other compounds contained in the crude extract. Compound **5** (IC_{50} = 4 μg mL^{-1}) was also as active as the reference drug potassium antimony(III) tartrate (IC_{50} = 3 μg mL^{-1}) against *Leishmania amazonensis* intracellular amastigotes (Da Silva Machado et al. 2011); additionally, dos Santos et al. (2010) reported that **1** was active against *L. amazonensis* amastigotes (IC_{50} = 0.5 μM), while Veiga-Santos et al. (2010) mentioned its anti-*Trypanosoma cruzi* amastigote activity (IC_{50} = 1 μM). The potency of **1** was similar to the reference drug amphotericin B for *L. amazonensis* and 24 times more active than benznidazole for *T. cruzi*. In trypomastigotes of *T. cruzi*, **1** seems to cause depolarization of the mitochondrial membrane potential and increase the levels of reactive oxygen species (Desoti et al. 2012). Although the possible molecular target of **1** is the mitochondrion and considering that this organelle is present in both parasites and their hosts, the authors claim that this molecule does not show any cytotoxic effect, which could be explained based on the differences between parasite and mammalian mitochondria (Inoki et al. 1958; Stoppani et al. 1980; Barros-Alvarez et al. 2014; Docampo and Huang, 2015). Other works have reported the cytotoxicity of **1** (Lang et al. 2012; Campos et al. 2012).



1 2 3 4 5

The investigation of the antimicrobial activity of the major metabolites of *Laurencia majuscula*, **1**, and iso-obtusol (**6**) showed similar activity towards the clinical isolates *Klebsiella pneumonia*, *Salmonella* sp., and *Staphylococcus epidermidis* when compared to commercial antibiotics (Vairappan, 2003). In a subsequent work, this author reported the antibacterial activity of other *Laurencia* spp. halogenated sesquiterpenes, among them laurinterol (**7**), allolaurinterol (**3**), isolaurinterol (**8**), and cupalaurenol (**9**). These compounds showed wide spectra of activity against Gram-positive bacteria, including vancomycin-susceptible strains such as methicillin-resistant *Staphylococcus aureus*, penicillin-resistant *Streptococcus pneumoniae*, and *Enterococcus* strains, regardless their phenotype of resistance to vancomycin (Vairappan et al. 2004). Chen et al. (2016) isolated eight new halogenated chamigrane sesquiterpenes, a new bromocuparane, and nine known related metabolites from *Laurencia tristicha* collected in Taiwan and tested against *Enterobacter aerogenes*, *Yersinia enterocolitica*, and *Serratia marcescens*. The chamigrane **10** had half of the activity of ampicillin towards *Y. enterocolitica*, while the known secondary metabolites **11** and **12** were able to inhibit the growth of the bacteria *S. marcescens* similarly to ampicillin (Chen et al. 2016).



6 7 8 9 10 11 12

Davyt et al. (2001) isolated eight sesquiterpenes β-chamigrane-type from the dichloromethane extract of *Laurencia scoparia* and demonstrated their activity against the parasitant stage of the helminth model *Nippostrongylus brasiliensis*. The compounds **13–15** are novel NPs, while other **16–21** are well-known chamigranes. All compounds showed moderate in vitro anthelmintic activity (IC_{50} < 100 μM) and none of them was as active as the reference drug albendazole (IC_{50} = 0.34 μM). Based on the structure of the compounds, the authors also considered that between the

Table 2 Biological activities of terpenes, phenols, quinones, chromones, macrolides, alkaloids, polysaccharides, and lipids from macroalgae against bacteria, fungi, protozoa, and helminthes

Chemical type	Compound	Species of marine algae; phylum	Species	Activity IC_{50} or MIC (SI)[a] % of inhibition	Activity Reference drug or inhibition zone diameter	References
Terpenes are from 1 to 54	**1**	*Laurencia rígida* J. Agardh; Rhodophyta	*Mycobacterium tuberculosis* H37Rv (ATCC 7294)	32 μg mL^{-1} (ND)	rifampin 0.3 μg mL^{-1}	König et al. (2000)
		Laurencia majuscula Harvey, Rhodophyta	*Staphylococcus haemolyticus* (clinical strain)	7–12 mm (ND)	augmentin 19–24 mm latamoxef 19–24 mm cefaclor 19–24 mm	Vairappan (2003)
			Klebsiella pneumoniae (clinical strain)	19–24 mm (ND)	latamoxef 19–24 mm ceftriaxone 19–24 mm kanamycin 19–24 mm	
			Pseudomonas sp. (clinical strain)	12–18 mm (ND)	netilmicin 12–18 mm	
			Salmonella sp. (clinical strain)	25–30 mm (ND)	augmentin 19–24 mm latamoxef 19–24 mm cefaclor 19–24 mm ceftriaxone 19–24 mm kanamycin 19–24 mm	
			Staphylococcus aureus (clinical strain)	7–12 mm (ND)	latamoxef 12–18 mm cefaclor 12–18 mm ceftriaxone 12–18 mm netilmicin 12–18 mm	
			Staphylococcus epidermidis (clinical strain)	19–24 mm (ND)	augmentin 19–24 mm latamoxef 19–24 mm cefaclor 19–24 mm	
		Laurencia dendroidea (Hudson) J. V. Lamouroux; Rhodophyta	*Leishmania amazonensis* amastigotes	0.5 μM (3)	amphotericin B 0.3 μM	Dos Santos et al. (2010)
			Trypanosoma cruzi	1 μM (24)	benznidazole 24 μM	Veiga-Santos et al. (2010)
	2	*Laurencia rigida* J. Agardh; Rhodophyta	*Mycobacterium tuberculosis* H37Rv (ATCC 7294)	32 μg mL^{-1} (ND)	rifampin 0.3 μg mL^{-1}	König et al. (2000)
			Mycobacterium avium (ATCC 25291)	8 μg mL^{-1} (ND)	clarithromycin 1.0 μg mL^{-1}	
	3	*Laurencia obtusa* (Hudson) Lamouroux, Rhodophyta	*Mycobacterium tuberculosis* H37Rv (ATCC 7294)	16 μg mL^{-1} (ND)	rifampin 0.3 μg mL^{-1}	König et al. (2000)
		Laurencia majuscula Harvey, Rhodophyta	*Staphylococcus aureus* 209PJC-1 and Smith	3.1 μg mL^{-1} (ND)	vancomycin 0.4–0.8 μg mL^{-1}	Vairappan et al. (2004)
			Staphylococcus aureus SR313 (L-MRSA), SR3626 (H-MRSA), and SR3637 (H-MRSA)	3.1 μg mL^{-1} (ND)	vancomycin 0.8–1.6 μg mL^{-1}	
			Staphylococcus epidermidis ATCC14990	6.3 μg mL^{-1} (ND)	vancomycin 1.6 μg mL^{-1}	
			Staphylococcus haemolyticus ATCC29970	6.3 μg mL^{-1} (ND)	vancomycin 1.6 μg mL^{-1}	
			Streptococcus pyogenes C-203	1.6 μg mL^{-1} (ND)	vancomycin 0.4 μg mL^{-1}	
			Streptococcus pneumoniae Type 1	1.6 μg mL^{-1} (ND)	vancomycin 0.4 μg mL^{-1}	

Table 2 (continued)

