Chapter 4
Soft Coral Biodiversity in the Red Sea Family Alcyoniidae: A Biopharmaceutical and Ecological Perspective

Erick E. Dokalahy, H. R. El-Seedi and Mohamed Ali Farag

Abstract Seas cover over 70% of the Earth surface, and its total global biodiversity is estimated to have some 500 × 10^6 species of prokaryote and eukaryote organisms. Moreover, the Red Sea with a high percentage of endemic biota is an epicenter for marine biodiversity. Indeed, of the 180 soft coral species identified worldwide, approximately 40% are native to the Red Sea area. Such coral reef ecosystems support enormous biological diversity, including structural and functional complex benthic communities. The marine metabolome is quite complex, and its diversity exceeds that of mammals because the selection and retention of chemical diversity is a critical factor in an organism's adaptation and fitness and a primary reason for the large number of natural products. Only a few thousand compounds have been reported from the Red Sea of marine origin, and hence, it is believed to have an enormous potential as a provider for new bioactive metabolites. Marine natural products display an extraordinary chemical and pharmacological scope. This could be attributed to their necessity to release secondary metabolites as their own chemical defense tools to survive in extreme environment, to resist their predators, or to provide chemical communication in symbiotic relationships. The growing interest in marine natural products, particularly in the area of anticancer compounds, is attributed to the urgent therapeutic need in this area. The biological and chemical research of the coral reefs has made a remarkable progress as reviewed herein yet the support information of the biodiversity, functions profile and ecological landscapes still to be acquired. This chapter overviews current

E. E. Dokalahy · M. A. Farag (✉)
Pharmacognosy Department, College of Pharmacy, Cairo University,
Kasr el Aini St., P.B. 11562 Cairo, Egypt
e-mail: Mohamed.farag@pharma.cu.edu.eg

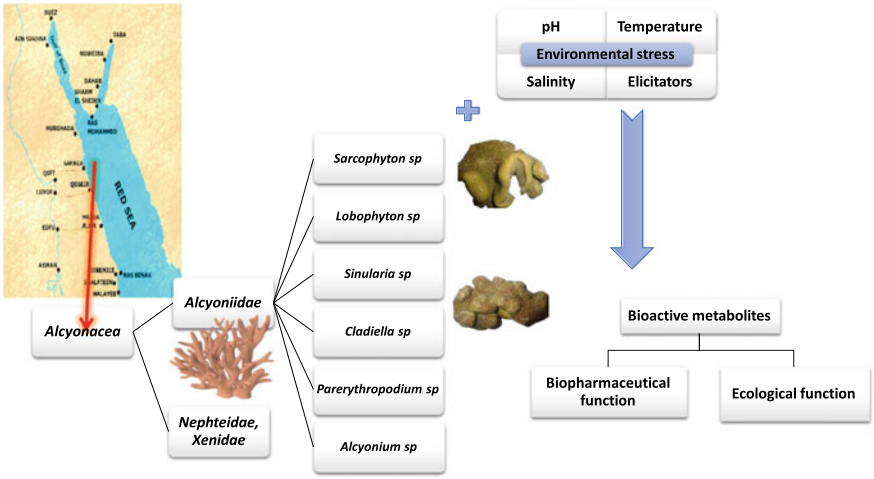
H. R. El-Seedi
Pharmacognosy Group, Department of Medicinal Chemistry,
Uppsala University, Biomedical Centre, Box 574, 751 23 Uppsala, Sweden

H. R. El-Seedi
International Research Center for Food Nutrition and Safety,
Jiangsu University, Zhenjiang 212013, China

K. G. Ramawat (ed.), *Biodiversity and Chemotaxonomy*, Sustainable
Development and Biodiversity 24, https://doi.org/10.1007/978-3-030-30746-2_4

research in octocoral order: *Alcyonacea* growing in the Red Sea area with focus on its medicinal potential within its chemical rich niche as well as their ecological functions. The chapter emphasizes also on the potential research areas for the marine natural products that are yet to be investigated.

Keywords Red sea · Alcyoniidae · Biopharmaceutical · Ecological functions



4.1 Introduction

The Red Sea has long been considered as an epicenter for marine biodiversity whether regarding its fish population (DiBattista et al. 2015), microbiome (Mustafa et al. 2016) or more for its hermaphytic corals. Among the animal phylum, octocorals or soft corals (Phylum *Cnidarian*, class *Anthozoa*, subclass Octocorallia or Alcyonaria) have emerged as potential animal source of vast research interest. Unlike the stony corals which are protected by a calcium carbonate skeleton, soft corals have a soft bodies supported by a spiny, minutes skeletal elements called sclerites. As a means to survive through the various stressors in marine life, protect themselves against predators, or communicate among symbiotic organisms (Farag et al. 2017b), octocorals have developed the machinery (Sammarco and Coll 1992) to produce a myriad of secondary metabolites such as ceramides (Cheng et al. 2009), sterols (Santalova et al. 2004), and predominantly terpenoid compounds and its derivatives (Hegazy et al. 2015) with interesting medicinal and ecological properties. As a matter of fact, the marine environment presents a great wealth of untapped natural sources of complex chemicals with potential biopharmaceutical

usage such as cytotoxicity (Ellithey et al. 2014), antitumor (Sarmiento-Vizcaíno et al. 2017), antimicrobial (Mariottini and Grice 2016) as well as their antifouling (Soliman et al. 2017), ichthyotoxic (Sammarco and Coll 1992), feeding deterrence (Kelman et al. 1999), and antimicrobial (Kelman et al. 2006) activities in the context of marine ecology.

Up to 40% of the 180 soft corals species identified worldwide are known to be endemic to the Red Sea area (Al-Lihaibi et al. 2014); however, the status of their research is still in its infancy with potential bioactive chemicals yet to be revealed. Berumen et al. (2013) conducted a comparative listing on the existing literature on the soft coral ecology performed in the Great Barrier Reef (GBR) in Australia, Caribbean Sea, and the Red Sea, suggesting that the majority focuses only on 2% of the Red Sea region. A guideline to pinpoint the future horizon of the soft coral research status in the Red Sea is needed to avoid replication of previously investigated corals and highlight the need of future unexplored research areas. Understanding of the Red Sea corals chemistry diversity and ecological function shall be of value to understand the influence of ecological relationships on corals and their change upon (man-made) environmental impact, i.e., global warming or pollution (Riegl et al. 2009). The main interaction between organisms but also within them is indeed of chemical nature. With regard to the Red Sea, Nature Middle East reports that the Red Sea is getting hotter at a rising temperature rate exceeding that of the global average. The Red Sea is already roughly 0.2 °C higher in temperature than the global average (Laylin 2011), which might seem like an insignificant number, but even small changes in temperature can have wide-ranging impacts on the overall ecosystem and marine life, and averages also conceal often more relevant hot spells. Corals, when exposed to seawater temperatures above normal levels for their region, will exhibit "bleaching"; i.e., they lose their zooxanthellae, which provide color to the host coral tissue, leaving the tissue transparent and ultimately leading to coral death (Wooldridge 2010; Sammarco and Strychar 2013). To understand how bleaching occurs in the host coral in terms of chemistry is also just at the beginning, with membrane lipids of symbiotic algae identified as a diagnostic parameter for the sensitivity to thermal bleaching in corals (Tchernov et al. 2004).

Searching literature on the Red Sea soft corals, family Alcyoniidae appeared as the most examined with a total of 39 soft coral species being studied belonging to the genus *Sarcophyton, Sinularia, Lobophyton, Alcyonium, Cladiella, and Parerythropodium* and suggesting that Alcyoniidae has received the most chemical investigation. Among these genotypes, most of the bioactive chemicals appeared to be associated with the genus *Sarcophyton* and in agreement with the review by Liang and Guo (2013). A comparative study on the bioactive terpenes from Red Sea marine organism starting from 1980 till 2014 has been reported by Hegazy et al. (2015). Nevertheless, several new coral species and novel chemicals are continuously being reported which warrants a more comprehensive review of the Red Sea octocorals.

To the best of our knowledge, this work represents not only the most comprehensive study of the Red Sea Alcyoniidae corals chemistry but also its biological and ecological functions. It compiles the reported secondary metabolites of the Red Sea Alcyoniidae family and is subdivided into two main sections including:

(1) reported bioactive components of each Alcyoniidae with a focus on their source followed by (2) ecological function. The chapter ends with a review of reported coral chemicals of yet no biological effects that are presented for researchers to consider in their future work.

4.2 Bioactive Secondary Metabolites of Red Sea *Alcyoniidae*

During the past 20 years, thousands of novel marine metabolites have been reported and assayed for anticancer activity based on their ability to either inhibit the proliferation, migration, tumor formation, the metastasis or even completely kill cancer cell. Extract and fractions from the Red Sea Alcyoniidae family has been assayed in the past decade for their potential source of anticancer and other biological properties (Hegazy et al. 2012). Terpenoids were the most studied among reported metabolites, particularly the cembranoid diterpenes found in abundance in the *Sarcophyton* (family Alcyoniidae). Cembranoids contain a 14-membered macrocyclic skeleton fused to a five-membered unsaturated lactone ring (Fig. 4.1, compound **10**) and exhibit a wide range of biological activities including most prominently antitumor activity (Hegazy et al. 2012). The furanocembranoid diterpene sarcophine (**10**) has been investigated since 1998 for its potential as a chemo-preventive agent and cytotoxic agent. The upcoming section highlights the anticancer activities reported of each Alcyoniidae genus, viz. *Sarcophyton*, *Sinularia*, *Cladiella, and Lobophyton* considering the wealth of cytotoxic activity reports for each genotype.

