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Diversity of source, chemistry, and bioactivities of secondary metabolites from algae-associated and sponge-associated fungi

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ABSTRACT

Marine-derived fungi have been evident sources of new secondary metabolites with an incredible diversity of structural and bioactivity. The accretion of research into discovering new secondary metabolites from marine-derived fungi has continued upward over the last few years. Marine-derived fungi have been found and isolated from various marine habitats, including sponges and algae. This review report displays the structures of new compounds isolated from algae-derived and sponge-derived fungi and their activities, covering the literature from 2017 to 2021. A total of 339 new compound structures were reported in this study, of which 169 compounds were distributed from algae-derived fungi and 170 were isolated from sponge-derived fungi. The compounds distributed were classified as alkaloids, aromatics, lactones, peptides, polyketides, pyrones, steroids, and terpenes isolated from *Trichoderma* sp., *Aspergillus* sp., *Penicillium* sp., *Alternaria* sp., *Talaromyces* sp., *Acremonium* sp., and *Pestalotiopsis* sp. Based on activity, these compounds have various activities such as antibacterial, cytotoxic, antioxidant, antifungal, anti-inflammatory, and butyrylcholinesterase inhibition. Several compounds showed stronger activity than the control. In the end, a review of this report can provide information on the great potential of discovering and developing new compounds to be used as led compounds derived from marine fungi.

INTRODUCTION

Marine microorganisms have been reported as one of the sources of compounds developed and used as drug agents, considering 75% of living organisms come from the marine environment (Saeed *et al*., 2021; Stincone and Brandelli, 2020). Previous reports supported the successful development of drugs from the marine environment has a success rate four times higher than other naturally derived compounds (Sigwart *et al*., 2021). Marine endophytic fungi are microorganisms that have produced potential compounds for drugs (El-Bondkly *et al*., 2021). Endophytic fungi have been discovered and isolated from various marine habitats, including sponges, mangroves, algae, and seagrasses, that have antifungal, anti-inflammatory, anticancer, antibacterial, antiviral, antiparasitic, immunosuppressive, and antioxidant activities (El-Bondkly *et al*., 2021).

Algal and sponges have much diversity and are important ecosystems in marine environments and even the world (Amelia *et al*., 2022; McCoy and Kamenos, 2015). Algae and sponges have benefited marine biotas such as fish and shellfish (Amelia *et al*., 2022; McCoy and Kamenos, 2015). In addition, algae and coral have long been used by humans in various fields, including the fishing industry, health, coastal protection, and tourism (Berdalet *et al*., 2016; Eastwood *et al*., 2017; Hoegh-Guldberg *et al*., 2007). For microorganisms, algae and sponges become ideal symbiosis places (Van de Water *et al*., 2018). Several studies have revealed communication between fungi and their symbiotic place, including algae and sponges (Zuluaga-Montero *et al*., 2010). However, the detailed symbiotic interactions between them are still not widely studied (Van de Water *et al*., 2018). The fungi isolated from algae

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or sponges are quite varied species-wise and produce quite various activities of secondary metabolites (Chen *et al*., 2022; Gao and Zhang, 2022).

A wide variety of algae-associated fungi and sponge-associated fungi has been isolated, producing new and known compounds (Chen *et al*., 2022; Gao and Zhang, 2022). The compounds have been reported to have biological activity, and some of them have become lead compounds to be developed and used in clinical applications (Saeed *et al*., 2021). In this review, we presented the diversity of sources, chemistries, and bioactivities of new compounds isolated from algae-associated and sponge-associated fungi gathered from the literature from 2017 to 2021. It covers 339 secondary metabolites focusing on the classification of compounds as fungi-producing, host-associated, and bioactive, and a comparison between algae-associated and sponge-associated fungi was made. Zhang *et al*. (2020) reviewed the diversity of bioactivity and structure of 571 metabolites from sponge-associated fungi and gathered the literature from 2010 to 2018. In another review in 2022, Gao and Zhang (2022) reported a total of 196 new metabolites isolated from algae-associated fungi covering from 2016 to 2021, including the chemical diversity and biological activities.

Algae-associated fungi

This review reported a total of 169 new secondary metabolites discovered from algae-associated fungi. According to structure, all the secondary metabolites can be classified as terpenes, alkaloids, aromatics, polyketides, lactones, and other compounds, which are dominated by terpenes 60% (Fig. 1A). Based on producing fungal strains, the secondary metabolites were isolated from various fungal species: *Trichoderma* sp., *Aspergillus* sp., and *Penicillium* sp. reflected predominant producers of the secondary metabolites, which were calculated for 54%, 12%, and 7%, respectively. On the other hand, the remaining secondary metabolites are scattered across 11 strains of fungal species, including the rare genera, such as *Chondrostereum* sp., *Alternaria* sp., *Nemania* sp., *Talaromyces* sp., *Acremonium* sp., *Eurotium* sp., *Pestalotiopsis* sp., *Stereum* sp., *Acrostalagmus* sp., *Pyrenochaetopsis* sp., and *Halosphaeriaceae* sp. (Fig. 1B).

Although the fungi are greatly disparate in terrestrial and marine environments, marine-derived fungi dominate fungal diversity. Environmental diversity, such as alterations in temperature, pressure, light, and mineral composition, such as salt levels, may affect the diversity of fungi inhabiting marine environments. Several studies have shown that the diversity of fungi varies according to their host genus. In this review, the variegated species to their algae-host genus were obtained from 21 algae. As depicted in Figure 2A, 18%, 15%, and 8% of these fungi are derived from *Rhodomela* sp., *Gracilaria* sp., and *Sargassum* sp., respectively, and others were isolated from *Laurencia* sp., *Chondria* sp., *Grateloupia* sp., *Chondrus* sp., *Pterocladiella* sp., *Ulva lactuca*, *Laminaria* sp., *Asparagopsis* sp., *Lomentaria* sp., *Coelarthrum* sp., *Mastophora rosea*, *Padina* sp., *Undaria pinnatifida*, *Ceramium japonicum*, *Codium fragile*, *Fucus vesiculosus*, *Enteromorpha prolifera*, and *Symphyocladia latiuscula*. Three of these algae are green algae, namely, *U. lactuca*, *C. fragile*, and *E. prolifera*, whereas the others are red and brown algae, and the red algae dominate as a source of fungi. The red and brown algae possess a high diversity of fungi that are the most important hosts of fungi from the marine. In contrast, the diversity of fungi from green algal is lower, which may be because of the comparatively short life cycle of green algae.

In addition to their classification as chemical, fungi-producing, and host-associated, these new secondary metabolites from algae-associated fungi possess exceptional biological activities. A total of 90 compounds were reported to have biological activities in which anti-marine-phytoplankton, antibacterial, and cytotoxicity activities are dominating capabilities in these new secondary metabolites with 21%, 11%, and 7%, respectively. Other activities include antimicroalgal, antioxidant, antifungal, anti-inflammatory, insecticidal, angiotensin-converting enzyme (ACE) inhibitory, acetylcholinesterase (AChE) inhibitory, and antiangiogenic (Fig. 2B).

Terpenes

Terpenes are a class of compounds that are widely produced by fungi and have diverse biological activities. Terpenes are reported to have antibacterial, antifungal, and antiviral activities. Some terpenes show a broad spectrum of antibacterial

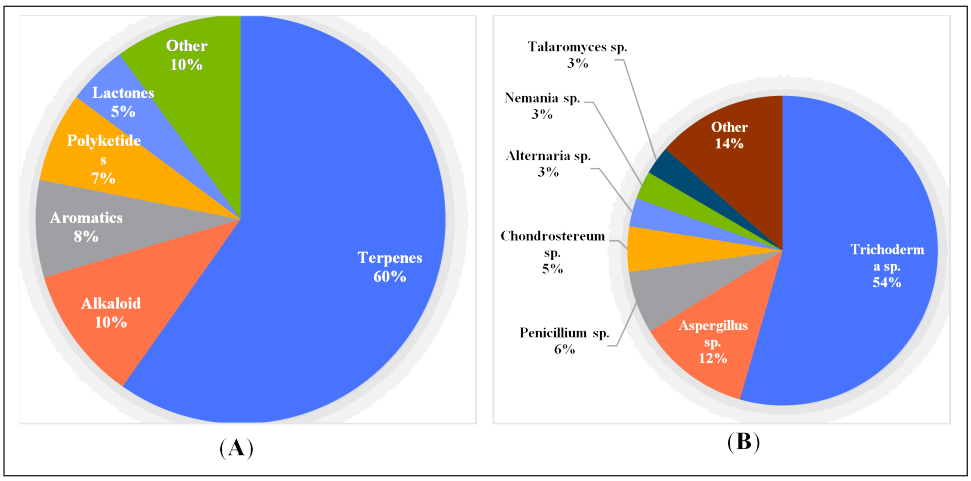

Figure 1. Distributions of new compounds produced algae-associated and their activities. Distribution of the secondary metabolites corresponding to the chemical structure (A) and fungi-producing (B).