Chemical type	Compound	Species of marine algae; phylum	Species	Activity IC_{50} or MIC (SI)[a] % of inhibition	Activity Reference drug or inhibition zone diameter	References
			Streptococcus pneumoniae SR16675-PRSP	3.1 μg mL^{-1} (ND)	vancomycin 0.4 μg mL^{-1}	
			Streptococcus mitis SR16376	3.1 μg mL^{-1} (ND)	vancomycin 0.8 μg mL^{-1}	
			Streptococcus faecalis SR1004	6.3 μg mL^{-1} (ND)	vancomycin 1.6 μg mL^{-1}	
			Streptococcus faecalis ATCC51299 (Van B), SR7914 (Van A)	6.3 μg mL^{-1} (ND)	vancomycin 12.5– > 50 μg mL^{-1}	
			Streptococcus faecium SR7917 (Van A)	6.3 μg mL^{-1} (ND)	vancomycin > 50 μg mL^{-1}	
	4	*Laurencia flexilis* Setchell, Rhodophyta	*Mycobacterium tuberculosis* H37Rv (ATCC 7294)	64 μg mL^{-1} (ND)	rifampin 0.3 μg mL^{-1}	König et al. (2000)
			Mycobacterium avium (ATCC 25291)	> 128 μg mL^{-1} (ND)	clarithromycin 1.0 μg mL^{-1}	
	5	*Laurencia dendroidea* (Hudson) J. V. Lamouroux; Rhodophyta	*Mycobacterium tuberculosis* H37Rv (ATCC 27294)	97.1 μg mL^{-1} (ND)	rifampicin 1 μg mL^{-1} (demonstrating 99.6% growth inhibition)	Ventura et al. (2015)
			Mycobacterium bovis Bacillus Calmette-Guerin (BCG)	31.4 μg mL^{-1} (75.8)	rifampicin 0.03 μg mL^{-1} (demonstrating 97.13% growth inhibition)	
	6	*Laurencia majuscula*	*Citrobacter freundii* (clinical strain)	7–12 mm (ND)	cefaclor 19–24 mm ceftriaxone 19–24 mm kanamycin 19–24 mm	Vairappan et al. (2003)
			Escherichia coli (clinical strain)	12–18 mm (ND)	augmentin 19–24 mm cefaclor 19–24 mm	
			Klebsiella pneumoniae (clinical strain)	19–24 mm (ND)	latamoxef 19–24 mm ceftriaxone 19–24 mm kanamycin 19–24 mm	
			Salmonella sp. (clinical strain)	19–24 mm (ND)	augmentin 19–24 mm latamoxef 19–24 mm cefaclor 19–24 mm ceftriaxone 19–24 mm kanamycin 19–24 mm	
	7	*Laurencia okamurae* Yamada; Rhodophyta	*Staphylococcus aureus* 209PJC-1 and Smith	3.1 μg mL^{-1} (ND)	vancomycin 0.4–0.8 μg mL^{-1}	Vairappan et al. (2004)
			Staphylococcus aureus SR313 (L-MRSA), SR3626 (H-MRSA), and SR3637 (H-MRSA)	3.1 μg mL^{-1} (ND)	vancomycin 0.8–1.6 μg mL^{-1}	
			Staphylococcus epidermidis ATCC14990	3.1 μg mL^{-1} (ND)	vancomycin 1.6 μg mL^{-1}	
			Staphylococcus haemolyticus ATCC29970	3.1 μg mL^{-1} (ND)	vancomycin 1.6 μg mL^{-1}	
			Streptococcus pyogenes C-203	1.6 μg mL^{-1} (ND)	vancomycin 0.4 μg mL^{-1}	
			Streptococcus pneumoniae Type 1	1.6 μg mL^{-1} (ND)	vancomycin 0.4 μg mL^{-1}	

Table 2 (continued)

Chemical type	Compound	Species of marine algae; phylum	Species	Activity IC_{50} or MIC (SI)[a] % of inhibition	Activity Reference drug or inhibition zone diameter	References
			Streptococcus pneumoniae SR16675-PRSP	3.1 μg mL^{-1} (ND)	vancomycin 0.4 μg mL^{-1}	
			Streptococcus mitis SR16376	3.1 μg mL^{-1} (ND)	vancomycin 0.8 μg mL^{-1}	
			Streptococcus faecalis SR1004	6.3 μg mL^{-1} (ND)	vancomycin 1.6 μg mL^{-1}	
			Streptococcus faecalis ATCC51299 (Van B), SR7914 (Van A)	3.1 μg mL^{-1} (ND)	vancomycin 12.5–> 50 μg mL^{-1}	
			Streptococcus faecium SR7917 (Van A)	3.1 μg mL^{-1} (ND)	vancomycin > 50 μg mL^{-1}	
	8	*Laurencia okamurae* Yamada; Rhodophyta	*Staphylococcus aureus* 209PJC-1 and Smith	6.3 μg mL^{-1} (ND)	vancomycin 0.4–0.8 μg mL^{-1}	
			Staphylococcus aureus SR313 (L-MRSA), SR3626 (H-MRSA), and SR3637 (H-MRSA)	6.3 μg mL^{-1} (ND)	vancomycin 0.8–1.6 μg mL^{-1}	
			Staphylococcus epidermidis ATCC14990	6.3 μg mL^{-1} (ND)	vancomycin 1.6 μg mL^{-1}	
			Staphylococcus haemolyticus ATCC29970	6.3 μg mL^{-1} (ND)	vancomycin 1.6 μg mL^{-1}	
			Streptococcus pyogenes C-203	3.1 μg mL^{-1} (ND)	vancomycin 0.4 μg mL^{-1}	
			Streptococcus pneumoniae Type 1	3.1 μg mL^{-1} (ND)	vancomycin 0.4 μg mL^{-1}	
			Streptococcus pneumoniae SR16675-PRSP	6.3 μg mL^{-1} (ND)	vancomycin 0.4 μg mL^{-1}	
			Streptococcus mitis SR16376	6.3 μg mL^{-1} (ND)	vancomycin 0.8 μg mL^{-1}	
			Streptococcus faecalis SR1004	6.3 μg mL^{-1} (ND)	vancomycin 1.6 μg mL^{-1}	
			Streptococcus faecalis ATCC51299 (Van B), SR7914 (Van A)	6.3 μg mL^{-1} (ND)	vancomycin 12.5–> 50 μg mL^{-1}	
			Streptococcus faecium SR7917 (Van A)	6.3 μg mL^{-1} (ND)	vancomycin > 50 μg mL^{-1}	
	9	*Laurencia okamurae* Yamada; Rhodophyta	*Staphylococcus aureus* 209PJC-1 and Smith	3.1–6.3 μg mL^{-1} (ND)	vancomycin 0.4–0.8 μg mL^{-1}	
			Staphylococcus aureus SR313 (L-MRSA), SR3626 (H-MRSA), and SR3637 (H-MRSA)	6.3 μg mL^{-1} (ND)	vancomycin 0.8–1.6 μg mL^{-1}	
			Staphylococcus epidermidis ATCC14990	6.3 μg mL^{-1} (ND)	vancomycin 1.6 μg mL^{-1}	
			Staphylococcus haemolyticus ATCC29970	6.3 μg mL^{-1} (ND)	vancomycin 1.6 μg mL^{-1}	
			Streptococcus pyogenes C-203	3.1 μg mL^{-1} (ND)	vancomycin 0.4 μg mL^{-1}	
			Streptococcus pneumoniae Type 1	3.1 μg mL^{-1} (ND)	vancomycin 0.4 μg mL^{-1}	
			Streptococcus pneumoniae SR16675-PRSP	3.1 μg mL^{-1} (ND)	vancomycin 0.4 μg mL^{-1}	
			Streptococcus mitis SR16376	6.3 μg mL^{-1} (ND)	vancomycin 0.8 μg mL^{-1}	

Table 2 (continued)

Chemical type	Compound	Species of marine algae; phylum	Species	Activity IC_{50} or MIC (SI)[a] % of inhibition	Activity Reference drug or inhibition zone diameter	References
			Streptococcus faecalis SR1004	6.3 μg mL^{-1} (ND)	vancomycin 1.6 μg mL^{-1}	
			Streptococcus faecalis ATCC51299 (Van B), SR7914 (Van A)	6.3 μg mL^{-1} (ND)	vancomycin 12.5–> 50 μg mL^{-1}	
			Streptococcus faecium SR7917(Van A)	6.3 μg mL^{-1} (ND)	vancomycin > 50 μg mL^{-1}	
	10	*Laurencia tristicha* C. K. Tseng, C. F. Chang, E. Z. Xia & B. M. Xia; Rhodophyta	*Yersinia enterocolitica* (ATCC23715) *Serratia marcescens* (ATCC25419)	4 μg mL^{-1} (ND) 2 μg mL^{-1} (ND)	ampicillin 8 μg mL^{-1} ampicillin 5 μg mL^{-1}	Chen et al. (2016)
	11	*Laurencia tristicha* C. K. Tseng, C. F. Chang, E. Z. Xia & B. M. Xia; Rhodophyta	*Serratia marcescens* (ATCC25419)	8 μg mL^{-1} (ND)	ampicillin 5 μg mL^{-1}	
	12	*Laurencia tristicha* C. K. Tseng, C. F. Chang, E. Z. Xia & B. M. Xia; Rhodophyta	*Yersinia enterocolitica* (ATCC23715)	3 μg mL^{-1} (ND)	ampicillin 8 μg mL^{-1}	
			Serratia marcescens (ATCC25419)	4 μg mL^{-1} (ND)	ampicillin 5 μg mL^{-1}	
	13 **14** **15** **16** **17** **18** **19** **20** **21**	*Laurencia scoparia*; Rhodophyta	*Nippostrongylus brasiliensis* L4	< 100 μM	albendazole 0.34 μM levamisole 0.21 μM febendazole 0.12 μM	Davyt et al. (2001)
	22			0.11 μM		Davyt et al. (2006)
	23	*Laurencia obtusa* Lamouroux; Rhodophyta	*Staphylococcus aureus* multidrug-resistant strains	0.1 μM (ND)	amoxicillin 0.1 μM	Bawakid et al. (2017)
	24		*Candida albicans*	8.3 μM (ND)	amphotericin B 4.6 μM	
	25	*Sphaerococcus coronopifolius* Stackhouse; Rhodophyta	*Staphylococcus aureus* SA1199B *Staphylococcus aureus* RN4220	0.5 μg mL^{-1} (ND) 1 μg mL^{-1} (ND)	norfloxacin 32 μg mL^{-1} norfloxacin 1 μg mL^{-1}	Smyrniotopoulos et al. (2008)
			Staphylococcus aureus EMRSA-15	0.5 μg mL^{-1} (ND)	norfloxacin 0.5 μg mL^{-1}	
			Staphylococcus aureus ATCC25943	0.5 μg mL^{-1} (ND)	norfloxacin 0.5 μg mL^{-1}	
			Staphylococcus aureus XU212 (TetK)	1 μg mL^{-1} (ND)	norfloxacin 8 μg mL^{-1}	
			Staphylococcus aureus EMRSA-16	0.3 μg mL^{-1} (ND)	norfloxacin 128 μg mL^{-1}	
	26		*Staphylococcus aureus* EMRSA-16 (mecA)	32 μg mL^{-1} (ND)	norfloxacin 256 μg mL^{-1}	Smyrniotopoulos et al. (2010)
	27			32 μg mL^{-1} (ND)	norfloxacin 256 μg mL^{-1}	

