Biological activities associated to the chemodiversity of the brown algae belonging to genus *Lobophora* (Dictyotales, Phaeophyceae)

Christophe Vieira, Julie Gaubert, Olivier de Clerck, Claude Payri, Gérald Culioli, Olivier Thomas

► To cite this version:

Christophe Vieira, Julie Gaubert, Olivier de Clerck, Claude Payri, Gérald Culioli, et al.. Biological activities associated to the chemodiversity of the brown algae belonging to genus *Lobophora* (Dictyotales, Phaeophyceae). *Phytochemistry Reviews*, 2017, 16 (1), pp.1-17. 10.1007/s11101-015-9445-x . hal-01767401

HAL Id: hal-01767401

<https://hal-amu.archives-ouvertes.fr/hal-01767401>

Submitted on 7 May 2018

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

1 **Biological activities associated to the chemodiversity of the brown algae**
2 **belonging to genus *Lobophora* (Dictyotales, Phaeophyceae)**

3
4 **Christophe Vieira · Julie Gaubert · Olivier De Clerck · Claude Payri · Gérald**
5 **Culioli · Olivier P. Thomas**

6
7 C. Vieira (✉)
8 Sorbonne Universités, UPMC Univ Paris 06, IFD, 4 Place Jussieu, 75252 PARIS
9 cedex 05, France

10 C. Vieira (✉) · Julie Gaubert · C. Payri
11 ENTROPIE, LabEx-CORAIL, Institut de Recherche pour le Développement, B.P.
12 A5, 98848, Nouméa Cedex, Nouvelle-Calédonie, France

13 C. Vieira (✉) · O. De Clerck
14 Phycology Research Group and Center for Molecular Phylogenetics and Evolution,
15 Ghent University, Krijgslaan 281 (S8), B-9000 Gent, Belgium

16 G. Culioli · O. P. Thomas
17 Université Nice Sophia Antipolis, Institut de Chimie de Nice, UMR 7272 CNRS,
18 Faculté des Sciences, Parc Valrose 06108 Nice, France

19 G. Culioli
20 Université de Toulon, MAPIEM, EA 4323, La Garde, France

21 O. P. Thomas
22 Institut Méditerranéen de Biodiversité et d'Ecologie marine et continentale (IMBE),
23 Aix Marseille Université, CNRS, IRD, Avignon Université, Station marine
24 d'Endoume, rue de la Batterie des Lions, 13007 Marseille, France
25 e-mail: cvcarp@gmail.com

26
27 **Running title** Bioactivity of natural products of the genus *Lobophora*

28
29
30

Abstract Although *Lobophora* belongs to a marine algal family (Dictyotaceae) that produces a large array of secondary metabolites, it has received little attention compared to other genera, such as *Dictyota*, in terms of natural compounds isolation and characterization. However, metabolites produced by *Lobophora* species have been found to exhibit a wide array of bioactivities including pharmacological (e.g. antibacterial, antiviral, antioxidant, antitumoral), pesticidal, and ecological. This review aims to report the state-of-the-art of the natural products isolated from *Lobophora* species (Dictyotales, Phaeophyceae) and their associated bioactivities. All bioactivities documented in the literature are reported, therefore including studies for which pure active substances were described, as well as studies limited to extracts or fractions. From the early 1980s until today, 49 scientific works have been published on *Lobophora* chemistry and bioactivity, among which 40 have reported bioactivities. Only six studies, however, have identified, characterized and tested no less than 23 bioactive pure compounds (three C₂₁ polyunsaturated alcohols, three fatty-acids, a macrolactone, 11 polyketides, a few sulfated polysaccharides, three sulfolipids, a tocopherol derivative). The present review intends to raise awareness of chemists and biologists given the recent significant taxonomic progress of this brown algal genus, which holds a promising plethora of natural products yet to be discovered with ecological and pharmacological properties.

Keywords Bioactivity · Brown algae · *Lobophora* · Natural products

53 **Abbreviations**

54	ACVr	Acyclovir-resistant
55	EC ₅₀	Half maximal Effective concentration
56	HCT-116	Human colon tumor
57	HEp-2	Human epithelial type 2
58	HIV	Human immunodeficiency virus
59	HL-60	Human promyelocytic leukemia cell line
60	HSV-1/2	Herpes simplex virus type 1 or 2
61	HT-29	Human colorectal adenocarcinoma cell line
62	IC ₅₀	Half maximal inhibitory concentration
63	LC ₅₀	Median lethal concentration
64	LD ₅₀	Median lethal dose
65	MCF-7	Human breast carcinoma cell line
66	MDCK	Madin-Darby canine kidney
67	MIC ₉₀	Minimal inhibitory concentration to inhibit the growth of 90%
68		of organisms
69	MZI	Mean zone of inhibition
70	RSV	Respiratory syncytial virus
71	SQDG	Sulfoquinovosyl diacylglycerol
72		

Introduction

The brown marine algal genus *Lobophora* J. Agardh (Dictyotales, Phaeophyceae) is distributed worldwide in tropical to temperate waters and represents an important algal component in coral reef ecosystems (Vieira et al. 2014; Bennett et al. 2010; De Ruyter van Steveninck and Breeman 1987; Diaz-Pulido et al. 2009). *Lobophora* belongs to the Dictyotaceae, a family which has proven to be a particularly rich and diverse source of natural products and predominantly diterpenes (Maschek and Baker 2008; Vallim et al. 2005; Blunt et al. 2015). These natural products have been particularly studied for their bioactivity for human health but also for their putative ecological role in nature. The terpenoids isolated from the Dictyotaceae exhibit various types of bioactivity such as feeding deterrence, antifungal, cytotoxic, antibiotic, anti-inflammatory, insecticidal or antiviral activities. However, while some genera have received much attention, notably *Dictyota* and *Dictyopteris* (Hay and Steinberg 1992; Paul et al. 2006; Paul and Ritson-Williams 2008), others like *Lobophora* raised less interest and a very limited number of natural products have already been described from algae of this genus. This limited attention may be explained by the taxonomic deficiency this genus has suffered from until recently. Indeed, only three *Lobophora* species were recognized until the end of the last century, with *Lobophora variegata* (Lamouroux) Womersley ex Oliveira being by far the most commonly reported species, apparently distributed in the world's oceans. This species has been cited in virtually all the chemical studies conducted on the genus *Lobophora* (Table 1). However, recent DNA-based studies (Sun et al. 2012; Vieira et al. 2014) have shed new light on *Lobophora* taxonomy. Today, 20 species are taxonomically accepted (Guiry and Guiry 2015) and 80 more have been estimated (Vieira 2015). The high genetic diversity recently unveiled within this genus presupposes that a richer chemodiversity is yet to be discovered. This review aims to report the state-of-the-art of the natural products isolated from *Lobophora* species (Dictyotales, Phaeophyceae) and their associated bioactivities. All bioactivities documented in the literature are reported in Table 1, therefore including studies for which pure active substances were described, as well as studies limited to extracts and/or fractions. The *Lobophora* natural products for which no bioactivity has yet been reported are presented in Table 2. *Lobophora* bioactive natural products reported here are presented in Figure 1.

Note that the recent taxonomic progress of the genus *Lobophora* naturally questions the validity of what has been nearly always reported as *L. variegata* based on external morphological criteria. Therefore, although referred to in the literature as *L. variegata* or in only one instance as *L. papenfussii*, we will presently simply make reference to the genus *Lobophora*.

Relevant literature was searched with the databases Marinlit, Google Scholar, ISI Web of Science, JSTOR and PubMed. A targeted search of English literature (i.e. papers with minimum an English title and abstract) was conducted using the key word ‘*Lobophora*’ followed by the search terms [activity or allelopath* or anti* or bioactiv* or chemi* or extract or metabolite or natural product]. An asterisk (*) is a wildcard character that means “any character”, which allows the database or search engine to look for multiple words that have different endings, e.g. bioactiv* captures [bioactive AND bioactivity].

Antimicrobial activities

Antimicrobial (anti-bacterial, -viral, -fungal or -protozoal) activities of extracts, fractions or compounds isolated from *Lobophora* species have been by far the most explored type of bioactivities searched for this genus. Like other eukaryotes, macroalgae harbor a large and diverse microbial community, which play important roles for the host (Egan et al. 2013). The selection of associated or symbiotic bacteria may be related to the production of specialized metabolites that play important functions against harmful marine microorganisms (Egan et al. 2013) as well as against some human pathogens.

Antibacterial activities

Organic extracts of *Lobophora* species have shown a broad-spectrum of antibacterial activities (Morrow et al. 2011; Engel et al. 2006; Manilal et al. 2012; Manilal et al. 2010a; Gutiérrez-Cepeda et al. 2015; Manilal et al. 2010b; Ballantine et al. 1987; Sivakumar 2014). Engel et al. (2006) considered two morphotypes of *Lobophora*, crustose and ruffled, which we strongly suspect to be two distinct species. Lipophilic and hydrophilic parts of organic extracts from both morphotypes resulted in growth inhibition of the bacteria *Pseudoalteromonas bacteriolytica*. However, the two morphotypes extracts yielded contrasting IC₅₀ values: the lipophilic parts showed

volumetric IC_{50s} of 1 and 0.24 (unitless) for the crustose and ruffled types, respectively, and the hydrophilic parts exhibited volumetric IC_{50s} of 0.51 and 0.67, respectively. It would therefore appear that these two different morphotypes have contrasting chemical production.