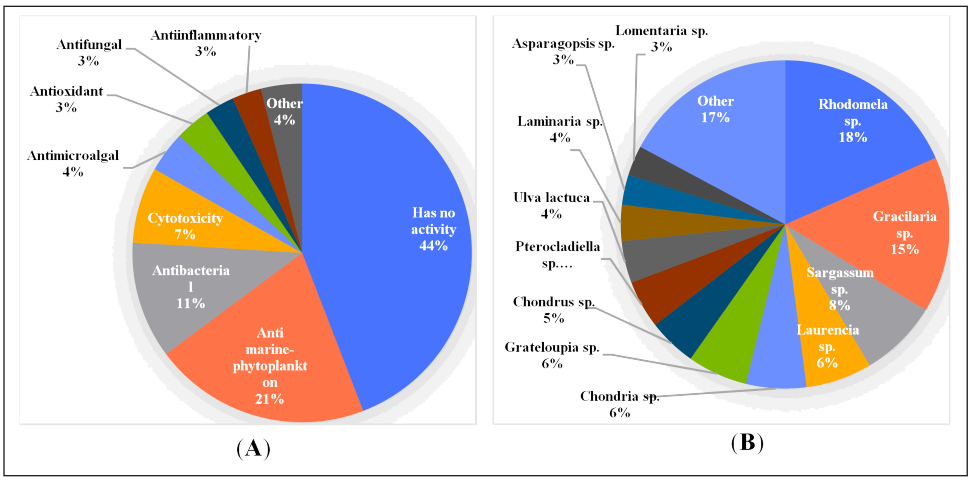

Figure 2. Distributions of new compounds produced algae-associated and their activities. Distribution of the secondary metabolites corresponding to the biological activity (A) and algae-associated (B).

activities. In this report, terpenes are the most widely isolated group of compounds from fungi symbiotic with algae, with as many as 101 compounds. A total of 78 compounds were reported isolated from the fungus *Trichoderma* spp., and others were isolated from *Alternaria alternata*, *Aspergillus sydowii*, *Chondrostereum* sp., *Nemania bipapillata*, and *Penicillium chrysogenum*. Based on biological activity, they are reported to have antibacterial, antifungal, antimicroalgal, anti-inflammation, antioxidant activities, and cytotoxicity and inhibition of marine phytoplankton. In this part, detailed descriptions of classified terpenes are provided below.

Sesquiterpenes

In this report, as many as 78 sesquiterpenes were reported to have been isolated from algae-associated fungi, with as many as 60 compounds isolated from the fungus *Trichoderma* spp. Sixteen compounds from the *Trichoderma* spp. were isolated from red alga *Rhodomela confervoides,* namely, 14-O-methyl CAF-603 (**1**), 14-O-methyltrichocarotin G (**2**), cadin-4-en-11-ol (**3**), cycloner-3-en -7,11-diol (**4**), isoepicyclonerodiol oxide (**5**), methylhydroheptelidate (**6**), norepicyclonerodiol oxide (**7**), trichobisabolin M (**8**) and N (**9**), and trichocadinin H-N (**10** – **16**). Compounds **1**, **2**, **4**, **6**, **7**, and **10**–**16** showed inhibition of the marine phytoplankton, and compounds **8** and **9** have antibacterial activities with minimal inhibitory concentration (MIC) values of 13 to 50 µg/ml (Liu *et al*., 2021; Song *et al*., 2020; Zou *et al*., 2021). Other reported 15 isolated compounds from the *Trichoderma* spp., obtained from *Gracilaria* sp, namely, trichocadinin A (**17**), trichocarotin A-H (**18** – **25**), 4-cadinen-11,12-dio (**26**), 4-cadinen-11,13-diol (**27**), and trichobisabolin I-L (**28**–**31**) (Fig. 3). Compounds **17**, **19**–**21**, and **24**–**31** showed inhibition of the marine phytoplankton (Shi *et al*., 2018; Song *et al*., 2019a, 2019b).

The *Chondria tenuissima*-associated fungi *Trichoderma brevicompactum* ADL-9-2 produced ten sesquiterpenes, namely, trichocuparin A-B (**32**–**33**) and trichodermarin G-N (**34**–**41**). Compounds **34**–**36**, **39**, and **40** showed antifungal and antimicroalgal activities, and compounds **37** and **38** showed antifungal activities (Shi *et al*., 2020). Furthermore, eight compounds have been isolated from *Trichoderma* spp., isolated from red algae *Chondrus ocellatus*, trichobisabolin A-H (**42**–**49**), of which compounds **45** and **49** showed inhibition of marine phytoplankton (Shi *et al*., 2019). The other 11 sesquiterpenes were isolated from 4 strains of *Trichoderma* spp. obtained from *Laminaria japonica*, *Grateloupia* sp., *Laurencia okamurai*, and *Sargassum* sp., namely, 10-cycloneren-3,5,7- triol (**50**), 11-methoxy-9-cycloneren-3,7-diol (**51**), 8-acoren-3,11-diol (**52**), methyl 3,7-dihydroxy-15-cycloneranate (**53**), 4-hydroxyepicyclonerodiol oxide (**54**), 5-hydroxyepicyclonerodiol oxide (**55**), trichodermol chlorohydrin (**56**), (10E)-isocyclonerotriol (**57**), (10Z)-isocyclonerotriol (**58**), 12-nor-11-acetoxybisabolen-3,6,7-triol (**59**), and bisabolan-1,10,11-triol (**60**) (Fig. 3). Compounds **50**–**53** showed inhibition of the marine phytoplankton, and compounds **56**, **59**, and **60** have antibacterial activity (Liu *et al*., 2020; Ma *et al*., 2021; Song *et al*., 2018a, 2018b).

Eighteen other sesquiterpenes were isolated from *Chondrostereum* sp. NTOU4203, *N. bipapillata* (AT-05), *P. chrysogenum* LD-201812, *A. sydowii* EN-434*, and *Stereum* sp. OUPS-124D-4, were obtained from the algae *Pterocladiella capillacea*, *Asparagopsis taxiformis*, *Grateloupia turuturu*, *S. latiuscula*, and *U. pinnatifida*, respectively. Namely, chondroterpene A-H (**61**–**68**), (+)-(2R,4S,5R,8S)-4-deacetyl-5-hydroxy-botryenalol (**69**), (+)-(2R,4R,5R,8S)-4-deacetyl-5-hydroxy-botryenalol (**70**), (+)-(2R,4S,5R,8R)-4-deacetyl-botryenalol (**71**), nemenonediol A – B (**72**–**73**), (2′R)-stachyline B (**74**), (2′R)-westerdijkin A (**75**), (7S,8S)-8-hydroxysydowic acid (**76**), (±)-(7 R*,10 R*)-10-hydroxysydowic acid (**77**), and dihydro-1,5-secovibralactone (**78**) (Fig. 3). Compound **61** showed inhibition of nitric oxide production in murine BV-2 microglial cells, and **76** inhibited AChE and butyrylcholinesterase (BuChE). Furthermore, compound **75** revealed selective cytotoxicity against **the** HepG2 cell line (IC_{50} = 22.0 µM) (Hsiao *et al*., 2017; Hu *et al*., 2020; Jiang *et al*., 2020; Medina *et al*., 2019; Yamada *et al*., 2018).

Diterpenes

Six diterpenes were reported to be isolated from *Trichoderma asperellum* A-YMD-9-2 and *Trichoderma harzianum* X-5 isolated from the red algae *Gracilaria verrucosa* and brown algae *L. japonica*, respectively, namely, trichaspside C-E (**79**–**81**), 3S-hydroxyharzianone (**82**), 3R-hydroxy-9R,10R-dihydroharzianone (**83**), and 11R-methoxy-5,9,13-proharzitrien-3-

ol (**84**) (Fig. 4). All the compounds showed inhibition of the marine phytoplankton (Song *et al*., 2018a, 2019b).

Meroterpenoids

Seventeen meroterpenoids were reported to have been isolated from two strains of fungi, *Alternaria* sp. and *Trichoderma* sp., which were isolated from *Lomentaria hakodatensis*, *R. confervoides*, and *Sargassum* sp., the compounds were sesteralterin (**85**), tricycloalterfurene A–D (**86**–**89**), trichobisabolin Q–Z (**90**–**99**), (7S)-1-hydroxy-3-p-menthen-9-oic acid (**100**), and (7R)-1-hydroxy-3-p-menthen-9-oic acid (**101**) (Fig. 5). Compounds **85** and **86** showed inhibition of the marine phytoplankton (Shi *et al*., 2017; Song *et al*., 2018b; Zou *et al*., 2021).

