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

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

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 C_{21} 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

Abbreviations

ACVr	Acyclovir-resistant
EC_{50}	Half maximal Effective concentration
HCT-116	Human colon tumor
HEp-2	Human epithelial type 2
HIV	Human immunodeficiency virus
HL-60	Human promyelocytic leukemia cell line
HSV-1/2	Herpes simplex virus type 1 or 2
HT-29	Human colorectal adenocarcinoma cell line
IC_{50}	Half maximal inhibitory concentration
LC_{50}	Median lethal concentration
LD_{50}	Median lethal dose
MCF-7	Human breast carcinoma cell line
MDCK	Madin-Darby canine kidney
MIC_{90}	Minimal inhibitory concentration to inhibit the growth of 90% of organisms
MZI	Mean zone of inhibition
RSV	Respiratory syncytial virus
SQDG	Sulfoquinovosyl diacylglycerol

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 IC_{50} 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 subtilus* (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 (MIC_{90}) 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 (EC_{50} 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 (EC_{50} 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 IC_{50} 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 IC_{50} of 1.39 µg ml-1 (Moo-Puc et al. 2008), an IC_{50} 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 LC_{50} 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 IC_{50} 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 IC_{50} of 3.9 µg ml-1, and a moderate activity against *T. vaginalis*

trophozoites with an IC_{50} of 8 μg 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 μg 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 μg ml-1) on the human colon tumor cell line HCT-116 (Kubanek et al. 2003), and sulfated polyscaccharides 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, nematicidal 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 ± 2.9% larval mortality at 500 ppm concentration; Bianco et al. 2013), and pupicidal potential against the urban mosquito *Culex quinquefasciatus* with a LD_{50} value of 683 µg ml-1 (Manilal et al. 2012). *Lobophora* methanolic extract presented a nematicidal activity against the plant-pathogenic nematode *Meloidogyne javanica* with a LD_{50} 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 an 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 ± 1.559 µg g-1 fresh weight of β-carotene, 0.697 ± 0.260 µg g-1 of retinol
300 equivalent and 4.722 ± 2.062 µg 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', c_1 and c_2, 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 c_1 and chlorophyll c_2 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 c_1 and c_2 (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 ± 0.05% of total content) and total carbohydrate
321 (19.34 ± 0.10%), and a low content of total lipid (0.27 ± 0.5%). While *Lobophora* has
322 a high fatty acid to total lipid ratio (58%), it has a low total lipid content (<50 mg g-1
323 dry weight) in comparison with other Dictyotales species (*Dictyota bartayresii*,
324 *Dictyota dichotoma*, and *Spatoglossum macrodontum*; total lipid content >100 mg g-1
325 dry weight) (Gosch et al. 2012). *Lobophora* is also rich in vitamins (especially
326 vitamin C, 23.430 ± 0.152 mg 100g-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 C_{21} 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

389 *Lobophora* has contrasting effects on coral larval recruitment. Birrell et al. (2008)
390 showed that *Lobophora* is able to enhance larvae settlement of *Acropora millepora* by
391 40%. On the contrary, Kuffner et al. (2006) showed that *Lobophora* causes either
392 recruitment inhibition or avoidance behavior in *P. astreoides* larvae. Diaz-Pulido et al.
393 (2010) also showed that *Lobophora* presented either no effect on 2-days-old larvae or
394 inhibitory effects on settlement of coral larvae. Similarly, Baird Morse (2004) showed
395 that *Lobophora* inhibited metamorphosis in coral larvae. Morse et al. (1996) found
396 that larvae of several Acroporids species did not settle in assays that included
397 *Lobophora* plants. Nevertheless, no compound, either acting as enhancers or
398 inhibitors, has already been identified.