Table 2 (continued)

Chemical type	Compound	Species of marine algae; phylum	Species	Activity IC_{50} or MIC (SI)[a] % of inhibition	Activity Reference drug or inhibition zone diameter	References
			Staphylococcus aureus EMRSA-16 (mecA)			
	28		*Staphylococcus aureus* EMRSA-16 (mecA)	64 μg mL^{-1} (ND)	norfloxacin 256 μg mL^{-1}	
	29		*Staphylococcus aureus* EMRSA-16 (mecA)	32 μg mL^{-1} (ND)	norfloxacin 256 μg mL^{-1}	
	30		*Staphylococcus aureus* (ATCC25923)	6.4 μM (ND)	ampicillin 0.1 μM	Rodrigues et al. (2015)
	31	*Jania rubens*, Rhodophyta	*Allolobophora caliginosa* adult worms	10% *w/v*	mebendazole 10%	Awad (2004)
	32					
	33					
	34					
	35					
	36					
	37					
	38	*Dilophus spiralis* (Montagne) Hamel; Phaeophyceae	*Dilophus spiralis* (Montagne) Hamel; Phaeophyceae	*Staphylococcus aureus* ERSA-16	16 μg mL^{-1} (ND)	Ioannou et al. (2011)
				Staphylococcus aureus SA1199B	128 μg mL^{-1} (ND)	
	39		*Staphylococcus aureus* ATCC25923	4 μg mL^{-1} (ND)	norfloxacin 0.5 μg mL^{-1}	
			Staphylococcus aureus EMRSA-15	2 μg mL^{-1} (ND)	norfloxacin 0.5 μg mL^{-1}	
			Staphylococcus aureus EMRSA-16	2 μg mL^{-1} (ND)	norfloxacin 128 μg mL^{-1}	
			Staphylococcus aureus RN4220	4 μg mL^{-1} (ND)	norfloxacin 0.5 μg mL^{-1}	
			Staphylococcus aureus SA1199B	2 μg mL^{-1} (ND)	norfloxacin 32 μg mL^{-1}	
			Staphylococcus aureus XU212	4 μg mL^{-1} (ND)	norfloxacin 8 μg mL^{-1}	
	40		*Staphylococcus aureus* ATCC25923	8 μg mL^{-1} (ND)	norfloxacin 0.5 μg mL^{-1}	
			Staphylococcus aureus EMRSA-15	8 μg mL^{-1} (ND)	norfloxacin 0.5 μg mL^{-1}	
			Staphylococcus aureus EMRSA-16	8 μg mL^{-1} (ND)	norfloxacin 128 μg mL^{-1}	
			Staphylococcus aureus RN4220	8 μg mL^{-1} (ND)	norfloxacin 0.5 μg mL^{-1}	
			Staphylococcus aureus SA1199B	16 μg mL^{-1} (ND)	norfloxacin 32 μg mL^{-1}	
			Staphylococcus aureus XU212	16 μg mL^{-1} (ND)	norfloxacin 8 μg mL^{-1}	
	41		*Staphylococcus aureus* ATCC25923	128 μg mL^{-1} (ND)	norfloxacin 0.5 μg mL^{-1}	
			Staphylococcus aureus EMRSA-15	64 μg mL^{-1} (ND)	norfloxacin 0.5 μg mL^{-1}	
			Staphylococcus aureus EMRSA-16	8 μg mL^{-1} (ND)	norfloxacin 128 μg mL^{-1}	
			Staphylococcus aureus RN4220	64 μg mL^{-1} (ND)	norfloxacin 0.5 μg mL^{-1}	
			Staphylococcus aureus SA1199B	32 μg mL^{-1} (ND)	norfloxacin 32 μg mL^{-1}	
			Staphylococcus aureus XU212	64 μg mL^{-1} (ND)	norfloxacin 8 μg mL^{-1}	

Table 2 (continued)

Chemical type	Compound	Species of marine algae; phylum	Species	Activity IC_{50} or MIC (SI)[a] % of inhibition	Activity Reference drug or inhibition zone diameter	References
	42		*Staphylococcus aureus* ATCC25923	32 μg mL^{-1} (ND)	norfloxacin 0.5 μg mL^{-1}	
			Staphylococcus aureus EMRSA-15	32 μg mL^{-1} (ND)	norfloxacin 0.5 μg mL^{-1}	
			Staphylococcus aureus EMRSA-16	8 μg mL^{-1} (ND)	norfloxacin 128 μg mL^{-1}	
			Staphylococcus aureus RN4220	64 μg mL^{-1} (ND)	norfloxacin 0.5 μg mL^{-1}	
			Staphylococcus aureus SA1199B	32 μg mL^{-1} (ND)	norfloxacin 32 μg mL^{-1}	
			Staphylococcus aureus XU212	64 μg mL^{-1} (ND)	norfloxacin 8 μg mL^{-1}	
	43		*Staphylococcus aureus* ATCC25923	64 μg mL^{-1} (ND)	norfloxacin 0.5 μg mL^{-1}	
			Staphylococcus aureus EMRSA-15	64 μg mL^{-1} (ND)	norfloxacin 0.5 μg mL^{-1}	
			Staphylococcus aureus EMRSA-16	16 μg mL^{-1} (ND)	norfloxacin 128 μg mL^{-1}	
			Staphylococcus aureus RN4220	64 μg mL^{-1} (ND)	norfloxacin 0.5 μg mL^{-1}	
			Staphylococcus aureus SA1199B	64 μg mL^{-1} (ND)	norfloxacin 32 μg mL^{-1}	
			Staphylococcus aureus XU212	64 μg mL^{-1} (ND)	norfloxacin 8 μg mL^{-1}	
	44		*Staphylococcus aureus* EMRSA-15	128 μg mL^{-1} (ND)	norfloxacin 0.5 μg mL^{-1}	
			Staphylococcus aureus EMRSA-16	4 μg mL^{-1} (ND)	norfloxacin 128 μg mL^{-1}	
	45		*Staphylococcus aureus* ATCC25923	8 μg mL^{-1} (ND)	norfloxacin 0.5 μg mL^{-1}	Ioannou et al. (2012)
			Staphylococcus aureus EMRSA-15	8 μg mL^{-1} (ND)	norfloxacin 0.5 μg mL^{-1}	
			Staphylococcus aureus EMRSA-16	2 μg mL^{-1} (ND)	norfloxacin 128 μg mL^{-1}	
			Staphylococcus aureus RN4220	8 μg mL^{-1} (ND)	norfloxacin 0.5 μg mL^{-1}	
			Staphylococcus aureus SA1199B	8 μg mL^{-1} (ND)	norfloxacin 32 μg mL^{-1}	
			Staphylococcus aureus XU212	8 μg mL^{-1} (ND)	norfloxacin 8 μg mL^{-1}	
	46		*Staphylococcus aureus* ATCC25923	4 μg mL^{-1} (ND)	norfloxacin 0.5 μg mL^{-1}	
			Staphylococcus aureus EMRSA-15	4 μg mL^{-1} (ND)	norfloxacin 0.5 μg mL^{-1}	
			Staphylococcus aureus EMRSA-16	2 μg mL^{-1} (ND)	norfloxacin 128 μg mL^{-1}	
			Staphylococcus aureus RN4220	2 μg mL^{-1} (ND)	norfloxacin 0.5 μg mL^{-1}	
			Staphylococcus aureus SA1199B	4 μg mL^{-1} (ND)	norfloxacin 32 μg mL^{-1}	
			Staphylococcus aureus XU212	4 μg mL^{-1} (ND)	norfloxacin 8 μg mL^{-1}	
	48	*Dictyota pfaffii* Schnetter; Phaeophyceae	*Leishmania amazonensis* amastigote	44 μM	amphotericin B 1 μM	Soares et al. (2012)
			Leishmania amazonensis amastigotes infected HIV-1 infected human macrophages	50 μM reduced by 60% the parasite burden[a] (ND)	amphotericin B 0.06 μg mL^{-1}	
	49	*Canistrocarpus cervicornis* (Kützing) De Paula and De Clerck; Phaeophyceae	*Leishmania amazonensis* promastigote	2 μg mL^{-1} (93)	amphotericin B 0.06 μg mL^{-1}	Dos Santos et al. (2011)
			Leishmania amazonensis intracellular amastigote	4 μg mL^{-1} (ND)	amphotericin B 0.3 μg mL^{-1}	
			Leishmania amazonensis axenic amastigote	12 μg mL^{-1} (ND)	amphotericin B 0.35 μg mL^{-1}	