Alkaloids

Alkaloids are a substantial and structurally diverse group of natural and liable for beneficial biological activities. Alkaloids have enthusiastically contributed to the development of drugs in various aspects, including synthesis, structural alteration, and substructures, which remain the focus of much research. The alkaloids were reported as compounds isolated from fungi in marine habitats. The unique complexity of structure causes the biological activity of alkaloids from marine fungi to be quite varied and strong. In this report, 18 alkaloids have been reported from algae-associated fungi along with their biological activities. *Penicillium* sp. strain KMM 4672 isolated from *Padina* sp. produced four diketopiperazine alkaloids, namely citriperazine A-D (**102**–**105**), which have cytotoxic activity in human prostate cell lines (Yurchenko *et al*., 2020). Li *et al*. (2021) reported that three diketopiperazines alkaloids were isolated from *Aspergillus creber* EN-602, obtained from the red algae *R. confervoides*, namely, 3-hydroxyprotuboxepin K (**106**), 3,15-dehydroprotuboxepin K (**107**), and versiamide A (**108**) (Fig. 6). Compound **106** had ACE inhibitory activity (IC_{50} = 22.4 µM and **107** and **108** had antimicrobial activity in the various aquatic bacteria (MIC = from 8 to 64 µg/ml).

In other reports, the *Sargassum*-associated fungi *T. asperellum* cf44-8 and *Eurotium cristatum* EN-220 were produced of diketopiperazine, oxazole, and piperazine alkaloid, namely, methylcordysinin A (**109**), 4-oxazolepropanoic acid (**110**), N-(40-hydroxyprenyl)-cyclo(alanyltryptophyl) (**111**), isovariecolorin I (**112**), 30-hydroxyechinulin (**113**), and 29-hydroxyechinulin (**114**), respectively. Compound **111** had the potential as an insecticidal agent and antioxidant, and **112** and **113** had the potential as insecticides (Du *et al*., 2017; Song *et al*., 2018b). Three indole diketopiperazine alkaloids and two diketopiperazine alkaloids were reported to have been isolated from *Acrostalagmus luteoalbus* TK-43 and *Aspergillus versicolor* OUCMDZ-2739, associated with the algae *C. fragile* and *E. prolifera*, respectively, namely (+)-acrozine A (**115**), acrozine B (**116**), acrozine C (**117**), 3-[6-(2-methylpropyl)-2-oxo-1H-pyrazin-3-yl]-propenamide (**118**), and (±)-brevianamide X (**119**) (Fig. 6). Compounds **115** and **116** show anti-AChE and antibacterial activity, respectively (Cao *et al*., 2019; Liu *et al*., 2019).

Aromatics compounds

Five aromatic anthraquinone compounds and three aromatic phenol compounds have been reported to be isolated from *Aspergillus terreus* EN-539 and *Talaromyces islandicus* EN-501, respectively, obtained from the algae *L. okamurai*, namely, 8-hydroxyconiothyrinone B (**120**), 8,11-dihydroxyconiothyrinone (**121**), 4R,8-dihydroxyconiothyrione B (**122**), 4S,8-dihydroxyconiothyrinone B (**123**), 4S,8-dihydroxy -10-O-methyldendryol E (**124**), and terreprenphenol A-C (**125** – **127**). All compounds (**120**–**127**) have been reported to have antibacterial activity, and compounds **121**–**124** had antibacterial and antioxidant activities (Li *et al*., 2017, 2019). Five other aromatic compounds were isolated from *Pestalotiopsis neglecta* SCSIO41403 and *P. chrysogenum* AD-1541 isolated from the algae *Coelarthrum* sp. and *G. turuturu*, including three carboxylic acids and two benzophenone, namely, pestallic acids F-G (**128**–**129**), neopestalone (**130**), and chryxanthone A-B (**131** – **132**), respectively (Fig. 7). Compound **131** had cytotoxic activity in five human tumor cell lines, A549, BT-549, HeLa, HepG2, and MCF-7 (IC_{50} = 41.7, 20.4, 23.5, 33.6, and 46.4 µM, respectively). Meanwhile, compound **132** has cytotoxic activity in the two human tumor cell lines, A549 and THP-1 (IC_{50} = 20.4 and 41.1 µM, respectively) (Wang *et al*., 2020; Zhao *et al*., 2018).

Lactones

Eight lactones, including three decalinoylspirotetramic acid derivatives, two diketomorpholines, carboxylic acid, isocoumarin, and steroid lactones, were isolated from *Pyrenochaetopsis* sp. FVE-001, *Aspergillus alabamensis* EN-548, *P. neglecta* SCSIO41405, *Trichoderma citrinoviride* A-WH-20-5, and *Trichoderma atroviride* RR-dl-3− 11, associated with *F. vesiculosus*, *C. japonicum*, *Coelarthrum* sp., *L. okamurai*, and *R. confervoides*, respectively: namely, pyrenosetin A-C (**133**–**135**), 4-epi-seco-shornephine A carboxylic acid (**136**), 4-epi-seco-shornephine A methyl ester (**137**), pestalotiopyrone N (**138**), trichophenol A9 (**139**), and 4-(p-hydroxyphenethoxy) demethylincisterol A3 (**140**) (Fig. 8). Compounds **133** and **134** had cytotoxic activity in the A-375 cell line (IC_{50} = 2.8 and 6.3 µM, respectively). Compound **136** had antibacterial activity on five aquatic bacteria, *Escherichia coli*, *Ed. ictaluri*, *M. luteus*, and *V. alginolyticus* (MIC = 64, 32, 32, and 64 µg/ml, respectively). Meanwhile, compound **137** had antibacterial activity on the three aquatic bacteria *E. coli*, *Ed. ictaluri*, and *M. luteus* (MIC = 16, 64, and 64 µg/ml, respectively) (Fan *et al*., 2020; Liu *et al*., 2020, 2021; Wang *et al*., 2020; Yang *et al*., 2018).

Polyketides

Twelve polyketides have been reported to be isolated in marine algae-associated fungi. Seven were highly oxygenated polyketides isolated from *Aspergillus giganteus* NTU967 collected from the green alga *U. lactuca*, namely, aspergilsmin A–G (**141**–**147**). Another five, including two azaphilone polyketides and one each of macrodiolide, lauric acid, and pentaketide polyketide, were isolated from *Penicillium sclerotiorum*, *Halosphaeriaceae* sp. OUPS-135D-4, *T. atroviride* RR-dl-3−12, and *P. chrysogenum* LD-201810, derived from *Grateloupia* sp., *Sargassum thunbergii*, *R. confervoides*, and *G. turuturu*, respectively: namely, 8a-epi-eupenicilazaphilone C (**148**), 8a-epi-hypocrellone A (**149**), halosmysin A (**150**), methyl 3,5-dihydroxydodecanoate (**151**), and penilactonol A (**152**) (Fig. 9). Compound **143** was reported to have cytotoxic activity in hepatocellular carcinoma and prostate cancer cells (SK-Hep-1 and PC-3, IC_{50} = 2.7–7.3 µM) and potential