4.2.1 Sarcophyton Genus Cytotoxic Effect

Sarcophyton (phylum, Cnidaria; class, Anthozoa; subclass, octocoralia; order Alcyonaceae; family, Alcyoniidae) is one of the genus that has been extensively

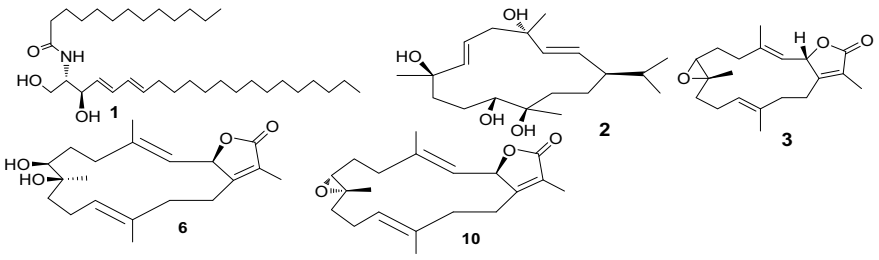


Fig. 4.1 Ceramide (**1**) and Cembranoid diterpenes (**2**, **3**, **6**, and **10**) from *S. auritum*

studied during the past three decades (Zubair et al. 2016) to include *Sarcophyton glaucum* (Abdel-Lateff et al. 2015; Eltahawy et al. 2014; Ne'eman et al. 1974), *Sarcophyton ehrenbergi* (Abou El-Ezz et al. 2013; Eltahawy et al. 2014; Hegazy et al. 2017), *S. trocheliophorum* (Řezanka and Dembitsky 2001; Shaaban et al. 2015), *S. auritum* (Eltahawy et al. 2014) for their antitumor and or cytotoxic activities.

Eltahawy et al. (2014, 2015) investigated the bioactive compounds of *Sarcophyton auritum* leading to the discovery of a ceramide (**1**) and four cembranoid diterpenes **2–3, 6, 10** found against two cancer lineHepG2 (liver cancer cell line) and MCF-7 (breast cancer cell line), Fig. 4.1. While **2 and 3**, reported for the first time, showed a moderate toxicity with an IC_{50} ranging from 19.7 to 21.1 μg/ml, whereas compound **6 and 10** were found the most and least cytotoxic.

The polar and non-polar extracts of *S. ehrenbergi* encompass a myriad of 10 or more ring-structured terpenoids such as cembranes (**4–10**), cembrenes (**11–13, 135–136**) diterpenoid, sesquiterpenes (**14**), bicyclic cembranolide (**15**), steroid (**16**), and tetraterpene (**17**), Fig. 4.2 with potential antiproliferative and cytotoxic activities toward selected cell lines (Hegazy et al. 2017). The antitumor activities of compounds **7–9** were assessed against breast carcinoma (MC-7), with IC_{50} values of 192.87, 68.57, and 114.41 μmol/mL, respectively. It is important to note that these compounds are novel to that species (Elkhateeb et al. 2014). A study by Hegazy et al. (2017) reported a variable antiproliferative activity of the cembrenes (**11–13, 135–136**), cembrane (**6**) diterpenoids, and the steroid (**16**) against three human tumor cell lines, viz. lung (A549), colon (Caco-2), and HepG2 coupled with a molecular docking technique study as the ring structure density plays a substantial role in the receptors/metabolites interaction and or binding. The first reported antiproliferative activity of **13** showed strong cytotoxicity with IC_{50} of 27.3 μM against A549 cell, whereas **13** and **16** showed a moderate inhibition against HepG2 cell line at IC_{50} of 53.8 and 56.8 μM, respectively.

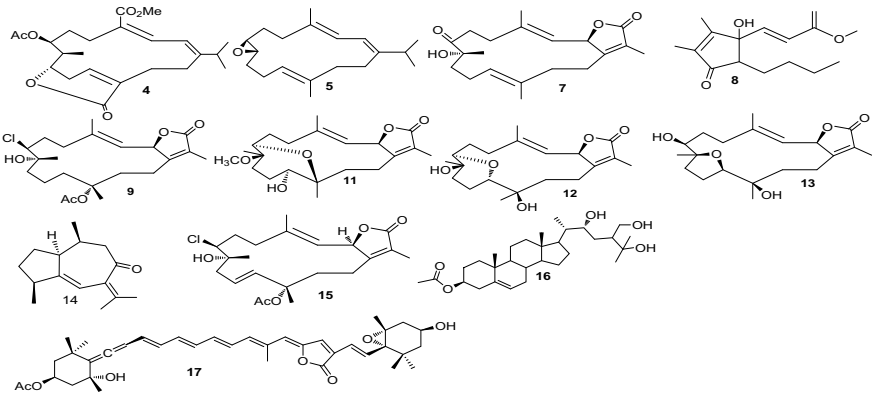


Fig. 4.2 Structure of metabolites from *S. ehrenbergi* **4–17**

Isolation attempt from the non-polar extract of *Sarcophyton glaucum* also provided different secondary metabolites class, namely cembranoids (**10, 18–28, 137–140**), a cembrene **29**, cembranolides **30–32**, sesquiterpenes **33–36, 135** and other miscellaneous classes **37–38**. Abou El-Ezz et al. (2013) assayed the cembranoid diterpenes (**10, 19, 22–25**) against several cancer cell lines. Among the most repeatedly isolated compounds from *Sarcophyton*, the furanocembranoid diterpene **10** has been massively reported by several researchers (Abou El-Ezz et al. 2013; Al-Footy et al. 2015; Eltahawy et al. 2014; Hegazy et al. 2015; Ne'eman et al. 1974; Shaaban et al. 2015; Shaker et al. 2010) to have a dry weight yields of 3% in *S. glaucum* and found most active against cholinesterase in vitro which warrants further development of its activity using combinatorial chemistry or structure active relationships SAR studies. Bioactive cembranoids **18, 22, and 23** were reported to exhibit a similar antitumor and cytotoxic activity toward the mouse melanoma B16F10 and monkey kidney CV-1 cell line. From an EtOAc extraction, bioactive sesquiterpene **35** was reported by Sawant et al. (2007) to exhibit a potent antiproliferative effect against the highly malignant mouse tumorous cell line (+SA mammary epithelial cells) at a dose 20 μM, while the dioxolane sesquiterpene alcohol **136** expressed no activity toward the tested cell line. Al-Lihaibi et al. (2014) reported also the isolation of cembranoids **19, 21, 26, 27,** and the sesquiterpene **34** from an organic (diethyl ether) extract of *S. glaucum* and tested their activity against five cancer lines, *viz*. MCF-7, HepG2, A549, PC-3, and VERO compared to the standard anticancer drug (Doxorubicin). Compounds **21, 26, 34** whose antiproliferative activity were related to their ability to induce cellular apoptosis were cytotoxic against HepG2 (IC_{50}20 μM), whereas metabolites **20, 27** exhibited a less potent against MCF-7 with an IC_{50} of 25 and 29 μM, respectively, as manifested by its much higher IC_{50} value in the micromolar range. Report on the ethyl acetate extract of the same *Sarcophyton* species let to the identification of five compounds including two new peroxide cembranoids **31–32**, two previously reported cembranoids **10, 30,** and a new cembrene derivative **29** (Hegazy et al. 2012). *In vitro* assay revealed that **29 and 31** exhibit a promising inhibitory effect on the cytochrome P450 1A activity (IC_{50} values: 2.7 and 3.7 nM) as well as gluthatione-*S*-transferase (GST) and quinone reductase (QR) inducing potential, which demonstrate their ability to affect the carcinogen metabolizing enzymes in Murine hepatoma cells (Hepa1c1c7).

The chloroform-methanol (1:1) extract and fraction of *Sarcophyton trocheliophorum* has been investigated by Hegazy et al. (2013), Al-Footy et al. (2015), Shaaban et al. (2016), El-Seedi et al. (2016) which has led to the isolation of metabolites (**10, 18, 29–30, 39- 46, 98, 141–148**) belonging to several chemical classes, namely pyrane-based cembranoids (**18, 39, 98**), bicyclo-(5,7)sesquiterpenes (**44, 143–146**), and cembranoid diterpenes (**10, 41, 98**). While their cytotoxicity preliminary testing in a brine shrimp assay showed no response except for **41** with a weak toxicity of 22.5% mortality rate, antitumor activity against two cell lines (Lymphoma and Erlish cell line) of the two diterpenes **10 and 41** exhibited strong effects with IC_{50} of 2.5–3.5 μM (Al-Footy et al. 2015). These results suggest that the application of general cytotoxic assays, i.e., shrimp bioassay, might evade the

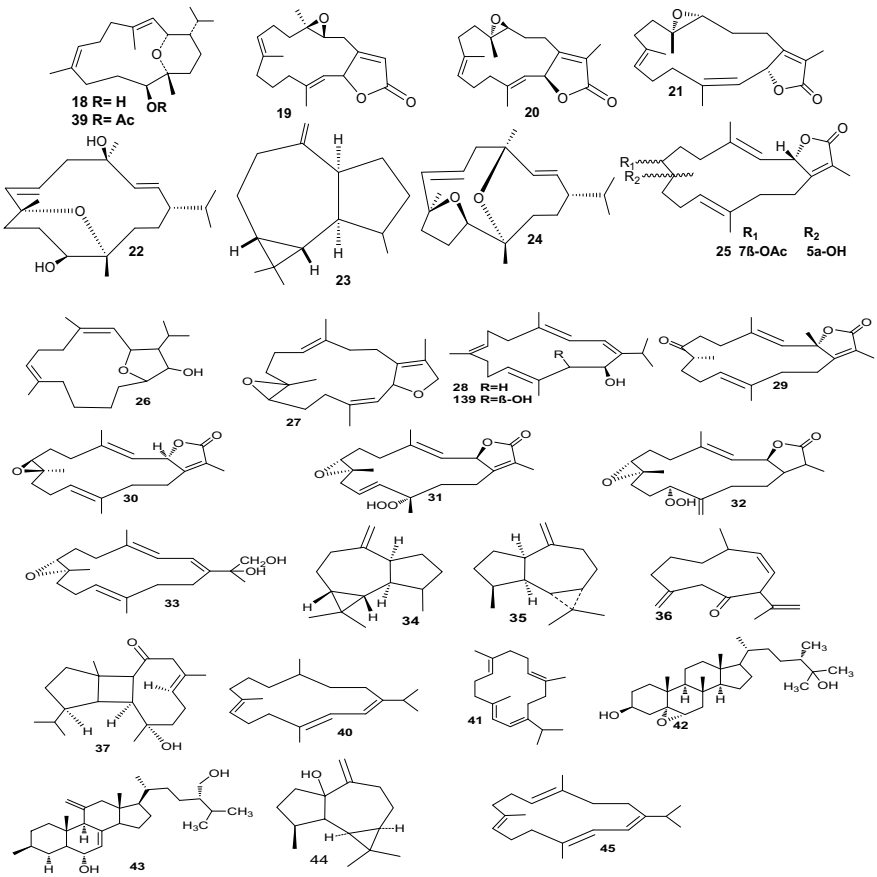


Fig. 4.3 Bioactive metabolites (**18–45**) reported from *S. trocheliophorum* and *S. glaucum*

detection of potential cytotoxic drugs in typical laboratory assays. While **29** and **30** were reported from *S. trocheliophorum* species for the first time, the cembranolide **151** has been isolated by Hegazy et al. (2015) for the first time in nature. Further analysis of its potential pharmacokinetic properties should be investigated (Fig. 4.3).