399 Deterrence function

400 *Lobophora* has been the subject of contradictory observations in terms of
401 susceptibility to herbivory. For example, while De Lara-Isassi et al. (2000) showed
402 ichthyotoxicity (from ethanol and acetone extracts) against the goldfish *Carassius*
403 *auratus*, Slattery Lesser (2014) concluded that *Lobophora* chemical defenses
404 (*Lobophora* crude extract and a purified SQDG) were inactive against the omnivorous
405 pufferfish (*Canthigaster rostrata*). The experiment of De Lara-Isassi et al. (2000),
406 which aimed at testing the ichthyotoxicity of phlorotannins, is nonetheless
407 ecologically poorly relevant since the goldfish is a freshwater fish. *Lobophora* feeding
408 deterrence potential was suggested based on the presence of phlorotannins and
409 terpenes (Targett and Arnold 1998; Amsler and Fairhead 2005), which may cause the
410 precipitation of proteins (Stern et al. 1996). Stern et al. (1996) isolated phlorotannins
411 from *Lobophora* and suggested several explanations for why the biological activity of
412 phlorotannins may vary as a function of the gut environment of marine herbivores. In
413 addition, Bolser Hay (1996) concluded that the greater consumption of temperate
414 (North Carolina) versus tropical (the Bahamas) *Lobophora* by the sea urchin *Arbacia*
415 *punctulata* was likely due to the higher concentrations of secondary metabolites such
416 as pholorotannins in *Lobophora* from the temperate regions than in tropical regions.
417 Weidner et al. (2004) showed that while *Lobophora* exhibited inducible defenses
418 following direct consumption by amphipods, the repulsive effects of the non-polar
419 extracts were overridden by counteracting effects of non-extracted chemicals, making
420 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 C_{21} 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	*L. variegata*	*Enterococcus faecalis, Escherichia coli, Staphylococcus aureus*	Lobophorols A-C, lobophopyranones A and B, lobophorones A-E	-	Gutiérrez-Cepeda et al. (2015)
Antibacterial	*L. variegata*	*Escherichia coli, Salmonella typhi, Klebsiella pneumonia, Vibrio cholera*	-	$CHCl_3$/MeOH	Sivakumar (2014)
Antibacterial	*L. variegata*	*Bacillus cereus, Micrococcus luteus, Salmonella typhimurium, Aeromonas hydrophila, Escherichia coli*	Mixture of fatty acids	MeOH	Manilal et al. (2012)
Antibacterial	*L. variegata*	Marine bacteria isolated from Caribbean macroalgae and corals	-	EtOAc/MeOH and then MeOH/H_2O	Morrow et al. (2011)
Antibacterial	*L. variegata*	Biofilm-forming bacteria	-	MeOH	Manilal et al. (2010a)
Antibacterial	*L. variegata*	*Vibrio parahaemolyticus, Vibrio vulnificus, Vibrio harveyi, Vibrio alcaligenes, Vibrio alginolyticus, Staphylococcus aureus, Pseudomonas aeruginosa, Bacillus subtilis, Klebsiella pneumoniae, Staphylococcus epidermidis*	-	MeOH	Manilal et al. (2010b)
Antibacterial	*L. variegata*	*Pseudoalteromonas bacteriolytica*	-	CH_2Cl_2/MeOH [divided into lipophilic (EtOAc) and hydrophilic (H_2O) parts]	Engel et al. (2006)
Antibacterial	*L. variegata*	*Bacillus subtilis, Enterococcus faecium, Mycobacterium smegmatis, Pseudomonas aeruginosa, Serratia marcescens, Staphylococcus aureus*	-	MeOH	Val et al. (2001)
Antibacterial	*L. variegata*	*Bacillus subtilis, Pseudomonas aeruginosa, Escherichia coli, Staphylococcus aureus, Candida albicans*	-	$CHCl_3$/MeOH	Ballantine et al. (1987)
Antibacterial	*L. papenfussii*	*Staphylococcus aureus, Bacillus subtilis, Escherichia coli, Enterobacter aerogenes, Pseudomonas aeruginosa, Candida albicans, Vibrio anguillarum*	2-(1'-Oxohexadecyl)-1,3,5-trihydroxybenzene	-	Gerwick Fenical (1982)
Antiviral	*L. variegata*	HIV	-	H_2O	Kremb et al. (2014)
Antiviral	*L. variegata*	HSV-1	-	CH_2Cl_2/MeOH	Soares et al. (2012)
Antiviral	*L. variegata*	HIV	Polysaccharide (galactofucan)		Queiroz et al. (2008)