The chloroform-methanolic extract of Caribbean *Lobophora* presented antibacterial activity against *Bacillus subtilis* (Ballantine et al. 1987). The organic extract of *Lobophora* samples from India showed a strong inhibition against *Salmonella typhi* and *Vibrio cholera* while being less active against *Klebsilla pneumonia* and *E.coli* (Sivakumar 2014). Val et al. (2001) did not observed any antimicrobial activity of the methanolic extract of *Lobophora* harvested in Canary Islands (Spain) against a panel of pathogen bacterial strains. Manilal et al. (2010a), Manilal et al. (2010b) and Manilal et al. (2012) showed that *Lobophora* methanolic extract exhibited a strong antibacterial activity against a wide array of bacteria including the biofilm-forming bacteria *Vibrio* sp., *Colwellia* sp. SW125 and *Pseudoalteromonas bacteriolytica*; the pathogenic bacterial strains *Aeromonas hydrophila*, *Bacillus cereus*, *Escherichia coli*, *Micrococcus luteus* and *Salmonella typhimurium*; the multiresistant human pathogens *B. subtilis*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *S. epidermidis*; and the shrimp pathogens *Vibrio parahaemolyticus*, *V. vulnificus*, *V. harveyi*, *V. alcaligenes* and *V. alginolyticus*. Manilal et al. (2012) characterized by gas chromatography seven fatty acids (palmitic, lauric, stearic, α -linolenic, oleic, myristic and hexadecatrienoic acids) from an active *Lobophora* fraction, thus suggesting that the antibacterial bioactivity could be attributed to the synergistic effects of these compounds. In fact, fatty acids, such as oleic, lauric and palmitic acids have already demonstrated antibacterial activity (Kabara et al. 1972). But while lauric and myristic acids presented inhibitory effect on the 11 bacterial strains tested by the authors, the effect of oleic acid was restricted to only one strain (*Streptococcus* group A) (Kabara et al. 1972). Morrow et al. (2011) showed that *Lobophora* organic extract induced a shift in the assemblage of bacteria associated to corals. Gerwick Fenical (1982) tested the *in vitro* antibacterial activity of a new aromatic polyketide identified from this species, 1-(2,4,6-trihydroxyphenyl)hexadecane-1-one (**1**), against a panel of six bacteria (*S. aureus*, *B. subtilis*, *E. coli*, *Enterobacter aerogenes*, *P. aeruginosa*, *Vibrio anguillarum*) but did not observe any effect. Similarly, Gutiérrez-Cepeda et al. (2015) identified 10 new polyketides (**13-22**) and tested the antimicrobial effect of seven of

them (**13-15**, **17-19** and **22**) against *Enterococcus faecalis*, *E. coli*, and *S. aureus*. The authors showed that the compounds **13** and **14** inhibited the growth of *S. aureus* by 100 ± 1% (average ± SD) and 65 ± 2%, respectively at 100 µg ml⁻¹ concentration. The minimum inhibitory concentration (MIC₉₀) of lobophorol A (**13**) against *S. aureus* was shown to be 25 µg ml⁻¹.

Antiviral activities

Lobophora aqueous extracts presented interesting bioactivities against a wide range of viruses. Some polysaccharides isolated from *Lobophora* exhibited antiviral activities against the herpes simplex virus types 1 and 2 (EC₅₀ 18.2 and 6.25 µg ml⁻¹, respectively), and a very low cytotoxicity to Vero, HEp-2, and MDCK cell lines as well as a moderate activity against respiratory syncytial virus (RSV) (Wang et al. 2008a). *Lobophora* aqueous extract exhibited anti-HSV properties (EC₅₀ 18.5 and 9 µg ml⁻¹ for HSV-1 and HSV-2, respectively) and a moderate anti-RSV activity (Wang et al. 2008b). The organic extract strongly inhibited HSV-1-ACVr (92% of inhibition) but did not inhibit at all HSV-2-ACVr (Soares et al. 2012). Queiroz et al. (2008) showed that a sulfated polysaccharide isolated from *Lobophora* (a galactofucan of 1400 kDa, with fucose, galactose, glucose and sulfate at molar ratio of 1:2:3:0.5), exhibited antiretroviral effect by inhibiting reverse transcriptase activity of human immunodeficiency virus. Kremb et al. (2014) showed that *Lobophora* aqueous extracts also inhibited HIV-1 infection at the level of virus entry into cells.

Antifungal activities

Some *Lobophora* extracts showed antifungal activities against a broad spectrum of fungi. The lipophilic part of an organic extract of the crustose type induced 100% growth inhibition of *Dendryphiella salina* (ascomycete) and the fungi-like *Halophytophthora spinosa* (oomycete), but no effect on *Lindra thalassiae* (ascomycete). On the other hand, the lipophilic extract of the ruffled type did not inhibit the growth of any of the three tested fungi. The hydrophilic extracts of both *Lobophora* types resulted in the growth inhibition by ca. 70% of only the oomycete *H. spinosa*. We notice here again that the different morphotypes of *Lobophora* have contrasting bioactivities against different micro-organisms (Engel et al., 2006). Gerwick Fenical (1982) tested the antifungal activity of the polyketide (**1**) against

Candida albicans, a causal agent of opportunistic oral and genital infections in humans, but did not observe any effect. Some *Lobophora* organic extracts also failed to inhibit the growth of *Aspergillus fumigatus*, *C. albicans* and *Saccharomyces cerevisiae* (Val *et al.*, 2001). Kubanek *et al.* (2003) identified a macrolactone polyketide named lobophorolide (**2**), which exhibited sub-micromolar activity against pathogenic and saprophytic marine fungi (*Dendryphiella salina*, *Lindra thalassiae* and *C. albicans*) with IC₅₀ values ranging from 0.034 to 1.3 µg ml⁻¹. Lobophorolide is structurally related to tolytoxin, scytophycins, and swinholides, macrolides previously isolated from terrestrial cyanobacteria, marine sponges and gastropods (Kubanek *et al.* 2003). These structural similarities raise the question of its origin, and the authors suggested that the molecule is more probably biosynthesized by *Lobophora* associated-bacteria.

Antiprotozoal activities

Lobophora extracts presented antiprotozoal activities against six protozoan parasites, namely *Trichomonas vaginalis* (a common and worldwide parasite which infects the urogenital tract of men and women), *Entamoeba histolytica* (parasite infecting humans and other primates), *Giardia intestinalis* (responsible for enteric protozoan infections), *Schizochytrium aggregatum* (marine protist), *Leishmania mexicana* (one of the causative species of leishmaniasis) and *Trypanosoma cruzi* (causative species of trypanomiasis). The organic extract exhibited anti-trichomonal activity with an IC₅₀ of 1.39 µg ml⁻¹ (Moo-Puc *et al.* 2008), an IC₅₀ of 3.2 µg ml⁻¹ against *Trichomonas vaginalis* (Cantillo-Ciau *et al.* 2010), and anti-leishmanial *in vitro* properties against *Leishmania mexicana* promastigote forms with a LC₅₀ value of 49.9 µg ml⁻¹ (Freile-Pelegrin *et al.* 2008). The same extract exhibited a moderate *in vitro* antiprotozoal activity against *Trypanosoma cruzi* with an IC₅₀ of 9.72 µg ml⁻¹ (León-Deniz *et al.* 2009). Cantillo-Ciau *et al.* (2010) identified three sulfoquinovosyldiacylglycerols (SQDGs; 1-*O*-palmitoyl-2-*O*-myristoyl-3-*O*-(6'''-sulfo- α -D-quinovopyranosyl)glycerol (**3**), 1,2-di-*O*-palmitoyl-3-*O*-(6'''-sulfo- α -D-quinovopyranosyl)glycerol (**4**) and 1-*O*-palmitoyl-2-*O*-oleoyl-3-*O*-(6'''-sulfo- α -D-quinovopyranosyl)glycerol (**5**) with antiprotozoal activity from a lipophilic fraction. SQDGs were shown to exhibit an *in vitro* antiprotozoal activity against *Entamoeba histolytica* with an IC₅₀ of 3.9 µg ml⁻¹, and a moderate activity against *T. vaginalis*

trophozoites with an IC_{50} of 8 $\mu\text{g ml}^{-1}$. Engel et al. (2006) observed differences in the antiprotozoal activities of both *Lobophora* types presented earlier. While both hydrophilic and lipophilic parts of the organic extract of the crustose type inhibited the growth of *Schizochytrium aggregatum*, only the lipophilic part of the ruffled type showed a significant inhibition (Engel et al. 2006).

