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**Review Article**

# Secondary Metabolites of the Soft Coral *Lobophytum pauciflorum*

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## Abstract

Secondary metabolites, derivatives of primary metabolites, are known for their biological activities. Marine organisms, especially marine invertebrates such as sponges, tunicates, soft corals, bryozoans, and nudibranchs are important source of secondary metabolites with diverse biological properties. Approximately 40,000 marine natural products have been identified from various marine resources. Soft corals are a group of invertebrates known for their production of a vast range of metabolites with great structural diversity. Among 39 genera of soft coral Alcyonacean, a total of eighteen different species of *Lobophytum* soft corals have been identified. Isolation of secondary metabolites from the genus *Lobophytum* is tremendously explored by researchers worldwide. This review compiles several secondary metabolites that have been isolated and published on the soft coral *L. pauciflorum*, including the compound structures and some notable bioactivity.

**Keywords***: Lobophytum pauciflorum,* soft coral, secondary metabolite, biological activity

## Introduction

The ocean constitutes a rich source of biologically and genetically diverse marine organisms, as a result of harsh chemical and physical marine environments, such as cold temperature, high pressure, and dark conditions of the ocean (Nikapitiya, 2012). Secondary metabolites are metabolic products

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derived from primary metabolites. Although they are considered non-essential for the vegetative growth, secondary metabolites take up adaptive roles such as defence mechanism, signalling molecules, symbiosis, metal transport, competition, etc. Secondary metabolites have long been harvested for their beneficial properties such as antimicrobial, antitumor and growth promoter (Thirumurugan et al., 2018). Marine organisms produce a range of bioactive secondary metabolites which are found to be chemically and biologically distinct from terrestrial originated metabolites (Hassan et al., 2016). Secondary metabolites are produced by both macro and micro marine organisms as part of their defence strategies, signalling molecule with their environment and in response to the food chain (Hanif et al., 2019).

Soft corals are a vital component of the coral reef ecosystem, and are known to be a vast source of secondary metabolites exhibiting diverse biological properties (Amir et al., 2012). To date, eight natural products derived from marine organism have been approved as drugs, seven of which are still in use until now (Hanif et al., 2019). In recent years, soft corals have become a new source of novel marine bioactive compounds in drug development research (Changyun et al., 2008). The genus *Lobophytum*, compromising of more than 20 different species present in tropical and subtropical waters, is known to be a rich source of macrocyclic cembranoids and metabolites with significant biological activities, such as anti-viral, anti-inflammatory and anti-tumour properties (Yan et al., 2010, Putra et al., 2016). *Lobophytum pauciflorum* (Figure 1) is a common species in the shallow waters of the Indo-West Pacific, and is also one of the most abundant soft coral species in the coral reefs of southern Taiwan (Fan et al., 2005, Wessels et al., 2017). Similar to most soft corals, *L. pauciflorum* is gonochoric in nature, with dimorphic polyps (Wessels et al., 2017). The secondary metabolite profile of male and female *L. pauciflorum* have been found to be different, hence indicating a physiological difference between sexes (Fleury et al., 2006). Nonetheless, physiological difference at the secondary metabolite levels between the sexes is yet unclear (Zhao et al., 2013). Distinction in the expression of the immune system between sexes was identified as one of the factors which gives rise to physiological differences in bilateral animals (Wessels et al., 2017). The immune system may also govern the microbiome of the soft coral (Margulis and Fester, 1991). However, exposure of *L. pauciflorum* of both sexes to short-term environmental stress was found to have no significant effect on the microbial communities of males and females, thus indicating the resilient nature of the microbiome towards short-term environmental stress (Wessels et al., 2017). Hence, the

difference in secondary metabolites levels between male and female *L. pauciflorum* still remains unclear.


**Figure 1.** Underwater colony of *L. pauciflorum* (photo credit Kishneth Palaniveloo).

This review discusses on the secondary metabolites that have been isolated, extracted and published on the soft coral *L. pauciflorum* and structures of these compounds are presented. In addition, the biological potential of *L. pauciflorum* and the isolated secondary metabolites are also reviewed.

