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REVIEW ARTICLE

Chemical and Bioactive Marine Natural Products of Coral-Derived Microorganisms (2015–2017)

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Abstract: Coral-derived microorganisms are known for their inherent ability to produce novel products of pharmaceutical importance. Nearly 260 marine natural products (MNPs) have been isolated from coral-derived microorganisms till 2014. In the last three years, 118 MNPs have been isolated from coral-associated microorganisms including 46 new compounds, two with a novel skeleton, and four new natural products. Most of them exhibited *in vitro* or *in vivo* activities against tumor cell lines, parasites, pathogenic bacteria, fungi and virus. We reviewed the natural products reported from 2015 to 2017 that have a wide range of bioactivities against different biological targets.

Keywords: Coral-derived microorganism, marine natural product, bioactivity, drug potential.

1. INTRODUCTION

The mysterious marine has afforded an unprecedented source of diverse natural products. More than thirty thousand marine natural products (MNPs) have been reported till 2017. These compounds showed potent antitumor, antibacterial, antiviral, antifungal, antiparasitic and anti-inflammatory properties [1]. Corals, the biomass abundant invertebrates in coral reef ecosystems, have drawn widespread attention for their abundant associated microorganisms and diverse bioactive natural products [2].

In the past decades, culture-free and cultivable techniques were used to study the population associated with the mucus and tissue of corals. Potentially, the coral-associated microorganism communities have functions relating to coral health, nutrition and disease. Focusing on the diversity and stability of these microorganisms is necessary for the conservation of marine ecosystem. In 2015, the biological and chemical diversity of coral-associated microorganisms has been reviewed [3]. Additional research on the diversity of corals and their associated microbial communities is well underway by researchers. During the last three years, more attention has been paid to explore microorganism resources of coral sources, including the diversity of coral associated bacteria [4–6], actinobacteria [7], and fungi [8,9], and the potential impacts of microorganisms on their coral hosts [10–13]. Microbial community inhabiting the surface mucus layer of corals is the most diverse with the production of PKS and NRPs compounds playing potential roles in coral defense [12]. Focusing on the diversity of coral-associated microorganisms can lead to the discovery of novel active metabolites with potential pharmacology applications.

The reported MNP numbers (see Fig. **1**) each year in the last three years are almost the same and many studies reported novel chemical structures and their biological activities. This review focuses on chemical diversity and pharmacological applications of these MNPs isolated from coral-derived microorganisms from 2015 to 2017.

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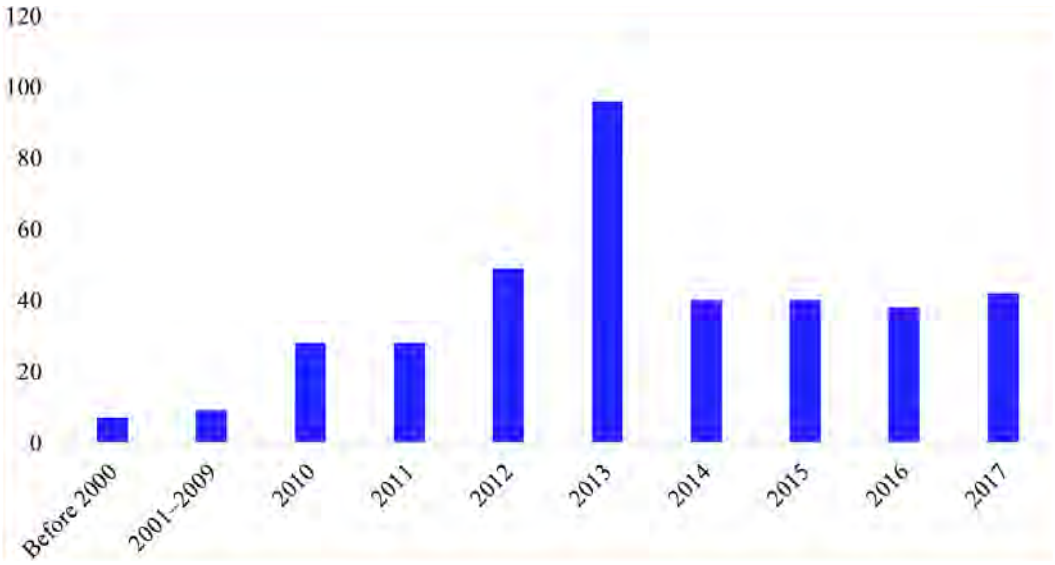


Fig. (1). The reported numbers of marine natural products isolated from coral-derived microorganisms.

2. CHEMICAL AND BIOACTIVE NATURAL PRODUCTS FROM CORAL-DERIVED MICROORGANISMS

From 2015 to 2017, 118 marine natural compounds have been isolated from coral-derived fungi and bacteria, including 46 new compounds, two compounds with new carbon skeleton and four new natural products (with *). These compounds were classified as alkaloids, peptides, polyketides, terpenoids, and others according to their structural features (see Fig. **2**). Of which the alkaloids and polyketides are still the two main classes. Alkaloids, peptides, and polyketides occupy a thematic position in pharmacological aspects. Pathogenic bacteria and fungi, virus, cancer cell lines, and enzymes relating to certain disease were used as models for bioassay. Herein, we summarize the structures and biological activities of natural products from coral-derived microorganisms. For convenient comparison, all the units were unified into "μM".