Additional pharmacological bioactivities

In addition to the antimicrobial activities presented above, *Lobophora* presented several additional bioactivities with some pharmacological potential, including anti-angiogenic, anticoagulant, anti-inflammatory antioxidant, cytotoxic (including antitumoral) and hemagglutinating activities. *Lobophora* extracts and sulfated polysaccharides were shown to exhibit anticoagulant (De Lara-Isassi et al. 2004; Medeiros et al. 2008; Castro et al. 2014b), antioxidant (Zubia et al. 2007; Paiva et al. 2011; Castro et al. 2014b; Sathyaseelan et al. 2015), anti-inflammatory (Paiva et al. 2011; Siqueira et al. 2011; Medeiros et al. 2008; Castro et al. 2014b), hemagglutinating (Lima Ainouz et al. 1992) as well as anti-angiogenic (Castro et al. 2014a) activities. *Lobophora* aqueous extract demonstrated low cytotoxic properties on human breast carcinoma MCF-7 cell lines, at a concentration of 200 $\mu\text{g ml}^{-1}$ (Wang et al. 2008b), and against the human nasopharyngeal carcinoma (KB) cell line (Moo-Puc et al. 2009). Semi-purified fractions of *Lobophora* also exhibited potential cytotoxic activity on a cultured human melanoma cancer cell line (Rocha et al. 2007). Lobophorolide (**2**) also showed antineoplastic activity (IC_{50} 0.03 $\mu\text{g ml}^{-1}$) on the human colon tumor cell line HCT-116 (Kubaneck et al. 2003), and sulfated polysaccharides presented anti-tumoral effects on human colon adenocarcinoma cell line HT-29 (Castro et al. 2014b). Several organic *Lobophora* extracts were active against P-388 lymphocytic leukemia and Ehrlich ascites tumor in mice (Kashiwagi et al. 1980). Queiroz et al. (2006) showed a cytotoxic action of *Lobophora* polysaccharides (a glucan and three galactofucans) on HL60 cells. The molecular mechanism of the cytotoxic effect of these polymers has not been clearly defined but this study suggested a possible involvement of phosphatases.

Pesticidal activities

Two studies assessed the pesticidal activities (i.e. pupicidal, nematocidal and phytotoxic activities) of *Lobophora* (Manilal et al. 2012; Bianco et al. 2013). *Lobophora* showed a larvicidal potential against the dengue mosquito *Aedes aegypti* ($52 \pm 2.9\%$ larval mortality at 500 ppm concentration; Bianco et al. 2013), and pupicidal potential against the urban mosquito *Culex quinquefasciatus* with a LD₅₀ value of 683 $\mu\text{g ml}^{-1}$ (Manilal et al. 2012). *Lobophora* methanolic extract presented a nematocidal activity against the plant-pathogenic nematode *Meloidogyne javanica* with a LD₅₀ value of 1.16 mg ml⁻¹; and a phytotoxic activities against several plant seeds (*Cicer arietinum*, *Vigna radiate* and *Cajanus cajan*), with a no growth response of *C. cajan*, *V. radiate* and *C. arietinum* at a seaweed extract concentration of 4, 6 and 8 mg ml⁻¹, respectively (Manilal et al. 2012). Manilal et al. (2012) have attributed these pesticidal activities to a synergistic effect between the fatty acids they have identified (see above).

Bromophenols production

Lobophora have been shown to produce bromophenols, a group of key flavor compounds in seafood. Chung et al. (2003) found four bromophenols in *Lobophora* namely 4-bromophenol (**9**), 2,4-dibromophenol (**10**), 2,6-dibromophenol (**11**), and 2,4,6-tribromophenol (**12**). These authors also showed that comparatively to two other brown algae, *Padina arborescens* and *Sargassum siliquastrum*, *Lobophora* presented the highest amount of bromophenols. Bromophenols have demonstrated a variety of biological activities including antioxidant, antimicrobial, anticancer, anti-diabetic, and anti-thrombotic effects (Liu et al. 2011). Nevertheless, to our knowledge no study has yet shown bioactivities for any of the four bromophenols isolated from *Lobophora*. Chkhikvishvili Ramazanov (2000) reported that the total phenolic substances content in *Lobophora* represent 1.2% of dry weight.

Edibility, nutritional and nutraceutical values

Widely consumed in some Asian countries (Zaneveld 1959), marine algae are well-known as a functional food for their richness in carotenoids, dietary fibers, essential fatty acids, lipids, minerals, polysaccharides, proteins and vitamins (Holdt and Kraan 2011; Plaza et al. 2008; Ito and Hori 1989; Dawczynski et al. 2007; Burtin 2003). However, only a handful of studies have been interested in testing the edibility and

294 nutritional value of *Lobophora*. Gerwick Fenical (1982) isolated one form of vitamin
 295 E (γ -tocopherol (**6**)) from *Lobophora*, which has distinct properties from the more
 296 common α -tocopherol (Jiang et al. 2001), the form of vitamin E that is preferentially
 297 absorbed and accumulated in humans (Rigotti 2007). Sousa et al. (2008) measured the
 298 content in β -carotene, retinol equivalent (vitamin A) and γ -tocopherol in *Lobophora*:
 299 $4.185 \pm 1.559 \mu\text{g g}^{-1}$ fresh weight of β -carotene, $0.697 \pm 0.260 \mu\text{g g}^{-1}$ of retinol
 300 equivalent and $4.722 \pm 2.062 \mu\text{g g}^{-1}$ of γ -tocopherol. *Lobophora* presented the lowest
 301 γ -tocopherol concentration amongst other Phaeophyceae (i.e. *Dictyopteris delicatula*,
 302 *Dictyota dichotoma*, *Padina gymnospora* and *Sargassum cymosum*). Hegazi (2002)
 303 analyzed the pigment composition of *Lobophora* from the Red Sea and fourteen
 304 compounds were reported: chlorophylls a, a', c₁ and c₂, fucoxanthin, violaxanthin,
 305 flavoxanthin, fucoxanthol, antheraxanthin, 9-cis-neoxanthin, diatoxanthin, zeaxanthin,
 306 β -carotene and phaeophytin a. fucoxanthin, flavoxanthin, diatoxanthin and zeaxanthin
 307 are typical xanthophylls of Chromophyta, while chlorophyll c₁ and chlorophyll c₂ are
 308 the characteristic chlorophylls of this algal group. In *Lobophora* chlorophyll a is the
 309 most important (0.27 mg g^{-1}), followed by chlorophylls c₁ and c₂ (0.001 mg g^{-1} each).
 310 Among the carotenoids, fucoxanthin was the dominant pigment (0.12 mg g^{-1}),
 311 followed by β -carotene (0.06 mg g^{-1}) and violaxanthin (0.04 mg g^{-1}). Carotenoids
 312 such as fucoxanthin, β -carotene and violaxanthin have demonstrated the ability to act
 313 as antioxidants, and to prevent the development of different degenerative diseases and
 314 health conditions in humans, including age-related macular degeneration, cataract,
 315 certain cancers, rheumatoid arthritis, muscular dystrophy and cardiovascular problems
 316 (Kim and Pangestuti 2011; Ibañez and Cifuentes 2013; Ahmed et al. 2013).
 317 Thennarasan (2015) analyzed the biochemistry of *Lobophora*, i.e. the composition in
 318 fatty acids, minerals, sterols, total carbohydrates, total lipids, total proteins and
 319 vitamins (Table 2). Results of this study showed that *Lobophora* presents a high
 320 content of total protein ($23.13 \pm 0.05\%$ of total content) and total carbohydrate
 321 ($19.34 \pm 0.10\%$), and a low content of total lipid ($0.27 \pm 0.5\%$). While *Lobophora* has
 322 a high fatty acid to total lipid ratio (58%), it has a low total lipid content ($<50 \text{ mg g}^{-1}$
 323 dry weight) in comparison with other Dictyotales species (*Dictyota bartayresii*,
 324 *Dictyota dichotoma*, and *Spatoglossum macrodontum*; total lipid content $>100 \text{ mg g}^{-1}$
 325 dry weight) (Gosch et al. 2012). *Lobophora* is also rich in vitamins (especially
 326 vitamin C, $23.430 \pm 0.152 \text{ mg } 100\text{g}^{-1}$), fatty acids (omega fatty acid), and minerals

(calcium, 135.4 ± 0.20 mg 100g⁻¹). de Alencar et al. (2011) have not found histamine and tyramine, amines that can cause intoxication symptoms, in quantities high enough to cause pharmacological actions in *Lobophora*. *Lobophora* appears to be a source of carbonyl compounds (e.g. aldehydes and ketones) (Mota da Silva et al. 2006). While many aldehydes and ketones are used as food flavorings (e.g. propanal, propanone) and preservatives (e.g. formaldehyde), some aldehydes can also act as mutagens and carcinogens (Leikauf 1992; Goldschmidt 1984). For instance, formaldehyde is classified as a “probable human carcinogen” (Thrasher and Kilburn 2001), and acetaldehyde can induce nasal carcinomas (Miyake and Shibamoto 1995).

Ecological roles

Fewer are the studies targeted towards understanding the ecological roles of *Lobophora* metabolites. Three main ecological roles have been investigated, namely antifouling, feeding deterrence, and effects on benthic competitors.