Table 2 (continued)

Chemical type	Compound	Species of marine algae; phylum	Species	Activity IC_{50} or MIC (SI)[a] % of inhibition	Activity Reference drug or inhibition zone diameter	References
	50	*Bifurcaria bifurcata* R. Ross; Phaeophyceae	*Plasmodium falciparum* *Trypanosoma brucei*	2.6 μg mL^{-1} (22) 13.7 μg mL^{-1} (4)	artemisinin 2 ng mL^{-1} melarsoprol 4 ng mL^{-1}	Gallé et al. (2013)
			Trypanosoma cruzi	18 μg mL^{-1} (3)	benznidazole 6 ng mL^{-1}	
	51	*Bifurcaria bifurcata* R. Ross; Phaeophyceae	*Leishmania donovani* amastigote *Trypanosoma cruzi* trypomastigote	19 μg mL^{-1} (3) 48 μg mL^{-1} (1)	miltefosin 0.1 μg mL^{-1} benznidazole 0.6 μg mL^{-1}	Smyrniotopoulos et al. (2017)
			Trypanosoma brucei rhodesiense bloodstream	12 μg mL^{-1} (5)	melarsoprol 10 ng mL^{-1}	
			Plasmodium falciparum	0.7 μg mL^{-1} (877)	chloroquine 50 ng mL^{-1}	
	54	*Lessonia vadosa* Searles; Phaeophyceae	*Leishmania infantum* promastigote *Leishmania infantum* amastigote	45 μM (> 2) ~ 10 μM (> 10)	amphotericin B 0.1 μM amphotericin B 0.2 μM	Becerra et al. (2015)
			Leishmania amazonensis promastigote	55 μM (> 2)	amphotericin B 0.1 μM	
			Leishmania amazonensis amastigotes	~ 8 μM (> 12)	amphotericin B 0.2 μM	
Phenols, quinones, chromones, and other related metabolites	**55**	*Sargassum heterophyllum* (Turner) C. Agardh (Sargassaceae)	*Plasmodium falciparum*	5 μg mL^{-1} (ND)	chloroquine 9.3 ng mL^{-1}	Afolayan et al. (2008)
		Sargassum macrocarpum C. Agardh; Phaeophyceae	*Staphylococcus aureus* (ATCC6538P)	32 μg mL^{-1} (ND)	vancomycin 1 μg mL^{-1}	Horie et al. (2008)
	56			8 μg mL^{-1} (ND)		
	57			16 μg mL^{-1} (ND)		
	58			2 μg mL^{-1} (ND)		
	59	*Sargassum macrocarpum* C. Agardh; Phaeophyceae	*Propionibacterium acnes* ATCC 11827 *Propionibacterium acnes* ATCC 25742	15 μg mL^{-1} (ND) 15 μg mL^{-1} (ND)	clindamycin 30 ng mL^{-1} clindamycin 67 ng mL^{-1}	Kamei et al. (2009)
	60	*Symphyocladia latiuscula* (Harvey) Yamada; Rhodophyta	*Candida albicans* (ATCC10231)	25 μg mL^{-1} (ND)	fluconazole 0.5 μg mL^{-1}	Xu et al. (2014)
	61	*Symphyocladia latiuscula* (Harvey) Yamada; Rhodophyta	*Candida albicans* (ATCC10231)	12.5 μg mL^{-1} (ND)	fluconazole 0.5 μg mL^{-1}	Xu et al. (2014)
	62	*Caulerpa racemosa*; Chlorophyta	*Candida glabrata* (ATCC 537) *Trichophyton rubrum* (Cmccftla)	4 μg mL^{-1} (ND) 16 μg mL^{-1} (ND)	amphotericin B 4 μg mL^{-1} amphotericin B 1 μg mL^{-1}	Liu et al. (2013)
			Cryptococcus neoformans (ATCC 32609)	4 μg mL^{-1} (ND)	amphotericin B 2 μg mL^{-1}	
	63	*Stypopodium zonale* (J. V. Lamouroux) Papenfuss; Phaeophyceae	*Leishmania amazonensis* amastigotes	20 μM (8.4)	amphotericin B 1 μM	Soares et al. (2016)
	64			23 μM (11.5)	inhibits 60% the parasite burden	
	65	*Cystoseira baccata* (S.G. Gmelin) P.C.; Phaeophyceae	*Leishmania infantum* promastigote *Leishmania infantum* amastigote	50 μM (2.6) 25 μM (5.2)	miltefosin 23 μM miltefosin 20 μM	De Souza et al. (2017)
	66	*Sargassum heterophyllum* (Turner) C. Agardh (Sargassaceae)	*Plasmodium falciparum*	6.5 μg mL^{-1} (ND)	chloroquine 9.3 ng mL^{-1}	Afolayan et al. (2008)
	67			0.8 μg mL^{-1} (11)		
	68			1.3 μg mL^{-1} (54)		

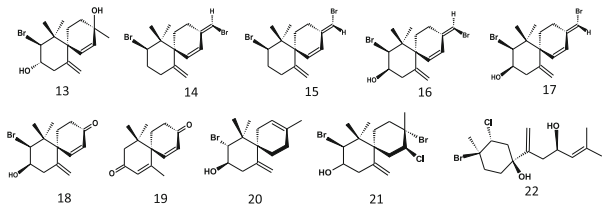
Table 2 (continued)

Chemical type	Compound	Species of marine algae; phylum	Species	Activity IC_{50} or MIC (SI)[a] % of inhibition	Activity Reference drug or inhibition zone diameter	References
Macrolides	**69**	*Callophycus serratus*; Rhodophyta	*Plasmodium falciparum*	0.4 μM (38)	amodiaquine 7.8 nM	Stout et al. (2011)
	70			0.3 μM (ND)		
	71			0.8 μM (ND)		
	72			0.6 μM (ND)		
	73			0.2 μM (104)		
Alkaloids	**74**	*Laurencia similis* K. W. Nam & Y. Saito; Rhodophyta	*Bacillus subtilis*	8 μM (ND)	penicillin 125 ng mL^{-1}	Li et al. (2016)
			Bacillus thuringiensis	8 μM (ND)	penicillin 64 μg mL^{-1}	
			Staphylococcus aureus	2 μM (ND)	penicillin 0.3 μg mL^{-1}	
			Agrobacterium tumefaciens	4 μM (ND)	penicillin 250 μg mL^{-1}	
			Pseudomonas lachrymans	8 μM (ND)	penicillin 250 μg mL^{-1}	
			Ralstonia solanacearum	4 μM (ND)	penicillin 250 μg mL^{-1}	
			Xanthomonas vesicatoria	8 μM (ND)	penicillin 250 μg mL^{-1}	
Lipids	**75**	*Laurencia okamurai;* Rhodophyta	*Candida glabrata* (ATCC537)	4 μg mL^{-1} (ND)	amphotericin B 1 μg mL^{-1} fluconazole 2 μg mL^{-1} ketoconazole 0.5 μg mL^{-1} voriconazole 30 ng mL^{-1}	Feng et al. (2015)
	76		*Cryptococcus neoformans* (ATCC 32609)	8 μg mL^{-1} (ND) 16 μg mL^{-1} (ND)	amphotericin B 1 μg mL^{-1} amphotericin B 1 μg mL^{-1} fluconazole 1 μg mL^{-1}	
	77	*Chondria crassicaulis* Harv. Rhodophyta	*Cryptococcus neoformans* (ATCC 32609)	32 μg mL^{-1} (ND)	amphotericin B 0.5 μg mL^{-1}	Tong et al. (2017)
	78, 79, 80 mixture	*Lobophora variegate*	*Giardia intestinalis* trophozoites	20.9 μg mL^{-1}	metronidazole 0.5 μg mL^{-1}	Cantillo-Ciau (2010)
			Entamoeba histolytica trophozoites	3.9 μg mL^{-1}		
			Trichomonas vaginalis trophozoites	8.0 μg mL^{-1}		
			Entamoeba histolytica			
Polysaccharides	**Fucoidan**	*Undaria pinnatifida*; Phaeophyceae	*Plasmodium falciparum*	> 50 μg mL^{-1}	chloroquine 24 ng mL^{-1}	Chen et al. (2009)
		Sargassum wightii	*Vibrio cholerae*	31.3 μg mL^{-1}	tetracycline 500 μg mL^{-1}	Maradhupandi and Kumar (2013)
			P. aeruginosa	62.5 μg mL^{-1}		
Other metabolites	**81**	*Laurencia scoparia*; Rhodophyta	*Nippostrongylus brasiliensis* L4	< 100 μM	albendazole 0.3 μM levamisole 0.2 μM febendazole 0.1 μM	Davyt et al. (2001)

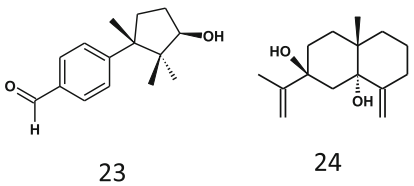
ND not determined

[a] Selective index

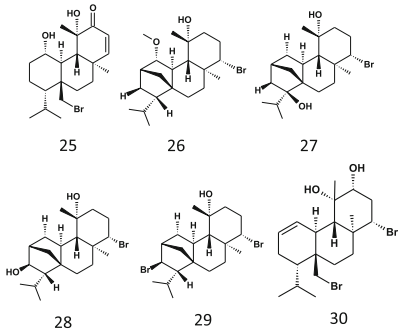
isomeric pairs, **14**–**15** and **16**–**17**, the *Z*-isomers **14** and **16** were more active than the *E*-isomers **15** and **17** (Davyt et al. 2001). The same authors (2006) reported the isolation of three new halogenated *β*-bisabolene sesquiterpenoids from *L. scoparia*. Compound **22** exhibited weak in vitro anthelmintic activity against parasitant stage (L4) *N. brasiliensis* (IC_{50} = 0.11 mM) when compared to the positive control reported in the previous work (Davyt et al. 2001, 2006).