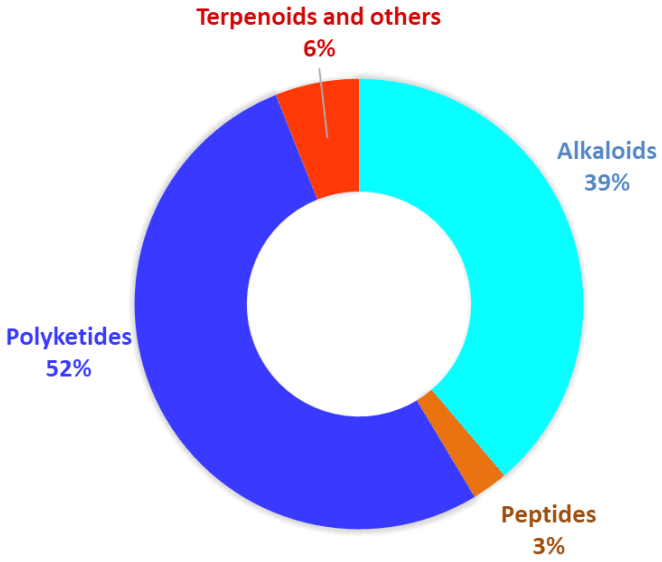


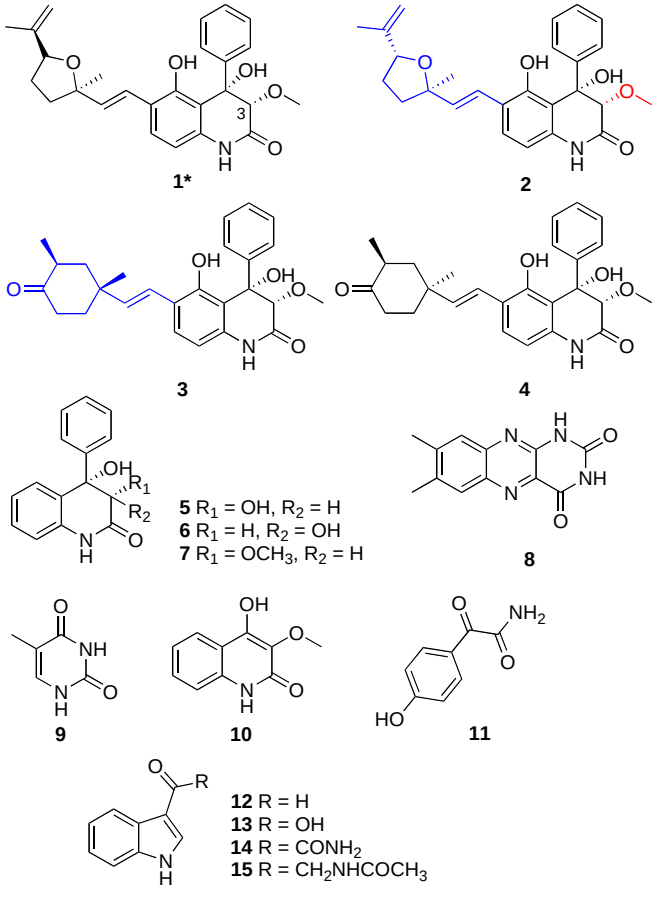
Fig. (2). Percentage distribution of marine natural products isolated from coral-derived microorganisms based on their putative biogenetic origin.

2.1. Alkaloids

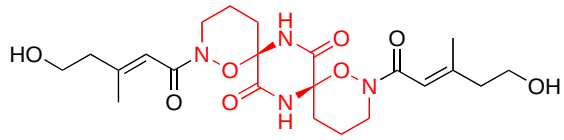
The abundant alkaloid family consists of quinolones, piperazines, indoles, and azole derivatives. These compounds displayed potential in antiviral, antipathogenic microbial, cytotoxic, and antifouling aspects.

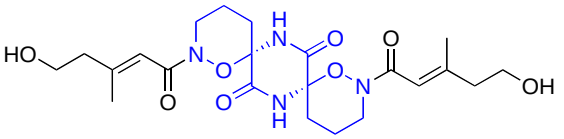
The fungus *Scopulariopsis* sp. (TA01-33) showed producing alkaloids of novel structures (gorgonian coral *Carijoa* sp., South China Sea, China). Fumiquinazoline L, with a heptacyclic skeleton formed *via* a bridging hemiaminal linkage, was obtained by fermentation in liquid potato medium [14]. Additionally, a series of dihydroquinolins containing terpenoid chain were isolated by solid rice fermentation, including scopuquinolone A (**1**), aniduquinolone A (**2**), aflaquinolones A, D, F, and G (**3**–**6**), and 6-deoxyaflaquinolone E (**7**) [15,16]. Compounds **2**–**5** and **7** exhibited potent antifouling activity against larval settlement of the barnacle *Balanus amphitrite* with very low EC_{50} values of 17.50 *p*M, 28.00 *n*M, 2.80 *n*M, 0.86 μM, and 1.04 μM, and very high therapeutic ratios (LC_{50}/EC_{50} 1200, 205, 57, 91, and 89). Compounds **2** and **3** showed potent and promising antifouling candidates for developing environmentally-benign antifoulants. Structure-activity relationships (SAR) of these compounds indicated that lipophilicity of the

cycloaliphatic ring is crucial for antifouling activity, and *S* configuration of C-3 enhances bioactivity. The fungus *Scopulariopsis* sp. (ST-F1) produced diverse alkaloids (**8**–**15**) by different fermentation medium (hard coral *Stylophora* sp., Red Sea, Egypt). Lumichrome (**8**) was obtained from solid rice medium [17], 5-methyluracil (**9**), 4-hydroxy-3-methoxy-2(1*H*)-quinolinone (**10**), 4-hydroxyphenylgly oxylic acid amide (**11**), indole-3-carboxaldehyde (**12**), indole-3-carboxylic acid (**13**), (1*H*-indol-3-yl) oxoacetamide (**14**), and *N*-acetyl-*β*-oxotryptamine (**15**) were isolated from solid white bean medium [18]. Compounds **8**–**15** were evaluated for their cytotoxicity against mouse lymphoma cells (L5178Y), anti-tubercular activity against *Mycobacterium tunerculosis*, and antibacterial activity against pathogenic bacteria *Staphylococcus aureus*, and *Acinetobacter baumannii* at 10 μg/mL. However, no obvious activities were observed.



The fungus *Pestalotiopsis* sp. (ZJ-2009-7-6) fermented in rice-$CaCl_2$-KBr solid fermentation (soft coral *Sarcophyton* sp., South China Sea, China) produced a pair of enantiomeric alkaloid dimers, (+)- and (−)-pestaloxazine A (**16** and **17**) [19]. The compounds featured an unprecedented symmetric spiro-[oxazinane-piperazinedione] skeleton. Compounds **16** and **17** exhibited potent antiviral activity against enterovirus 71 (EV71) with IC_{50} values of 14.20 and 16.10 μM, respectively.