Antiviral	*L. variegata*	Herpes simplex virus type 1 and 2 (HSV-1 and -2), respiratory syncytial virus (RSV)		H_2O	Wang et al. (2008b)
Antifungal	*L. variegata*	*Dendryphiella salina*, *Halophytophthora spinosa*	-	CH_2Cl_2/MeOH [divided into lipophilic (EtOAc) and hydrophilic (H_2O) parts]	Engel et al. (2006)
Antifungal	*L. variegata*	*Dendryphiella salina, Lindra thalassiae, Candida albicans*	Lobophorolide	-	Kubanek et al. (2003)
Antifungal	*L. variegata*	*Aspergillus fumigatus, Candida albicans, Saccharomyces cerevisiae*	-	MeOH	Val et al. (2001)
Antiprotozoal	*L. variegata*	*Trichomonas vaginalis, Entamoeba histolytica, Giardia intestinalis*	Mixture of sulfoquinovosyl-diacylglycerols (SQDGs)	CH_2Cl_2/MeOH	Cantillo-Ciau et al. (2010)
Antiprotozoal	*L. variegata*	*Trypanosoma cruzi*	-	CH_2Cl_2/MeOH	León-Deniz et al. (2009)
Antiprotozoal	*L. variegata*	*Trichomonas vaginalis*	-	CH_2Cl_2/MeOH	Moo-Puc et al. (2008)
Antiprotozoal	*L. variegata*	*Leishmania mexicana*	-	CH_2Cl_2/MeOH	Freile-Pelegrin et al. (2008)
Antiprotozoal	*L. variegata*	*Schizochytrium aggregatum*	-	CH_2Cl_2/MeOH [divided into lipophilic (EtOAc) and hydrophilic (H_2O) parts]	Engel et al. (2006)
Other pharmacological activities					
Anti-angiogenic	*L. variegata*	Embryonated chicken eggs	Sulfated polysaccharides (fucans)	-	Castro et al. (2014a)
Anticoagulant	*L. variegata*	Human plasma	Sulfated polysaccharides (fucans)	-	Castro et al. (2014b)
Anticoagulant	*L. variegata*	Human plasma	Sulfated polysaccharide (fucoidan)	-	Medeiros et al. (2008)
Anticoagulant	*L. variegata*	Human plasma	-	H_2O (Phosphate buffer)	De Lara-Isassi et al. (2004)
Anti-inflammatory	*L. variegata*	Male Swiss-Webster mice	Sulfated polysaccharides (fucans)	-	Castro et al. (2014b)
Anti-inflammatory	*L. variegata*	Wistar rats	Sulfated polysaccharides (fucans)	-	Paiva et al. (2011)
Anti-inflammatory	*L. variegata*	Wistar rats	Sulfated polysaccharide (fucan)	-	Siqueira et al. (2011)
Anti-inflammatory	*L. variegata*	Wistar rats	Sulfated polysaccharide (fucoidan)	-	Medeiros et al. (2008)
Antioxidant	*L. variegata*	Chemical test	3-(2-methoxy-4-((2,5,6,8a-tetramethyl-1,4,8,8a-tetrahydronaphthalen-1-yl)methyl)phenyl)propanoate	H_2O/MeOH	Sathyaseelan et al. (2015)
Antioxidant	*L. variegata*	Wistar rats	-	-	Paiva et al. (2011)
Antioxidant	*L. variegata*	Chemical test	-	CH_2Cl_2/MeOH	Zubia et al. (2007)