4.2.2 Sinularia Genus Cytotoxic Effect

Sinularia genus reported anticancer effects include firstly that if (El Sayed and Hamann 1996) from *Sinularia gardineri*'s EtOH extract leading to the isolation of a sesquiterpene (**47**), a new heptacyclic norcembranoid dimer (**48**), a known norcembranoid **152** lacking a methyl group at C_4 and a C_4 norcembranoid **153**. Cytotoxicity assay of **47** and **48** were found effective against four cancer cell lines,

i.e., murine leukemia (P-388), A549, human colon carcinoma (HT-29), and human melanoma cells (MEL-28) with an IC_{50} ranging from 1 to 5 μg/mL. Investigation on *Sinularia polydactyla* extract uncovered five steroids (**49–53**), two sesquiterpenes (**54, 55**), and a cembranoid diterpene (**56**) with varied cytotoxic efficacies. Metabolites (**41, 49–51, 54–55**) (Shaaban et al. 2013b) exhibited marginal cytotoxic effect toward brine shrimp assay with 4–7% mortality rate at 10 μg/mL except for (**49**), displaying 24%. (Aboutabl et al. 2013) unraveled the antitumor and cytotoxic effects of (**49–54**) against three human cancer lines, viz. liver ($HepG_2$), colon (HCT-116), and epidermoid larynx carcinoma (Hep2). While the crude extract **57** of the same species *Sinularia polydactyla* was active on all cell lines, **56** showed a strong and selective toxicity toward Hep2 (IC_{50} 1.0 μg/mL) suggestive for a synergized effect for all chemicals in crude extract to function independently against several cell lines as commonly reported in plant extracts. The bioactive sterols isolated from *Sinularia terspilli* (Mohammed et al. 2017) included eight compounds (**58–62, 159–161**). Strong cytotoxicity with more than 80% inhibition was observed for **58, 60–62** when tested against K-562 versus **58 and 62** found active against human leukemia cell lines HL60 and K562, with IC_{50} values of 0.002–0.025 μM, comparable to that of taxol drug. The first report on the cytotoxicity of a *Cnidarian* species extract of *Sinularia maxima* (**63**) was made by Ellithey et al. (2014) with a potent cytotoxic effect against leukemia (U937) and cervical cancer (HeLa) cells lines (Fig. 4.4).

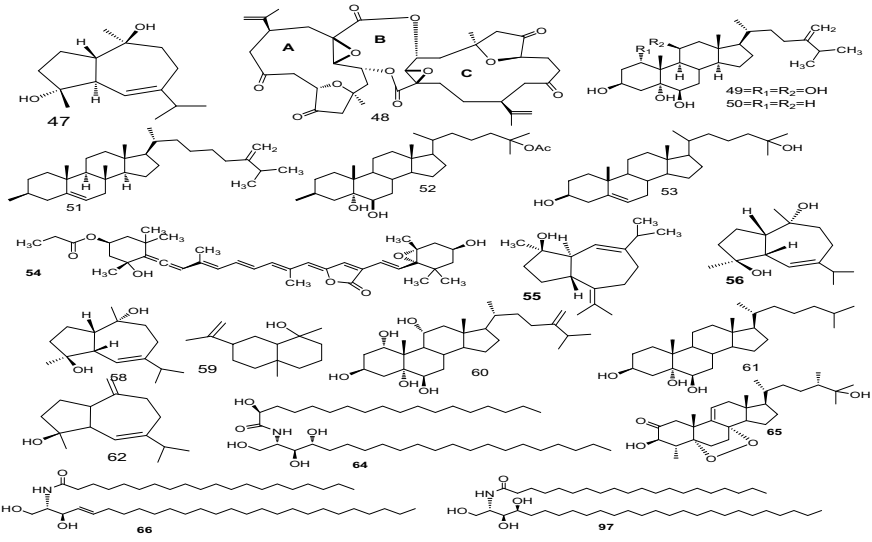


Fig. 4.4 Bioactive metabolites reported from *Sinularia* genus

4.2.3 Cladiella Genus Cytotoxic Effect

Study on *Cladiella pachyclados* (Hassan et al. 2010) suggested that next to *Sarcophyton*, *Cladiella* genus is a rich source of a diterpenes with five isolated new (**71–85**) and 11 known (**76–85, 106**) eunicellin-based diterpenoid characterized by the presence of a cladiellane-based skeleton which contains a C_2 and C_9 ether bridge (Fig. 4.5). Three biological assays, namely the MTT, wound-healing, and Cultrex Basement Membrane extract cell invasion assays were performed to assess their cytotoxic potential. Antimigration and antimetastatic assays of the tested compounds suggested the anti-evasive potential of **73, 76, 83,** and **85** compared to the 200 μM dose of the positive drug 4-hydroxyphenylmethylene hydantoin (PMH). This report was the first to reveal for the effect of the eunicellin-based diterpenoid class as anti-invasive or acting as an antimigration of different cancer lines and suggest for searching of other more active agents of that class.

4.2.4 Lobophyton Genus Cytotoxic Effect

A study of the methanol extract of *L. crassum* by Aboutabl et al. in (2017) revealed for five polyhydroxysterols **98–100, 161–162** and a sesquiterpene **86**. Biological evaluation of compounds against three human cancer lines, viz. $HepG_2$, Hep-2, and HCT-116, revealed a strong cytotoxic effect of **99** toward $HepG_2$, Hep-2, and HCT-116, with IC_{50} values of 1.9, 5.8, and 6.4 μM, respectively. On the other hand, compounds **86, 98, and 100** expressed a selective affinity to HepG2 compared to the other cell lines with a respective IC_{50}values of 1.9, 3.0 and 3.7 μM. Reports on the organic extract of *Lobophyton* species are also reported in

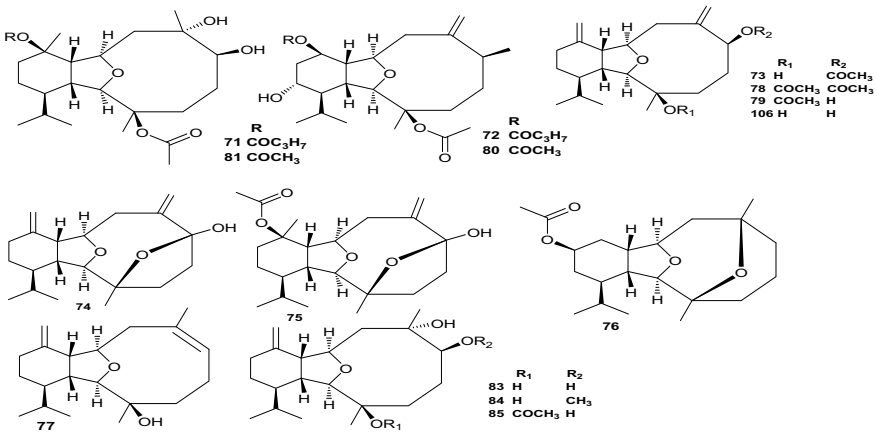


Fig. 4.5 Eunicellin-based diterpenoid from *Cladiella pachyclados*

Table 4.2 (**107–133, 161–162**) for which no reported bioactivity made. Research on *Lobophyton* species producing antiproliferatives cembranolides (Peng et al. 2018) and antiviral seco-cembranoids (Cheng et al. 2014) in other geographical location such as Dongsha Atoll in Taiwan, further investigation on the biopharmaceutical potential of the Red Sea *Lobophyton* are suggested especially considering that coral metabolism varies according to its environmental conditions (Farag et al. 2016, 2018). Other secondary metabolites isolated from other Alcyoniidae Family such as *A. flaccidum*, *A. utinomii,* and *Sarcophyton* sp are reported in Table 4.2 (Fig. 4.6).

4.2.5 Red Sea Alcyoniidae Corals Antimicrobial Effect

Octocorals, as a response to the marine extreme environment, have adapted its metabolism in a distinct way compared to that of hard corals, especially considering their anatomical structure lacking a hard protective shell. Moreover, like other coelenterate, their unique cavity opening used as food ingestion and waste disposal made them more vulnerable to microbial contamination. Consequently, octocorals produce a plethora of secondary metabolites as their own chemical antimicrobial defense tools compared to the stony corals found to exhibit less antimicrobial activity against marine bacteria (Kelman et al. 2006). Those metabolites present an untapped potential to combat the emerging antibiotic resistance by bacteria due to the abusive use of antibiotics over the past 60 years (Al-Footy et al. 2015). Marine scientists have investigated the antibacterial, antiviral, and antifungal of crude extract or metabolites of the Red Sea soft corals (Kelman et al. 2006) and the next section outlines corals effect against different microorganisms.