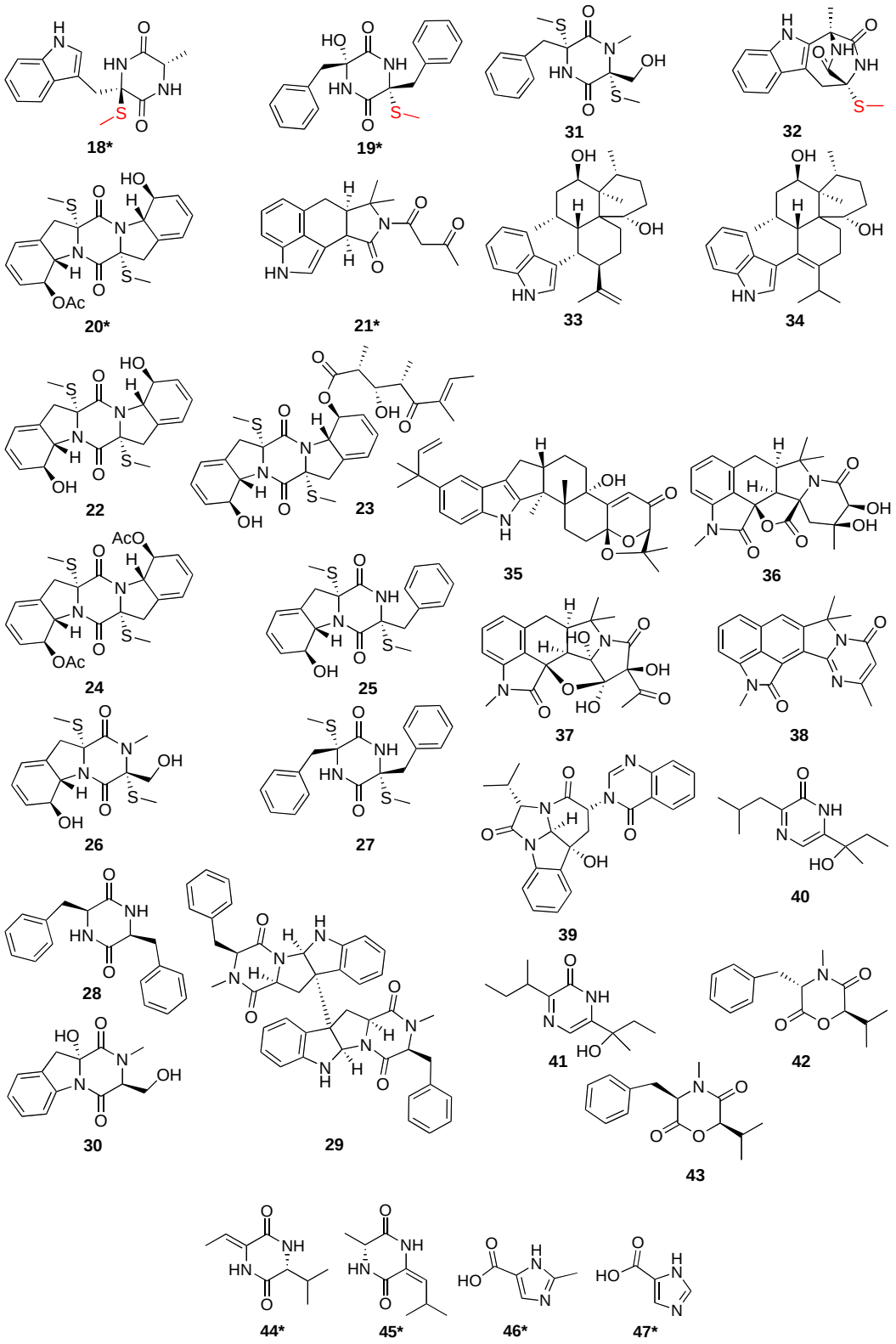


The soft coral derived fungi *Pseudallescheria ellipsoidea* (F42-3), *P. boydii* (F19-1), and *Dichotomomyces* sp. (L-8) produced different chemical classes of alkaloids (**18**–**43**) (soft coral *Lobophytum crissum*, South China Sea, China). These alkaloids were pseudellone D (**18**) [20], pseuboydones C–E (**19**–**21**), boydines A and B (**22**, **23**), haematocin (**24**) [21], phomazine B (**25**), bisdethiobis (methylthio) gliotoxin (**26**), *cyclo*-(2,2'-dimethylthio)-Phe-Phe (**27**), *cyclo*-(Phe-Phe) (**28**), ditryptophenaline (**29**), dichotocejpin C (**30**) [22], *bis*-*N*-norgliovictin (**31**), lasiodipline F (**32**) [20], 24,25-dehydro-10,11-dihydro-20-hydroxyaflavinin (**33**), aflavinine (**34**), *β*-aflatrem (**35**), cyclopiamide E (**36**), speradines B and C (**37**, **38**), pseudofischerine (**39**), 4-(1-hydroxy-1-methylpropyl)-2-isobutyl-pyrazin-2(1*H*)-one (**40**), 4-(1-hydroxy-1-methyl-propyl)-2-secbutylpyrazin-2(1*H*)-one (**41**) [22], (*S*, *R*)-bassiatin (**42**), and (*R*, *R*)-bassiatin (**43**) [20]. Compounds **19**, **28**, **33**, **34**, and **38** exhibited strong toxic activity against the fall armyworm *Spodoptera frugiperda* Sf9 cells with IC_{50} values of 0.70, 0.80, 0.50, 0.40, and 0.90 μM [21]. Compound **24** showed moderate inhibitory activity against human breast cancer MDA-MB-435 cell line with an IC_{50} of 7.34 μM [22].

A coral-derived bacterium *Brevibacterium* sp. (L-4) produced four known alkaloids, brevibactins B and C (**44**, **45**), 2-methyl-3*H*-imidazole-4-carboxylic acid (**46**), and 3*H*-imidazole-4-carboxylic acid (**47**) (unknown coral, South China Sea, China) [23]. These compounds were reported as natural products for the first time.