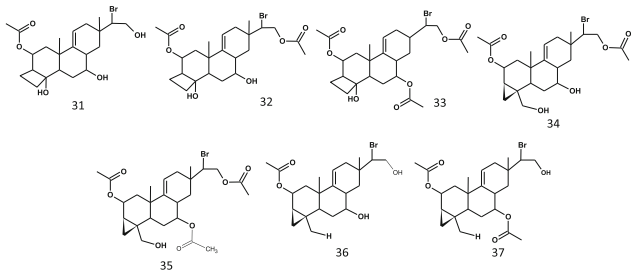
Bawakid et al. (2017), working with *Laurencia obtusa* from the Saudi Red Sea, isolated four new sesquiterpenes and further evaluated against multidrug-resistant bacteria strains including *S. aureus*, *Enterococcus faecalis*, and *Pseudomonas aeruginosa*. They showed that compound **23** (MIC = 0.09 μM) was as active as amoxicillin when tested towards *S. aureus*, while the eudesmane sesquiterpene **24** (MIC = 8.3 μM) showed nearly half of the anticandidal activity of amphotericin B (MIC = 4.7 μM).



Smyrniotopoulos et al. (2008) investigated *Sphaerococcus coronopifolius* from Corfu Island, Greece, and isolated six bromoditerpenes, including four new compounds further tested against a panel of methicillin- and multidrug-resistant *S. aureus* strains. The new compound **25** was active against all tested strains, presenting MIC values ranging from 0.2 to 1 μg mL^{-1}, overwhelming the positive control norfloxacin. In face of the less active bromoditerpenes, the authors argue that the presence of α,β-unsaturated ketone at C-12 might be contributing to the observed activity, with this compound being capable of undergoing Michael-type additions to this moiety via attack at C-14 by biological nucleophiles (Smyrniotopoulos et al. 2008). Following the investigation, four new tetracyclic bromoditerpenes (**26**–**29**) modified at C-12 have also shown antibacterial activity against the same panel of *S. aureus* strains; however, this activity was only four to 16 times higher than norfloxacin, contrary to previous work that showed **25** was 64 to 512 times more active than the same standard drug (Smyrniotopoulos et al. 2010). These findings are corroborated by Rodrigues et al. (2015) who showed other bromoditerpenes without ketone at C-12 are not active against bacteria species including *E. coli and P. aeruginosa*, while the known compound **30** was only as effective as ampicillin when tested against *S. aureus*.

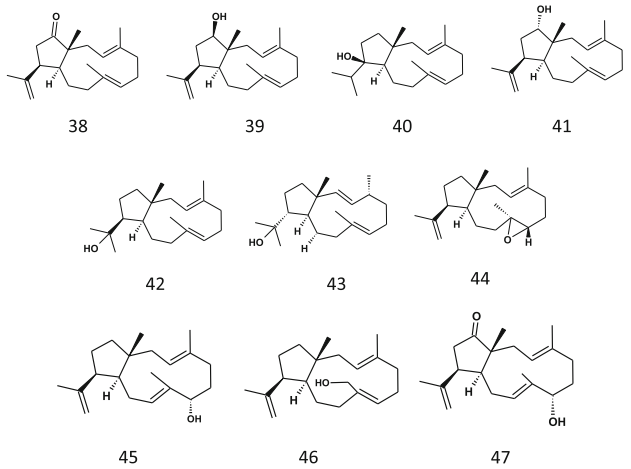


Awad (2004) isolated novel brominated diterpenes parguerene and isoparguerene from the red alga *Jania rubens*, collected from the Red Sea coasts, Egypt. The compounds were identified as isoparguerol (**31**), isoparguerol-16-acetate (**32**), isoparguerol-7, 16-diacetate (**33**), parguerol-16-acetate (**34**), parguerol-7, 16-diacetate (**35**), deoxyparguerol (**36**), and deoxyparguerol-7-acetate (**37**) and tested for anthelmintic activities against the earthworms *Allolobophora caliginosa*. Compounds **31**–**35** were more effective than **36** and **37** and gave high anthelmintic activity when compared with the same concentration (10%) of the reference drug mebendazole.



Ioannou et al. (2011) isolated 17 dolabellanes, including eight novel compounds, from the brown alga *Dilophus spiralis* (synonym: *Dictyota spiralis* Montagne) from Elafonissos Island, Greece (Guiry and Guiry, 2018). The compounds were tested against a panel of six strains of *S. aureus* presenting different phenotypes regarding drug susceptibility. Compound **38** bears a ketone group at C-14 and was eight times more active than norfloxacin against the methicillin-resistant strain, EMRSA-16, and its alcohol derivative **39** was the most active compound against all six strains; however, when compared to the reference drug, **39** was more effective than norfloxacin (64 times) only for the EMRSA-16 strain. The most active compounds against EMRSA-16 bear a hydroxyl group at C-12 (**40**), C-14 (**39** and **41**), or C-18 (**42** and **43**), suggesting that these structural features seem to be

important for the activity of these dolabellanes against the strain EMRSA-16; nevertheless, these structure-activity relationships (SAR) are not essential, since compound **44** bears an epoxide function instead of a double bond at C-7, unlikely the aforementioned structural feature. Compound **40** was moderately active against all tested strains and differs from **39** by the position of the hydroxyl group. Following the exploitation of the same alga *D. spiralis*, Ioannou et al. (2012) isolated 13 other novel minor dolabellanes, which were tested against the same panel of *S. aureus* strains from their previous work (Ioannou et al. 2011). Among all tested compounds, only **45** and **46** were 64 times more active than norfloxacin against EMRS-16 as well as to two other multidrug-resistant strains and were as active as the standard drug. Regarding the SAR, the author suggests that the allylic hydroxyl group at C-7 might be contributing to the antibacterial activity; additionally, compounds presenting a ketone group at C-14 such as **47** were inactive.

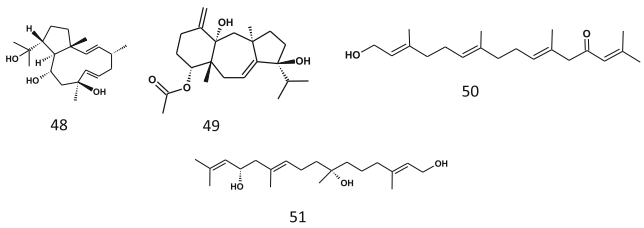


Soares et al. (2012) semi-synthesized dolabelladienetriol (**48**) after reduction of dolabellane diterpene 10,18-diacetoxy-8-hydroxy-2,6-dolabelladiene obtained from the brown algae *Dictyota pfaffi* as previously described (Barbosa et al. 2004). Compound **48** was active against promastigotes and intracellular amastigote forms of *L. amazonensis* and was also effective in reducing amastigotes in HIV-1-infected human macrophages.

Dos Santos et al. (2011) isolated the diterpene **49** from the brown alga *Canistrocarpus cervicornis*, collected in the coast of Paraíso Beach, Pernambuco State, Brazil, which showed a dose-dependent activity against promastigotes, axenic amastigotes, and intracellular amastigotes of *L. amazonensis*. Despite the fact that **49** was two times less active than amphotericin B, the compound presented an outstanding selective index (SI = 93), i.e., **49** was 93 times more selective to the parasite rather than to the J774G macrophages and it is suggested that the antileishmanial effect is also related to the depolarization of the mitochondrial membrane and membrane lipid peroxidation.

Gallé et al. (2013) demonstrated that eleganolone **50** obtained from the brown alga *Bifurcaria bifurcata* showed interesting anti-*Plasmodium falciparum* activity (IC_{50} = 2.6 μg mL^{-1}; SI = 22) and low cytotoxicity, being 22 times more selective to the parasite. Although **50** presented moderate activity against both *Trypanosoma brucei rhodesiense* (IC_{50} = 13.7 μg mL^{-1}; SI = 4) and *T. cruzi* (IC_{50} = 18 μg mL^{-1}, SI = 3), the diterpene was cytotoxic to the host cell, according to the obtained SI.