Antifouling

As an evolutionary response to the ecological disadvantages of epibiosis, most if not all macroalgae have developed antifouling chemical defenses. However, these antifouling defenses are not equally efficient across different algal taxa, and some may harbor a significant community of epiphytes. Such is the case of *Lobophora*, which blades act as an important living substratum (Fricke et al. 2011). Yet, the upper-side blade surface is generally less epiphytized than the underside surface. Two studies have been performed to assess the antifouling properties of compounds produced by *Lobophora* against mussels, barnacles and bacterial biofilm (Manilal et al. 2010a; Da Gama et al. 2008). The methanolic extracts showed considerable antifouling activity against biofilm forming bacteria, i.e. *Vibrio* sp. (11 ± 2.5 mm zone of inhibition (MZI)), *Colwellia* sp. SW125 (6 ± 2.1 mm MZI) and *Pseudoalteromonas* sp. SW124 (9 ± 1.5 mm MZI) (Manilal et al. 2010a). On the other hand, some *Lobophora* extract stimulated the attachment to the algal surface of the brown mussel *Perna perna*, and apparently did not show significant activity against the barnacle *Balanus amphitrite* and mussel *Mytilus edulis* attachment (data not presented; Manilal et al. 2010a). Although not clearly demonstrated, antifouling activities might be

attributable to phlorotannins, a class of molecules present in *Lobophora*, that have been reported to present antifouling activity (Amsler and Fairhead 2005).

Effects on benthic competitors

As a consequence of natural or anthropogenic perturbations of their environmental conditions, some coral reefs have shifted from a coral- to a macroalgal-dominance. *Lobophora* has been reported in such events and allelopathy has been suggested as a possible mechanism allowing the alga to outcompete corals in damaged reefs by causing bleaching and suppressing photosynthetic efficiency. Some authors (e.g. Longo and Hay 2014; Vieira et al. 2015; Antonius and Ballesteros 1998) observed that *Lobophora* contacting some corals (e.g. *Agaricia*, *Porites*, *Seriatopora*) was associated with more or less important bleaching. While an allelopathic mechanism has been suggested in the late 1990s (Antonius and Ballesteros 1998), it has only recently been experimentally tested (Rasher and Hay 2010b; Slattery and Lesser 2014; Vieira et al. in revision). Those latter studies clearly demonstrated that *Lobophora* possesses potentially adverse chemicals to several corals (*Porites cylindrica*, *Porites porites*, *Montastrea cavernosa*, *Acropora muricata*, *Stylophora pistillata* and *Montipora hirsuta*), although their actual efficiency *in situ* remains to be proven (Vieira et al. in revision). Slattery Lesser (2014) and Vieira et al. (in revision) identified four molecules with bleaching properties: SQDG (**3**) identified by Cantillo-Ciau et al. (2010) (Slattery and Lesser 2014), and three new C₂₁ polyunsaturated alcohols (**6-8**) (Vieira et al. in revision). Slattery Lesser (2014) experimentally showed that **3** presented bleaching activity against the coral *M. cavernosa*, and Vieira et al. (in revision) showed that the all lobophorenols (**6-8**) exhibited bleaching activities against the coral *A. muricata*. In Vieira et al. (in revision) a significant number of semi-purified fractions also exhibited a more or less significant activity against corals.

Lobophora natural compounds adversity towards corals may be indirect, by affecting the coral-associated bacterial community and notably by causing community shifts on *Montastraea faveolata* and *Porites astreoides* colonies (Morrow et al. 2012), and also causing a sublethal stress. No compounds with such effects have yet been identified, but only the aqueous extract has been found to show ecological effects.

Effects on coral larval recruitment

Lobophora has contrasting effects on coral larval recruitment. Birrell et al. (2008) showed that *Lobophora* is able to enhance larvae settlement of *Acropora millepora* by 40%. On the contrary, Kuffner et al. (2006) showed that *Lobophora* causes either recruitment inhibition or avoidance behavior in *P. astreoides* larvae. Diaz-Pulido et al. (2010) also showed that *Lobophora* presented either no effect on 2-days-old larvae or inhibitory effects on settlement of coral larvae. Similarly, Baird Morse (2004) showed that *Lobophora* inhibited metamorphosis in coral larvae. Morse et al. (1996) found that larvae of several Acroporids species did not settle in assays that included *Lobophora* plants. Nevertheless, no compound, either acting as enhancers or inhibitors, has already been identified.

Deterrence function

Lobophora has been the subject of contradictory observations in terms of susceptibility to herbivory. For example, while De Lara-Isassi et al. (2000) showed ichthyotoxicity (from ethanol and acetone extracts) against the goldfish *Carassius auratus*, Slattery Lesser (2014) concluded that *Lobophora* chemical defenses (*Lobophora* crude extract and a purified SQDG) were inactive against the omnivorous pufferfish (*Canthigaster rostrata*). The experiment of De Lara-Isassi et al. (2000), which aimed at testing the ichthyotoxicity of phlorotannins, is nonetheless ecologically poorly relevant since the goldfish is a freshwater fish. *Lobophora* feeding deterrence potential was suggested based on the presence of phlorotannins and terpenes (Targett and Arnold 1998; Amsler and Fairhead 2005), which may cause the precipitation of proteins (Stern et al. 1996). Stern et al. (1996) isolated phlorotannins from *Lobophora* and suggested several explanations for why the biological activity of phlorotannins may vary as a function of the gut environment of marine herbivores. In addition, Bolser Hay (1996) concluded that the greater consumption of temperate (North Carolina) versus tropical (the Bahamas) *Lobophora* by the sea urchin *Arbacia punctulata* was likely due to the higher concentrations of secondary metabolites such as phlorotannins in *Lobophora* from the temperate regions than in tropical regions. Weidner et al. (2004) showed that while *Lobophora* exhibited inducible defenses following direct consumption by amphipods, the repulsive effects of the non-polar extracts were overridden by counteracting effects of non-extracted chemicals, making live plants more nutritive. Nevertheless, toxicity of *Lobophora* extracts towards fish

has only been suggested, but not rigorously tested (De Lara-Isassi et al. 2000). Cetrulo Hay (2000) investigated the activation of chemical defenses in 42 species of seaweeds including *Lobophora*, but the latter, together with other Dictyotacean species, failed to show activation following damage by the spottail finfish *Diplodus holbrooki*, and the sea urchin *Lytechinus variegatus*.

Conclusion and prospects

The chemical content and associated bioactivities of *Lobophora* species started to be explored in the early 1980s. *Lobophora* exhibits a wide array of bioactivities such as pharmacological (e.g. antibacterial, antiviral, antioxidant, antitumoral), pesticidal, and ecological. The limited number of studies conducted on the subject showed that this alga is a promising functional food.

Most studies were performed with extracts and mainly focused on their pharmacological potential, whereas only few chemicals compounds have been characterized. Only six studies have identified, characterized and tested no less than 23 bioactive compounds (three C₂₁ polyunsaturated alcohols, three fatty-acids, a polyketide macrolactone, 11 polyketides, a few sulfated polysaccharides, three sulfolipids, a tocopherol derivative). Additional chemical studies are urgently required in order to fully characterize the compounds responsible for the large array of biological activities encountered. Furthermore, recent major progress in the taxonomy of this brown algal genus, suggests that a plethora of natural compounds is yet to be discovered within the 110 estimated species (Vieira 2015).

This review is written in this pivotal moment in the chemical knowledge of *Lobophora*, and aims at triggering the interest of chemists, biologists and pharmacologists in exploring this mine of natural compounds still largely under-explored.

Compliance with ethical standards

Conflicts of interest The authors state no conflict of interest and have received no payment for the preparation of this manuscript.

451 Table 1. *Lobophora* natural products and associated bioactivities.

Bioactivity	Species	Biological target	Molecule	Type of extract	Reference
Antimicrobial activities					
Antibacterial	<i>L. variegata</i>	<i>Enterococcus faecalis</i> , <i>Escherichia coli</i> , <i>Staphylococcus aureus</i>	Lobophorols A-C, lobophopyranones A and B, lobophorones A-E	-	Gutiérrez-Cepeda et al. (2015)
Antibacterial	<i>L. variegata</i>	<i>Escherichia coli</i> , <i>Salmonella typhi</i> , <i>Klebsiella pneumonia</i> , <i>Vibrio cholera</i>	-	CHCl ₃ /MeOH	Sivakumar (2014)
Antibacterial	<i>L. variegata</i>	<i>Bacillus cereus</i> , <i>Micrococcus luteus</i> , <i>Salmonella typhimurium</i> , <i>Aeromonas hydrophila</i> , <i>Escherichia coli</i>	Mixture of fatty acids	MeOH	Manilal et al. (2012)
Antibacterial	<i>L. variegata</i>	Marine bacteria isolated from Caribbean macroalgae and corals	-	EtOAc/MeOH and then MeOH/H ₂ O	Morrow et al. (2011)
Antibacterial	<i>L. variegata</i>	Biofilm-forming bacteria	-	MeOH	Manilal et al. (2010a)
Antibacterial	<i>L. variegata</i>	<i>Vibrio parahaemolyticus</i> , <i>Vibrio vulnificus</i> , <i>Vibrio harveyi</i> , <i>Vibrio alcaligenes</i> , <i>Vibrio alginolyticus</i> , <i>Staphylococcus aureus</i> , <i>Pseudomonas aeruginosa</i> , <i>Bacillus subtilis</i> , <i>Klebsiella pneumoniae</i> , <i>Staphylococcus epidermidis</i>	-	MeOH	Manilal et al. (2010b)
Antibacterial	<i>L. variegata</i>	<i>Pseudoalteromonas bacteriolytica</i>	-	CH ₂ Cl ₂ /MeOH [divided into lipophilic (EtOAc) and hydrophilic (H ₂ O) parts]	Engel et al. (2006)
Antibacterial	<i>L. variegata</i>	<i>Bacillus subtilis</i> , <i>Enterococcus faecium</i> , <i>Mycobacterium smegmatis</i> , <i>Pseudomonas aeruginosa</i> , <i>Serratia marcescens</i> , <i>Staphylococcus aureus</i>	-	MeOH	Val et al. (2001)
Antibacterial	<i>L. variegata</i>	<i>Bacillus subtilis</i> , <i>Pseudomonas aeruginosa</i> , <i>Escherichia coli</i> , <i>Staphylococcus aureus</i> , <i>Candida albicans</i>	-	CHCl ₃ /MeOH	Ballantine et al. (1987)
Antibacterial	<i>L. papenfussii</i>	<i>Staphylococcus aureus</i> , <i>Bacillus subtilis</i> , <i>Escherichia coli</i> , <i>Enterobacter aerogenes</i> , <i>Pseudomonas aeruginosa</i> , <i>Candida albicans</i> , <i>Vibrio anguillarum</i>	2-(1'-Oxohexadecyl)-1,3,5-trihydroxybenzene	-	Gerwick Fenical (1982)
Antiviral	<i>L. variegata</i>	HIV	-	H ₂ O	Kremb et al. (2014)
Antiviral	<i>L. variegata</i>	HSV-1	-	CH ₂ Cl ₂ /MeOH	Soares et al. (2012)
Antiviral	<i>L. variegata</i>	HIV	Polysaccharide (galactofucan)		Queiroz et al. (2008)