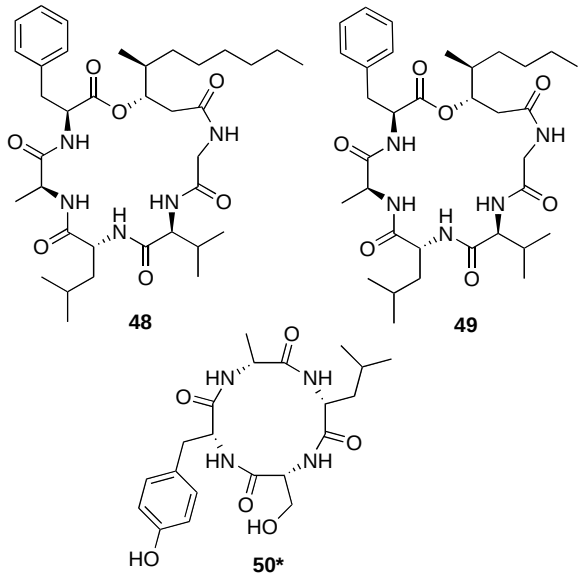
2.2. Peptides

In addition to diverse alkaloids, the cyclohexadepsipeptides, scopularides A and B (**48**, **49**),



were also obtained from the *Scopulariopsis* sp. (ST-F1) fungus [17]. Coincidentally, **48** and **49** were first isolated from the same genus *Scopulariopsis* (sponge *Tethya aurantium*, Limski Fjord, Croatia) [24]. Moreover, the cyclotetrapeptide brevibactin A (**50**) was obtained from the bacterium *Brevibacterium* sp. (L-4) (unknown coral, South China Sea, China) [23]. Compound **48** exhibited strong cytotoxic activity against the murine lymphoma cells (L5178Y) with an IC_{50} of 1.20 μM. Additionally, compounds **48** and **49** inhibited the

growth of pancreatic cancer cells (Colo357 and Panc89) and colon cancer cells (HT29) at 10 μg/mL, with inhibitory ratio of 36% (**48**)/26% (**49**) (Colo357), 42% (**48**)/49% (**49**) (Panc89), and 37% (**48**)/24% (**49**) (HT29). Elementary SAR of **48** and **49** suggested that the length of the aliphatic side chain (lipophilicity) is important for the cytotoxicity [17, 25].

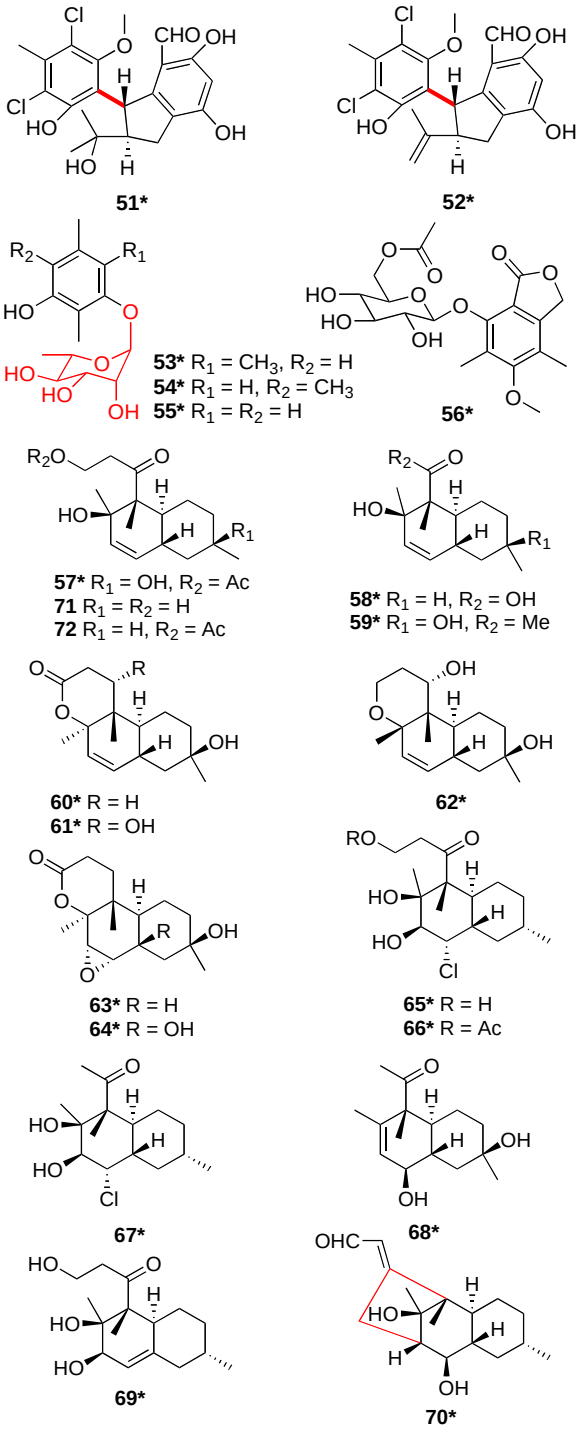


2.3. Polyketides

The polyketides are a large family with diverse structures, including quinones, macrolides, γ-pyrones, benzene derivatives, fatty acids, and others. The polyketide family is of great value in the field of antibiotic, antiviral, antitumor, antiparasitic, and antiinflammation.

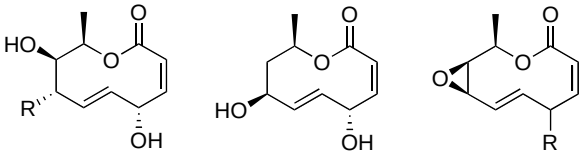
Dichlorinated diphenylmethanes (±)-pestalachlorides C and D were obtained from the fungus *Pestalotiopsis* sp. (ZJ-2009-7-6) fermented by liquid potato medium in 2013. Further investigation on the fungal strain ZJ-2009-7-6 by fermentation in rice solid medium led to the isolation of other new compounds, including two new (±)-pestalachlorides E and F (**51**, **52**) [26], three new rhamnosylated phenols pestarhamnoses A–C (**53**–**55**) [27], and a new phthalide derivative pestalotiolide A (**56**) [28]. Compounds (±)-**51** and (±)-**52** exhibited potent antifouling activity against the larval settlement of the barnacle *Balanus amphitrite* with EC_{50} values of 3.75 and 1.30 μM, and high therapeutic ratios with LC_{50}/EC_{50} > 30.3 and 18.2. Compound **56** exhibited anti-EV71 activity, with an IC_{50} of 27.70 μM.

The fungus *Libertasomyces* sp. (DYZ-027) was the source of diverse novel *trans*-fused decalins, libertalides A-N (**57**−**70**), and the known aspermytin A (**71**) and aspermytin A acetate (**72**) (soft coral *Sinularia sandensis*, South China Sea, China) [29]. Compound **70** is characterized by α-enol ether bridge conjugating with an aldehyde group. Immunoregulatory activity of this chemical class was reported for the first time. Compounds **58**, **64**, and **71** significantly induced the proliferation of $CD3^+$ T cells, and **61**, **65**, **68** and **72** increased the $CD4^+/CD8^+$ ratio obviously.