## Secondary Metabolites Isolated from *L. Pauciflorum*

### *Diterpenes*

Cembranoid diterpenes are fourteen carbocyclic ring structures with an isoprenoid skeleton (Rodrigues et al., 2019). Among the earliest investigations on *L. pauciflorum* was the investigation into the bioactivity of terpenes from the species from Japan. Isolation through repeated silica gel column chromatography revealed the presence of two cembranoid diterpenes of a 13-membered carbocyclic ring system, both with α-methylene-γ-lactone ring (Yamada et al., 1980a). Cembranolides containing a tricyclic system were also isolated by Japanese researchers. Similar to the previously isolated compounds, these compounds possessed the α-methylene-γ-lactone ring moiety as well, along with a trisubstituted epoxide and the common 14-membered carbocyclic ring. (Yamada et al., 1980a).

In 1983, Kinamoni et al. reported the isolation of cembranoids nephthenol (**1**) from the Red sea variety of *L. pauciflorum*. Nephthenol (**1**) was first isolated

and characterized in 1974 by Schmitz et al., from the soft coral *Nephthea* sp. collected from the Marshall Islands. The Australian variety of this soft coral species were discovered to produce the cembranes, 14-hydroxycembra-1,3,7,11-tetraene (**2**) and 15-hydroxycembra-1,3,7,11-tetraene (**3**) (Bowden et al., 1987). Later in the 1990s, an antipode, lobocalone (**4**) was reported to be isolated from *L. pauciflorum* from the Indian waters (Anjaneyulu & Rao, 1995). This compound was also isolated from the soft coral *L. caledonense* from the South China Sea by Su et al., in 1993, and from the gorgonian *Eunicea fusca* (Gopichand & Schmitz, 1978). In addition, a group of Fujisawa pharmaceutical companies in 1993 isolated four additional cembranoids (Anjaneyulu & Rao, 1995). The group also reported the isolation of six steroids from *L. pauciflorum*. Further studies on *L. pauciflorum* lead to the isolation of a 10-membered-ring diterpene, cyclolobatriene (**5**) of an Okinawan variety of the soft coral. Cyclolobatriene (**5**) was isolated together with the known compounds lobatriene (**6**), eunicol (**7**) and fuscol (**8**) (Govindam et al., 2012). Lobatriene (**6**) has been previously reported to be isolated from the soft coral *Sinularia flexibilis*, and eunicol (**7**) was previously reported from the same soft coral species and reported by Coll et al. in 1986. In this study, *L. pauciflorum* samples were extracted with methanol, and the methanol extract was gone through a silica-gel flash column chromatography, which uses 40 µm silica gel Hi-Flash column of size L (26 mm i.d. x 100 mm), and recycling HPLC with a LC-8A pump. The extracts of compounds **5-7** were colourless viscous oil, while compound **8** was in a colourless oil form. These compounds are of germacrene nature.

The secondary metabolites of the soft coral *L. pauciflorum* mainly comprise lobane-type compounds instead of cembranoid diterpenes. Previous records of lobanes being isolated from the genus *Lobophytum* has been reported by Raju et al. (1994) from the Andaman and Nicobar waters with the isolation of 15-nor-13-keto-ß-elemene (**9**), 17,18-epoxyloba-8,10,13(15)-triene-16-ol (**10**) and loba-8,10,13(15)-triene-16,17,18-triol (**11**). The lobane 15-nor-13-keto-ß-elemene (**9**) had been previously isolated from a gorgonian, *Eunicea fusca* (Raju et al., 1994) and was also reported from *L. pauciflorum* by Rao in 1990. The structures of compounds **1** – **11** are shown in Figure 2.

*L. pauciflorum* from the waters of Philippines yielded an additional four lobanes, lobatriene (**6**) that was oddly named as epoxylobatrienol, its acetate (**12**), lobatrienediol (**13**), its acetate (**14**), methoxy lobatetraene (**15**) and oxepin lobatrientriol (**16**). Interestingly, the compound lobatetraene (**15**) was reported as fuscol (**8**), a compound being isolated from the gorgonian *Eunicea fusca* and re-isolated from the soft coral *L. microlobulatum* (Bonnard et al., 2010).