Antiviral	<i>L. variegata</i>	Herpes simplex virus type 1 and 2 (HSV-1 and -2), respiratory syncytial virus (RSV)		H ₂ O	Wang et al. (2008b)
Antifungal	<i>L. variegata</i>	<i>Dendryphiella salina</i> , <i>Halophytophthora spinosa</i>	-	CH ₂ Cl ₂ /MeOH [divided into lipophilic (EtOAc) and hydrophilic (H ₂ O) parts]	Engel et al. (2006)
Antifungal	<i>L. variegata</i>	<i>Dendryphiella salina</i> , <i>Lindra thalassiae</i> , <i>Candida albicans</i>	Lobophorolide	-	Kubaneck et al. (2003)
Antifungal	<i>L. variegata</i>	<i>Aspergillus fumigatus</i> , <i>Candida albicans</i> , <i>Saccharomyces cerevisiae</i>	-	MeOH	Val et al. (2001)
Antiprotozoal	<i>L. variegata</i>	<i>Trichomonas vaginalis</i> , <i>Entamoeba histolytica</i> , <i>Giardia intestinalis</i>	Mixture of sulfoquinovosyl-diacylglycerols (SQDGs)	CH ₂ Cl ₂ /MeOH	Cantillo-Ciau et al. (2010)
Antiprotozoal	<i>L. variegata</i>	<i>Trypanosoma cruzi</i>	-	CH ₂ Cl ₂ /MeOH	León-Deniz et al. (2009)
Antiprotozoal	<i>L. variegata</i>	<i>Trichomonas vaginalis</i>	-	CH ₂ Cl ₂ /MeOH	Moo-Puc et al. (2008)
Antiprotozoal	<i>L. variegata</i>	<i>Leishmania mexicana</i>	-	CH ₂ Cl ₂ /MeOH	Freile-Pelegrin et al. (2008)
Antiprotozoal	<i>L. variegata</i>	<i>Schizochytrium aggregatum</i>	-	CH ₂ Cl ₂ /MeOH [divided into lipophilic (EtOAc) and hydrophilic (H ₂ O) parts]	Engel et al. (2006)

Other pharmacological activities					
Anti-angiogenic	<i>L. variegata</i>	Embryonated chicken eggs	Sulfated polysaccharides (fucans)	-	Castro et al. (2014a)
Anticoagulant	<i>L. variegata</i>	Human plasma	Sulfated polysaccharides (fucans)	-	Castro et al. (2014b)
Anticoagulant	<i>L. variegata</i>	Human plasma	Sulfated polysaccharide (fucoidan)	-	Medeiros et al. (2008)
Anticoagulant	<i>L. variegata</i>	Human plasma	-	H ₂ O (Phosphate buffer)	De Lara-Isassi et al. (2004)
Anti-inflammatory	<i>L. variegata</i>	Male Swiss-Webster mice	Sulfated polysaccharides (fucans)	-	Castro et al. (2014b)
Anti-inflammatory	<i>L. variegata</i>	Wistar rats	Sulfated polysaccharides (fucans)	-	Paiva et al. (2011)
Anti-inflammatory	<i>L. variegata</i>	Wistar rats	Sulfated polysaccharide (fucan)	-	Siqueira et al. (2011)
Anti-inflammatory	<i>L. variegata</i>	Wistar rats	Sulfated polysaccharide (fucoidan)	-	Medeiros et al. (2008)
Antioxidant	<i>L. variegata</i>	Chemical test	3-(2-methoxy-4-((2,5,6,8a-tetramethyl-1,4,8,8a-tetrahydronaphthalen-1-yl)methyl)phenyl)propanoate	H ₂ O/MeOH	Sathyaseelan et al. (2015)
Antioxidant	<i>L. variegata</i>	Wistar rats	-	-	Paiva et al. (2011)
Antioxidant	<i>L. variegata</i>	Chemical test	-	CH ₂ Cl ₂ /MeOH	Zubia et al. (2007)

Antioxidant	<i>L. variegata</i>	Chemical test	Sulfated polysaccharides (fucans)	-	Castro et al. (2014b)
Cytotoxic	<i>L. variegata</i>	Human nasopharyngeal carcinoma (KB) cell line	-	CH ₂ Cl ₂ /MeOH	Moo-Puc et al. (2009)
Cytotoxic	<i>L. variegata</i>	C32 human melanoma cells	-	Acetone and H ₂ O	Rocha et al. (2007)
Cytotoxic	<i>L. variegata</i>	Human promyelocytic leukemia HL-60 cells	Polysaccharides (a glucan and three galactofucans)	-	Queiroz et al. (2006)
Cytotoxic	<i>L. variegata</i>	Human colon tumor cell line HCT-116	Lobophorolide	-	Kubaneck et al. (2003)
Cytotoxic	<i>L. variegata</i>	Murine P-388 lymphocytic leukemia, Ehrlich ascites tumor cells	-	<i>n</i> -Hexane, CHCl ₃ and then ButOH	Kashiwagi et al. (1980)
Cytotoxic	<i>L. variegata</i>	Vero, HEp-2 and MDCK cells	-	H ₂ O	Wang et al. (2008a)
Cytotoxic	<i>L. variegata</i>	Human breast carcinoma MCF-7 cells	-	H ₂ O	Wang et al. (2008a)
Cytotoxic	<i>L. variegata</i>	Human colon tumor cell line HT-29	Sulfated polysaccharides (fucans)	-	Castro et al. (2014b)
Hemagglutinating	<i>L. variegata</i>	Chicken, goat, pig, rabbit and human erythrocytes	-	H ₂ O (NaCl)	Lima Ainouz et al. (1992)

Pesticidal activities

Pupicidal	<i>L. variegata</i>	<i>Culex quinquefasciatus</i>			
Nematicidal	<i>L. variegata</i>	<i>Meloidogyne javanica</i>	Fatty acids	MeOH	Manilal et al. (2012)
Phytotoxic	<i>L. variegata</i>	<i>Cicer arietinum</i> , <i>Vigna radiata</i> and <i>Cajanus cajan</i> seeds			
Larvicidal	<i>L. variegata</i>	<i>Aedes aegypti</i>	-	CH ₂ Cl ₂ /MeOH	Bianco et al. (2013)

Ecological roles

Antifouling	<i>L. variegata</i>	<i>Perna perna</i>	-	CH ₂ Cl ₂ /MeOH or CH ₂ Cl ₂	Da Gama et al. (2008)
Antifouling	<i>L. variegata</i>	<i>Balanus amphitrite</i> , <i>Mytilus edulis</i>	-	MeOH	Manilal et al. (2010a)
Bleaching	<i>L. variegata</i>	<i>Porites cylindrica</i>	-	MeOH [Lipophilic (EtOAc) part]	Rasher Hay (2010a)
Bleaching	<i>L. variegata</i>	<i>Montastrea cavernosa</i>	SQDG	CH ₂ Cl ₂ /MeOH	Slattery Lesser (2014)
Cell lysis	<i>L. variegata</i>	<i>Agelas clathrodes</i>	SQDG	CH ₂ Cl ₂ /MeOH	Slattery Lesser (2014)
Ichtyotoxic	<i>L. variegata</i>	-	Phlorotannins	-	Stern et al. (1996)
Ichtyotoxic	<i>L. variegata</i>	<i>Carassius auratus</i>	-	Acetone, EtOH and H ₂ O	De Lara-Isassi et al. (2000)
Ichtyotoxic	<i>L. variegata</i>	<i>Lytechinus variegatus</i> , <i>Diplodus holbrooki</i>	-	CH ₂ Cl ₂ /MeOH	Cetrulo Hay (2000)
Settlement enhancement	<i>L. variegata</i>	<i>Acropora millepora</i>	-	Seawater (waterborne extract)	Birrell et al. (2008)