The soft coral *Sarcophyton* sp. (GX-WZ-20080011) was the source of many bioactive fungi including *Al-*

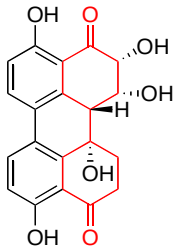
ternaria sp. (ZJ-2008003) [30], *Aspergillus elegans* (ZJ-2008010) [31], *Lophiostoma* sp. (ZJ-2008011) [32], and *Alternaria* sp. (ZJ-2008017) [33]. The *Alternaria* sp. (ZJ-2008003) fungus produced a class of antibiotic quinones, while *Aspergillus elegans* (ZJ-2008010) was the source of cytochalasin antifoulants. Chemical investigation of the *Lophiostoma* sp. (ZJ-2008011) fungus led to the isolation of a series known antibiotic macrolides, (3*Z*,4*S*,5*S*,6*E*,7*S*,8*S*,9*S*,10*R*)-8-chloro-5,8,9,10-tetrahydro-5,9-dihydroxy-10-methyl-2*H*-oxecin-2-one (**73**), modiolide A (**74**), curvulides B1 and B2 (**75**, **76**), and curvulalide (**77**). Compound **73** displayed moderate antibacterial activity against *Bacillus cereus* and *Escherichia coli* with MICs of 3.12 and 6.25 μM, respectively. Compound **74** exhibited weak antibacterial activity against *Micrococcus luteus* and antifungal activity against *Neurospora crassa*. [34] Furthermore, the known head-to-head perylenes 7-*epi*-8-hydroxyaltertoxin I (**78**), stemphytriol (**79**), altertoxin I (**80**), stemphyltoxin II (**81**), and a head-to-tail stemphyperylenol (**82**) were obtained from *Alternaria* sp. (ZJ-2008017). Compound **80** exhibited strong teratogenicity against zebrafish embryo (Danio rerio) with an IC_{50} of 12.89 μM. Compound **80** also showed potent antifouling activity against the settlement of the barnacle *B. amphitrite* with an IC_{50} of 0.77 μM.



73 R = Cl
77 R = OH

74

75 R = β-OH
76 R = α-OH



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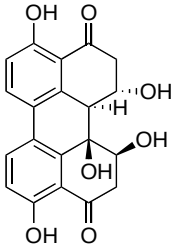

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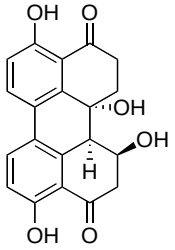

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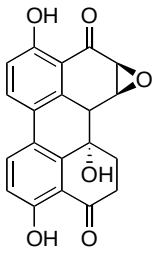

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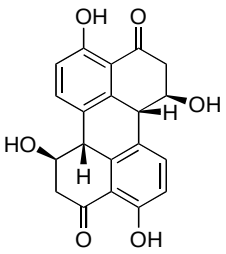
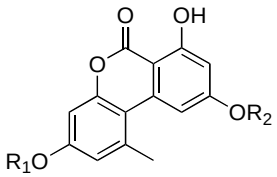
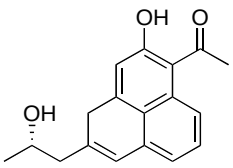


82

Bioassay-guided investigation of the fungus *Alternaria alternata* led to the isolation of three known antiviral compounds, alternariol-9-methyl ether-3-*O*-sulphate (**83**), alternariol-9-methyl ether (**84**), and alternariol (**85**) (soft coral *Litophyton arboretum*, Egyptian Red Sea, Egypt) [35]. Compounds **84** and **85** showed strong antiviral activity against HCV NS3-NS4A (IC_{50} 118.38 and 46.51 μM), while compound **83** was weak in the bioassay. The inhibitory activity against HCV NS3NS4A for these compounds would be reinforced by the increasing of free hydroxyl groups in the structure and weakened by the removal or blockade of the free hydroxyl groups. Once the hydroxyl groups were sulfonated or methylated, activities of compounds **84** and **85** decreased markedly. Furthermore, **84** and **85** were proved to be non-selective protease inhibitors of human trypsin. Additionally, the actinomycete *Streptomyces griseorubens* sp. (ASMR4) produced a new alternariol analogue 8-hydroxy-2-(2-hydroxypropyl)-7-acetyl-1-oxaphenalene (**86**) (unknown soft coral, Egyptian Red Sea, Egypt) [36]. However, **86** was inactive against the tested bacteria and cancer cell lines.