4.2.5.1 Antibacterial Activity

Early investigation of the Red Sea soft corals antibacterial effect dates back to the 1990 to encompass mostly extracts of coral species from three different genotypes (*Sinularia, Sarcophyton, and Lobophyton*) that has been tested against marine bacteria and human pathogens. Compound (**45**) isolated by Gomaa et al. (2016) from n-hexane extract of *Sarcophyton trocheliophorum* was found active against several pathogens, namely *Bacillus cereus, Salmonella typhi, Escherichia coli, Staphylococcus aureus,* and *Pseudomonas aeruginosa*. Biological octocorals' antibacterial agents mostly belonged to diterpenoids (**39**) (Al-Footy et al. 2015), sesquiterpenoids (**62, 86–88**), and steroids (**89, 90**) (Al-Footy et al. 2016). In (2006), Kelman compared the antibacterial activity of two different cnidarian orders, namely scleractinian and alcyonacean. Results revealed that the majority of the Red Sea soft corals (*Litophyton arboreum, Rythisma fulvum, Heteroxenia fuscescens, Sarcophyton glaucum, Dendronephthya hemprichi, Xenia macrospiculata*) were 83% more active against marine bacteria *Arthrobacter* sp. (two strains)

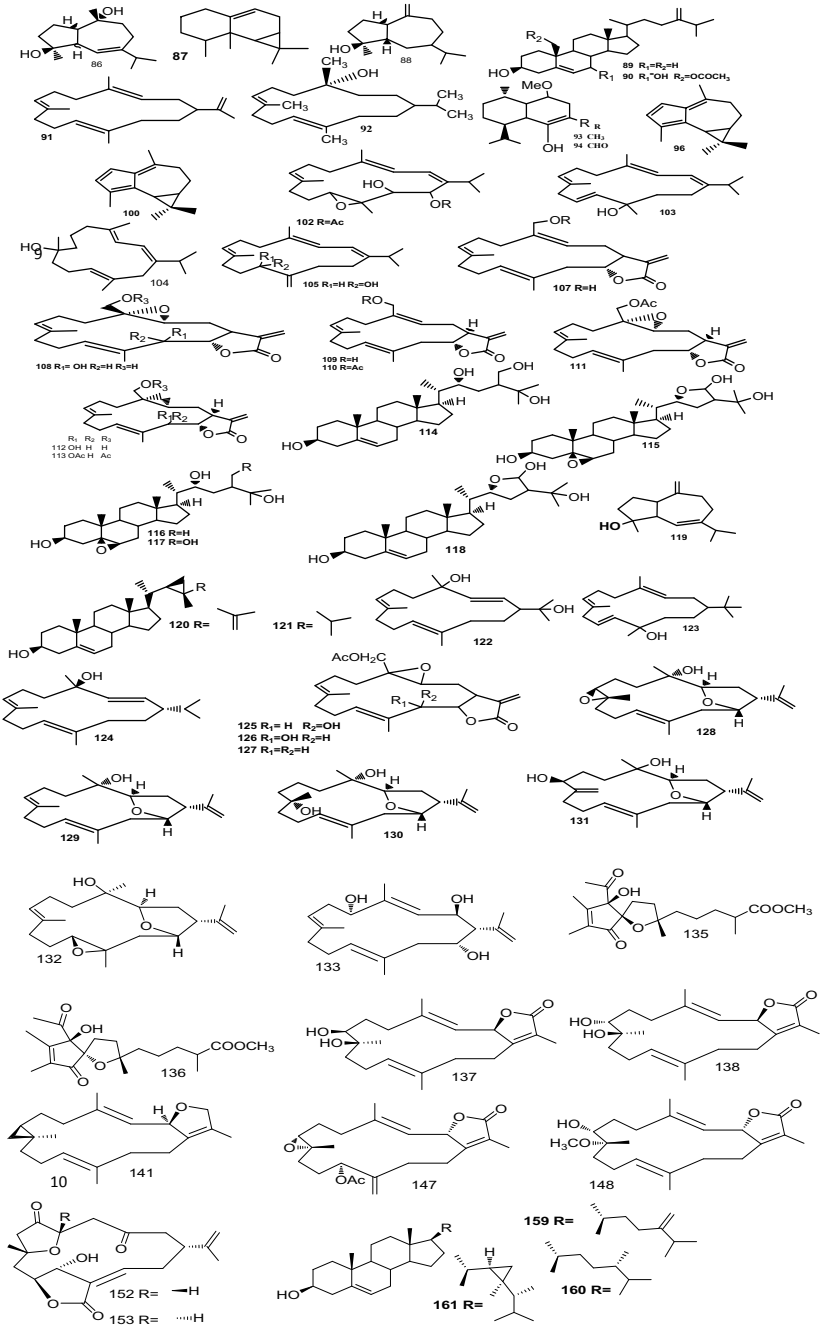


Fig. 4.6 Bioactive metabolites from *Lobophyton* (**87–92**, **103–133**) and *Sarcophyton* (**135–141**) and *Sinularia* metabolites with non-reported activity

compared to hard corals which have mainly developed other strategies to combat microbial invasion in the marine environment (Kelman et al. 2006).

Collected off the Saudi Arabia Red Sea coast, sesquiterpenes (**62, 86–88**) and steroids (**89, 90**) isolated from *Lobophyton* sp. extract exhibited a weaker antibacterial activity compared to sesquiterpene (**91**) and the steroid (**42–43**) as assessed against some gram-positive bacteria (*S. aureus, S. epidermis, and S. pneumonia*) and gram-negative bacteria (*P. aeruginosa*). A further study on *Sarcophyton trocheliophorum* extract showcased the isolation of two cembranoids (**10, 39**) and two pyrane-based cembranoid (**18, 40**) exhibiting significant antibacterial activity, especially against *S. aureus, Acinetobacter spp.*, and MRSA with (MICs) ranging from 1.5 to 4.3 μM (Al-Footy et al. 2015). Aboutabl et al. (2013) assessed the effect of *S. polydactyla* extract against gram-positive bacteria, reporting that compound **53** displayed a moderate antimicrobial activity. Crude extract and fractions including the steroids (**42, 43**) were reported to possess different responses toward *S. aureus* by Shaaban et al. (2013a). While the keto-hydroxysterol **43** showed high antimicrobial activity, oxirane containing compound **42** and the crude extract were found inactive.

Kelman et al. (1998) assessed the extract of several developmental stages of the soft coral *P. fulvum fulvum* against *Vibrio* sp strain from a necrotic coral and other coral associated bacterial strains. The sensitivity toward the *Vibrio* sp with an MIC of 1.25 mg/mL suggested that in general corals do not have a broad-spectrum antibacterial activity against the growth of common, co-occurring, and potentially harmful bacteria, but has a specific activity. Nevertheless, such hypothesis needs to be proved by assaying larger specimens of coral species against several pathogens.

Recently, investigation in the Egyptian Red Sea was done by Soliman et al. (2017) on the methanol extract derived from soft coral species, viz. *S. glaucum, S. cruciate, H. fuscescens,* and *S. compressa* against selected marine bacteria (*P. aeruginosa* ATCC653, *Staphylococcus aureus* ATCC6538, and *Escherichia coli, P. aeruginosa* ATCC6539) using a microdilution broth susceptibility test. The *S. compressa* extract (**67**) showed the strongest effect as revealed from its low MIC/MBC values ranging from 0.5 to 1/1 to 10 mg/mL followed by *S. cruciate* (**68**) and *S. glaucum* (**38**) with a MIC/MBC of 5–50/10–100 mg/mL, whereas *H. fuscescens* exhibited no activity.

4.2.5.2 Antiviral Activity

As a potential marine drug source of antimicrobials, the Red Sea Alcyoniidae coral extracts also demonstrated their capacity to encompass strong antiviral metabolites, though with much less evidence-based assays compared to that derived from antibacterial. Ahmed et al. (2013) reported two classes of compounds, ceramides and sterols to exhibit an antiviral effect against H5N1 virus from *S. candidula*. Bioactivity guided fractionation of the EtOAc extract against influenza H5N1 led to the isolation of three bioactive ceramides (**64, 66** and **97**) and a polyhydroxylated sterol (**65**). All compounds managed to reduce the virus titer by 55.16%, 48.81%,

10.43%, and 15.76% at a dose of 1 ng/mL comparable to the standard drug Zanamivir, while the crude extract expressed a complete inhibition at 12 µg/mL.

In search of anti-HIV/AIDS drugs from marine resources, Ellithey et al. (2014) assessed the response of Red Sea organisms' extracts (**63**) toward the inhibition of HIV-1 reverse transcriptase (RT) and protease (PR) enzymes. Although extracts exhibited no significant effect against HIV-1 RT enzymes, inhibitory activities against HIV-1 PR were shown from the soft corals *S. heterospiculata* (8.6 µg/mL), *L. arboreum* (12 µg/mL), and *S. maxima* (13.1 µg/mL). These results highlight the bioactivity of the crude extract of the tested marine organism, and calling for a further bioassay guided fractionation to identify their active site as potential anti-HIV agents.