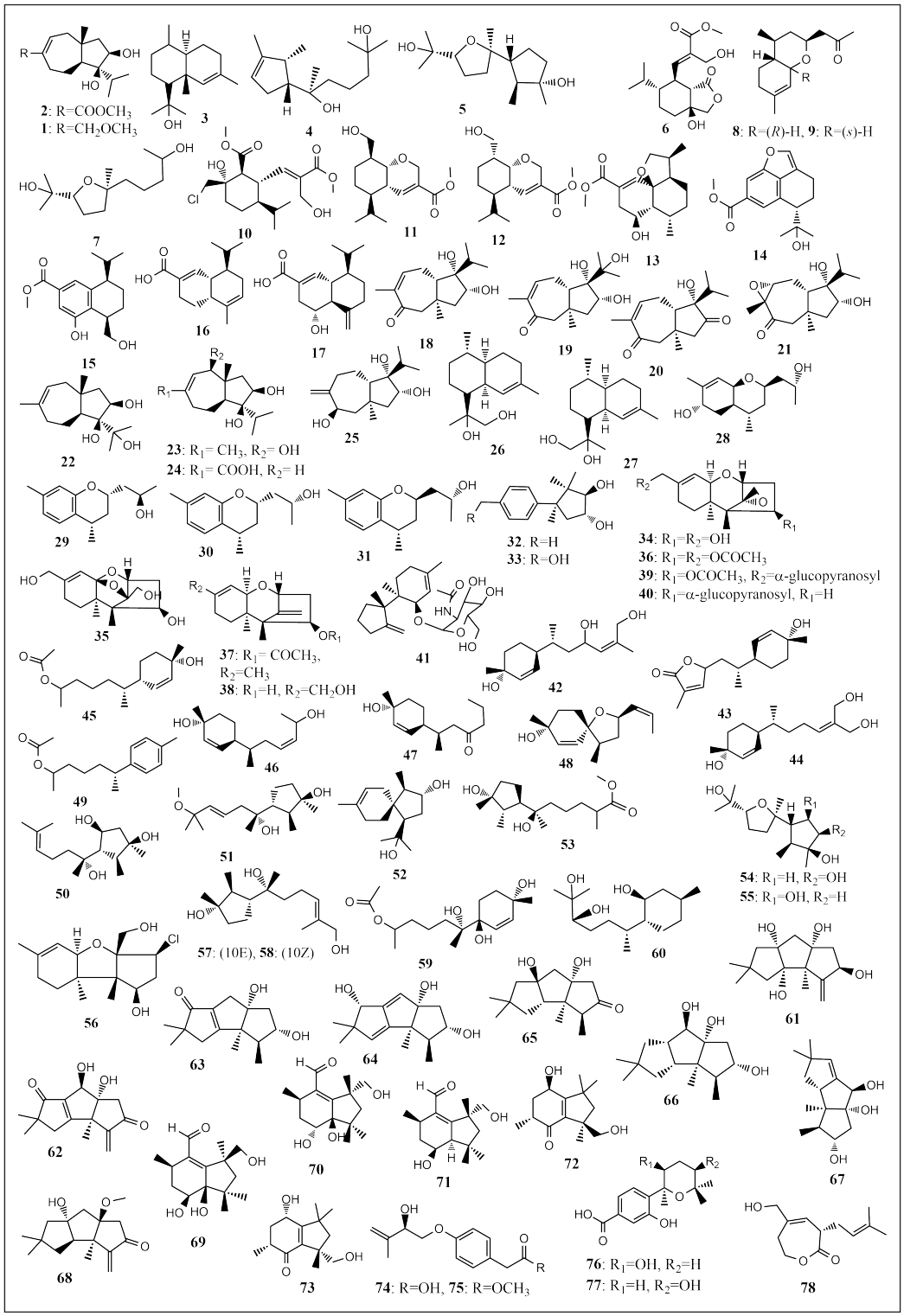

Figure 3. Structures of **1–78**.

activity as an antiangiogenic. The **149** had selective toxicity in the neuroblastoma SH-SY5Y cell line and selective inhibition of TNF-α-induced NFκB phosphorylation. Compound **150** showed potent cytotoxic activity against three leukemia cell lines (murine P388, human HL-60, and murine L1210, IC_{50} = 2.2–11.7 μM) (Chen *et al*., 2020; Jiang *et al*., 2020; Liu *et al*., 2021; Wang *et al*., 2021a; Yamada *et al*., 2020).

Other compounds

Seventeen other compounds have been reported to be isolated from the fungus *T. asperellum* A-YMD-9-2, *Acremonium* sp. NTU492, *Stereum* sp. OUPS-124D-1, *T. asperellum* cf44-6, and *A. alabamensis* EN-549, derived from *G. verrucosa*, *M. rosea*, *U. pinnatifida*, *Sargassum* sp., and *C. japonicum*, respectively. The compounds included seven cycloneranes, namely, 3,7,11-tri-

hydroxycycloneran-10-one (**153**), cycloneran-3,7,10,11-tetraol (**154**), cycloneran-3,7,11-triol (**155**), 11,12,15-trinorcycloneran-3,7,10-triol (**156**), 7,10S-epoxycycloneran-3,15-diol (**157**), 7,10R-epoxycycloneran-3,15-diol (**158**), and (10Z)-15-acetoxy-10-cycloneren-3,7-diol (**159**); four peptides, namely, acrepeptin A-D (**160**–**163**); three carboxylic acids, namely, sterepinic acids A-C (**164**–**166**); two trichodenones, namely, dechlorotrichodenone C (**167**) and 3-hydroxytrichodenone C (**168**); and one steroid, namely, 28-acetoxy-12β,15α,25-trihydroxyergosta-4,6,8(14),22-tetraen-3-one (**169**) (Fig. 10). Compounds **153**–**159** and **167**–**168** have anti-marine-phytoplankton. Meanwhile, compounds **167–169** have antibacterial activity (Hsiao *et al*., 2020; Song *et al*., 2018b, 2019c; Yamada *et al*., 2018; Yang *et al*., 2018).

Sponge-associated fungi

In recent years, an augmentative number of studies highlighted that many active secondary metabolites from sponges are of microorganism origin due to similar chemical structures found in terrestrial microorganisms. Of many marine organisms, sponges are considered the most prolific source of therapeutic compounds as these animals harbor many secondary metabolites, many of which are worthwhile for human health. Sponge-associated fungi are a group of microorganisms found to produce secondary metabolites.

In this report, 170 new secondary metabolites were reported to have been isolated from various marine sponge-associated fungi and were found in 18 genera. Most of the new secondary metabolites found in sponge-associated fungi are produced by *Aspergillus* sp. (32%), while *Penicillium* sp. and *Talaromyces* sp. account for about 11% and 10% of the new secondary metabolites reported. The rest were found from the fungi *Setosphaeria* sp., *Pestalotiopsis* sp., *Acremonium* sp., *Alternaria* sp., *Didymellaceae* sp., *Cymostachys* sp., *Eupenicillium* sp., *Cladosporium* sp., *Fusarium* sp., *Trichoderma* sp. *Arthrinium* sp, *Pleosporales* sp., *Ascomycota* sp., *Daldinia eschscholtzii* sp., and *Neosartorya fennelliae* sp. (Fig. 11A). The fungi were derived from three sponges: *Callyspongia* sp. (29%), *Phakellia fusca* (16%), and *Axinella cannabina* (9%). The rest were derived from *Xestospongia testudinaria*, *Plakortis simplex*, *Aaptos*, *Isopod*, *Haliclona* sp., *Paratetilla* sp., *Agelas oroides*, *N. chaliniformis*, *Petrosia* sp., *Stylissa* sp., *Chalinidae, Epipolasis* sp., *Mycale* sp., *Phyllospongia foliascens*, *Reniochalina* sp., *Sarcotragus muscarum*, *Stelletta* sp., *Aka coralliphaga*, and *Hymeniacidon perleve* (Fig. 11B).

The new secondary metabolites produced by sponge-associated fungi are a diverse array of structures observed. The majority of the new secondary metabolites are lactones (19%), polyketides (18%), alkaloids (16%), and aromatics (16%) (Fig. 12A). In addition to the diverse structures, the new secondary metabolites derived from sponge-associated fungi exhibit diverse and pronounced biological activities. Antimicrobial activity and cytotoxicity are the most prominent activities, as indicated by 12 and 11% of the new secondary metabolites. Other activities include IL-6 immune-suppressive, antifungal, anti-inflammatory, NF-α immune-suppressive, antioxidant, alpha-glucosidase inhibitors, anti-BChE, anti-Aβ fibrillization, anti-*Mycobacterium tuberculosis*, and antiviral effects (Fig. 12B).

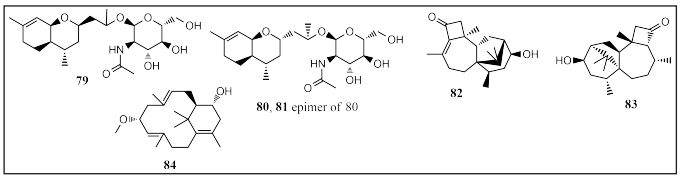

Figure 4. Structures of **79**–**84**.

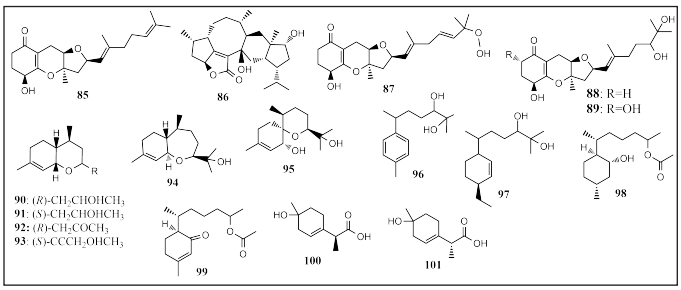

Figure 5. Structures of **85**–**101**.

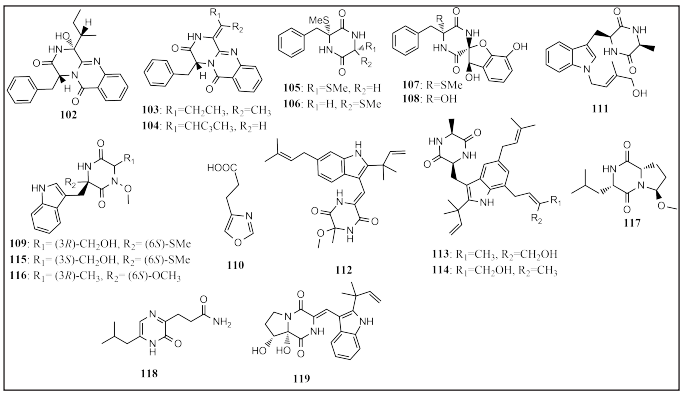

Figure 6. Structures of **102**–**119**.