Shift of coral-associated bacteria	<i>L. variegata</i>	<i>Montastraea faveolata</i> , <i>Porites astreoides</i>	-	EtOAc/MeOH and then EtOH/H ₂ O	Morrow et al. (2012)
Sublethal stress response	<i>L. variegata</i>	<i>Montastraea faveolata</i> , <i>Porites astreoides</i>	-	EtOAc/MeOH and then EtOH/H ₂ O	Morrow et al. (2012)

452 Table 2. *Lobophora* natural products for which bioactivity has not been tested in
 453 the study.

Molecule	Species	Reference
Volatile carbonyl compounds		
Acetaldehyde	<i>Lobophora variegata</i>	Mota da Silva et al. (2006)
Butanal	<i>Id.</i>	<i>Id.</i>
Formaldehyde	<i>Id.</i>	<i>Id.</i>
Hexanal	<i>Id.</i>	<i>Id.</i>
Pentanal	<i>Id.</i>	<i>Id.</i>
Propanal	<i>Id.</i>	<i>Id.</i>
Propanone	<i>Id.</i>	<i>Id.</i>
Fatty acids		
Docosahexaenoic acid (DHA)	<i>Lobophora variegata</i>	Thennarasan (2015)
Eicosapentaenoic acid (EPA)	<i>Id.</i>	<i>Id.</i>
Hexadecatrienoic acid	<i>Id.</i>	Manilal et al. (2012)
Lauric acid	<i>Id.</i>	<i>Id.</i>
Linoleic acid	<i>Id.</i>	Thennarasan (2015)
Margaric acid	<i>Id.</i>	<i>Id.</i>
Myristic acid	<i>Id.</i>	Manilal et al. (2012)
Oleic acid	<i>Id.</i>	Thennarasan (2015), Manilal et al. (2012)
Palmitic acid	<i>Id.</i>	<i>Id.</i>
Stearic acid	<i>Id.</i>	<i>Id.</i>
Stearidonic (moroticic) acid	<i>Id.</i>	Thennarasan (2015)
α -Linolenic acid	<i>Id.</i>	Thennarasan (2015), Manilal et al. (2012)
Phenols		
Phenolic substances	<i>Lobophora variegata</i>	Chkhikvishvili Ramazanov (2000)
4-Bromophenol	<i>Lobophora</i> sp.	Chung et al. (2003)
2,4,6-Tribromophenol	<i>Id.</i>	<i>Id.</i>
2,4-Dibromophenol	<i>Id.</i>	<i>Id.</i>
2,6-Dibromophenol	<i>Id.</i>	<i>Id.</i>
Polyphenols	<i>Lobophora variegata</i>	(Rao and Untawale 1991)
Photosynthetic pigment		
9'- <i>Cis</i> -Neoxanthin	<i>Lobophora variegata</i>	(Hegazi 2002)
Antheraxanthin	<i>Id.</i>	<i>Id.</i>
Chlorophyll <i>a</i>	<i>Id.</i>	<i>Id.</i>
Chlorophyll <i>a</i> '	<i>Id.</i>	<i>Id.</i>
Chlorophyll c1	<i>Id.</i>	<i>Id.</i>
Chlorophyll c2	<i>Id.</i>	<i>Id.</i>
Diatoxanthin	<i>Id.</i>	<i>Id.</i>
Flavoxanthin	<i>Id.</i>	<i>Id.</i>
Fucoxanthin	<i>Id.</i>	<i>Id.</i>
Fucoxanthol	<i>Id.</i>	<i>Id.</i>
Phaeophytin <i>a</i>	<i>Id.</i>	<i>Id.</i>
Violaxanthin	<i>Id.</i>	<i>Id.</i>
Zeaxanthin	<i>Id.</i>	<i>Id.</i>
β -carotene	<i>Id.</i>	Sousa et al. (2008), (Hegazi 2002)
Vitamins		
Vitamin A	<i>Lobophora variegata</i>	Thennarasan (2015), Sousa et al. (2008)

Vitamin B1	<i>Id.</i>	Thennarasan (2015)
Vitamin B2	<i>Id.</i>	<i>Id.</i>
Vitamin B3 (niacinamide)	<i>Id.</i>	<i>Id.</i>
Vitamin B5 (calcium pantothenate)	<i>Id.</i>	<i>Id.</i>
Vitamin B6	<i>Id.</i>	<i>Id.</i>
Vitamin B9 (folic acid)	<i>Id.</i>	<i>Id.</i>
Vitamin B12	<i>Id.</i>	<i>Id.</i>
Vitamin C	<i>Id.</i>	<i>Id.</i>
Vitamin D	<i>Id.</i>	<i>Id.</i>
Vitamin E	<i>Id.</i>	<i>Id.</i>
γ -Tocopherol	<i>Lobophora papenfussii, L. variegata</i>	Gerwick Fenical (1982), Sousa et al. (2008)
Sterols		
Campesterol	<i>Lobophora variegata</i>	Thennarasan (2015)
Stigmastanol (sitostanol)	<i>Id.</i>	<i>Id.</i>
β -sitosterol	<i>Id.</i>	<i>Id.</i>

References

- Ahmed F, Fanning K, Schuhmann H, Netzel M, Schenk PM (2013) Microalgae: a valuable source of natural carotenoids with potential health benefits. In: Yamaguchi M (Ed.) Carotenoids: Food Sources, Production and Health Benefits. Nova Science Publishers, Hauppauge, NY, USA
- Amsler CD, Fairhead VA (2005) Defensive and sensory chemical ecology of brown algae. *Adv Bot Res* 43:1-91
- Antonius A, Ballesteros E (1998) Epizoisism: a new threat to coral health in Caribbean reefs. *Rev Biol Trop* 46:145-56
- Baird AH, Morse AN (2004) Induction of metamorphosis in larvae of the brooding corals *Acropora palifera* and *Stylophora pistillata*. *Mar Freshwat Res* 55:469-72
- Ballantine DL, Gerwick WH, Velez SM, Alexander E, Guevara P (1987) Antibiotic activity of lipid-soluble extracts from Caribbean marine algae. *Hydrobiologia* 151:463-69
- Bennett S, Vergés A, Bellwood D (2010) Branching coral as a macroalgal refuge in a marginal coral reef system. *Coral Reefs* 29:471-80
- Bianco EM, Pires L, Santos GK, Dutra KA, Reis TN, Vasconcelos ER, Cocentino AL, Navarro DM (2013) Larvicidal activity of seaweeds from northeastern Brazil and of a halogenated sesquiterpene against the dengue mosquito (*Aedes aegypti*). *Ind Crop Prod* 43:270-75
- Birrell CL, McCook LJ, Willis BL, Harrington L (2008) Chemical effects of macroalgae on larval settlement of the broadcast spawning coral *Acropora millepora*. *Mar Ecol Prog Ser* 362:129-37
- Blunt JW, Copp BR, Keyzers RA, Munro MH, Prinsep MR (2015) Marine natural products. *Nat Prod Rep* 32:116-211
- Bolser RC, Hay ME (1996) Are tropical plants better defended? Palatability and defenses of temperate vs. tropical seaweeds. *Ecology* 77:2269-86
- Burtin P (2003) Nutritional value of seaweeds. *EJEAFChe* 2:498-503
- Cantillo-Ciau Z, Moo-Puc R, Quijano L, Freile-Pelegrín Y (2010) The tropical brown alga *Lobophora variegata*: A source of antiprotozoal compounds. *Mar Drugs* 8:1292-304
- Castro LSEPW, de Sousa Pinheiro T, Castro AJG, Santos MdSN, Soriano EM, Leite EL (2014a) Potential anti-angiogenic, antiproliferative, antioxidant, and anticoagulant activity of anionic polysaccharides, fucans, extracted from brown algae *Lobophora variegata*. *J Appl Phycol* 27:1315-25
- Castro LSEW, Pinheiro TS, Castro AJ, Dore CM, da Silva NB, Alves MGdCF, Santos MSN, Leite EL (2014b) Fucose-containing sulfated polysaccharides from brown macroalgae *Lobophora variegata* with antioxidant, anti-inflammatory, and antitumoral effects. *J Appl Phycol* 26:1783-90
- Cetrulo GL, Hay ME (2000) Activated chemical defenses in tropical versus temperate seaweeds. *Mar Ecol Prog Ser* 207:243-53
- Chkhikvishvili ID, Ramazanov ZM (2000) Phenolic substances of brown algae and their antioxidant activity. *Appl Biochem Microbiol* 36:289-91
- Chung HY, Ma WCJ, Ang PO, Kim J-S, Chen F (2003) Seasonal variations of bromophenols in brown algae (*Padina arborescens*, *Sargassum siliquastrum*, and *Lobophora variegata*) collected in Hong Kong. *J Agric Food Chem* 51:2619-24
- Da Gama BA, Carvalho AG, Weidner K, Soares AR, Coutinho R, Fleury BG, Teixeira VL, Pereira RC (2008) Antifouling activity of natural products from Brazilian seaweeds. *Bot Mar* 51:191-201
- Dawczynski C, Schubert R, Jahreis G (2007) Amino acids, fatty acids, and dietary fibre in edible seaweed products. *Food Chem* 103:891-99