4.2.5.3 Antifungal Activity

To evade the predation and infection of soft corals from fungi that may affect their marine life, Alcyoniidae family produce various antifungal biomolecules, viz. terpenes and steroids that can be exploited as therapeutic agents in the pharmaceutical industry for humans (Mohammed 2012). Fungi may be opportunistic pathogens in corals under environmental stress. Abou El-Ezz et al. (2013) evaluated the methanol extract of *Sarcophyton glaucum* for its antifungal activity. Compared to isolated metabolites, crude extract showed no obvious biological activity. In contrast, cembrane-based diterpene **40** and **10** with a MIC of 0.68 µM were found active against fungal pathogens *Candida albicans, Aspergillus flavus* and with an IC_{50} of 20 µg/mL against *Cryptococcus neoformans*, respectively. Al-Footy et al. (2015) assessed compounds isolated from the lipophilic extract of *Sarcophyton trocheliophorum* against *Aspergillus flavus* and *C. Albicans*. While compound **40** exhibited a low antifungal activity with an MIC of 0.68 µM, other pyrane-based cembranoid (**18 and 39**), cembranoid **10,** and a sesquiterpene **44** did not exhibit any response. Analyzing biological structure–activity relationships (SAR) among coral terpenoids analogues also may help identify more biologically active antifungal drugs and reveal crucial structural motifs that promote an antimicrobial effect.

In a similar location, another species *S. gardineri* was investigated (El Sayed and Hamann 1996) for its effect against *C. albicans* B311 and *C. neoformans* (El Sayed and Hamann 1996). The heptacyclic norcembranoid dimer **48** showed a growth inhibition results comparable to amphotericin B. In contrast, sesquiterpene **47** and cembranolides (**159–160**) were not able to inhibit fungal growth. Investigating the lipophilic extract of *S. terspili*, Mohammed et al. (2017) reported that the sterol (**61**) exhibited a moderate activity on the fungus *C. neoformans* with an IC_{50} value of 9.6 µg/mL. The assessment of lypophilic extract in all studies seems rational as to identify positive antifungal hits considering the lypophilicity of the fungal cell wall, a prerequisite type for a chemical to penetrate first prior to exerting a killing effect (Georgopapadakou 1995).

4.2.5.4 Antileishmanial Effect

Leishmaniasis is a disease that is more peculiar to the Third World countries, with an increasing mortality and morbidity rate in Africa, Asia, and Latin America caused by the protozoan *Leishmania* which uses mosquito as its principal vector to human from rodents (Rocha et al. 2005). The need for an effective drug to cure the disease aside from vaccine treatment prompted the search of bioactive chemicals of marine origin. *S. terspilli*, endemic to the Red Sea in Hurgada Egypt, has been reported by Mohammed et al. (2017) as a source of three bioactive sesquiterpenes [**58, 59,** and **62**] and sterols [**60, 61, 146, 159** and **161**]. In vitro culture of *Leishmania donovani* promastigotes was tested against isolated compounds, with sesquiterpenes [**58, 59**] and sterols [**60, 61**] exhibiting antileishmanial activity with IC_{50} values ranging from 10 to 30 μg/mL (Mohammed et al. 2017).

4.2.6 Red Sea Alcyoniidae Miscellaneous Biological Effects

Aside from the previously reported cytotoxic and antimicrobial activities for Red Sea Alcyoniidae family, other activities such as antiepileptic, anxiolytic, anti-inflammatory, and antimalarial activities were reported but to less extent. Eltahawy et al. (2014) examined the effect of crude polar extract and fractions of *S. auritum* enriched in ceramides. In vivo screening of the antiepileptic properties using PZP-induced seizure model, ceramide [**1**] was found successful to antagonize the lethality of pentylenetetrazole in mice. Moreover, the same compound was assessed in vitro of the light–dark transition box and elevated plus maze and confirming its anxiolytic activity.

A semi-synthesized products from furanocembranoid diterpenes (**10**) of *S. glaucum* were reported to exhibit potential anti-inflammatory effects. Sawant et al. (2006) reported the first anti-inflammatory activity of **10**, in addition to its hydroxylated semi-synthetic derivatives, found effective to release inflammatory mediators such as thromboxane B2 and superoxide anion in activated rat neonatal microglia. A promising result with an improved bioactivity of the sulfur derivative of **10** was found to also exhibit strong anti-inflammatory effect on highly malignant +SA mammary epithelial cell proliferation. In general and although in some cases, drug leads from marine resources fail to exhibit a prominent effect, semi-synthesis or biotransformation of these chemicals could present more efficacious drugs and with less side effects. As an example, the bioconversion of the *S. glaucum* fractions (**10, 40, 136**) using preparative scale fermentation by three selected fungus (*Absidia glauca* ATCC 22752, *Rhizopus arrhizus* ATCC 11145, and *Rhizopus stolonifer* ATCC 24795) resulted in extracts with improved functionality compared to the resulting metabolites (El Sayed et al. 1998) (Tables 4.1 and 4.2).

Table 4.1 List of Red Sea Alcyoniidae natural products, extracts and their reported bioactivities

N°	Molecules	Bioactivity	Biological target	Source	Reference
	Metabolites isolated from Sarcophyton sp				
1	N-((2S0,3*R*,4*E*,6*E*)-1,3-Dihydroxyhenicosa-4,6-dien-2-yl)tridecanamide	Anticonvulsant, anxiolytic	–	*S. auritum*	Eltahawy et al. (2015)
2	(1*R*,2*E*,4*S*,6*E*,8*R*,11*R*,12*R*)-2,6-Cembradiene-4,8,11,12-tetrol	Cytotoxic	MCF-7, HepG2	*S. auritum*	Eltahawy et al. (2014)
3	2-Epi-sarcophine	Id.	MCF-7, HepG2	*S. auritum*	Eltahawy et al. (2014)
4	(+)-Emblide	Antiproliferative	KB cell	*S. ehrenbergi*	Shaker et al. (2010)
5	(+)-7,8-Epoxy-7,8- dihydrocembrene	Id	HUVEC, K562 cell	*S. ehrenbergi*	Shaker et al. (2010)
6	7α,8β-Dihydroxy-deepoxysarcophine	Id.	HepG2, MCF-7, B16F10	*S. ehrenbergi*	Abou El-Ezz et al. (2013), Eltahawy et al. (2014), Hegazy et al. (2017)
7	7-Keto-8α-hydroxy-deepoxysarcophine	Cytotoxic	MCF-7	*S. ehrenbergi*	Elkhateeb et al. (2014)
8	(*E*)-Methyl-3-(5-butyl-1-hydroxy-2,3-dimethyl-4-oxocyclopent-2-enyl)acrylate	Id.	MCF-7	*S. ehrenbergi*	Elkhateeb et al. (2014)
9	7β-Chloro-8α-hydroxy-12-acetoxy deepoxysarcophine	Id.	MCF-7	*S. ehrenbergi*	Elkhateeb et al. (2014)
10	Sarcophine	Antifungal, antibacterial, antitumor, cytotoxic, antipredator, anti-acetylcholine	*Cryptococcus neoformans*, CV-1 cells, Erlish cell line, MCF-7, HepG2	*S. glaucum, S. auritum, S. ehrenbergi*	Abou El-Ezz et al. (2013), Al-Footy et al. (2015), Eltahawy et al. (2014), Hegazy et al. (2015), Ne'eman et al. (1974), Shaaban et al. (2015), Shaker et al. (2010)
11–13	Sarcoehrenbergilid A-C	Antiproliferative	HepG2	*S. ehrenbergi*	Hegazy et al. (2017)
14	Guajacophine	Moderate antiproliferative and cytotoxic	HUVEC, K-562, and HeLa cell lines	*S. ehrenbergi*	Shaker et al. (2010)

(continued)

Table 4.1 (continued)

N°	Molecules	Bioactivity	Biological target	Source	Reference
15	Sarcoglaucol-16-one	Antiproliferative, cytostatic	HM02, HepG2, MCF7	*S. ehrenbergi*	Shaker et al. (2010)
16	Sardisterol	Cytotoxic	A549	*S. ehrenbergi*	Hegazy et al. (2017)
17	Peridinin	Antiproliferative, cytotoxic, antitumor	HUVEC, K-562, Hela, DLD	*S. ehrenbergi*	Shaker et al. (2010)
18	Sarcotrocheliol	Antibacterial, cytotoxic	*S. aureus, Actinobacter spp and MRSA*, MCF-7 cell	*S. trocheliophorum, S. glaucum*	Abdel-Lateff et al. (2015), Al-Footy et al. (2015)
19	Sarcophytolide	Antimicrobial, antitumor, cytotoxic	*S. aureus, P. aeruginosa* and *S. cerevisiae*, B16F10, CV-1 cells	*S. glaucum*	Abou El-Ezz et al. (2013), Badria et al. (1997)
20–21	Sarcophytolide B, C	Antitumor, cytotoxic	MCF-7, HepG2	*S. glaucum*	Al-Lihaibi et al. (2014)
22	(1*S*,2*E*,4*R*,6*E*,8*R*,11*S*,12*R*)-8,12-Epoxy-2,6-cembradiene-4,11-diol	Antitumor	B16F10	*S. glaucum*	Abou El-Ezz et al. (2013)
23	(1*S*,4*R*,13*S*)-Cembra-2*E*,7*E*,11*E*-trien-4,13-diol	Cytotoxic, antitumor	CV-1 cells, B16F10 cells	*S. glaucum*	Abou El-Ezz et al. (2013)
24	(1*S*,2*E*,4R,6*E*,8*S*,11*R*,12*S*)-8,11-Epoxy-4,12-epoxy-2,6-cembradiene	Cytotoxic	CV-1 cells, B16F10 cells	*S. glaucum*	Abou El-Ezz et al. (2013)
25	7β-Acetoxy-8α-hydroxydeepoxysarcophine	Id.	HepG2, HCT-116, and HeLa cells	*S. glaucum*	Hegazy et al. (2011a)
26	Sarcophytolol	Id.	HepG2	*S. glaucum*	Al-Lihaibi et al. (2014)
27	Deoxosarcophine	Potent cytotoxic	MCF-7, HCT116, MCF-7	*S. glaucum*	Abdel-Lateff et al. (2015), Al-Lihaibi et al. (2014)
28	Sarcophytol A	Antitumor	C3H/HeNCrj mice3 and *N*-methyl-*N*-nitrosurea-induced large bowel cancer in rats	*S. glaucum*	El Sayed et al. (1998)
29	8-Epi-Sarcophinone	Antitumor	Cyp1A	*S. glaucum, S. trocheliophorum*	Hegazy et al. (2012, 2013)
30	Ent-sarcophine	Antitumor	Cyp1A	*S. glaucum, S. trocheliophorum*	Hegazy et al. (2012, 2013)
31	12(*S*)-Hydroperoxylsarcoph-10-ene	Antitumor	Cyp1A	*S. glaucum*	Hegazy et al. (2012)