83 R_1 = SO_3H, R_2 = CH_3
84 R_1 = H, R_2 = CH_3
85 R_1 = R_2 = H

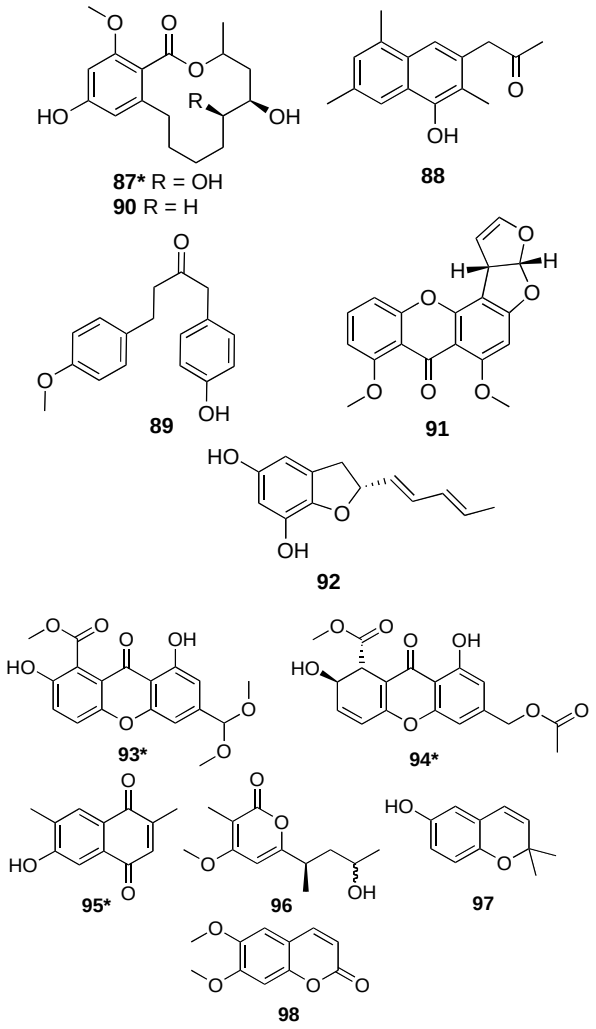


86*

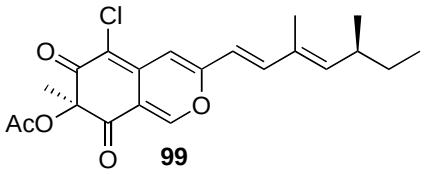
Chemical investigation of the fungi *Pseudallescheria ellipsoidea* (F42-3) [20], *P. boydii* (F19-1) [21], and *Dichotomomyces* sp. (L-8) [22] led to the isolation of diverse polyketides, including (5*S*,6*S*)-dihydroxylasiodiplodin (**87**), dichotones A and B (**88** and **89**), (5*S*)-hydroxylasiodiplodin (**90**), *O*-methyl sterigmatocystin (**91**), asperfuran (**92**). Compound **91** was first isolated from a toxigenic fungus *Aspergillus flavus* [37]. However, **91** has not shown any toxicity. While, its demethylated natural product sterigmatocystin exhibited strong activity against the growth of transplanted leukemias P-388 and L1210 in mice, and toxic to humans [38].

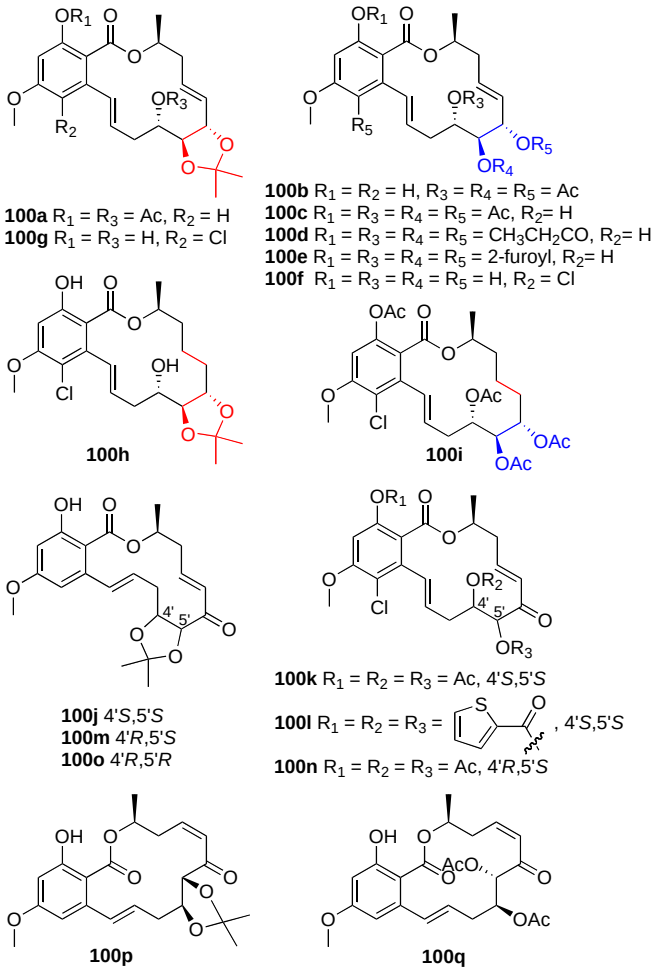
Diverse polyketides were obtained from the fungus *Scopulariopsis* sp. (ST-F1) cultivated in different fermentation media [17,18], including 12-dimethoxypinselin (**93**), 12-*O*-acethyl-AGI-B4 (**94**), 6-hydroxy-2,7-dimethyl-1,4-naphthoquinone (**95**), scopupyrone (**96**), 6-hydroxy-2,2-dimethyl-2*H*-chromene (**97**), and scoparone (**98**). However, they were inactive in cytotoxic and antibacterial assays.

The fungus *Penicillium sclerotiorin* (CHNSCLM-0013) produced the known (+)-sclerotiorin (**99**) with high yields (gorgonian coral *Anthogorgia ocbracea*,



South China Sea, China) [39]. Compound **99** and its semi-synthetic derivatives exhibited strong antifouling activity against the larval settlement of the barnacle *Balanus amphitrite* with low EC_{50} values ranging from 1.21 to 46.67 μM, and high therapeutic ratios with LC_{50}/EC_{50} of 20–106. Protein kinase G (PknG) is an important enzyme in the survival of the Mycobacterium in the host macrophages, and targeting the PknG is an effective strategy for developing anti-TB leads [40]. Compound **99** exhibited strong inhibitory activity against PknG with an IC_{50} value of 76.5 μM [41]. Interestingly, **99** reduced mycobacterial growth in infected macrophages without side-effect on macrophages. Further investigation of these compounds may lead to the development of novel anti-TB agents.

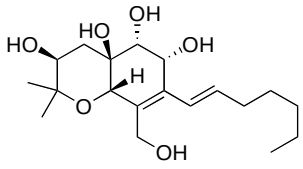




In the previous study, a series of 14-membered resorcylic acid lactones, with potent antifouling activity, have been isolated from the gorgonian *Dichotella gemmacea* (GX-WZ-20080034) derived fungi *Cochliobolus lunatus* (ZJ-2008002) [42]. Recently, new research advances of these compounds have been made [43]. A series of derives (**100a**–**100q**) were semi-synthesized from cochliomycin A and zeaenol. Compounds **100a**–**100c**, **100p** exhibited strong antiplasmodial activity against *Plasmodium falciparum* with IC_{50} values of 1.84, 8.36, 6.95, and 8.95 μM, and very high therapeutic indices (CC_{50}/IC_{50} > 180). The acetonide functionality in **100a** improved the IC_{50} value approximately 4-fold over that of **100c** with the acetoxy groups at C5'-C6', suggesting that the acetonide functionality might contribute to the antiplasmodial activity. Compounds **100a**, **100g**–**100l**, **100p**, and **100q** displayed obvious antileishmanial activity against *Leishmania donovani* with IC_{50} values of 1.24–9.22 μM. Additional toxicity against mammalian kidney cells (Vero) were screened *in vitro*. Compounds **100a**–**100c** showed pronounced selectivity indices (SI > 300) representing po-

tentially promising antiplasmodial and antiplasmodial leads for further research.