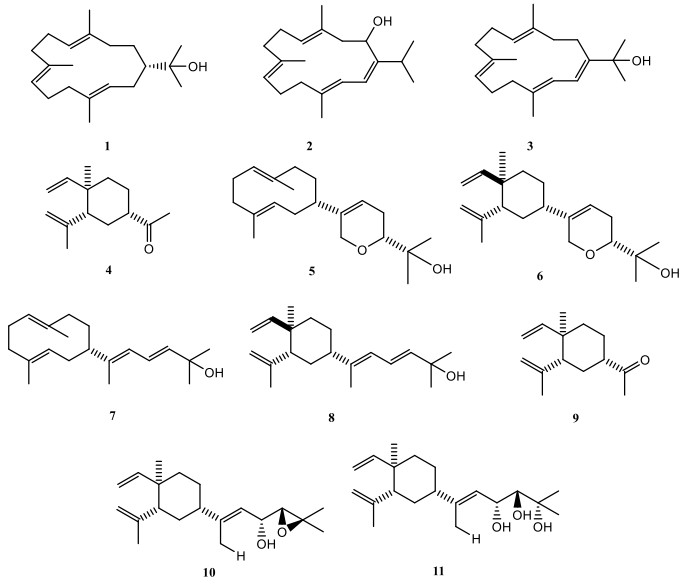


**Figure 2.** Lobane type diterpene and other derivatives isolated from *L. pauciflorum*.

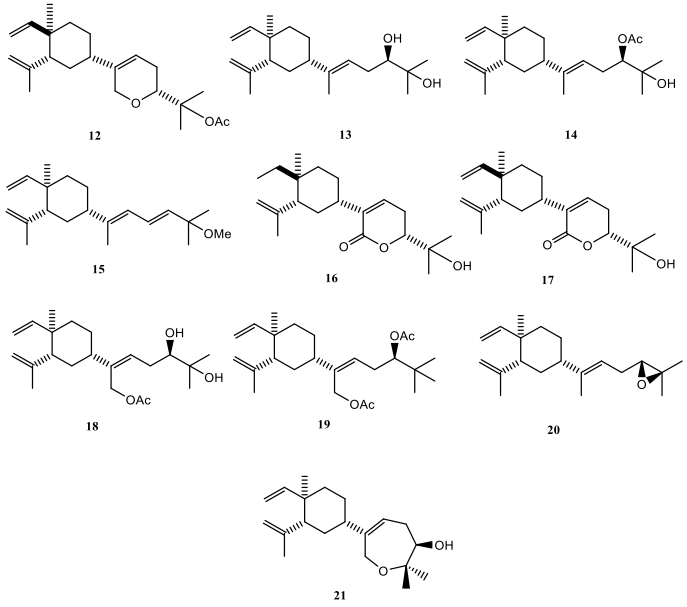


**Figure 3.** The structures of compounds **12 – 21**.

The compounds lobatrienediol (**13**), lobatrienolide (**17**), lobatrientriol monoacetate (**18**), lobatrienetriol diacetate (**19**) and lobatriene epoxide (**20**) were also isolated along with two compounds, lobatrienol (**21**) and lobatriene (**6**), previously reported from *Sinularia flexibilis*. These compounds were tested for their biological properties (Edrada et al., 2000). Structures of the isolated lobanes and other derivatives from *L. pauciflorum* are shown in Figure 3.

*Biscembranoids*

Biscembranoids are constituents consisting of two cembranes linked together, and *L. pauciflorum* is reported to be a rich source of biscembranoids. In 2010, 27 iso-biscembranoids from *L. pauciflorum* in Chinese waters were reported. Lobophytones A (**22**) - $Z_1$ (**48**) was isolated from *L. pauciflorum* by Yan et al. between 2010 and 2011. The lobophytones were reported in four separate publications (Yan et al., 2010a; 2010b; 2010c; 2011). The first report involves lobophytones A (**22**) - G (**28**) (Figure 4), followed by lobophytones H (**29**) - N (**35**) (Figure 5), lobophytones O (**36**) - T (**41**) (Figure 6) and lobophytones U (**42**) - $Z_1$ (**48**) (Figure 3 and 4). In the final report, Yan and co-workers reported additional metabolites methyl sartortuoate (**49**) and nyalolide (**50**). The biscembranoids of this soft coral was suggested to be different than the usual tetraterpenoids due to the antipodal Diels-Alder cycloaddition between cembranoid-diene and cembranoid-dienophile. Several stereoisomers were also identified among the lobophytones. Lobophytone G (**28**) was suggested to be a stereoisomer of lobophytone F (**27**) (Yan et al., 2010a) and lobophytone L (**33**) is a stereoisomer of K (**32**). Lobophytone U (**42**) was similar to lobophytones A (**22**) and B (**23**), except for the presence of hydroxy moiety at C-33. Lobophytone V (**43**) likewise was similar to lobophytone A (**22**) but contained an additional oxygen atom and a methine group.