Antioxidant	*L. variegata*	Chemical test	Sulfated polysaccharides (fucans)	-	Castro et al. (2014b)
Cytotoxic	*L. variegata*	Human nasopharyngeal carcinoma (KB) cell line	-	CH_2Cl_2/MeOH	Moo-Puc et al. (2009)
Cytotoxic	*L. variegata*	C32 human melanoma cells	-	Acetone and H_2O	Rocha et al. (2007)
Cytotoxic	*L. variegata*	Human promyelocytic leukemia HL-60 cells	Polysaccharides (a glucan and three galactofucans)	-	Queiroz et al. (2006)
Cytotoxic	*L. variegata*	Human colon tumor cell line HCT-116	Lobophorolide	-	Kubanek et al. (2003)
Cytotoxic	*L. variegata*	Murine P-388 lymphocytic leukemia, Ehrlich ascites tumor cells	-	*n*-Hexane, $CHCl_3$ and then ButOH	Kashiwagi et al. (1980)
Cytotoxic	*L. variegata*	Vero, HEp-2 and MDCK cells	-	H_2O	Wang et al. (2008a)
Cytotoxic	*L. variegata*	Human breast carcinoma MCF-7 cells	-	H_2O	Wang et al. (2008a)
Cytotoxic	*L. variegata*	Human colon tumor cell line HT-29	Sulfated polysaccharides (fucans)	-	Castro et al. (2014b)
Hemagglutinating	*L. variegata*	Chicken, goat, pig, rabbit and human erythrocytes	-	H_2O (NaCl)	Lima Ainouz et al. (1992)
Pesticidal activities					
Pupicidal	*L. variegata*	*Culex quinquefasciatus*			
Nematicidal	*L. variegata*	*Meloidogyne javanica*	Fatty acids	MeOH	Manilal et al. (2012)
Phytotoxic	*L. variegata*	*Cicer arietinum, Vigna radiate* and *Cajanus cajan* seeds			
Larvicidal	*L. variegata*	*Aedes aegypti*	-	CH_2Cl_2/MeOH	Bianco et al. (2013)
Ecological roles					
Antifouling	*L. variegata*	*Perna perna*	-	CH_2Cl_2/MeOH or CH_2Cl_2	Da Gama et al. (2008)
Antifouling	*L. variegata*	*Balanus amphitrite, Mytilus edulis*	-	MeOH	Manilal et al. (2010a)
Bleaching	*L. variegata*	*Porites cylindrica*	-	MeOH [Lipophilic (EtOAc) part]	Rasher Hay (2010a)
Bleaching	*L. variegata*	*Montastrea cavernosa*	SQDG	CH_2Cl_2/MeOH	Slattery Lesser (2014)
Cell lysis	*L. variegata*	*Agelas clathrodes*	SQDG	CH_2Cl_2/MeOH	Slattery Lesser (2014)
Ichtyotoxic	*L. variegata*	-	Phlorotannins	-	Stern et al. (1996)
Ichtyotoxic	*L. variegata*	*Carassius auratus*	-	Acetone, EtOH and H_2O	De Lara-Isassi et al. (2000)
Ichtyotoxic	*L. variegata*	*Lytechinus variegatus, Diplodus holbrooki*	-	CH_2Cl_2/MeOH	Cetrulo Hay (2000)
Settlement enhancement	*L. variegata*	*Acropora millepora*	-	Seawater (waterborne extract)	Birrell et al. (2008)

Shift of coral-associated bacteria	*L. variegata*	*Montastraea faveolata, Porites astreoides*	-	EtOAc/MeOH and then EtOH/H_2O	Morrow et al. (2012)
Sublethal stress response	*L. variegata*	*Montastraea faveolata, Porites astreoides*	-	EtOAc/MeOH and then EtOH/H_2O	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	*Lobophora variegata*	Mota da Silva et al. (2006)
Butanal	*Id.*	Id.
Formaldehyde	*Id.*	Id.
Hexanal	*Id.*	Id.
Pentanal	*Id.*	Id.
Propanal	*Id.*	Id.
Propanone	*Id.*	Id.
Fatty acids		
Docosahexaenoic acid (DHA)	*Lobophora variegata*	Thennarasan (2015)
Eicosapentaenoic acid (EPA)	*Id.*	Id.
Hexadecatrienoic acid	*Id.*	Manilal et al. (2012)
Lauric acid	*Id.*	Id.
Linoleic acid	*Id.*	Thennarasan (2015)
Margaric acid	*Id.*	Id.
Myristic acid	*Id.*	Manilal et al. (2012)
Oleic acid	*Id.*	Thennarasan (2015), Manilal et al. (2012)
Palmitic acid	*Id.*	Id.
Stearic acid	*Id.*	Id.
Stearidonic (moroctic) acid	*Id.*	Thennarasan (2015)
α-Linolenic acid	*Id.*	Thennarasan (2015), Manilal et al. (2012)
Phenols		
Phenolic substances	*Lobophora variegata*	Chkhikvishvili Ramazanov (2000)
4-Bromophenol	*Lobophora* sp.	Chung et al. (2003)
2,4,6-Tribromophenol	*Id.*	Id.
2,4-Dibromophenol	*Id.*	Id.
2,6-Dibromophenol	*Id.*	Id.
Polyphenols	*Lobophora variegata*	(Rao and Untawale 1991)
Photosynthetic pigment		
9'-*Cis*-Neoxanthin	*Lobophora variegata*	(Hegazi 2002)
Antheraxanthin	*Id.*	Id.
Chlorophyll *a*	*Id.*	Id.
Chlorophyll *a'*	*Id.*	Id.
Chlorophyll c1	*Id.*	Id.
Chlorophyll c2	*Id.*	Id.
Diatoxanthin	*Id.*	Id.
Flavoxanthin	*Id.*	Id.
Fucoxanthin	*Id.*	Id.
Fucoxanthol	*Id.*	Id.
Phaeophytin *a*	*Id.*	Id.
Violaxanthin	*Id.*	Id.
Zeaxanthin	*Id.*	Id.
β-carotene	*Id.*	Sousa et al. (2008), (Hegazi 2002)
Vitamins		
Vitamin A	*Lobophora variegata*	Thennarasan (2015), Sousa *et al.* (2008)