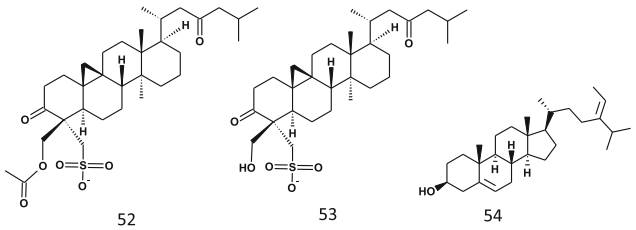
Smyrniotopoulos et al. (2017) isolated bifurcatriol (**51**) from the Irish brown alga *B. bifurcata*. Compound **51**, which has two stereogenic centers, was tested towards the protozoa *P. falciparum* (IC_{50} = 0.65 μg mL^{-1}; SI = 877), *T. brucei rhodesiense* (IC_{50} = 12 μg mL^{-1}; SI = 5), *T. cruzi* (IC_{50} = 48 μg mL^{-1}, SI = 1), and *Leishmania donovani* (IC_{50} = 19 μg mL^{-1}; SI = 3). Compound **51** did not present wide spectra of action, being more active only against the malaria parasite; additionally, although **51** was not as active as chloroquine (IC_{50} = 50 μg mL^{-1}), its selectivity was outstanding (SI = 877).



Puglisi et al. (2004) isolated the triterpene sulfate cycloartanone capisterones A (**52**) and B (**53**) from the green alga *Penicillus capitatus*, collected in Sweetings Cay, Bahamas. In order to search for efflux pumps inhibitors, Li et al. (2006) tested these compounds towards a panel of different fungi, including *Candida albicans*, *Candida glabrata*, *Candida krusei*, *Cryptococcus neoformans*, and *Aspergillus fumigatus* as well as against two fluconazole-resistant strains of *Saccharomyces cerevisiae* overexpressors of the efflux pumps *CDR1* and *MDR1* of *C. albicans.* Interesting, both **52** and **53** were able to reverse the drug resistance phenotype of the *S. cerevisiae* strains; however, they did not present any antifungal activity against the other fungi species tested, which suggests that these compounds might be acting as efflux pumps inhibitors.

Becerra et al. (2015) obtained fucosterol (**54**) from the brown alga *Lessonia vadosa* from Patagonia, through green extraction methods. The triterpene presented antileishmanial activity towards *Leishmania infantum* (IC_{50} = 10 μM; SI > 10) and *L. amazonensis* (IC_{50} = 8 μM; SI > 12). Although its efficacy is low compared to amphotericin B (IC_{50} < 0.2 μM),

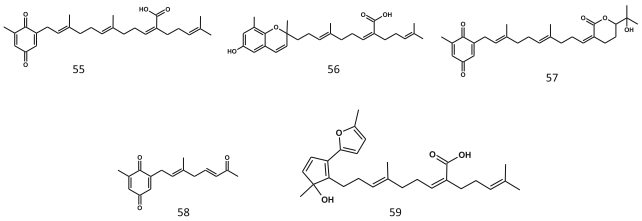
the SI values higher than ten turn it an interesting scaffold for the drug development process.



Phenols, quinones, chromones, and other related metabolites

The brown alga *Sargassum sagamianum* from Japan afforded the known sargaquinoic acid (**55**) and sargachromenol (**56**) and two new sargaquinoic acid derivatives, 15′-hydroxysargaquinolide (**57**), and the product of its oxidative cleavage (**58**). The antibacterial assays were performed against *S. aureus* and showed that these compounds present MIC values ranging from 2 to 32 μg mL^{-1}, and among them, **58** was the most potent (MIC = 2 μg mL^{-1}), considering the positive control vancomycin (MIC = 1 μg mL^{-1}) (Horie et al. 2008).

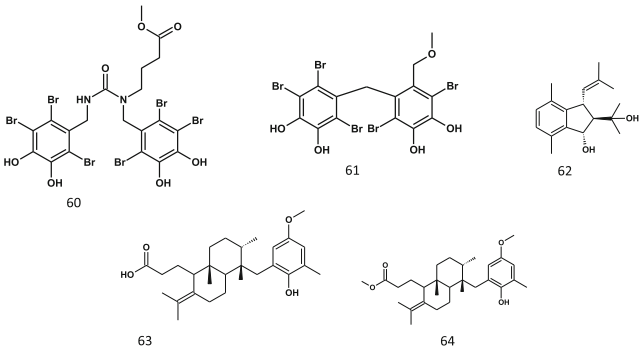
Kamei et al. (2009) isolated from *Sargassum macrocarpum* from Japan, sargafuran (**59**), a compound presenting a similar side chain to sargaquinoic acid (**55**) and sargachromenol (**56**). The compound **59** presented bactericidal activity against *Streptococcus pyogenes* that causes acne, unlikely clindamycin, known to have only bacteriostatic activity. The bactericidal activity of **59** is highlighted because it might contribute to minimize the emergence of resistant strains.



From another red alga, *Symphyocladia latiuscula*, collected at Qindao, China, Xu et al. (2014) isolated bromophenols that presented antifungal activity towards *C. albicans*. The new metabolite **60** showed mild antifungal activity (MIC = 25 μg mL^{-1}), while the known compound **61** was two times more active (MIC = 12.5 μg mL^{-1}) than **60**; however, both bromophenols were less active than the positive control fluconazole (MIC = 0.5 μg mL^{-1}).

Liu et al. (2013) showed that the isolated prenylated *p*-xylene caulerprenylol B (**62**) from the green alga *Caulerpa racemosa* from China was as active as amphotericin B (MIC$_{80}$ = 4 μg mL^{-1}) against *C. neoformans* (MIC$_{80}$ = 4 μg mL^{-1}) and only two times lower than the reference drug (MIC$_{80}$ = 2 μg mL^{-1}) for *C. glabrata* (MIC$_{80}$ = 4 μg mL^{-1}). Considering the dermatophyte fungus *Tricophyton rubrum*, the activity (MIC$_{80}$ = 16 μg mL^{-1}) was only 16 times lower than the control (MIC$_{80}$ = 1 μg mL^{-1}).

Soares et al. (2016) studying the lipophilic extract from the brown *Stypopodium zonale*, collected in Brazil, described the isolation of meroditerpenoid atomaric acid (**63**) and its methyl ester derivative (**64**). Both compounds showed comparable anti-*L. amazonensis* amastigote activity (IC$_{50}$ = 20 μM) but 20 times lower than amphotericin B. Although the activity of the compounds is mild, they were at least eight times more selective to the parasite, which might be interesting in terms of further drug development process.



de Sousa et al. (2017) described bioactivity-driven fractionation of the hexane extract from the brown alga *Cystoseira baccata* collected in Portugal and reported the anti-*L. infantum* activity of the meroditerpenoid tetraprenyltoluquinol (**65**). This compound was nearly as active (IC$_{50}$ = 25 μM) as miltefosine (IC$_{50}$ = 20 μM) against intracellular *L. infantum* amastigotes and was five times more selective to the parasite than to the host cells.

Afolayan et al. (2008) isolated the tetraprenylated toluquinols, sargaquinoic acid (**55**), sargahydroquinoic acid (**66**), and sargaquinol (**67**) and the carotenoid pigment fucoxanthin (**68**) from the brown alga *Sargassum heterophyllum*, collected in of South Africa. The compounds were tested towards the parasite *P. falciparum*, and although all of them presented antiplasmodial activity, the most active were **67** (IC$_{50}$ = 0.8 μg mL^{-1}) and **68** (IC$_{50}$ = 1.3 μg mL^{-1}), considering the activity of chloroquine (IC$_{50}$ = 9 ng mL^{-1}), being **68** the most selective to the parasite (SI = 54).

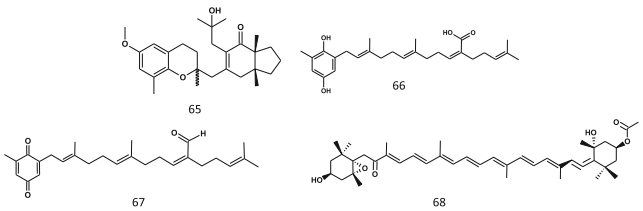
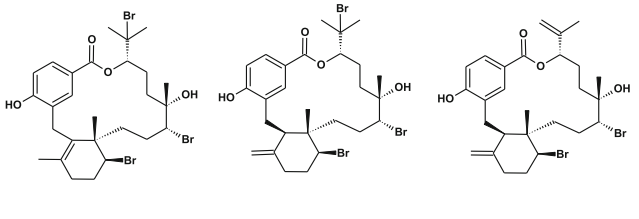


Table 3 Representative patents regarding green extraction methods used on seaweeds