Alkaloids

Twenty-nine alkaloids have been reported to be isolated from sponge-associated fungi *Alternaria* sp., *Aspergillus* sp., and *Penicillium* sp., derived from the sponges *Callyspongia* sp., *Epipolasis* sp., *Isopods*, and *P. fusca,* respectively. Twelve alkaloids were reported to be piperazine alkaloids, namely, pyranamides A-D (**170**–**173**), secopyranamide C (**174**), protuboxepins F-J (**175** – **179**), and solitumines A-B (**180**–**181**). Nine pyrrolidine alkaloids included preussins C– I (**182**–**188**) and (11R)/(11S)-preussins J–K (**189**–**190**). Four indole alkaloids included candidusin D (**191**) and solitumidines A-C (**192**–**194**). Three thiazole alkaloids included altenusinoides A– B (**195**–**196**) and methyl 2-(6-hydroxybenzothiazol-4-yl) acetate (**197**) (Fig. 13). Compounds **176**, **182**, and **191** have cytotoxic activity. Meanwhile, **183**–**190** have been reported to have IL-6 immune-suppressive activity (IC_{50} = 22, 8.2, 9.9, 0.11. 14, 0.19, 2.3, and 16 μM, respectively) (Buttachon *et al*., 2018; Chen *et al*., 2018; Gu *et al*., 2018a; Luo *et al*., 2019a; Rodríguez *et al*., 2020).

Aromatic

Twenty-eight aromatic compounds have been reported to be isolated from sponge-associated fungi consisting of phenol,

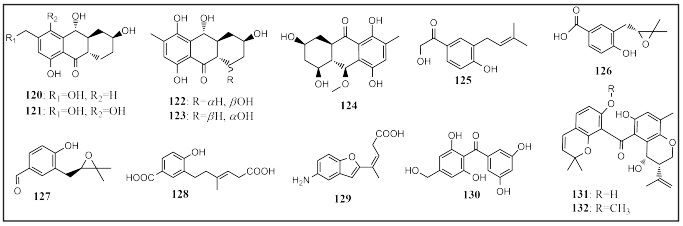

Figure 7. Structures of **120–132**.

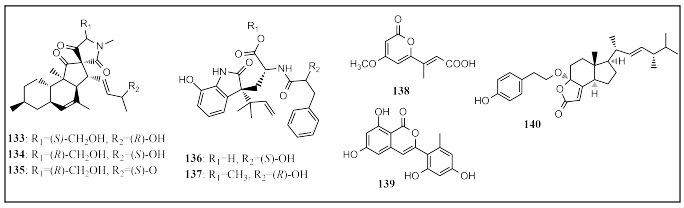

Figure 8. Structures of **133–140**.

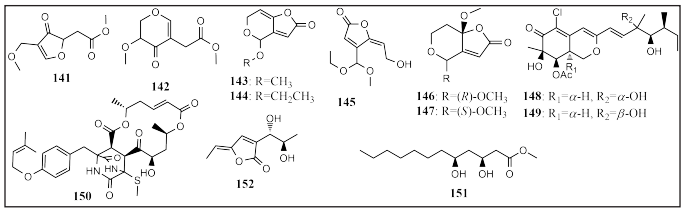

Figure 9. Structures of the **141–152**.

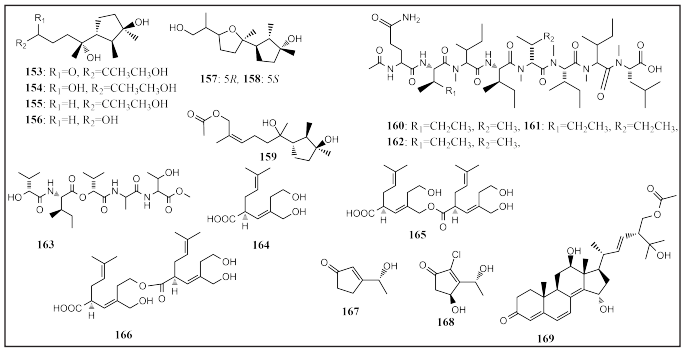

Figure 10. Structures of **143–169**.

benzofuran, anthraquinone, epimer, chromone, amino acid, anthracenedione, and ether. Thirteen phenols were isolated from *Didymellaceae* sp. SCSIO F46, *Alternaria* sp. SCSIO41014, *A. sydowii* J05B-7F-4, and *Ascomycota* sp. VK12 derived from the sponge *Callyspongia* sp., *Stelletta* sp., and unidentified sponges, respectively, namely, 1-hydroxy-6-methyl-11-methoxy-8-hydroxymethylxanthone (**198**), 7-(2-hydroxyphenyl) butane-7,8,9-triol (**199**), coleophomones E and F (**200** and **201**), diorcinols F and L (**202** and **203**), boric acid E (**204**), alternariphent A (**205**), β-d-glucopyranosyl aspergillusene A (**206**), and (3R)-(3′,5′-dihydroxyphenyl)butan-2-one (**207**) (Fig. 14). Compound **203** was reported to have promising cytotoxic activity against four tumor cell lines (Huh-7, HeLa, DU145, and HL60, IC_{50} = 5.7–9.6 μM), and **204** had promising COX-2 inhibitory activity (IC_{50} = 3.3 μM). Compound **207** displayed cytotoxic activity on three human cancer cell lines (HepG2, MCF-7, and SK-Mel2, IC_{50} = 65.9, 57.7, and 96.5 μM) and has promising NO inhibitory activity against lipopolysaccharide (LPS)-stimulated BV2 cells (IC_{50} = 76.5 μM) (Liu *et al*., 2017; Pang *et al*., 2018c; Quang *et al*., 2021; Tian *et al*., 2018). Wang *et al.* (2017, 2020, 2021a, 2021b) reported six phenol benzofurans isolated from the marine sponge-associated fungus *Cymostachys* sp. NBUF082 was obtained from the *Aaptos sponge*, namely, cymopolyphenols A–F (**208–213**), with compounds **208** and **210–213** being weakly antimicrobial (MIC =16–64 μg/ml).

Two reports from different research teams, Artasasta *et al.* (2021) and Sibero *et al.* (2019) have successfully isolated five anthraquinones from fungal fermentation. Three anthraquinones were isolated from *N. chaliniformis*-associated fungi *Aspergillus nomius* NC06 and two anthraquinones were isolated from *Xestospongia* sp.-associated fungi *Fusarium* sp. KJMT.FP.4.3, namely, oxisterigmatocystin J–L (**214** – **216**) and karimunones A and B (**217** and **218**), respectively. Compounds **214** and **215** had cytotoxic activity against HT29 colon cancer cells (IC_{50} = 6.28, and 15.14 μM). Meanwhile, compound **218** had antibacterial activity on resistant bacteria (*Salmonella enterica* ser. Typhi, MIC = 125 μg/ml). Seven other aromatic compounds, consisting of two epimers, two chromones, one amino acid, one aromatic, and one anthracenedione, were isolated from *P. fusca*-associated fungi *Pestalotiopsis heterocornis* XWS03F09, *Haliclona*-associated fungi *Aspergillus* sp. LS57, *Haliclona*-associated fungi *D. eschscholtzii* KJMT FP 4.1, *Isopod*-associated *Penicillium solitum* IS1-A f, *Stylissa flabelliformis*-associated fungi *Talaromyces stipitatus* KUFA 0207, and *A. oroides*-associated fungi *Penicillium canescens* 4.14.6a, respectively: namely, heterocornol O and P (**219** and **220**), aspergilluone A (**221**), karimanone (**222**), solitumidine D (**223**), bis(1,4,5-trihydroxy-7-methylanthraquinone) (**224**), and diphenyl ether (**225**) (Fig. 14). Compounds **219** and **220** had cytotoxic activities on four cancer cell lines (BGC-823, Ichikawa, HepG2, and 7860, IC_{50} = 22.1–54.3 μM). Compound **221** had anti-*M. tuberculosis* (MIC = 32 μg/ml, *in vitro*) and antibacterial activity on three bacterial [*Staphylococcus aureus* (ATCC 6,538), *Bacillus subtilis* (JCM 1,465) and *E. coli* (JCM 1,649), MIC = 64, 8, 128 μg/ml, respectively]. Compound **222** showed antibacterial activity on multidrug-resistant bacterial *S. enterica* ser. Typhi (MIC = 125 μg/ml) (Artasasta *et al*., 2021; Frank *et al*., 2019; Lei *et al*., 2019; Liu *et al*., 2017, 2021; Noinart *et al*., 2017; Pang *et al*., 2018c; Quang *et al*., 2021; Rodríguez *et al*., 2020; Sibero *et al*., 2019, 2020; Tian *et al*., 2018; Wang *et al*., 2021b).