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

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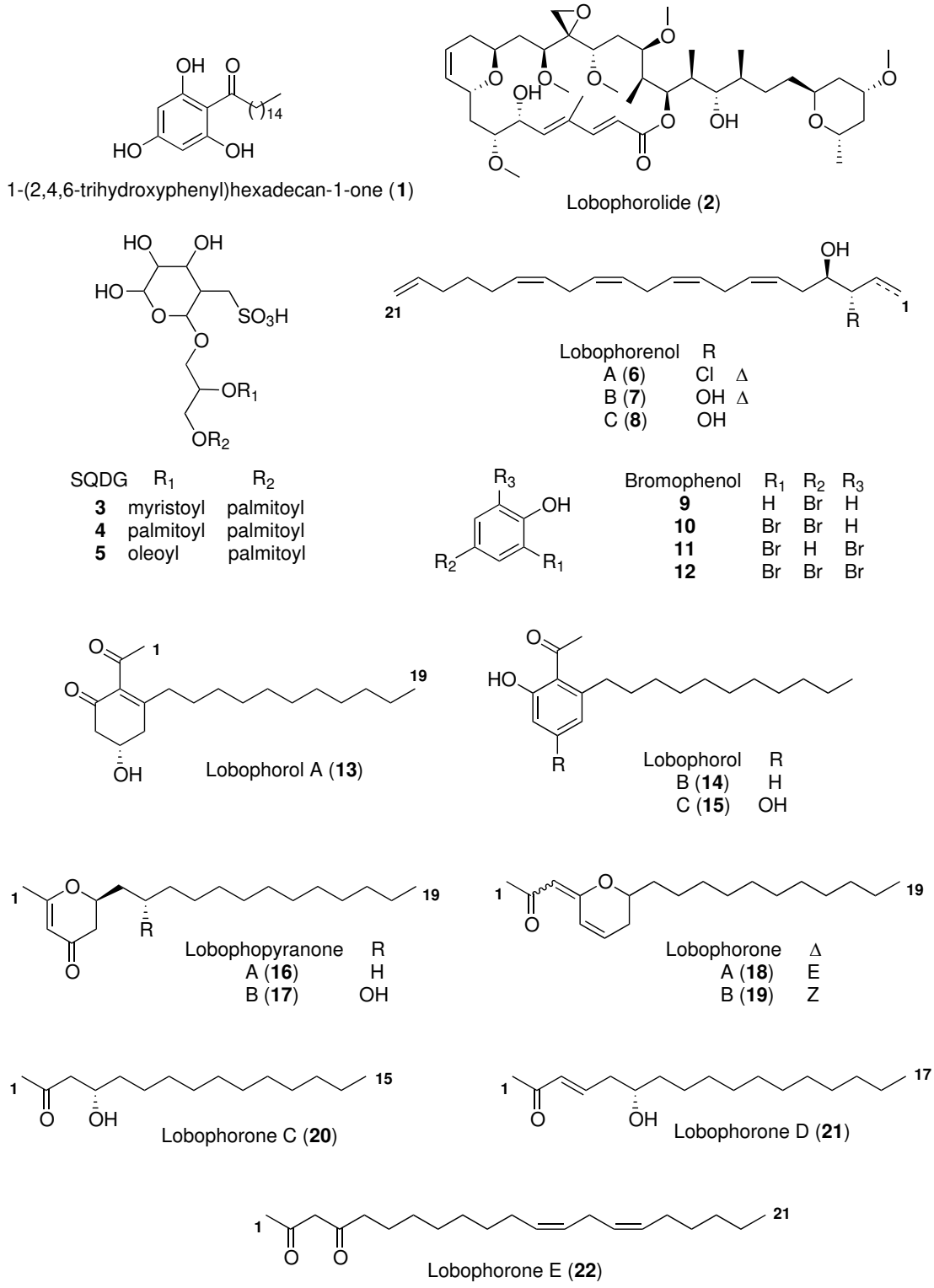

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722 **Fig. 1** Chemical structure of the natural products isolated from different species of *Lobophora*
723 (Cantillo-Ciau et al. 2010; Chung et al. 2003; Gerwick and Fenical 1982; Gutiérrez-Cepeda et al. 2015;
724 Kubanek et al. 2003; Vieira et al.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

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