Title of invention	Brief description	Patent number	Applicants	Publication date	Reference
Extraction method and apparatus of the fucoxanthin from seaweed	The invention comprises a method wherein a high-pressure fluid, a supercritical fluid, or a subcritical fluid is used to extract fucoxanthin from seaweed	JP2010006783	Kagawa Industry Support Foundation	01/14/2010	Quitain et al. (2010)
Method for extracting chlorophyll and carotenoid pigments from seaweeds, crustacea, and echinodermata using supercritical and subcritical carbon dioxides with entrainer	The invention comprises a method wherein a mixture of supercritical fluid and ethanol is used to extract chlorophyll and carotenoid pigments from seaweed and others	KR1020020000660	Chun, Byung Soo	01/05/2002	Chun and Hong (2002)
Vitiligo covering composition and preparation method thereof	The invention comprises an extract composition wherein a mixture of extracts from seaweeds of different *phylum* plus beets extract has a vitiligo-covering effect. The extraction methods include ultrasonic extraction and supercritical fluids	CN102793640	Hu Fagang	11/28/2012	Fagang and Xiaoli (2012)
Method for producing D-cysteinolic acid extract	The invention comprises a method wherein a D-cysteinolic acid extract derived from seaweed is produced by carbon dioxide in a supercritical state	JP2004143112	Mitsubishi Heavy Ind LTD	05/20/2004	Shin (2004)
Method for preparing fucoxanthin from kelp seaweeds	The invention comprises a method for preparing fucoxanthin from kelp seaweeds wherein subcritical water extraction was part of the process	CN106518814	Daxinganling Lingoberry Boreal Biotech CO., LTD	03/22/2017	Dekun and Xuehui (2017)
Seaweed flavor powder	The invention comprises a process that provides a rich aroma and taste of seaweed powder wherein part of the extraction process is microwave-assisted	CN101919541	Guangzhou University	12/22/2010	Yaming et al. (2010)
Method for extracting and purifying fucoxanthin	The invention comprises a method for extracting and purifying fucoxanthin from a brown seaweed wherein ethanol solvent extraction is microwave-assisted	CN104327017	Wuhan University	02/04/2015	Yongmei et al. (2015)
Preparation method of seaweed whole active substances	The invention comprises a preparation method of seaweed active substances realizing a sequential extraction from a small polarity solvent (ethanol) through mixed solvents (ethanol and water) until high polarity (water)	CN106942739	Fujian Agriculture And Forestry University	07/14/2017	Bin et al. (2017)
Cosmetic composition containing seaweed extract	The invention comprises a cosmetic composition containing a water-extracted mixture of 3 seaweeds	WO2015099280	Ecomine CO., LTD	07/02/2015	Moon et al. (2015)
Antioxidant extract from brown macroalgae and method for obtaining same	The invention comprises a method for obtaining antioxidants extracts through a ultrasound-assisted continuous aqueous extraction	EP2997963 US20160074317 WO2014167162	Univ Santiago Compostela	03/23/2016 (EP) 03/17/2016 (US) 10/16/2014 (WO)	Jorge et al. (2014, 2016a, 2016b)
Method and device for non-thermal extraction of phytochemicals from macroalgae	The invention comprises a method for the extraction of a phytochemical from a seaweed by applying electric field	WO2017081677	Ramot At Tel-Aviv University LTD	05/18/2017	Golberg (2017)

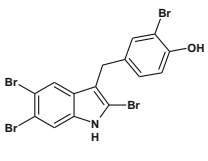
Macrolides

Stout et al. (2011) reported the antiplasmodial activity of bromophycolide A and their semisynthetic derivatives isolated from the Fijian red algae *Callophycus serratus*. The bromophycolide A **69** (IC_{50} = 0.5 μM) and the derivatives **70** (IC_{50} = 0.3 μM), **71** (IC_{50} = 0.8 μM), **72** (IC_{50} = 0.6 μM), and **73** (IC_{50} = 0.2 μM) were the most active compounds. The authors pointed out that the acylation of the phenol in the *p*-hydroxybenzoate group in **69–73** might be contributing to the slight increase in the activity of **73**. Moreover, **69** (IC_{50} = 0.4 μM) and **73** (IC_{50} = 0.3 μM) were also active against *P. falciparum* chloroquine-resistant parasites, indicating that bromophycolide A might not be substrate to efflux pumps, which are known to be involved in parasite resistance to chloroquine. In addition to the low toxicity of these compounds over mammalian cells, the author's data support the hypothesis that the structure of bromophycolides might be considered as inhibitors of heme crystallization, similarly to artemisin.



Alkaloids

From the red alga *Laurencia similis*, Li et al. (2016) isolated four new minor brominated indole related alkaloids and tested them against three Gram-positive and four Gram-negative bacterial strains. Brominated indole **74** presented MIC values ranging from 2 to 4 μg mL^{-1} and was at least 31 times more potent than penicillin (MIC = 250 μg mL^{-1}) for all Gram-negative bacteria tested; however, no remarkable effect was observed for any of the compounds considering the Gram-positive strains.

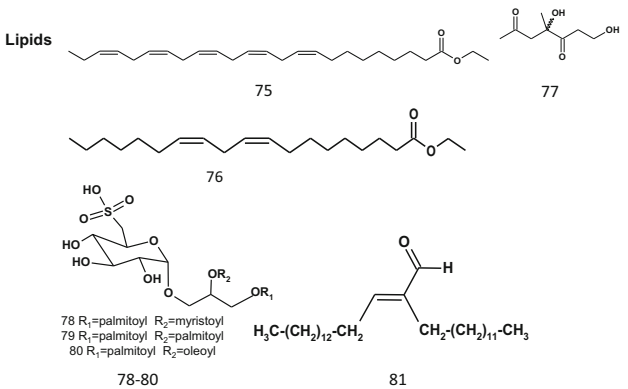


Lipids

Feng et al. (2015) isolated polyunsaturated fatty acid ethyl esters from the red alga *Laurencia okamurai* collected in the coast of China. The isolated metabolites were tested against *C. glabrata*, *T. rubrum*, and *C. neoformans*. The novel compound **75** was the most active towards *C. glabrata*, although showing only moderate activity (MIC_{80} = 4 μg mL^{-1}) when compared to the reference drugs amphotericin B (MIC_{80} = 1 μg mL^{-1}), fluconazole (MIC_{80} = 2 μg mL^{-1}), and ketoconazole (MIC_{80} = 0.5 μg mL^{-1}). On the other hand, **75** was about 130 times less potent than voriconazole. Compounds **75** (MIC_{80} = 8 μg mL^{-1}) and **76** (MIC_{80} = 16 μg mL^{-1}) had also a slight activity against *C. neoformans*, considering the positive controls amphotericin B (MIC_{80} = 1 μg mL^{-1}) and fluconazole (MIC_{80} = 1 μg mL^{-1}).

Another red alga from China, *Chondria crassicaulis*, was investigated by Tong et al. (2017) and afforded two pairs of rare racemic lipids, derivatives of heptanediones. These compounds were tested against different clinical isolates, including four species of *Candida*. One of the racemic heptanedione derivatives, **77**, had moderate activity against *C. neoformans* (MIC_{80} = 32 μg mL^{-1}) considering the antifungal effect of amphotericin B (MIC_{80} = 0.5 μg mL^{-1}).

A mixture of three sulfoquinovosyl-diacylglycerols **78–80** isolated from the chloroform fraction of the total extract of the brown alga *Lobophora variegata* showed good activity against *Entamoeba histolytica* (IC_{50} = 3.9 μg mL^{-1}), moderate activity against *Trichomonas vaginalis* (IC_{50} = 8.0 μg mL^{-1}), and good selectivity to the parasite (SI > 10); however, the mixture was not as effective as the reference drug metronidazole (Cantillo-Ciau et al. 2010).



Polysaccharides

Maradhupandi and Kumar (2013) investigated a fucoidan isolated from *Sargassum wightii* that contains 52.7% of fucose

and 29.3% of sulfate. It was tested against several bacteria and the best activities, superior to the control tetracycline (MIC = 500 μg mL^{-1}), were obtained for *Vibrio cholerae* (MIC = 31.3 μg mL^{-1}) and *P. aeruginosa* (MIC = 62.5 μg mL^{-1}). The original fucoidans from *Saccharina* (*Laminaria) japonica* showed no antibacterial activity at the concentration of 10 mg mL^{-1}, but interestingly, the products of depolymerization (fractions with molecular weight ranging from < 6 up to > 80 kDa) showed some activity against *S. aureus* and *E. coli* with the best results associated to the fraction with lower molecular weight (Liu et al. 2017). Based on their results and considering the literature reports for fucoidans from other algae, the authors suggest that both sulfate content and molecular weight are the main factors that contribute to the antibacterial activity of fucoidans.

Chen et al. (2009) showed the antiplasmodial activity of the sulfated polysaccharide fucoidan obtained from the brown alga *Undaria pinnatifida*, showing the anti-*P. falciparum* activity of this compound (IC_{50} = 2 μg mL^{-1}). The in vivo analyses demonstrated that at a dose of 100 mg kg^{-1} day^{-1}, it was able to reduce the parasite burden by 37% in *Plasmodium berghei*-infected BALB/c mice, while the dose of 5 mg kg^{-1} day^{-1} of chloroquine was three times more effective, showing 94% of parasite burden reduction.