Similarly, lobophytone W (**44**) possessed an oxymethylene attached to C-27, while lobophytone X (**45**) lacked the hydroxy group in the compound. Lobophytone Z (**47**), on the other hand is a dehydroxylated derivative of lobophytone A (**22**), while lobophytone G (**28**) is chemically related to lobophytone W (**44**) with variations in rings B and C of the biscembranoid. Lobophytone Y (**46**) is structurally similar to methyl sartortuoate (**49**), while lobophytone J (**31**) is structurally related to the biscembrane nyalolide (**50**) that was reported by Yan et al. in 2011. Chemical structures of compounds **42-50** are shown in Figure 7.

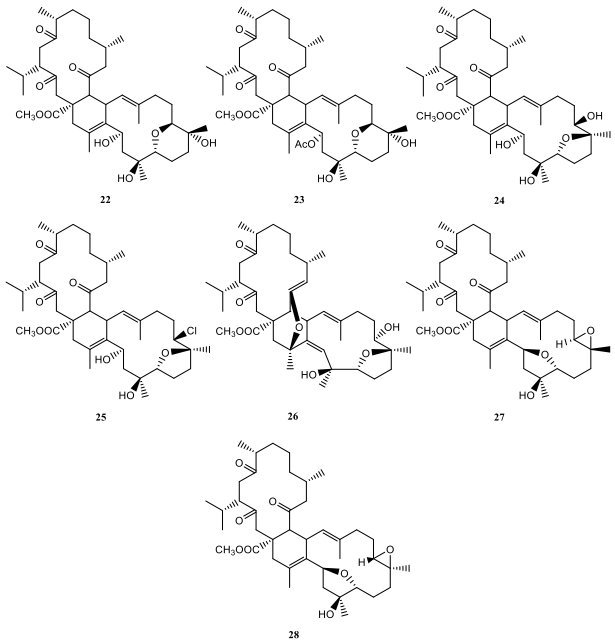


**Figure 4.** Biscembranoids lobophytones A (**22**) - G (**28**) from *L. pauciflorum*.

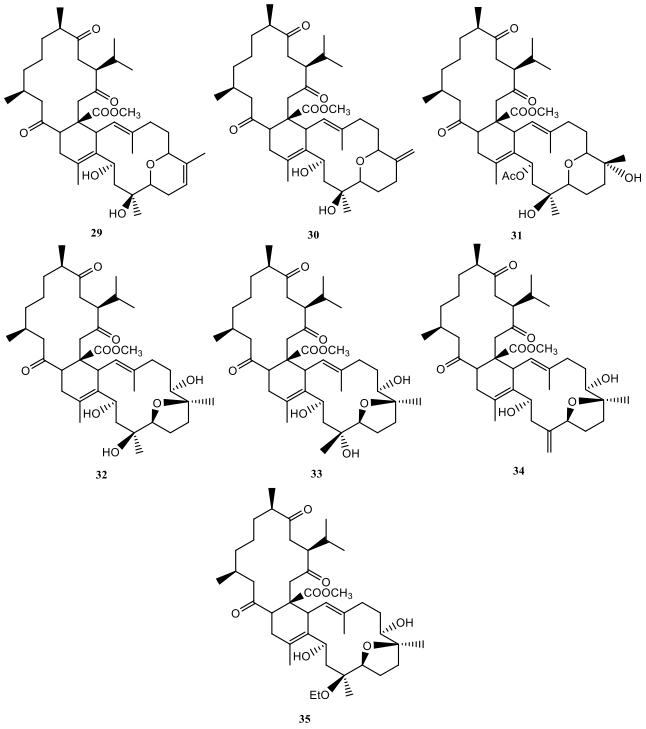


**Figure 5.** Biscembranoids lobophytones H (**29**) - N (**35**) from *L. pauciflorum*.

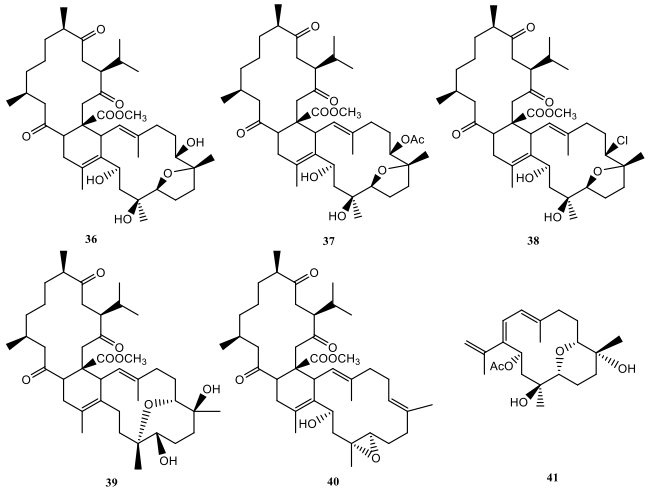


**Figure 6.** Biscembranoids lobophytones O (**36**) - T (**41**) from *L. pauciflorum*.

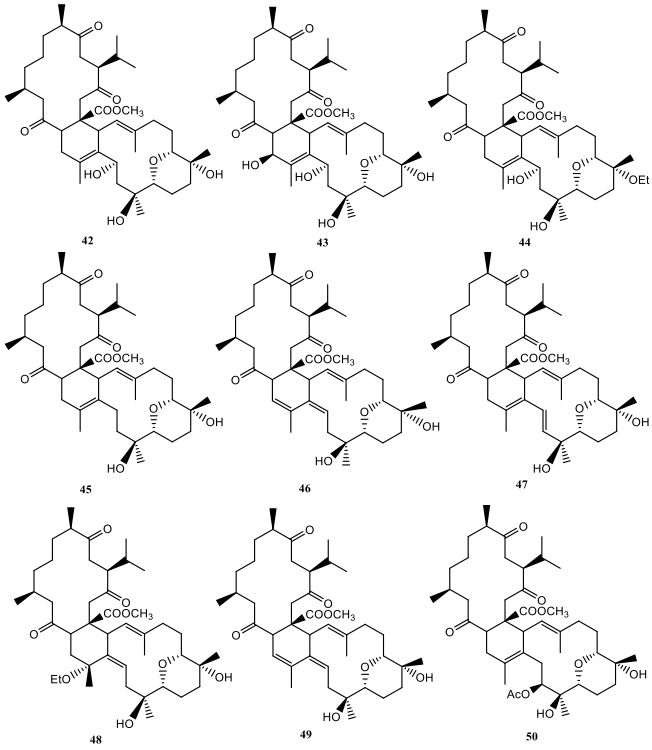


**Figure 7.** The structures of compounds (**42-50**) from *L. pauciflorum*.

*Sterol*

Steroids are structures with a cyclopentane polyhydrogen phenanthrene skeleton and three side chains. Despite being widely found in animals and plants, marine steroids are found to be more diverse in their structure compared to terrestrial phytosterols (Zhang et al., 2019). Lobosterol (**51**) was the first sterol to be isolated and reported from the soft coral *L. pauciflorum*, which contains a 3β,4β,5β-trihydroxy system (Tursch, 1976). This is followed by isolation of several polyhydroxysteroids from *L. pauciflorum* in the Okinawan waters (Yamada et al., 1980b). These polyhydroxysteroids include 24ξ-methylcholastane-3β,5α,6β,25-tetrol (**52**), 24ξ-methylcholastane-1β,3β,5α,6β-tetrol (**53**), 24-methylenecholastane-1β,3β,5α,6β-tetrol (**54**), and 24ξ-methycholestane-3β,5α,6β,25-tetrol 25-monoacetate (**55**). Compound **55** was previously isolated from *Sarcophyton elegans* (Moldowan et al., 1974).