Lactones

Thirty-three lactones were reported from various marine sponge-associated fungi, including fifteen isolated from *Talaromyces rugulosus* derived from *A. cannabina* and ten compounds from *Setosphaeria* sp. SCSIO41009 was obtained from *Callyspongia* sp., namely, lactone acid n-butyl ester (**226**), 4-methoxylactone acid n-butyl ester (**227**), lactone diacid 7-O-n-butyl ester (**228**), lactone diacid (**229**), (3S)-cis-resorcylide (**230**), (3S,7S)-7-hydroxyresorcylide (**231**), (3S,7R)-7-hydroxyresorcylide (**232**), (3S,7S)-7-methoxyresorcylide 9 (**233**), (3S,7R)-7-methoxyresorcylide (**234**), (3S,7S)-7-O-n-butylresorcylide (**235**),

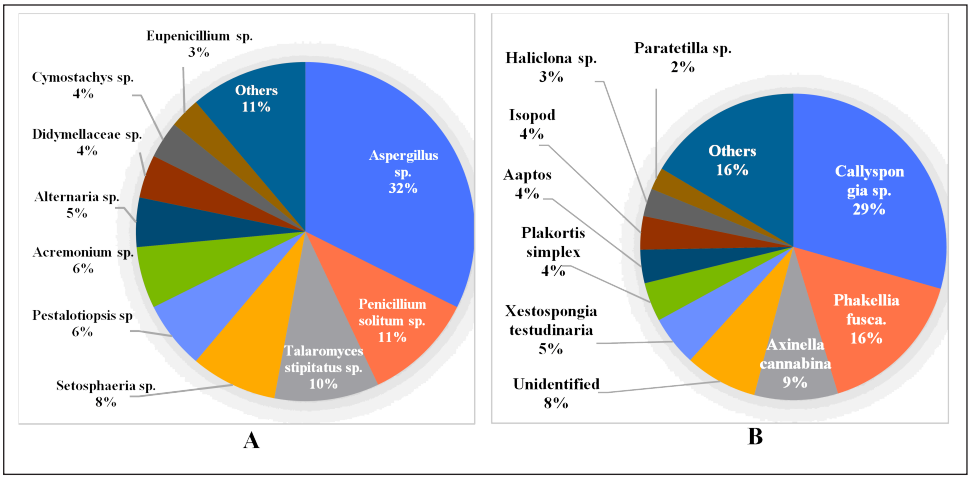

Figure 11. Distributions of sponge-associated new compounds. Distribution of the fungi-producing (A) and sponge-associated (B) secondary metabolites.

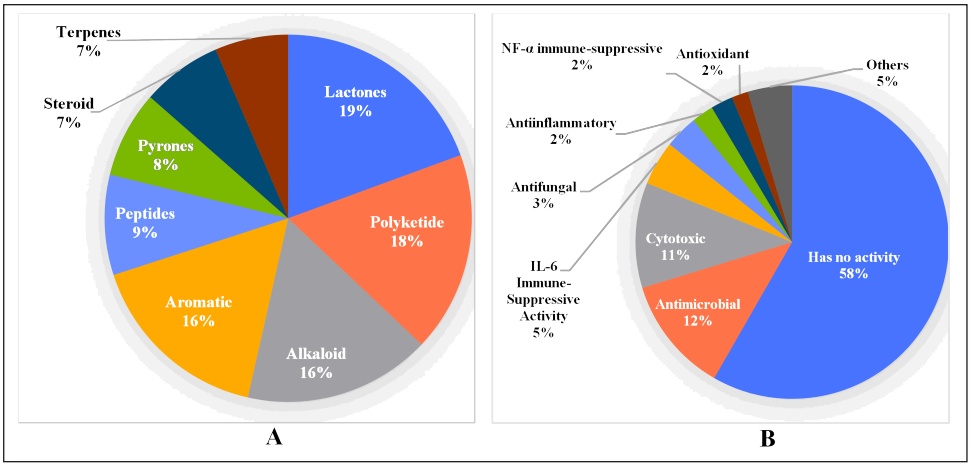

Figure 12. Distributions of sponge-associated new compounds. Distribution of the secondary metabolites corresponding to the chemical structure (A) and biological activity (B).

(3S,7R)-7-O-n-butylresorcylide (**236**), talarodilactone A and B (**237** and **238**), thalumarin A and B (**239** and **240**), setosphalide A and B (**241** and **242**), 5-O-desmethylcolletotrialide (**243**), (S)-colletotrialide (**244**), exserolide I–K (**245**–**247**), 5-hydroxy-3-methoxy-5-methyl-4-butylfuran-2(5H)- one (**248**), and botryorhodine I and J (**249** and **250**), respectively (Fig. 15). Compounds **237** and **238** have potential cytotoxicity in the murine lymphoma (L5178Y cell line, IC_{50} = 3.9 and 1.3 µM, respectively), and **249** and **250** have antifungal activities on two fungal pathogens (*Colletotrichum asianum* and *Colletotrichum acutatum* MIC = 0.16, 0.63, of 0.31, and 0.63 mg/ml, respectively) (Küppers *et al*., 2017; Pang *et al*., 2018d).

The other eight lactones were isolated from the sponge-associated fungus *Alternaria* sp. SCSIO41014, *A. terreus*, *Cladosporium* sp. SCSIO41010, *N. fennelliae* KUFA 0811, and *P. heterocornis* derived from the sponges *Callyspongia* sp., *A. coralliphaga*, and *P. fusca*, namely, nordihydroaltenuenes A (**251**), isoochracinate A (**252**), asperteretal D (**253**), asperteretal E (**254**), (3R)-3-(2-hydroxypropyl)-6,8-dihydroxy-3,4-dihydroisocoumarin

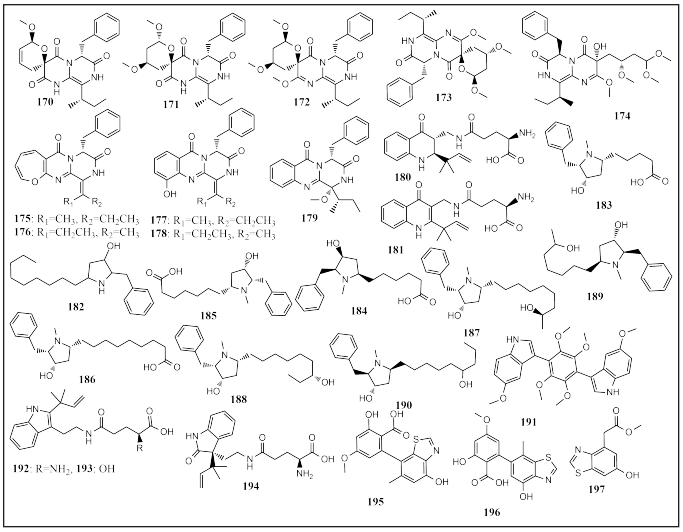

Figure 13. Structures of **170**–**197**.

(**255**), paecilin E (**256**), and pestaloisocoumarin A and B (**257** and **258**) (Fig. 15). The **253** and **254** had a potential for inhibition of a-glucosidase (IC_{50} = 8.65 to 20.3 mM) and **256–258** have antibacterial effects on Gram-positive bacteria (MIC = 25 to 100 µg/ml).

Peptides

Eleven peptides were reported from sponge-associated including eight compounds from *P. fusca*-associated fungi *Acremonium persicinum* F10, namely, acremonpeptide E and F (**259** and **260**), Al (III)-acremonpeptide E and F (**261** and **262**), aselacin D (**263**), Fe (III)-acremonpeptide E and F (**264** and **265**), and Ga (III)-acremonpeptide E (**266**). Seven compounds were isolated from *Aspergillus* derived from sponges *Petrosia* sp., *Reniochalina* sp., and *Callyspongia* sp., namely, petrosamides A–C (**267–269**), sclerotiotide L (**270**), violaceomide A (**271**), and aspergillamides C and D (**272** and **273**) (Fig. 16). Compounds **267–269** expressed inhibition of pancreatic lipase (IC_{50} = 7.6, 1.8, and 0.5 µM, respectively) and compound **271** inhibition of IL-10 expression induced of LPS on THP-1 cells (Li and Li, 2021; Liu *et al*., 2018; Luo *et al*., 2019b; Tang *et al*., 2020).

Polyketides

Thirty new polyketides have been isolated from sponge-associated fungi, including nine compounds from *Aspergillus* sp., eight compounds from *Penicillium* sp., and six compounds from *Pestalotiopsis* sp. The fungi were obtained from *X. testudinaria*, *Stelletta* sp., *Paratetilla* sp., *A. oroides*, *P. fusca*, and unidentified sponges: namely, (+)1-O-demethylvariecolorquinones A (**274**), eurobenzophenone A–C (**275–277**), euroxanthone A and B (**278** and **279**), aspergchromone A and B (**280** and **281**), diorcinolic acid (**282**), sclerotiorin A–D (**283–286**), bromophilone A and B (**287** and **288**), penicitrinone G (**289**), erubescensoic acid (**290**), pestalotiopol A–D (**291–294**), and heterocornol M and N (**295** and **296**), respectively (Fig. 17). The **276** and **278** showed inhibition of NF-κB and NO production in SW480 and BV2 microglia cells, respectively, induced by LPS. Compounds **289–290** have antibacterial activity and **291–292** have cytotoxic activities against BGC-823, SMMC-7721, Ichikawa, and 7,860 human cancer cell lines (IC_{50} = 16.5 to 52.1 µM). Meanwhile, **295** showed cytotoxic activities against HepG2 and BGC-823 human cancer cell lines (IC_{50} = 20.4 and 61.1 µM) (Du *et al*., 2018; Frank *et al*., 2019; Jia *et al*., 2019; Kumla *et al*., 2019; Lei *et al*., 2019, 2020; Liu *et al*., 2017; Sabdaningsih *et al*., 2020; Wang *et al*., 2017).