(continued)

Table 4.1 (continued)

N°	Molecules	Bioactivity	Biological target	Source	Reference
32	11(*S*)-Hydroperoxylsarcoph-12(20)-ene	Cytotoxic	Cytochrome P450 1A	*S. glaucum*	Hegazy et al. (2012)
33	Sarcophinediol	Cytotoxic	HCT116, HepG2	*S. glaucum*	Abdel-Lateff et al. (2015)
34	10(14)-Aromadendrene	Cytotoxic, antitumor	PC-3, HepG2	*S. glaucum*	Al-Lihaibi et al. (2014)
35	(+)-alloaromadendrene	Antiproliferative	+ SA mammary epithelial cells at a dose of 20 μM	*S. glaucum*	Sawant et al. (2007)
36	6-Oxo-germacra-4(15),8,11-triene	Cytotoxic	HCT116	*S. glaucum*	Abdel-Lateff et al. (2015)
37	Sarcoglane	Cytotoxic	Fertilized sea urchin eggs	*S. glaucum*	Fridkovsky et al. (1996)
38	Crude extract	Antibacterial, antifouling paint formulation	*P. aeruginosa* ATCC6538, *S. aureus* ATCC6538, *E. coli*	*S. glaucum*	Soliman et al. (2017)
39	Sarcotrocheliol acetate	Antibacterial, cytotoxic	*S. aureus, Actinobacter* spp *and MRSA*	*S. trocheliophorum*	Al-Footy et al. (2015)
40	Cembrene C	Antifungal	*E. coli, P. aeruginosa, K. pneumonia, S. aureus, and S. epidermidis, E. coli*	*S. trocheliophorum*	Al-Footy et al. (2015)
41	(*Z*)-Cembrene C	Weak cytotoxic	Brine shrimp	*S. trocheliophorum*	Shaaban et al. (2015)
42–43	Zahramycins A-B	Antibacterial, antibiotic	Gram +ve bacteria *S. aureus* and *B. subtilis*	*S. trocheliophorum*	Shaaban et al. (2013a)
44	Palustrol	Antitumor, antiproliferative, antifungal, antibacterial	Lymphoma and Erlish Cell line	*S. trocheliophorum*	Al-Footy et al. (2015)
45	(5*S*)-3-[(3*E*,5*S*)-5-Hydroxy-3-hepten-6-yn-1-yl]-5-methyl-2(5H)-furanone	Antibacterial	Pathogenic bacterial strains, i.e., *B. cereus, S. typhi, E. coli, S. aureus and P. aeruginosa*	*S. trocheliophorum*	Gomaa et al. (2016)
46	Crude extract	Antifouling	–	*S. trocheliophorum*	Mohamed Ali and Soliman (2010)
47	Guaianediol	Cytotoxic	P-388, A549, HT-29, MEL-28	*S. trocheliophorum*	El Sayed and Hamann (1996)

(continued)

Table 4.1 (continued)

N°	Molecules	Bioactivity	Biological target	Source	Reference
	Metabolites from Sinularia sp.				
48	Singardin	Cytotoxic	P-388, A549, HT-29, MEL-28, *C. albicans* B311 and *C. neoformans*	*S. gardineri*	El Sayed and Hamann (1996)
49	24-Methylenecholestane-1α, 3β,5α,6β,11α-pentol	Cytotoxic	Brine shrimp	*S. polydactyla*	Shaaban et al. (2013b)
50	24-Methylenecholestane-3β,5α, 6β-triol	Cytotoxic	Brine shrimps (4–7% mortality at 10 μg/mL)	*S. polydactyla*	Shaaban et al. (2013b)
51	Hurgadacin	Cytotoxic	Brine shrimps (4–7% mortality at 10 μg/mL)	*S. polydactyla*	Shaaban et al. (2013b)
52	24-Methylcholestane-3β,5α,6β,25-tetrol 25-monoacetate	Cytotoxic, antitumor	Hep2 and HCT	*S. polydactyla*	Aboutabl et al. (2013), Hegazy et al. (2015)
53	24-Methylcholestane-5-en-3β,25-diol	Antimicrobial	Gram +ve: *Bacillus subtilis* and *Bacillus megaterium*	*S. polydactyla*	Aboutabl et al. (2013)
54	Peridinin	Cytotoxic	Brine shrimps (4–7% mortality at 10 μg/mL)	*S. polydactyla*	Shaaban et al. (2013b)
55	Lactiflorenol	Cytotoxic	Brine shrimps (4–7% mortality at 10 μg/mL)	*S. polydactyla*	Shaaban et al. (2013b)
56	Durumolide C	Selective toxicity	HepG2	*S. polydactyla*	Aboutabl et al. (2013)
57	Crude extract	Antibiotic, antifouling	Fungus *R. solani*	*S. polydactyla*	Mohamed Ali and Soliman (2010)
58	1S, 4S, 5S, 10R-4, 10-guaianediol	Antileishmanial, strong cytotoxic	*Leishmania donovani*, K562	*S. terspillii*	Mohammed et al. (2017)
59	5,7 Eduesm- 11(13) en-4-ol	Weak antileishmanial	*L. donovani*	*S. terspillii*	Mohammed et al. (2017)
60	Ergost-24(28)-ene-1, 3, 5, 6, 11-pentol (1α, 3β, 5α, 6β, 11α)	Weak antileishmanial, antifungal, cytotoxic	*L. donovani, C. neoformans*, HL60	*S. terspillii*	Mohammed et al. (2017)
61	Ergost-24(28)-ene-3, 5, 6-triol (3β, 5α, 6β)-triol	Antileishmanial, cytotoxic	*L. donovani*, K562, HL60	*S. terspillii*	Mohammed et al. (2017)

(continued)

Table 4.1 (continued)

N°	Molecules	Bioactivity	Biological target	Source	Reference
62	Alismol	Strong cytotoxic (>80%inhibition), High antibacterial	K562, Gram +ve (*S. aureus, S. S. epidermis and S. pneumonia*) and Gram −ve (*P. aeruginosa*)	*S. terspillii, Lobophytum sp*	Al-Footy et al. (2016), Mohammed et al. (2017)
63	Crude extract	Moderate cytotoxic	U937 and HeLa	*S. maxima*	Ellithey et al. (2014)
64	(*R*)-20-Hydroxy-N-[(2S,3S,4R)-1,3,4-trihydroxypentacosan-2-yl] nonadecanamide	Antiviral	Influenza H5N1, 100% inhibition at 1 μg/mL	*S. candidula*	Ahmed et al. (2013)
65	3b-25-Dihydroxy-4-methyl-5a,8a-epidioxy-2-ketoergost-9-ene	Antiviral	Id.	*S. candidula*	Ahmed et al. (2013)
66	*N*-[(2S,3R,E)-1,3-Dihydroxyhexacos-4-en-2-yl] icosanamide	Antiviral	Id.	*S. candidula*	Ahmed et al. (2013)
67	Crude extract	Antibacterial	–	*S. compressa*	Soliman et al. (2017)
68	Crude extract	Antifouling paint formulation	–	*S. cruciata*	Soliman et al. (2017)
69	Crude extract	Selective antifouling	–	*S. heterospiculata*	Mohamed Ali and Soliman (2010)
70	Crude extract	Antifouling activity	–	*S. variabilis*	Mohamed Ali and Soliman (2010)
	Metabolites from Cladiella sp				
71–75	Pachycladins A-E	Antimigration, antimetastatic	PC-3	*C. pachyclados*	Hassan et al. (2010)
76	(+)-Polyanthelin A	Antimigration, antimetastatic	PC-3	*C. pachyclados*	Hassan et al. (2010)
77	(6Z)-Cladiellin (cladiella-6*Z*,11(17)-dien-3-ol)	Antimigration	PC-3	*C. pachyclados*	Hassan et al. (2010)
78	3,6-Diacetyl cladiellisin	Antitumor, antimigration	PC-3	*C. pachyclados*	Hassan et al. (2010)
79	3-Acetylcladiellisin	Antimigration	PC-3	*C. pachyclados*	Hassan et al. (2010)
80–81	Klysimplexin E-F	Antimigration	PC-3	*C. pachyclados*	Hassan et al. (2010)
82	Patagonicol	Antitumor, anti-invasive	PC-3	*C. pachyclados*	Hassan et al. (2010)

(continued)

Table 4.1 (continued)