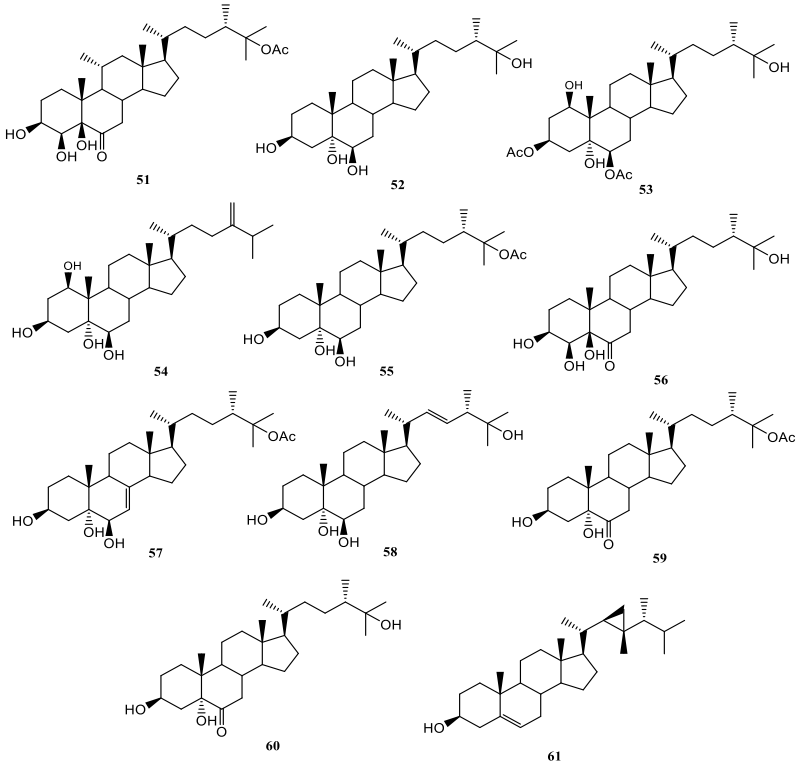


**Figure 8.** Polyhydroxysteroids (**51-61**) isolated from *L. pauciflorum*.

Reports on the isolation of sterols from *L. pauciflorum* continued with the isolation of additional five steroids from the soft coral variety of the Andaman and Nicobar Islands. These steroids, 25-deacetylobosterol (**56**), (24*S*)-24-methylcholest-7-en-3β,5α,6β,25-tetrol-25-monoacetate (**57**), (24*S*)-24-methylchoiest-22*E*-ene-3β,5α,6β,25-tetrol (**58**), (24*S*)-24-methylcholestane-3β,5α,25-triol-6-one-25-monoacetate (**59**) and its C-25 deacetoxy analogue (**60**). The steroids were isolated along wtih lobosterol (**51**) and two diterpene lobanes (Rao et al., 1990). In 2016, Hassan et al. isolated six known compounds from the marine soft coral *L. pauciflorum*. Among the identified compounds is the sterol gorgost-5-ene-3β-ol (**61**). Figure 8 represents the chemical structures of polyhydroxysteroids from *L. pauciflorum*.

## Biological Properties of *L. Pauciflorum* and Isolated Compounds

The cytotoxicity of polar and nonpolar extracts of freeze-dried *L. pauciflorum* using 50:50 ethanol-water and 50:50 ethyl acetate-methanol was investigated using brine shrimp *Artemia salina* lethality test. The polar extract of *L. pauciflorum* exhibited shrimp mortality activity of 90.7% at 1000-ppm concentration after 6 hours of exposure, and 100% mortality effect after 24-hour exposure. Moderate cytotoxicity activity of 89.1% was observed for the non-polar extract at 1000-ppm. However, it is notable that *L. pauciflorum* had the highest activity among the other three soft corals that were investigated which are *Sinularia flexibilis* (70.2%), *Sarcophyton glaucum* (69.2%), and *Lobophytum crissum* (33.3%) (Luyao et al., 2019a). Antioxidant and antimicrobial activities of polar and non-polar extracts of *L. pauciflorum* collected from the Coast of Agusan del Norte, Philippines was investigated by Luyao et al., in 2019. The total antioxidant capacity was expressed as Ascorbic Acid Equivalence (AAE) and Butylated Hydroxytoluene Equivalence (BHTE). Non-polar extract and polar of *L. pauciflorum* exhibited an AAE value of 54.58 and 53.59, respectively at 200 ppm. A BHTE value of 125.85 and 113.41 was observed for non-polar and polar extracts, respectively at 200 ppm. The DPPH radical scavenging activity (%) of non-polar and polar *L. pauciflorum* extract exhibited an activity of 1.49% and 2.88% at 500 ppm. *Lobophytum pauciflorum* displayed a minimal yet active effect towards the growth of gram-positive and gram-negative bacteria, *B. subtilis* and *E. coli*. However, no antifungal activity was observed against the tested *Aspergillus niger* and *Saccharomyces cerevisiae*.