Seven other polyketides were produced by the fungus *Trichoderma* sp. SCSIO41004, *Alternaria* sp. SCSIO41014, and *Pleosporales* sp. NBUF144 derived from *Callyspongia* sp. and *Chalinidae*, namely, 5,7-dihydroxy-3-methyl -2-(2-oxopropyl)naphthalene-1,4-dione (**297**), 7-acetyl-1,3,6-trihydroxyanthracene-9,10- dione (**298**), trichbenzoisochromen A (**299**), altertoxin VII (**300**), butyl xanalterate (**301**), 2′-hydroxy bisdechlorogeodin (**302**), and globosuxanthone F (**303**) (Fig. 17). Compounds **300** and **303** exerted cytotoxic activities; the **300** was cytotoxic against three tumor cell lines (K562, SGC-7901, and BEL-7402, IC_{50} = 26.58, 8.75, and 13.11 µg/ml) and the **303** had strong cytotoxicity against human acute lymphatic leukemia cells (CCRF-CEM, IC_{50} = 0.46 µM) (Pang *et al*., 2018a, 2018c; Zhou *et al*., 2021).

Pyrones

Thirteen pyrones group compounds have been isolated from sponge-associated fungi, *Aspergillus flocculosus*, *Aspergillus*

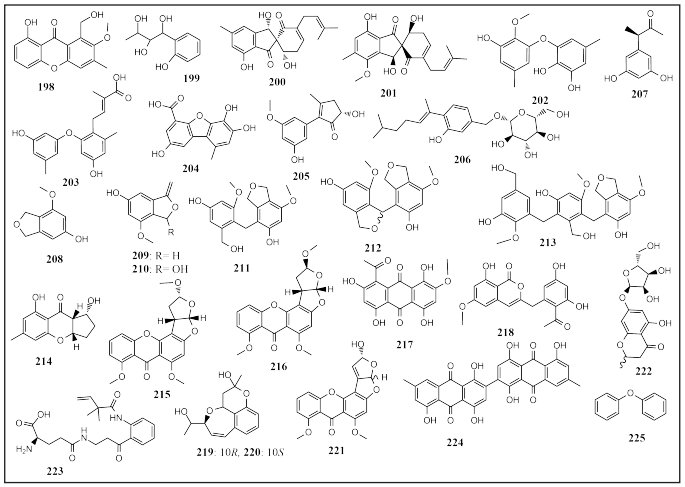

Figure 14. Structures of **198–225**.

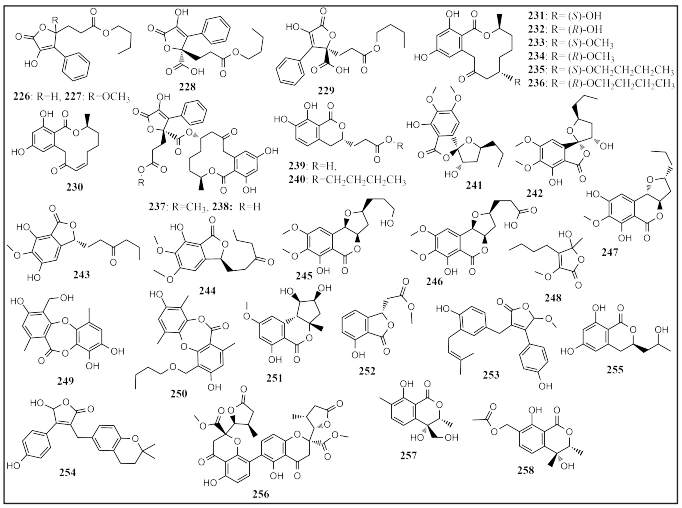

Figure 15. Structures of **226–258**.

niger, *Fusarium lateritium* 2016F18-1, *P. chrysogenum* 14XS09-2, *Penicillium erubescens* KUFA 0220, and *Setosphaeria* sp., SCSIO41009 obtained from the sponges *Stylissa* sp., *Haliclona* sp., *P. foliascens*, *P. simplex*, and *Callyspongia* sp., namely, ochraceopone F (**304**), nipyrone A-C (**305–307**),13-dehydroxy-1,11-deacetylpyripyropene A (**308**), 1-deacetylpyripyropene A (**309**), 1 (**310**), 2 (**311**), SPF-3059-26, and setosphapyrone A-D (**313–316**) (Fig. 18). Compounds **305** and **306** showed antibacterial activites against pathogenic bacteria (*S. aureus*, *E. coli*, *B. subtilis* MRSA, and *M. tuberculosis*, MIC = 32–128 µM), compound **307** had strong antibacterial activity (*S. aureus* and *B. subtilis*, MIC = 8 and 16 µM), and compound **312** had antibacterial in the *E. coli* ATCC 25922 (MIC = 64 mg/l) (Cao *et al*., 2017; Ding *et al*., 2019; Kumla *et al*., 2019; Pang *et al*., 2018d; Shin *et al*., 2018).

Steroids

Twelve steroids have been reported to be isolated from various sponge-associated fungi *Cladosporium* sp. SCSIO41009, *Aspergillus* sp. LS116, *T. stipitatus* KUFA 0207, and *Aspergillus fumigatus* HNMF0047 derived from *Callyspongia* sp., *Haliclona* sp., *S. flabelliformis*, and unidentified sponges, respectively,

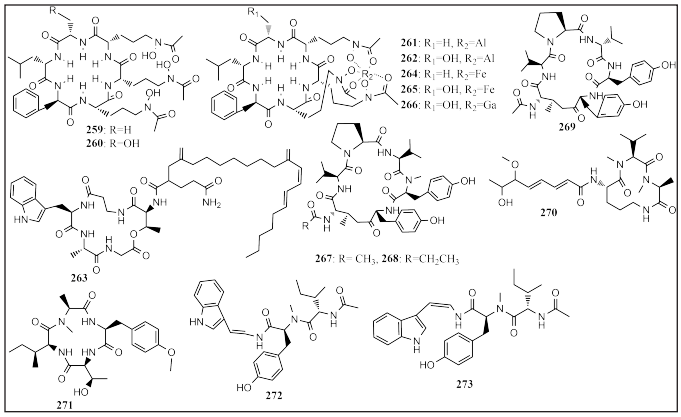

Figure 16. Structures of **259**–**273**.

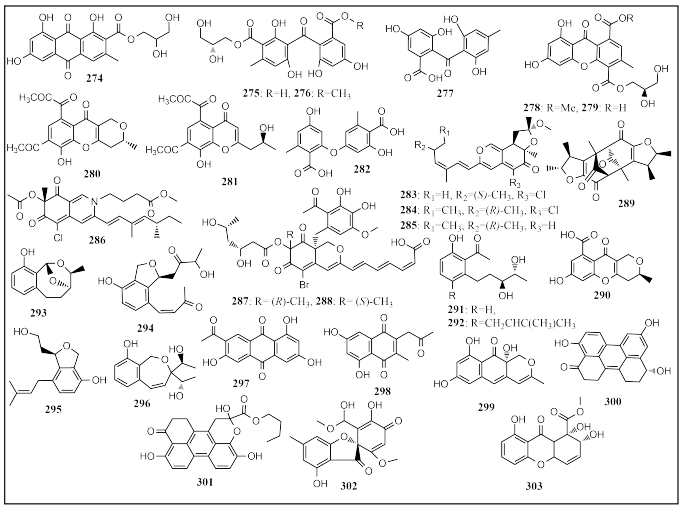

Figure 17. Structures of **274**–**303**.

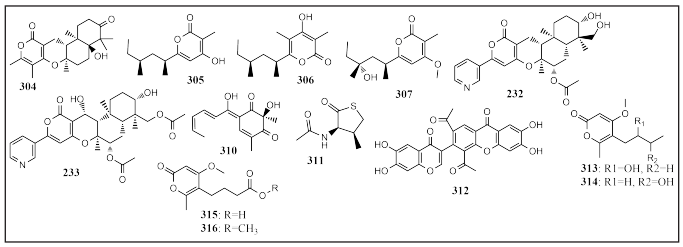

Figure 18. Structures of **304**–**316**.

namely, 16-O-deacetylhelvolic acid 21,16-lactone (**317**), 6-O-propionyl-6,16-O-dideacetylhelvolic acid 21,16-lactone (**318**), 1,2-dihydro-6,16-O-dideacetylhelvolic acid 21,16-lactone (**319**), 1,2-dihydro-16-O-deacetylhelvolic acid 21,16-lactone (**320**), 16-O-propionyl-16-O-deacetylhelvolic acid (**321**), 6-O-propionyl-6-O-deacetylhelvolic acid (**322**), and 24-epi-6β,16β-diacetoxy-25-hydroxy-3,7-dioxo-29-nordammara-1,17(20)-diene-21,24-lactone (**323**), and three compounds have been confirmed as oxygenated steroids produced by the SCSIO41008 strain, namely, cladosporisteroid A–C (**324**–**326**).