507 de Alencar DB, Pires-Cavalcante KMS, de Sousa MB, Viana FA, Saker-Sampaio S
 508 (2011) Biogenic amines in marine macroalgae of the state of Ceará, Brazil.
 509 Rev Ciênc Agron 42:349
 510 De Lara-Isassi G, Alvarez-Hernandez S, Collado-Vides L (2000) Ichthyotoxic activity
 511 of extracts from Mexican marine macroalgae. J Appl Phycol 12:45-52
 512 De Lara-Isassi G, Alvarez-Hernández S, Quintana-Pimentel A (2004) Screening for
 513 anticoagulant substances in some marine macroalgae. Detección de
 514 sustancias anticoagulantes en algunas macroalgas marinas. Hidrobiológica
 515 14:47-54
 516 De Ruyter van Steveninck E, Breeman A (1987) Deep water populations of
 517 *Lobophora variegata* (Phaeophyceae) on the coral reef of Curaçao: influence
 518 of grazing and dispersal on distribution patterns. Mar Ecol Prog Ser 38:241-
 519 50
 520 Diaz-Pulido G, Harii S, McCook L, Hoegh-Guldberg O (2010) The impact of benthic
 521 algae on the settlement of a reef-building coral. Coral Reefs 29:203-08
 522 Diaz-Pulido G, McCook LJ, Dove S, Berkelmans R, Roff G, Kline DI, Weeks S,
 523 Evans RD, Williamson DH, Hoegh-Guldberg O (2009) Doom and boom on a
 524 resilient reef: climate change, algal overgrowth and coral recovery. PLoS One
 525 4:e5239
 526 Egan S, Harder T, Burke C, Steinberg P, Kjelleberg S, Thomas T (2013) The
 527 seaweed holobiont: understanding seaweed–bacteria interactions. FEMS
 528 Microbiol Rev 37:462-76
 529 Engel S, Puglisi MP, Jensen PR, Fenical W (2006) Antimicrobial activities of extracts
 530 from tropical Atlantic marine plants against marine pathogens and
 531 saprophytes. Mar Biol 149:991-1002
 532 Freile-Pelegrin Y, Robledo D, Chan-Bacab M, Ortega-Morales B (2008)
 533 Antileishmanial properties of tropical marine algae extracts. Fitoterapia
 534 79:374-77
 535 Fricke A, Titlyanova T, Nugues M, Bischof K (2011) Depth-related variation in
 536 epiphytic communities growing on the brown alga *Lobophora variegata* in a
 537 Caribbean coral reef. Coral Reefs 30:967-73
 538 Gerwick W, Fenical W (1982) Phenolic lipids from related marine algae of the order
 539 Dictyotales. Phytochemistry 21:633-37
 540 Goldschmidt BM (1984) Role of aldehydes in carcinogenesis. J Environ Sci Health C
 541 2:231-49
 542 Gosch BJ, Magnusson M, Paul NA, Nys R (2012) Total lipid and fatty acid
 543 composition of seaweeds for the selection of species for oil- based biofuel
 544 and bioproducts. Gcb Bioenergy 4:919-30
 545 Guiry M, Guiry G (2015) AlgaeBase. World-wide electronic publication, National
 546 University of Ireland, Galway.
 547 Gutiérrez-Cepeda A, Fernández JJ, Norte M, Montalvão S, Tammela P, Souto ML
 548 (2015) Acetate-derived metabolites from the brown alga *Lobophora variegata*.
 549 J Nat Prod 78:1716-22
 550 Hay M, Steinberg P (1992) The chemical ecology of plant-herbivore interactions in
 551 marine versus terrestrial communities. In: Gerald A R May R B Eds.
 552 Herbivores: their interactions with secondary plant metabolites.
 553 Hegazi MM (2002) Separation, identification and quantification of photosynthetic
 554 pigments from three red sea seaweeds using reversed-phase high-
 555 performance liquid chromatography. Egypt J Bio 4:1-6
 556 Holdt SL, Kraan S (2011) Bioactive compounds in seaweed: functional food
 557 applications and legislation. J Appl Phycol 23:543-97
 558 Ibañez E, Cifuentes A (2013) Benefits of using algae as natural sources of functional
 559 ingredients. J Sci Food Agric 93:703-09
 560 Ito K, Hori K (1989) Seaweed: chemical composition and potential food uses. Food
 561 Rev Int 5:101-44

562 Jiang Q, Christen S, Shigenaga MK, Ames BN (2001) γ -Tocopherol, the major form
563 of vitamin E in the US diet, deserves more attention. *Am J Clin Nutr* 74:714-
564 22

565 Kabara JJ, Swieczkowski DM, Conley AJ, Truant JP (1972) Fatty acids and
566 derivatives as antimicrobial agents. *Antimicrob Agents Chemother* 2:23-28

567 Kashiwagi M, Mynderse J, Moore R, Norton T (1980) Antineoplastic evaluation of
568 Pacific basin marine algae. *J Pharm Sci* 69:735-38

569 Kim S-K, Pangestuti R (2011) Biological activities and potential health benefits of
570 fucoxanthin derived from marine brown algae. *Adv Food Nutr Res* 64:111

571 Kremb S, Helfer M, Kraus B, Wolff H, Wild C, Schneider M, Voolstra CR, Brack-
572 Werner R (2014) Aqueous extracts of the marine brown alga *Lobophora*
573 *variegata* inhibit HIV-1 infection at the level of virus entry into cells. *PLoS One*
574 9:e103895

575 Kubanek J, Jensen PR, Keifer PA, Sullards MC, Collins DO, Fenical W (2003)
576 Seaweed resistance to microbial attack: a targeted chemical defense against
577 marine fungi. *Proc Natl Acad Sci U S A* 100:6916-21

578 Kuffner IB, Walters LJ, Becerro MA, Paul VJ, Ritson-Williams R, Beach KS (2006)
579 Inhibition of coral recruitment by macroalgae and cyanobacteria. *Mar Ecol*
580 *Prog Ser* 323:107-17

581 Leikauf GD (1992) Formaldehyde and other aldehydes. *Environmental toxicants:*
582 *human exposures and their health effects*, Third Edition:257-316

583 León-Deniz LV, Dumonteil E, Moo-Puc R, Freile-Pelegrin Y (2009) Antitrypanosomal
584 in vitro activity of tropical marine algae extracts. *Pharm Biol* 47:864-71

585 Lima Ainouz I, Holanda Sampaio A, Barros Benevides N, Ponte Freitas A, Costa F,
586 Carvalho M, Pinheiro-Joventino F (1992) Agglutination of enzyme treated
587 erythrocytes by Brazilian marine algal extracts. *Bot Mar* 35:475-80

588 Liu M, Hansen PE, Lin X (2011) Bromophenols in marine algae and their
589 bioactivities. *Mar Drugs* 9:1273-92

590 Longo G, Hay M (2014) Does seaweed–coral competition make seaweeds more
591 palatable? *Coral Reefs*:1-10

592 Manilal A, Selvin J, Thajuddin N, Sujith S, Panikkar M, Idhayadhulla A, Kumar RS
593 (2012) Biopotentials of marine alga, *Lobophora variegata* collected from the
594 south Indian littoral. *Thalassas* 28:47-54

595 Manilal A, Sujith S, Sabarathnam B, Kiran GS, Selvin J, Shakir C, Lipton AP (2010a)
596 Antifouling potentials of seaweeds collected from the southwest coast of
597 India. *World J Agric Sci* 6:243-48

598 Manilal A, Sujith S, Selvin J, Seghal Kiran G, Shakir C, Premnath Lipton A (2010b)
599 Antimicrobial potential of marine organisms collected from the southwest
600 coast of India against multiresistant human and shrimp pathogens. *Sci Mar*
601 (Barc) 74:287-96

602 Maschek JA, Baker BJ (2008) The chemistry of algal secondary metabolism. In:
603 Amsler C D (Ed.) *Algal chemical ecology*. Springer Berlin Heidelberg,

604 Medeiros V, Queiroz K, Cardoso M, Monteiro G, Oliveira F, Chavante S, Guimaraes
605 L, Rocha H, Leite E (2008) Sulfated galactofucan from *Lobophora variegata*:
606 anticoagulant and anti-inflammatory properties. *Biochemistry (Moscow)*
607 73:1018-24

608 Miyake T, Shibamoto T (1995) Quantitative analysis by gas chromatography of
609 volatile carbonyl compounds in cigarette smoke. *J Chromatogr* 693:376-81

610 Moo-Puc R, Robledo D, Freile-Pelegrin Y (2008) Evaluation of selected tropical
611 seaweeds for *in vitro* anti-trichomonal activity. *J Ethnopharmacol* 120:92-97

612 Moo-Puc R, Robledo D, Freile-Pelegrin Y (2009) In vitro cytotoxic and
613 antiproliferative activities of marine macroalgae from Yucatán, Mexico
614 Actividad citotóxica y antiproliferativa in vitro de macroalgas marinas de
615 Yucatán, México. *Cienc Mar* 35:345-58