Recently, fungi *Eutypella* sp. (ZJ-20080090) and *Phoma* sp. (TA07-1) from the same coral *D. gemmacea* produced new compounds, cytosporin L (**101**) [44] and phomaethers A–C (**102**–**104**) [45]. Compound **101** showed moderate antiviral activity against the respiratory syncytial virus (RSV, IC_{50} 70.01 μM). Additionally, **101** also displayed moderate antibacterial activity towards *Micrococcus lysodeikticus* and *Enterobacter aerogenes* with the same MIC values of 3.12 μM. Compounds **102** and **104** displayed moderate antibacterial activity against *S. albus*, *S. aureus*, and *E. coli* (MIC 0.31–1.25 μM).



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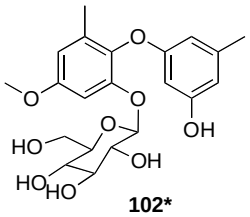
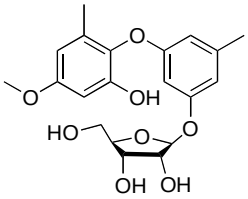


102*



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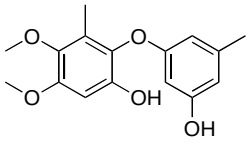
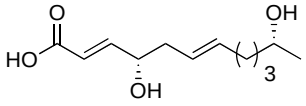


104*

A series of hexaketides, including two new cladospolides E and F (**105** and **106**), and four known secopatulolides A and C (**107** and **108**), 11-hydroxy-γ-dodecalactone (**109**) and iso-cladospolide B (**110**), were obtained from the fungus *Cladosporium* sp. (TZP-29) (unknown soft coral, South China Sea, China) [46]. Compounds **105**–**110** were tested for their lowering effects against oleic acid-elicited lipid accumulation in HepG2 liver cells. Compounds **105** and **107**–**109** significantly decreased the lipid accumulation with IC_{50} values of 12.10, 8.40, 13.10, and 7.10 μM, respectively.

The actinomycete *Streptomyces* sp. (M-207), isolating from a deep-sea coral sample, produced a new lobophorin K (**111**) (gorgonian coral *Lophelia pertusa*, Cantabrian Sea) [47]. Compound **111** showed moderate cytotoxic activity against human immortalized hepatocyte (THLE-2) cell line with an IC_{50} value of 6.30 μM. Compound **111** also displayed selective activity against a series of methicillin-sensitive *Staphylococcus aureus* with MIC_{90} ranging from 34.13 to 68.26 μM.



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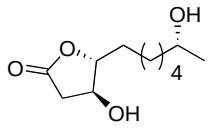

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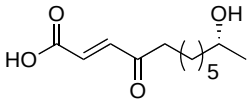
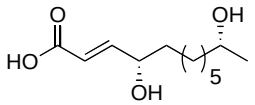


107



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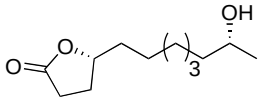

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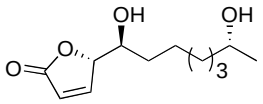

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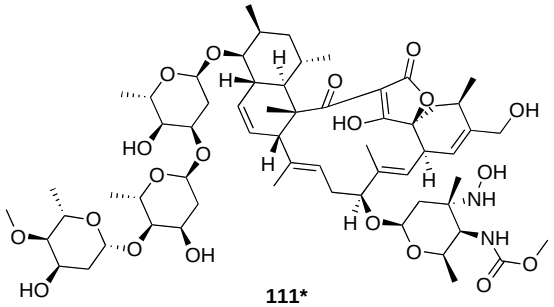
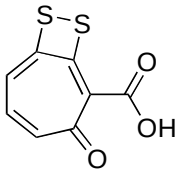


111*

TDA (**112**), with strong inhibition against coral pathogens *Vibrio coralliilyticus* and *V. owensii* was isolated from a reef-building coral-associated bacterium *Pseudovibrio* sp. (scleractinian coral *Pocillopora damicornis*, Great Barrier Reef, Australia) [48]. Research conjectured that **112** may derive from dimethylsulfoniopropionate (DMSP). The catabolism precursor was produced in high concentrations by reef-building corals and played a role in structuring coral bacterial communities, then prevented coral diseases [49].

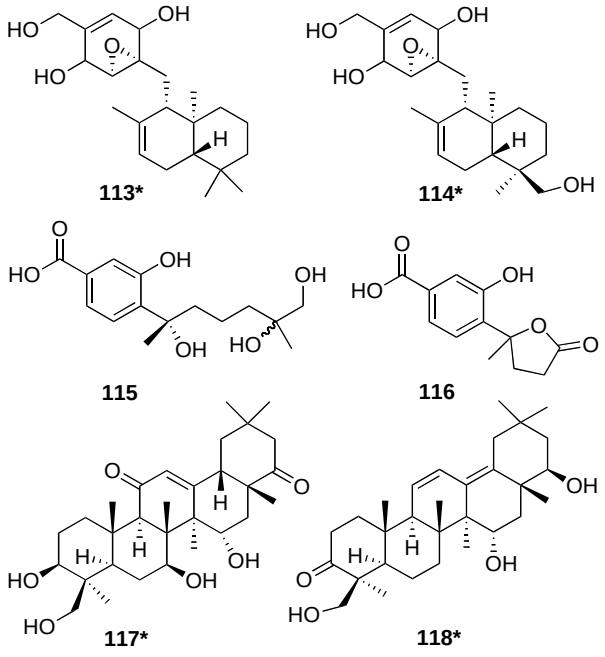


112*

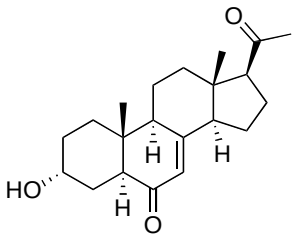
2.4. Terpenoids and Steroids

A soft coral-derived fungus *Lophiostoma* sp. (ZJ-2008011) [32] led to the isolation of craterellins A and D (**113**, **114**). Compound **113** displayed moderate antibacterial activity against *Bacillus cereus*, *Escherichia coli*, *Staphylococcus aureus*, and *Micrococcus luteus* with MICs of 3.12, 6.25, 6.25, and 6.25 μM. Another two sesquiterpenoids, 11,12-dihydroxysydonic acid (**115**) and 1-hydroxyboivinianic acid (**116**), were