N°	Molecules	Bioactivity	Biological target	Source	Reference
83–84	Sclerophytin A-B	Antimigration, antimetastatic	PC-3	*C. pachyclados*	Hassan et al. (2010)
85	Sclerophytin F methyl ether	Antimigration	PC-3	*C. pachyclados*	Hassan et al. (2010)
86	Alismoxide	Antibacterial, selective cytotoxic	Gram +ve (*S. aureus, S. S. epidermis and S. pneumonia*) and Gram −ve (*P. aeruginosa*); HepG2	*C. pachyclados, L. crasssum*	Aboutabl et al. (2017), Hassan et al. (2010)
	Metabolites from Lobohyton sp. and Parerythropodium sp				
87	Aristol-9-ene	Antibacterial	Id	*Lobophytum sp*	Al-Footy et al. (2016)
88	Nardol	Antibacterial	Id	*Lobophytum sp*	Al-Footy et al. (2016)
89	Chalinasterol	Antibacterial	Id	*Lobophytum sp*	Al-Footy et al. (2016)
90	Nephalsterol C	Antibacterial	Id	*Lobophytum sp*	Al-Footy et al. (2016)
91	Cembrene A	cytotoxicity	*Artemia salina* and Erhlich carcinoma cells	*Lobophytum sp*	Al-Footy et al. (2016)
92	Epi-thunbergol	Mass Spawning	–	*L. crassum*	Coll et al. (1995)
93	5-Hydroxy-8-methoxy-calamenene	Specie recognition	–	*P. fulvum fulvum gray morph*	Kelman et al. (2000)
94	5-Hydroxy-8-methoxy-calamenene and 5- hydroxy-8-methoxy-calamenene-6-al	Specie recognition	–	*P. fulvum fulvum gray morph*	Kelman et al. (2000)
95	Crude extract	Feeding deterrence, antibacteria	–	*P. fulvum fulvum gray morph*	Kelman et al. (2000)
96	Fulfulvene	Antibacteria, chemical defense, allelopathy	–	*P. fulvum fulvum Yellow morph*	Kelman et al. (2000)
97	N-[(2*S*,3*S*,4*R*)-1,3,4-trihydroxyhexacosan-2-yl] icosanamide	Antivirus	Influenza H5N1, 100% inhibition at 1 μg/mL	*S. candidula*	Ahmed et al. (2013)
98	24-Methylenecholest-5-ene-1α,3β,11α-triol 1-acetate	Selective cytotoxic	HepG2	*L. crassum*	Aboutabl et al. (2017)
99	24-Methylenecholest-5-ene-3β-ol	Strong cytotoxic	HepG2, Hep-2 and HCT-116	*L. crassum*	Aboutabl et al. (2017)
100	24-Methylenecholestane-3β,5α,6β-triol	Selective cytotoxic	HepG2 IC_{50} 3.00 μM	*L. crassum*	Aboutabl et al. (2017)

4.3 Ecological Functions of the Red Sea *Alcyoniidae* Secondary Metabolites

Soft corals, deprived from a protective exoskeleton, constitute an important class of marine invertebrates which have sophisticated biochemical as well as physiological mechanisms, enabling them to produce elaborate bioactive compounds endowed with structural diversity either on their surface of secreted to their surrounding for purposes such as survival against various stresses, protection against predation, competition, or chemical communication in symbiotic relationships (Farag et al. 2017a). Soft corals belonging to the genus *Sarcophyton* are among the largest biodiversity contributors to many tropical coral habitats including the Red Sea and the Indo-Pacific region. Being a geologically "young" sea that is the Red Sea located in the warmest zone on Earth, unraveling the ecological importance or its benthic organism will be an asset to the global understanding of such marine environment. However, the status of the reef ecology research in the zone lag behind compared to the progress accomplished in other coastal regions, viz. GBR, Caribbean and the China Sea. Berumen et al. (2013) reported that almost half of the research related to the ecological aspect of the Red Sea is done in the Gulf of Eilatre presents only 2% of the Red Sea surface. Herein, we review the reported ecological function, viz. feeding deference, antibacterial, antifouling in Red Sea Alcyoniidae as well as their interaction among their benthic environment.

4.3.1 Predator Defense

Being sessile organisms located at the Seabed, soft corals cannot readily escape in time when attacked by their predators. Their chemical defense strategy relies therefore on secreting metabolites that display ichthyotoxic and antifeeding properties (Changyun et al. 2008). In (1974), Kashman and coworkers reported from *Sarcophyton glaucum* the isolation of furanocembranoid diterpenes **10** with remarkable yields of up to 3% dry weight, with (**10**) being suggested as a toxin that constitutes the major chemical defenses against coral natural predators (El Sayed et al. 1998; Hegazy et al. 2012; Kashman et al. 1974). To counteract cembrane diterpene, i.e., sarcophine toxicity inside corals themselves, cyclopropane-containing sterols found in corals (Farag et al. 2016) are suggested to be linked with coral adaptation to the membranolytic activities of their own toxins, that is, cembranoids. Such phenomenon, which involves the interdependent presence of two different types of secondary metabolites in an organism, that is, a "biochemical coordination" of the type "membranolytic toxins-unusual sterols," is evidenced for several marine sponges (Santalova et al. 2004).

With regard to antifeedant chemicals, the palatability of the Red Sea soft coral *Parerythropodium fulvum fulvum* on two generalist reef fish species *Thallasonia klunzingen* and *T. Lunare* was tested by Kelman et al. (1999). A comparative feeding assay of the coral organic extract and its sclerite were examined, with

Table 4.2 Red Sea Alcyoniidae metabolites for which bioactivity has yet to be reported, for structures refer to Fig. 4.6

N°	Identification	Coral source	Reference
101	(*Z*)-cembrenene C	*S. trocheliophorum*	Shaaban et al. (2015)
102	Flaccidoxide	*A. flaccidum*	Kashman et al. (1981)
103–105	Alcyonol A, B, C	*A. utinomi*	Hegazy et al. (2015), Kinamoni et al. (1983)
106	Cladiellisin	*C. pachyclados*	Hassan et al. (2010)
107	(3*E*,7*E*,11*E*)-18-Hydroxy-3,7,11,15(17) cembratetraen-16-14-olide	*L. crassum*	Kinamoni et al. (1983)
108	(7*E*,11*E*)-13,18-Dihydroxy-3,4-epoxy-7,11,15(17)-cembratrien-16,14-olide	*L. crassum*	Kinamoni et al. (1983)
109	3-Deoxy-20-acetylpresinularolide B	*L. crassum*	Hegazy et al. (2015)
110	3-Deoxypresinularolide B	*L. crassum*	Hegazy et al. (2015)
111	Labolide	*L. crassum*	Hegazy et al. (2015)
112	Sinularolide C	*L. crassum*	Hegazy et al. (2015)
113	Sinularolide C diacetate	*L. crassum*	Hegazy et al. (2015)
114	(22*R*,24*E*)-24-Methylcholest-5-en-3β,22,25,28-tetraol	*L. depressum*	Hegazy et al. (2015)
115	(22*R*,24*E*,28*E*)-5β,6β-Epoxy-22,28-oxido-24 methyl-5α-cholestan-3β,25,28-triol	*L. depressum*	Hegazy et al. (2015)
116	5β,6β - Epoxy - 24b – methylchloestan -3β, 22(R),25-triol	*L. depressum*	Hegazy et al. (2015)
117	Depresosterol	*L. depressum*	Hegazy et al. (2015)
118	Lobophytosterol	*L. depressum*	Hegazy et al. (2015)
119	(+)-Alismol	*L. Lobophyton*	Hegazy et al. (2016b)
120	Gorgostan-5,25-dien-3b-ol	*L. Lobophyton*	Hegazy et al. (2016b)
121	Gorgosterol	*L. Lobophyton*	Hegazy et al. (2016b)
122–123	Pauciflorol A, B	*L. pauciflorum*	Hegazy et al. (2015), Kinamoni et al. (1983)
124	Tumbergol	*L. pauciflorum*	Hegazy et al. (2015)
125	(7*E*,11*E*)-18-Acetoxy-3,4-epoxy-13-hydroxy-7,11,15 (17)-cembratrien-16,14-olide	*L. crassum*	Kashman et al. (1981)
126	(7*E*,11*E*)-18-Acetoxy-3,4-epoxy-13-epihydroxy-7,11,15-(17)-cembratrien-16,14-olide	*L. crassum*	Kashman et al. (1981)
127	Lobolide	*L. crassum*	Kashman et al. (1981)
128–133	Lobophylins A, B, C, F, G, H	*L. crassum*	Mohammed et al. (2017)
134	1,4-Peroxymuurol-5-ene	*S. ehrenbergi*	Shaker et al. (2010)

(continued)

Table 4.2 (continued)

N°	Identification	Coral source	Reference
135–136	Sinulolide A, B	*S. ehrenbergi*	Hegazy et al. (2017)
137	2*R*,7*R*,8*R*-Dihydroxydeep oxysarcophine	*S. glaucum*	Hegazy et al. (2011a, b)
138	7α,8β-Dihydroxydeep oxysarcophine	*S. glaucum*	Hegazy et al. (2011a, b)
139	Sarcophytol B	*S. glaucum*, *A. flaccidum*	El Sayed et al. (1998), Kashman et al. (1981)
140	Dioxosarcoguaiacol	*S. glaucum*	Sawant et al. (2007)
141	(+)-Sarcophytoxide	*S. ehrenbergi*, *S. trocheliophorum*	Shaaban et al. (2015), Shaker et al. (2010)
142	16-Oxosarcophytonin E	*S. trocheliophorum*	Hegazy et al. (2013)
143	Bisabolene	*S. trocheliophorum*	Shaaban et al. (2015)
144	Alloaromadendrene	*S. trocheliophorum*	Shaaban et al. (2015)
145	Caryophyllene	*S. trocheliophorum*	Shaaban et al. (2015)
146	ß-Elemene	*S. trocheliophorum*	Shaaban et al. (2015)
147–148	Trochelioid A, B	*S. trocheliophorum*	Hegazy et al. (2013)
149	Cholesterol	*S. candidula*	Abou El Ezz et al. (2015)
150	24-methylene cholesterol	*S. candidula, S. terspilli*	Abou El Ezz et al. (2015), Mohammed et al. (2017)
151	Chimyl alcohol	*S. candidula*	Abou El Ezz et al. (2015)
152	5-Epi-sinuleptolide	*S. gardineri*	El Sayed and Hamann (1996)
153	Sinuleptolide	*S. gardineri*	El Sayed and Hamann (1996)
154	Ineleganolide	*S. polydactyla*	Hegazy et al. (2016a)
155	Scabrolide F	*S. polydactyla*	Hegazy et al. (2016a)
156–158	Sinularcasbane M, N, O	*S. polydactyla*	Hegazy et al. (2016a)
159	24-Methylenecholesterol	*S. terspilli*	Mohammed et al. (2017)
160	24α-Methyl cholesterol	*S. terspilli*	Mohammed et al. (2017)
161	Gorgosten-5(*E*)-3β-ol	*S. terspilli*	Mohammed et al. (2017)
162	24-Methylenecholest-5-ene-1α,3β,11α-triol	*L. crassum*	Aboutabl et al. (2017)
163	24-Methylenecholestane-1α,3β,5α,6β,11α-pentol	*L. crassum*	Aboutabl et al. (2017)

feeding deterrence found to be more associated with the organic extract. Further experimentation on the embryo expressed a higher response of deterrence mainly attributed to the mucus covering it that is likely to encompass more chemically active substance with antipredatory properties, with chemical structure or active substances yet to be elucidated. Compound [**96**] isolated from the yellow morph *Parerythropodium fulvum fulvum* was found active protectant of the coral species against two fish species (Kelman et al. 1999).