Two other steroids produced by strains LS116 and KUFA 0207, namely, aspergillsteroid (**327**) and tharosterone (**328**), respectively (Fig. 19). In terms of the biological activity of all alkaloids, compounds **321**, **322**, and **327** had antibacterial activity, while compound **325** had antiviral activity, and **327**, **328**, and **325** had stronger activity against *S. agalactiae* (MIC = 16, 2, and 8 µg/ml, respectively) and **325** against *V. harveyi* (MIC =16 µg/ml) and **325** has activity against H3N2 (IC50 = 16.2 µM) (Kong *et al*., 2018; Noinart *et al*., 2017; Pang *et al*., 2018b; Xu *et al*., 2020).

Terpenes

Eleven terpenes, including meroterpenoids and sesquiterpenes isolated from sponge-associated fungi, including two meroterpenoids from *Arthrinium* sp., four meroterpenoids from *Eupenicillium* sp. 6A-9, two sesquiterpenes from *A. persicinum* KUFA 1007, and others from *P. heterocornis* and *Trichoderma* sp. HPQJ-34, were obtained from the sponges *S. muscarum*, *P. simplex*, *Mycale* sp., *P. fusca*, and *H. perleve*, namely, spiroarthrinol A and B (**329** and **330**), 1-methoxy-hydropreaustinoid A1 (**331**), 22-deoxy-10-oxominiolutelide B (**332**), eupeniacetal A and B (**333** and **334**), hydroberkeleyone B (**335**), acremine S and T (**336** and **337**), isopolisin B (**338**), and 5-hydroxycyclopeni cillone (**339**) (Fig. 20). Compounds **331** and **333**–**335** have immune-suppressive activity (TNF-α, 22.6, 43.1, 28.5, and 42.3 µM, respectively). The **336** and **337** have AChE and BuChE inhibitory activity (% inhibition at 6.6 µM = 10.42, 14.08, 30.71, and 10.53, respectively). Compound **357** has antibacterial activity against *S. aureus* and *B. subtilis* (MIC = 25 to 100 µg/ml) and **339** has antioxidative, anti-Aβ fibrillization, and neuroprotective activities (Alves *et al*., 2019; Elissawy *et al*., 2017; Fang *et al*., 2017; Gu *et al*., 2018b; Lei *et al*., 2017).

Comparative of algae-associated and sponge-associated fungi

Algae- and sponge-associated fungi are the two groups of endophytic fungi found to produce new secondary metabolites. As shown in Figure 21, *Trichoderma* is described as the greatly predominant producers of new secondary metabolites from algae-associated fungi, while *Aspergillus* sp. is predominant in sponge-associated fungi. *Penicillium* sp. and *T. stipitatus* sp. are fungi that constantly produce new secondary metabolites. The remaining new secondary metabolites were produced by 28 fungi. Although fungi are highly disparate in terrestrial and marine habitats, marine-derived fungi possess more diversity. As noted before, drivers of nutrition, heat, air pressure, and light may affect the diversity of marine-derived fungi. Moreover, several reviews have indicated that the diversity of marine-derived fungi varied according to their host genus. In this review, the fungal producers of new secondary metabolites were explored from 21 algae and 23 sponges.

In this review, new secondary metabolites produced by algae- and sponge-derived fungi possessed a high structural diversity. A total of 339 new secondary metabolites were isolated from algae-derived fungi and sponge-derived fungi, which are categorized into terpenes, alkaloids, aromatics, polyketides, lactones, peptides, and steroids. Terpenoids produced the most algae-associated fungi and the least sponge-associated fungi, while lactones, polyketides, alkaloids, and aromatics were produced equally by sponge-associated fungi, as represented in Figure 22.

In addition to the high structural diversity, the new secondary metabolites derived from algae-associated fungi and sponge-associated fungi show diverse and apparent biological activities. As represented in Figure 23, 173 (34%) new secondary

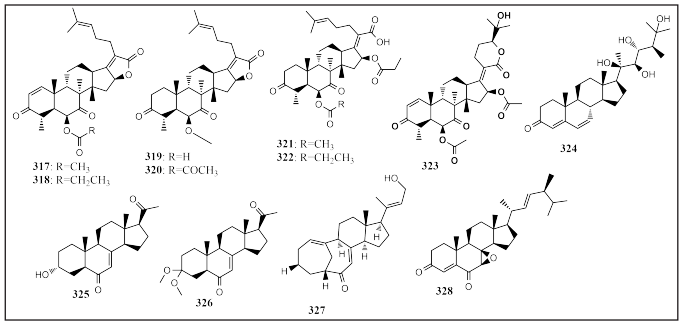

Figure 19. Structures of **317**–**328**.

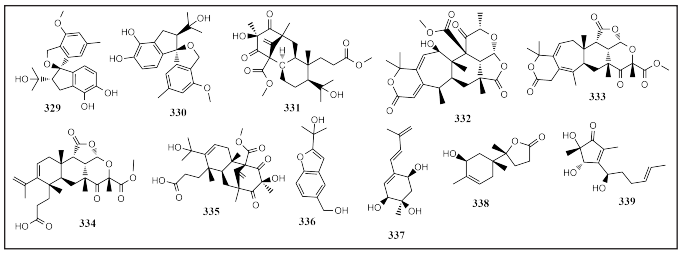

Figure 20. Structures of **329**–**339**.

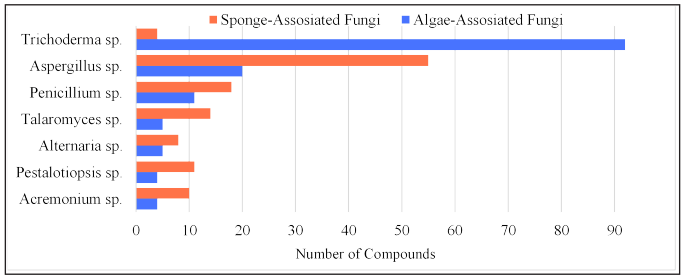

Figure 21. Comparison of fungal producers of new secondary metabolites.

metabolites isolated from algae-associated fungi and sponge-associated fungi are found to possess considerable biological activities, of which 73 new secondary metabolites exhibit potent antibacterial and cytotoxicity activity. Moreover, some of the new secondary metabolites are shown to have one or more varieties of biological activities and are shown to have moderate to potent bioactivities. These strong bioactivities create some of the new secondary metabolite preferable candidates for developing new drugs, agrochemicals, and lead compounds in the future.

CONCLUSION

Marine algae and sponges are exceptional fungal sources for producing new secondary metabolites. From 2017 to 2021, natural product research into algae-derived fungi and sponge-derived fungi led to 339 new secondary metabolites. These new secondary metabolites were observed to have significantly varied in structure and various bioactivities. These new secondary metabolites have great potential in treating diseases. However, the bioactivities of these new secondary metabolites were exclusively *in vitro* tested; thus, there is more interest in *in vivo* studies for the molecular mechanism. Furthermore, there is great potential in discovering and developing new compounds to be used as led

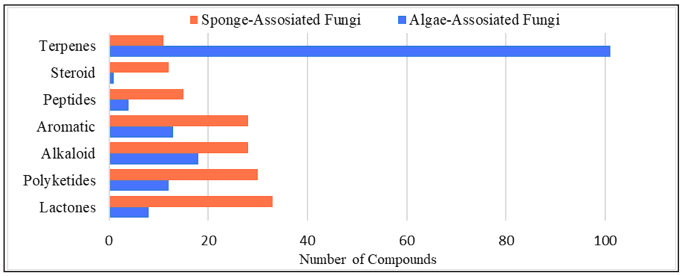

Figure 22. Comparison of secondary metabolites corresponding to the chemical structure.

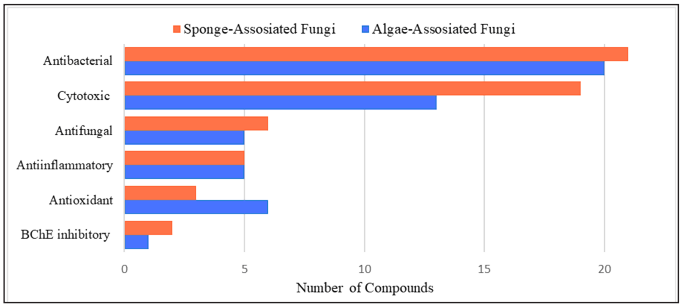

Figure 23. Comparison of biological activities isolated from algae-associated fungi and sponge-associated fungi.

compounds derived from algae-associated and sponge-associated fungi.

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AUTHOR CONTRIBUTIONS

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work. All the authors are eligible to be an author as per the international committee of medical journal editors (ICMJE) requirements/guidelines.

CONFLICTS OF INTEREST

There are no conflicts of interest to report.

ETHICAL APPROVALS

This study does not involve experiments on animals or human subjects.

DATA AVAILABILITY

All data generated and analyzed are included in this research article.

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