isolated from the fungus *Scopulariopsis* sp. (ST-F1) culturing by solid rice medium [17]. Interestingly, triterpenoids, 3*β*,7*β*,15*α*,24-tetrahydroxyolean-12-ene-11,22-dione (**117**) and 15*α*,22*β*,24-trihydroxyolean-11,13-diene-3-one (**118**) were isolated from the fungus ST-F1 by fermentation in solid white bean medium [18]. Compounds **115**–**118** showed weak cytotoxicity against murine lymphoma cells (L5178Y) and antimycobacterial against *Mycobacterium tuberculosis*.



Bioassay-guided investigation of the fungus *Cladosporium* sp. (WZ-2008-0042) led to the isolation of a new pregnane, 3*α*-hydroxy-7-ene-6,20-dione (**119**) (gorgonian coral *Dichotella gemmacea*, South China Sea, China) [50]. Compound **119** strongly inhibited respiratory syncytial virus (RSV) with an IC_{50} of 0.12 *m*M, with the therapeutic ratio (TC_{50}/IC_{50}) of 9.92.



CONCLUSION AND FUTURE PERSPECTIVES

It should be mentioned that the diverse abundance of natural products from coral-derived microorganisms were discovered and studied. In the complex marine ecosystems, bioactive metabolites were inherent for host protection against fouling organisms and pathogens. These chemical defense compounds also showed pharmaceutical activities. For example, aniduquinolone A, cochliomycin A, sclerotiorin, pestalachlorides, and TDA exhibited potent activity against coral pathogens and fouling organisms. Chemical modification and broad bioassay revealed their potential in pharmaceutical applications against pathogenic bacteria, virus, tumor, and parasites. However, the mechanism of active compounds remains largely unexplored.

Fungi still play a predominant role in the research on natural products of coral-derived microorganisms, while tremendous cultivation of new genera and other taxa of fungi and bacteria have yet to be discovered (see Fig. **3**). Bioactivity screening is built on the diversity and yields of compounds, and OSMAC (one strain for many compounds) has been fully developed in the study. For example, pestalachorides (**51** and **52**) were isolated from the fungus *Pestalotiopsis* sp. (ZJ-2009-7-6) both in liquid potato and solid rice mediums, rhamnosylates (**53**–**55**) were obtained in solid rice medium. Interestingly, new skeleton alkaloids (**16** and **17**) were obtained from this fungal strain ZJ-2009-7-6 cultivated in solid rice medium by adding $CaCl_2$ and KBr. An array of alkaloids (**1**–**7**) was isolated from the fungus *Scopulariopsis* sp. (TA01-33) in solid and liquid mediums. Alkaloids (**8**–**15**), peptides (**48** and **49**), polyketides (**93**–**98**), and terpenoids (**115**–**118**) were isolated from *Scopulariopsis* sp. (ST-F1) by fermentation in both rice and white bean solid mediums, only with terpenoid types differ from sesquiterpenes and triterpenoids, respectively. Though numerous microbial secondary metabolites of coral-derived microorganisms have been isolated, the number of new groups awaiting discovery remains unknown. Gene sequencing technology provides an integrated database for mapping out the biosynthetic pathways of natural products, and identifying the gene clusters will improve the biosynthesis of novel compounds *in vitro* or *in vivo*.

Further investigation of these microorganisms by different techniques can discover novel active metabolites with potential pharmacology applications. In recent years, various novel bioinformatics approaches including molecular networking (MN) and in-silico fragmentation tools (LC-MS) have emerged and provide a new perspective for metabolite identification and dereplication in natural products research. Specifically, integration of different techniques, such as combining the MN with bioassay screening or extensive in-silico MS/MS fragmentation, may enable the targeted isolation of natural products possessing both novel chemical structures and desired biological activities.

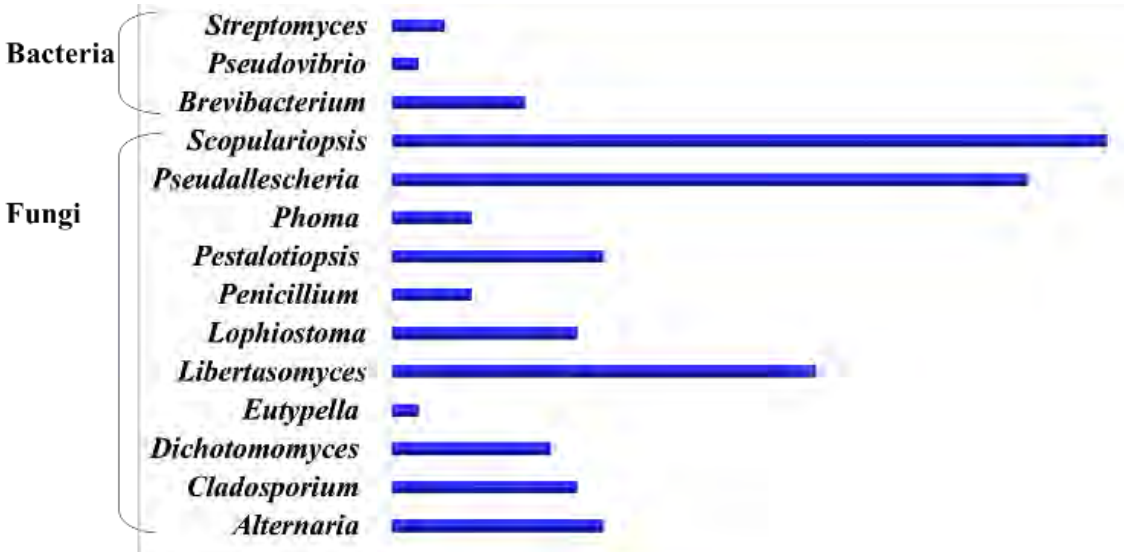


Fig. (3). The distribution of marine nature products from coral-derived microorganisms.

CONSENT FOR PUBLICATION

Not applicable.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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