4.3.2 Interspecific Competition for Space

The competition for living space is frequent among benthic marine organisms in which a taxon can outcompete another one through the secretion of specific allelochemicals to a non-recognized species (Changyun et al. 2008). Allelochemicals are also found in terrestrial plants and to function in weed management system (Asaduzzaman et al. 2015). Nevertheless, much less is known regarding allelochemicals functioning in corals. This interspecific interaction is suggested to provide a margin and enough space to soft coral to grow with enough food (Sammarco et al. 1983).

A self/non self-mechanism was demonstrated by Frank et al. (1996) on the soft coral *P. fulvum fulvum*. This allogeneic recognition study, the first in Alcyoniidae family, consists of a tissue to tissue contact between 13 large colonies. While the isogenic repaired and fused themselves perfectly, the allogeneic species had two different responses. Allogeneic encounters were experimentally arranged in Eilat, Red Sea for the first time in the Alcyonacea (Frank et al. 1996). Two allopathic responses were observed in which the first exhibited a retreat growth ending with a separated two growing organisms. In contrast, the other reaction consisted of a unilateral or reciprocal tissue overgrowth.

4.3.3 Antifouling Activity

Antifouling property is the ability to hinder the growth or settlement of a biofilm on a given surface. The current method, of interest in the Naval industry to coat ships, requires the use of toxic chemicals mixed with the external paints which is not only expensive but ecologically unfriendly (Soliman et al. 2017). Following the observation that no organisms attach to soft corals bodies due to their chemical secretion (Changyun et al. 2008), they have been regarded as a potential source of environmentally friendly antifouling chemicals.

A MeOH:DCM extract from five soft corals species *Sinularia variabilis, S. polydactyla, S. heterospiculata, L arboretum, and S trocheliophorum* were studied as a paint formulation for their antifouling properties (Mohamed Ali and Soliman 2010) against the main fouling organism barnacle *Balanus amphitrite* and the tube worm *Hydroides elegans*. The responses were taken at 7, 17, 31, and 62 days post-exposure where the mass of the remaining fouling organism was measured. While the *S. heterospiculata* and *S. variabilis* exhibited the highest response to both fouling organisms, *S. polydactyla* was responsive to the barnacle only. Further analysis to identify the chemical nature of the antifouling agent should now follow in that crude extract (Mohamed Ali and Soliman 2010). A similar investigation was performed assessing seven Red Sea soft coral extracts by Soliman et al. (2017) where an Alcyoniidae *S. compressa* and a xenidae *H. fuscescens* were the most responsive to the marine biofouling barnacle and tubeworms.

4.3.4 *Alcyoniidae Interaction and Biodiversity in Its Benthic Environment*

Soft coral communication within its surrounding environment is of chemical nature, and besides their protective function, those chemicals have another purposes for coral life. In (2000), a study by Kelman et al. of the major secondary metabolite of *P. fulvum fulvum* led to the discovery of their intraspecific variation toward different geographical location. Fulfulvene **96** and calamenene (**93–94**) were, respectively, dominant of the yellow and gray morph of the soft coral found in the Red Sea, at Eilat. Following an ESI-MS analysis of the each colored species, a qualitative difference on their metabolic profile was noticed. Compound [**104**] occurred at 10.1 ± 4.1 and $2.9 \pm 3.8\%$ of crude organic extract in the shallow and deep colonies, respectively. This result corroborates with the compositional differences observed among *Sarcophyton* sp collected from different sites along the Egyptian Red Sea coast (Farag et al. 2016). The specific metabolites that contributed to discriminate between soft corals of *S. ehrenbergi* from the three different growing habitats belonged to cembrane-type diterpenes. Furthermore, compared to wild corals, aquarium grown species were found being less enriched in cembranoids and more enriched in oxylipids (Farag et al. 2016). Cembranoids therefore play an ecological role in coral life as discussed above and are more likely to be produced at higher levels where corals are under more stressful marine conditions compared to corals grown in an aquarium tank. This study is also the first to derive *Sarcophyton* species relatedness based on metabolite data not only from Red Sea area, as molecular phylogenetic analyses alone so far have been insufficient to clearly identify *Sarcophyton* species. The lack of understanding in both intraspecific variations of diagnostic morphological characters within that genus in addition to a lack of solid taxonomic and ecological work on *Sarcophyton* poses problems to derive a clear phylogenetic-based analysis.

Biopharmaceutical production of soft corals marine products or chemical, in order to give an efficient product, requires an in vitro culture followed by manipulation of the cultural parameters such as pH, temperature, nutrition, and chemical elicitors to enhance the production of the targeted molecule (Farag et al. 2017b). This method is already applied in the biomedical field and the extraction of natural compounds from endophyte, microorganisms or plants, whereas a promising research has been applied by Farag et al. (2016). The comparison between elicitations of several Red Sea corals produced varied responses where the oxylipins, viz. methyl jasmonate (MeJa) and its animal analogue prostaglandin (PG) showed higher product levels than other tested chemical elicitors. As a continuity of the report by Farag et al. (2017a), more analysis was done on two soft corals from the Red Sea. The effect of oxylipins on soft corals metabolism resulted in an upregulation of campestene-triol and a cembranoid in *Sarcophyton glaucum* compared to the use of geranylgeranyl phosphate (GGP) and arachidonic acid (AA) or wounding.

4.4 Conclusion and Future Perspectives

This review reports on the potential ecological and biological role of many coral metabolites influencing stress responses, virulence, and their further effects in humans as drug leads for treatment of various ailments. Improvement of coral-producing organisms and active constituents yield in natural extracts is ongoing challenge facing the nutraceutical industry. The production of metabolites in marine animals is also often low and depends greatly on ecological conditions where it survives. The response of sessile marine animals to stress conditions compared to plants is indeed in contrast much less explored. The biotechnological production of valuable secondary metabolites in coral using in vitro cultures is an attractive alternative, which has yet to be examined at a commercial scale. In addition, a detailed dissection of coral secondary metabolome is required to understand how coral metabolic responses are elicited. This issue is complicated considering that the exact origin of coral bioactive chemicals is not identified especially with coral acting as a holobiont encompassing several living organism algae, fungi, and bacteria, a challenge to decipher each organism role in producing these assortments of chemicals. Despite increasing reports, many aspects of corals metabolic pathways, regulation and perception, are still poorly characterized. The combined analysis of metabolic and gene expression profiles will likely be an increasingly powerful approach to identify candidate genes involved in the production and regulation of biologically active coral compounds. Classifying the Red Sea corals based on the characteristic metabolite signature of each species will bridge the gap between the complex relationship between the coral host and their symbiont as well as the chemical signature of the Alcyoniidae family. Moreover, systematic use of ^{13}C-mass isotopomers and ^{13}C-labeling associated with MS analysis should lead to progress in characterization of biochemical pathways involved in coral secondary metabolites production. This could also be facilitated by simultaneous monitoring, directly in crude extracts without the need for fractionation, of a large number of metabolites by spectroscopic techniques. An extended investigation on the chemical ecology of the Red Sea coral should also gain more attention as its unique environment and to impact its genetic makeup and adaptation differently from that of the other coastal regions. Finally, the Alcyoniidae family encompasses a wide array octocoral organism identified along the Red Sea that have yet to be reported for in terms of its chemical composition compared to results from other generic species. Therefore, identification and profiling of less investigated species in the Red Sea will provide a rich database of marine metabolites in that region.

The biological and chemical research of the coral reefs has made a remarkable progress as reviewed herein yet the support information of the biodiversity, functions profile and ecological landscapes still to be acquired. Flora, fauna, and fisheries are facing future threats by human activities such as heavy harvesting and environmental impact including global warming, habitats destruction and pollution. The decrease in water quality, salinity, and substrate changes are some of the factors

that influenced negatively the oceans and could be easily translated to the reef corals, and thus, loss would be able to predict accompanied with shifting of the biodiversity and biological activity. Protecting the marine and particularly the corals natural properties is a multi-dimensional task where molecular biology and genomics could play a central role to report the configuration and accommodate the unique features. The first step is to identify the underlying biological and ecological processors/indices and create an evidence-based foundation for the coral population.

We anticipate that the future management and policy tools should be directed to restore the coral ecosystem. Future studies should attribute to the consistent complexity of the coral different habitats, and this is something we attempt to address in our ongoing projects in order to identify habitat indices and quantitative measures for the habitats structure. Future classification, mapping, and management could be planned to incorporate the importance of the coral community but also to assure the conservation and stability of the ecosystem. Identifying and monitoring the coral stock status at both national and international scales would aid the global goal to preserve the marine ecosystem and the parallel human activities in particular fisheries. The food web structure including fisheries is known as the ocean-based stocks where dietary nutrients, food security, and drug developments are all common features. Thus, the complementary expansion into the coral habitual complexity, sustainability in parallel to fisheries conservation would be highly recommended.

Acknowledgements M. A. Farag acknowledges the funding received from the Alexander von Humboldt foundation, Germany. H. R. El-Seedi is very grateful to the Swedish Research links grant 2016-05885 (VR for the years 2017–2019) for generous financial support and to Jiangsu University, China for Adjunct Professor fellowship.

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