616 Morrow K, Paul V, Liles M, Chadwick N (2011) Allelochemicals produced by
617 Caribbean macroalgae and cyanobacteria have species-specific effects on
618 reef coral microorganisms. *Coral Reefs* 30:309-20

619 Morrow KM, Ritson-Williams R, Ross C, Liles MR, Paul VJ (2012) Macroalgal
620 extracts induce bacterial assemblage shifts and sublethal tissue stress in
621 Caribbean corals. *PLoS One* 7:e44859

622 Morse AN, Iwao K, Baba M, Shimoike K, Hayashibara T, Omori M (1996) An ancient
623 chemosensory mechanism brings new life to coral reefs. *Biol J Bull* 191:149-
624 54

625 Mota da Silva V, Da Cunha Veloso MC, Teixeira Sousa E, Vieira Santos G, Accioly
626 MC, Afonso De Pereira P, De Andrade JB (2006) Determination of 11 low-
627 molecular-weight carbonyl compounds in marine algae by high-performance
628 liquid chromatography. *J Chromatogr Sci* 44:233-38

629 Paiva AAdO, Castro AJ, Nascimento MS, Will LSE, Santos ND, Araújo RM, Xavier
630 CA, Rocha FA, Leite EL (2011) Antioxidant and anti-inflammatory effect of
631 polysaccharides from *Lobophora variegata* on zymosan-induced arthritis in
632 rats. *Int Immunopharmacol* 11:1241-50

633 Paul VJ, Puglisi MP, Ritson-Williams R (2006) Marine chemical ecology. *Nat Prod*
634 *Rep* 23:153-80

635 Paul VJ, Ritson-Williams R (2008) Marine chemical ecology. *Nat Prod Rep* 25:662-
636 95

637 Plaza M, Cifuentes A, Ibáñez E (2008) In the search of new functional food
638 ingredients from algae. *Trends Food Sci Technol* 19:31-39

639 Queiroz K, Assis C, Medeiros V, Rocha H, Aoyama H, Ferreira C, Leite E (2006)
640 Cytotoxicity effect of algal polysaccharides on HL60 cells. *Biochemistry*
641 (Moscow) 71:1312-15

642 Queiroz K, Medeiros V, Queiroz L, Abreu L, Rocha H, Ferreira C, Juca M, Aoyama
643 H, Leite E (2008) Inhibition of reverse transcriptase activity of HIV by
644 polysaccharides of brown algae. *Biomed Pharmacother* 62:303-07

645 Rao CK, Untawale A (1991) Polyphenols content of Indian seaweeds. *Mahasagar*
646 24:99-102

647 Rasher DB, Hay ME (2010a) Chemically rich seaweeds poison corals when not
648 controlled by herbivores. *Proc Natl Acad Sci U S A* 107:9683-88

649 Rasher DB, Hay ME (2010b) Seaweed allelopathy degrades the resilience and
650 function of coral reefs. *Commun Integr Biol* 3:564-66

651 Rigotti A (2007) Absorption, transport, and tissue delivery of vitamin E. *Mol Aspects*
652 *Med* 28:423-36

653 Rocha FD, Soares AR, Houghton PJ, Pereira RC, Kaplan MAC, Teixeira VL (2007)
654 Potential cytotoxic activity of some Brazilian seaweeds on human melanoma
655 cells. *Phytother Res* 21:170-75

656 Sathyaseelan T, Murugesan S, Sivamurugan V (2015) Structural identification and
657 antioxidant properties of methanolic extract of brown algae *Lobophora*
658 *variegata* (JVF Lamouroux) Womersley ex EC Oliveira. *Int J Innov Pharma*
659 *Biosci Res Technol* 2:165-78

660 Siqueira RC, da Silva MS, de Alencar DB, Pires AdF, de Alencar NM, Pereira MG,
661 Cavada BS, Sampaio AH, Farias WR, Assreuy AMS (2011) In vivo anti-
662 inflammatory effect of a sulfated polysaccharide isolated from the marine
663 brown algae *Lobophora variegata*. *Pharm Biol* 49:167-74

664 Sivakumar S (2014) In vitro activity of seaweed extracts collected from Gulf of
665 Mannar coast islands Tamilnadu on clinical isolates. *Int J Pharm Biol Arch* 5

666 Slaterry M, Lesser MP (2014) Allelopathy in the tropical alga *Lobophora variegata*
667 (Phaeophyceae): mechanistic basis for a phase shift on mesophotic coral
668 reefs? *J Phycol* 50:493-505

669 Soares AR, Robaina M, Mendes GS, Silva TS, Gestinari L, Pamplona OS,
670 Yoneshigue-Valentin Y, Kaiser CR, Romanos MTV (2012) Antiviral activity of

671 extracts from Brazilian seaweeds against herpes simplex virus. Rev Bras
 672 Farmacogn 22:714-23
 673 Sousa MBd, Pires KMdS, Alencar DBd, Sampaio AH, Saker-Sampaio S (2008) α -
 674 and β -carotene, and α -tocopherol in fresh seaweeds. Food Sci Technol
 675 (Campinas) 28:953-58
 676 Stern JL, Hagerman AE, Steinberg PD, Mason PK (1996) Phlorotannin-protein
 677 interactions. J Chem Ecol 22:1877-99
 678 Sun Z, Hanyuda T, Lim P-E, Tanaka J, Gurgel CFD, Kawai H (2012) Taxonomic
 679 revision of the genus *Lobophora* (Dictyotales, Phaeophyceae) based on
 680 morphological evidence and analyses *rbcL* and *cox3* gene sequences.
 681 Phycologia 51:500-12
 682 Targett NM, Arnold TM (1998) Minireview—predicting the effects of brown algal
 683 phlorotannins on marine herbivores in tropical and temperate oceans. J
 684 Phycol 34:195-205
 685 Thennarasan S (2015) Biochemical composition of marine brown alga *Lobophora*
 686 *variegata* from Mandapam in the South East Coast of Tamil Nadu. Int J
 687 Pharm Pharm Sci 5:25-29
 688 Thrasher JD, Kilburn KH (2001) Embryo toxicity and teratogenicity of formaldehyde.
 689 Arch Environ Health: Int J 56:300-11
 690 Val A, Platas G, Basilio A, Cabello A, Gorrochategui J, Suay I, Vicente F, Portillo E,
 691 Río M, Reina G (2001) Screening of antimicrobial activities in red, green and
 692 brown macroalgae from Gran Canaria (Canary Islands, Spain). Int Microbiol
 693 4:35-40
 694 Vallim MA, De Paula JC, Pereira RC, Teixeira VL (2005) The diterpenes from
 695 Dictyotacean marine brown algae in the Tropical Atlantic American region.
 696 Biochem Syst Ecol 33:1-16
 697 Vieira C (2015) *Lobophora* biotic interactions and diversification. Ph. D. Doctoral
 698 dissertation, Ph. D. thesis, Université Pierre et Marie Curie, France.
 699 Vieira C, D'hondt S, De Clerck O, Payri CE (2014) Toward an inordinate fondness for
 700 stars, beetles and *Lobophora*? Species diversity of the genus *Lobophora*
 701 (Dictyotales, Phaeophyceae) in New Caledonia. J Phycol 50:1101-19
 702 Vieira C, Payri C, De Clerck O (2015) Overgrowth and killing of corals by the brown
 703 alga *Lobophora hederacea* (Dictyotales, Phaeophyceae) on healthy reefs in
 704 New Caledonia: a new case of the epizooism syndrome. Phycol Res 63:152-
 705 53
 706 Vieira C, Thomas OP, Culioli G, Houlbreque F, De Clerck O, Payri C (in revision)
 707 Allelopathic interactions between the brown algal genus *Lobophora*
 708 (Dictyotales, Phaeophyceae) and scleractinian corals. Scientific Reports
 709 Wang H, Chiu L, Ooi VE, Ang PO (2008a) Seaweed polysaccharides with anticancer
 710 potential. Bot Mar 51:313-19
 711 Wang H, Ooi EV, Ang Jr PO (2008b) Antiviral activities of extracts from Hong Kong
 712 seaweeds. J Zhejiang Univ-SCI A 9:969-76
 713 Weidner K, Lages BG, da Gama BA, Molis M, Wahl M, Pereira RC (2004) Effects of
 714 mesograzers and nutrient levels on the induction of defenses in several
 715 Brazilian macroalgae. Mar Ecol Prog Ser:113-25
 716 Zaneveld JS (1959) The utilization of marine algae in tropical South and East Asia.
 717 Econ Bot 13:89-131
 718 Zubia M, Robledo D, Freile-Pelegrin Y (2007) Antioxidant activities in tropical marine
 719 macroalgae from the Yucatan Peninsula, Mexico. J Appl Phycol 19:449-58
 720

Fig. 1 Chemical structure of the natural products isolated from different species of *Lobophora* (Cantillo-Ciau et al. 2010; Chung et al. 2003; Gerwick and Fenical 1982; Gutiérrez-Cepeda et al. 2015; Kubanek et al. 2003; Vieira et al. in revision).