The seven isolated compounds lobatriene (**8**), lobatrienediol (**13**), lobatrienolide (**17**), lobatrientriol monoacetate (**18**), lobatrienetriol diacetate (**19**), lobatriene epoxide (**20**) and lobatrienol (**21**) were tested for their bioactivity. Lobane was tested for its biological potential and lobatrienol (**21**) was found to possess

antibacterial and anti-fungal activities by inhibiting the gram-positive bacteria *Bacillus subtilis* and *Saccaromyces cerevisiae* as well as the phytopathogenic fungus *Candida cucumerinum* (Edrada et al., 2000). Cytotoxicity test using brine shrimp assay were also conducted. Lobatriene epoxide (**20**) displayed the highest cytotoxicity activity with $IC_{50}$ value of 0.64 µg/mL along with lobatetraene (**15**) at 4.18 µg/mL (Edrada et al., 1998). Bioassay-guided screening of *n*-hexane, dichloromethane, ethyl acetate and methanol fractions of *L. pauciflorum* for anti-inflammatory activity revealed its significant activity against cyclooxygenase enzymes COX-1 and COX-2. The hexane, dichloromethane showed significant anti-inflammatory activity against COX-1 compared to the positive control, and indomethacin had $IC_{50}$ values of 0.59, 1.37 and 1.52 mM respectively. The *n*-hexane, dichloromethane, ethyl acetate showed significant anti-inflammatory activity against COX-2 compared to positive control Celecoxib, with an $IC_{50}$ value of 0.12, 0.33, 0.61 and 0.43 mM respectively. Spectroscopic analysis isolated two active compounds which were identified to be nephthenol (**1**) and gorgost-5-ene-3β-ol (**61**) (Hassan et al., 2016).

Biscembranoids lobophytone Q (**38**) exhibited inhibition towards lipopolysaccharide (LPS) induced nitric oxide (NO) production in macrophages with $IC_{50}$ of 2.8 µM. In addition, this compound together with lobophytone T (**41**) inhibited the growth of *Staphylococcus aureus, S. pneumoniae* and *Saccaromyces cerevisiae* at a concentration of 20 µg/mL (Yan et al., 2010c). Similar to lobophytone Q (**38**), lobophytone Z (**47**) exhibited inhibition towards LPS induced NO production in macrophages with $IC_{50}$ of 2.6 µM while the other compounds displayed $IC_{50}$ values in the range of 3-5 µM. Lobophytone U (**42**) also was able to inhibit the growth of *S. aureus* and *S. pneumoniae* (Yan et al., 2011). The reported biological activity of *L. pauciflorum* and the active compounds is summarised in Table 1.

**Table 1.** Summary of *L. pauciflorum* biological activities and the active compounds.

| Biological activity | Active compound | Reference |
|---|---|---|
| Antibacterial | Lobatrienol (**21**) | Edrada et al., 2000 |
| Antifungal | Lobatrienol (**21**) | Edrada et al., 2000 |
| Anti-inflammatory | Nephthenol (**1**)<br>Gorgost-5-ene-3β-ol (**61**) | Hassan et al., 2016 |
| Antimicrobial | Lobophytone Q (**38**) | Yan et al., 2010c |
| | Lobophytone T (**41**) | Yan et al., 2011 |
| | Lobophytone U (**42**) | Luyao et al., 2019b |
| | Lobophytone Z (**47**) | |
| Antioxidant | - | Luyao et al., 2019 |
| Cytotoxicity | Lobatriene epoxide (**20**) | Edrada et al., 1998,<br>Luyao et al., 2019a |

## Conclusion

*Lobophytum pauciflorum* is a source of a range of secondary metabolites that have diverse bioactivities. In this review, we report that three classes of secondary metabolites, namely diterpenes, biscembranoids, cembrene and sterols, have been isolated from the soft coral species *L. pauciflorum* and their bioactivity. It was observed that reports on *L. pauciflorum* focus more on the structural diversity of secondary metabolites rather than their bioactivity. Further extensive study is required to explore the biological potential of the secondary metabolites isolated from the soft coral species *L. pauciflorum*.

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