Other metabolites

A long chain aldehyde, (2*E*)-2-tridecylheptadec-2-enal (**81**), isolated from the dichloromethane extract of the red alga *L. scoparia* showed moderate in vitro anthelmintic activity (IC_{50} < 100 μM) against the parasitant stage of *N. brasiliensis*; nevertheless, the compound was not as active as the reference drugs (e.g., albendazole, IC_{50} = 0.34 μM) (Davyt et al. 2001).

Patents

Over 2000 patents were searched considering the use of macroalgae as raw material for production of bioactive compound but none publication was found regarding NTDs. Furthermore, when being less restrictive, just eight patents were found when considering macroalgae as the resource of bioactive compound for medicinal preparations against viruses, parasites, and bacteria (Table 3). Despite the aforementioned data regarding the seaweeds, bioactive compounds, and the very low number of registered and published patents, it is evident that this research field is being underexplored.

Discussion

Macroalgae are very important for the marine environment and are responsible for nitrate assimilation and O_2 production, while simultaneously removing CO_2 from the atmosphere. The compounds isolated from algae have sophisticated chemical structures and present great potential, considering the several published studies and patents regarding chemicals extracted from this marine source and registered for human health and nutrition (Cardozo et al. 2007; Torres et al. 2014).

It is a fact that the world population is increasing rapidly and, therefore, the demands for agricultural and food, new drugs for pharmaceutical purposes, metabolites for cosmetic, subproducts for the bioenergy industry, and many others are increasing and algae products and their metabolites can fulfill the gap of such demands. The bioactive compounds from marine algae herein described are very interesting for the pharmaceutical and medical areas, including drugs for NDs.

This review highlights the efforts of many research groups in finding bioactive compounds from marine algae to control NDs and circumvent the huge medical problem associated to the appearance of resistant pathogens. Indeed, Li et al. (2006) showed the potential of triterpenes obtained from the green alga *P. capitus* in inhibiting efflux pumps, membrane proteins known to be involved in multidrug resistance. Nevertheless, none of the compounds herein reported have been further evaluated in any clinical tests. A part of the problem is the reliance on the relative potency of the compounds or toxicity in comparison to the reference drugs, which make them not attractive to pharmaceutical companies in order to consider them as potential drug leads. Moreover, at least for some promising compounds, the small amounts of purified compounds are not sufficient for further evaluation in in vivo studies (Reichelt and Borowitzka, 1984). Thus, to circumvent this issue, many efforts have been made in the synthesis and structural modification of marine bioactive compounds such as trabectedin (Cuevas and Francesch, 2009) and discodermolide (Freemantle, 2004; Mickel et al. 2004), two anticancer agents that proceed thorough clinical trials. Trabecterin (Yondelis®) was approved by FDA in 2015 for the treatment of sarcomas (Barone et al. 2017), while discodermolide failed at phase II/III due to their presented low efficacy and high toxicity (Freemantle, 2004; Mickel et al. 2004).

Considering the chemical diversity observed among algal metabolites that were active against the etiological agents of NDs as their model microorganisms and the fewer studies approaching their mechanisms of action, it is not possible to suggest features of structure-bioactivity. Ogungbe and Setzer (2016) reviewed molecular targets for *Leishmania*, *Trypanosoma*, and *Plasmodium* spp. parasites and showed that several classes of phytochemicals, including

geranylgeraniol, steroids, and phenols, presented an antioxidant enzyme, trypanothione reductase, as their target. In silico studies of algal metabolites could afford interesting insights concerning potential molecular targets such as those conducted by Passalacqua et al. (2015), who performed docking analyses followed by dynamic simulation to investigate the molecular interactions and structural patterns that are crucial for the semisynthetic antileishmanial 2',4'-dihydroxychalcone targets the parasite glycolytic enzyme glycerol-3-phosphate dehydrogenase.

In response to this growing application, with a very high economic impact, it is imperative to take actions for the sustainable utilization and preservation of the natural resources. For this, farming cultivation of algae in open ponds, photobioreactors, or in tanks using IMTA has been stimulated by different governmental policies, and allied, modern, and environmentally green extraction methods are definitely changing the concept from wild harvesting to the sustainable production of algae in large scale (Laurens et al. 2017). Moreover, the advancement of genetic techniques will allow isolation and expression of biosynthetic gene clusters important for production of therapeutically relevant secondary metabolites and the heterologous cloning of these genes in yeast or microalgae will represent a new frontier for natural products' drug discovery.

Despite the London Declaration of 2012 (Molyneux, 2016) and all the efforts of WHO, Research and Development commitments of pharmaceutical companies, and the huge diversity of NPs, this review revealed that we are far from the ideal scenario considering the search for new alternatives for treatment of NDs, especially those caused by helminthes. Part of the problem relies on the early stage drug discovery, which is a challenging step for most of the helminthes that, unlike protozoa or bacteria, present complex life cycles and do not have simple assays for drug screening. Indeed, drug discovery and development programs do not yet exist for any of the major helminth diseases, and only few works regarding bioactive NPs were found to be mildly effective against the nematode *N. brasiliensis*, known to infect only rodents. Although the use of *N. brasiliensis* as platform for drug discovery might be justified by its simple life cycle, similarity to other nematodes, and its use in animal models (Dominguez et al. 2000), the drug discovery process for helminthes has been very slow. Therefore, more investment in the development of new and easy screening assays to find new therapeutic options to control these diseases is mandatory.

A low-cost and simple visual imaging system to automate and quantify screening of filariasis based on their movement has been proposed to search for new antifilarials (Marcellino et al. 2012). For trematodes, the use of larval stages has been an alternative that allows the assessment of large numbers of worms (Abdulla et al. 2009). Nevertheless, although these achievements represent an important progress to the field of anti-helminthic discovery, these new assays are not comparable to the high throughput levels already established for the assays developed for the protozoa parasites *Plasmodium* spp., *Trypanosoma* sp., and *Leishmania* spp. (Hudson and Nwaka, 2007). However, this scenario might be circumvented with the development of new approaches such as High Content Screening (HCS), recently developed for *Schistosoma* parasites and other helminths (Marcelino et al. 2012; Abdulla et al. 2009; Paveley, 2012). Although HCS is slower when compared to HTS, it allows a more detailed phenotypic screening and better understanding of drug effects. Recently, a label-free HCS using automatic bright field image analysis was proposed for the assessment of anti- *S. mansoni* compounds. This system can be adapted to several other species of helminthes, which turns this assay into a promising alternative for drug discovery (Paveley et al. 2012).

Even though phenotypic visual analysis is still the method of choice in many bioactive compound screening programs, target-based approaches must urgently be considered to be explored for scientists working on marine NPs. Simeonov et al. (2008) screened more than 71,000 synthetic compounds for thioredoxin/glutathione reductase and peroxiredoxin activity, principal components of the defense system of *Schistosoma*, and showed interesting hits presenting IC_{50} values in the nanomolar range. This change of paradigm from phenotypic cell to target-based approach will definitely contribute to the discovery of more suitable bioactive NPs to combat these parasites. For this, other molecular targets are still necessary and the use of the technology of RNA interference (RNAi) has been very helpful for target identification and validation (Grant 2007; Geldhof et al. 2007; Grant e Behm, 2007; Yoshino et al. 2010; Maule et al. 2011; Dalzell et al. 2012; Crowther et al. 2014; Gosbert et al. 2014; He et al. 2018). Besides, the search for new potential targets must consider not only their importance in pathogen survival and/or virulence but also their "druggability", which might impair their use in HTS (Crowther et al. 2014).

Conclusion and perspectives

This review has highlighted the progress of early phase drug discovery for infectious diseases using as starting point the inexhaustible source of secondary metabolites, the marine macroalgae, and their potential for pharmaceutical application as well as some aspects of sustainable practices of cultivation and green extraction methods. From the 81 bioactive compounds highlighted in this review, 54 are terpenes and 14 are phenols, quinones, or related compounds, while macrolides, alkaloids, lipids, and polysaccharides were less reported. Among terpenes, the halogenated sesquiterpenes from *Laurencia* species (Rhodophyta) were the compounds that showed broad activity profile (antibacterial and antiparasitary)

while non-halogenated diterpenes from the brown alga *D. spiralis* and bromoditerpenes from the red alga *S. coronopifolius* presented only reports for antibacterial activity against MRSA strains. The genus *Sargassum* presented the highest number of compounds in the class of phenolic compounds, where the prenylated toluquinones/quinols should be highlighted for the antibacterial and antiplasmodial activities. Among the reports from *Laurencia* species, it was possible to observe that some of the scientific names do not correspond to the currently accepted taxa. For example, *Laurencia scoparia* J. Agardh. as well as *L. majuscula* (Harvey) A.H.S. Lucas and *L. obtusa* var. *majuscula* Harvey have as accepted name *Laurencia dendroidea* J. Agardh. The high phenotypical variation of the genus *Laurencia* leads to common misidentification of the algal material, but the correct identification of other algal species may also be a considerable challenge. Furthermore, this review has also revealed the plethora of different screening protocols, strains, and data presentation, which turn difficult literature comparison. Thus, the development of specific guidelines for screening protocols for each bioactivity is mandatory and urgent.

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