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Progress in the discovery of new bioactive substances from deep-sea associated fungi during 2020-2022

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The marine environment can harbor millions of macro- and micro-organisms. These habitats have gained more attention as it was found they produce a plethora of novel secondary metabolites. Recently, marine-derived fungi have become the hotspot in drug discovery and development. Deep-sea-associated fungi are an important group of marine fungi living in the ocean below 1000 m. The extreme living environment of high pressure and low temperature mean the deep-sea-associated fungi are difficult to collect but has resulted in the evolution of the special secondary metabolic genes in them. Although the vast majority of deep-sea fungi are undiscovered and very few natural products have been reported from them compared to the fungi derived from the near and shallow sea, they are still considered to be potential prolific sources of novel bioactive compounds that are of considerable interest for new drug leads. This review will expound on the sources of strains, chemical structures, and biological activity of 184 new natural products isolated from 46 deep-sea-associated fungi, which were reported from 2020-2022.

KEYWORDS

deep-sea fungi, chemical structures, marine natural products, new compounds, bioactivities

1 Introduction

Oceans cover more than 70% of the Earth's surface and provide 99% of the living space (Subramani and Sipkema, 2019). Animals, plants, and other organisms that live in the oceans, coastal areas, or brackish coastal water can harbor millions of bacteria, fungi, and many other organisms. Some of these marine species live in stressful habitats: high salinity, low temperature, high pressure, and low light conditions (Li et al., 2021; Wu et al., 2022b).

Importantly, a large number of species with high diversity survive under such conditions and produce fascinating and structurally complex natural products that are not found in terrestrial organisms. This may be due to the bioaccumulation of metabolites in marine microorganisms, as they adapt and survive in harsh conditions that differ from other habitats (Bhakuni and Rawat, 2005; Debbab et al., 2010). Therefore, the associated microorganisms could produce bioactive substances with unique structural skeletons and bioactivity. These metabolites also act as chemical defense mechanisms for marine organisms. This is especially true for soft-bodied organisms which lack structural defense mechanisms (Jensen and Fenical, 1994). For example, the sequence of malate dehydrogenase in mollusks in the Conch is produced by the organisms to adapt to high temperatures, while the Mariana lionfish genome species undergoes mutations in genes that regulate bone development and ossification, leading to an early termination of the calcification process of its bones, making most of its bones cartilage, in response to deep-sea pressure. The chlorine-secreting cells of barracuda gills can be flexibly adjusted to adapt to different salinities (Kobayashi and Yuki, 1954; Skinner, 1982; Liao et al., 2017).

Many deep-sea organisms need to coexist with microorganisms to survive in these harsh environments, such as sulfide-oxidizing bacteria symbiosis with tubular worms near deep-sea cold springs. Thus, it is known that bioactive metabolites discovered from marine organisms such as sponges and sea slugs are the products of microbial metabolism (Gerwick and Moore, 2012).

Studies on marine-derived microorganisms were intensively initiated in the nineties. Marine microorganisms quickly proved to be prolific sources of novel bioactive compounds that are of considerable interest as new drug leads in the pharmaceutical industry (Marmann et al., 2014). Although studies on marine microbial natural products are fascinating, there are some limitations as well. For example, only 5% of the marine microbes can be cultured with normal laboratory microbiological conditions and techniques, taxonomy is very poorly defined, and fermentation yields are very low. Also, the complexity of the molecule makes it difficult to resynthesize (Jimenez et al., 2009; Ameri, 2014). Even with these disadvantages, the development of microbial natural products with good bioactivity is of great interest.

Recently published research articles showed that most of the marine microbial metabolites are potent anticancer compounds and most of them are clinically used or under clinical trials. Already, 23 marine-inspired agents are in clinical use, of which 16 are of anticancer antitumor interest (Ameri, 2014; Almaliti and Gerwick, 2023). The most famous example of a marine microbial compound is salinosporamide A (marizomib), which is isolated from marine *Salinispora* bacteria and is a proteasome inhibitor that is currently undergoing clinical studies as a potential new anticancer drug (Marmann et al., 2014). Didemnin B and thiocoraline are two drug candidates that were identified from marine microorganisms and show potent antitumor anticancer activities. They are used for the treatment of different cancers at present (Ameri, 2014). Recently, in 2018, the novel diketopiperazine derivative plinabulin was discovered in marine *Aspergillus* sp. and is now in a worldwide phase III clinical trial for non-small cell lung carcinoma (Blayney et al., 2016).

Studies on microbial natural products have become a famous research area due to their ability to produce biologically active, biosynthetically rare, structurally diverse, and similar metabolites as the host. The ability to produce metabolites on a large scale without damaging the hosts, consumption of minimal period, and reproducibility are also advantageous qualities in this field of study. Thus, the secondary metabolites produced by marine microorganisms have unique and diverse structures, and significant biological activities, which have great potential for traditional Chinese medicine (Yin et al., 2023).

As an important component of the deep-sea microbial community, deep-sea fungi have attracted much attention from researchers due to their rich types of secondary metabolites, high emergence rates, and significant biological activity (Gozari et al., 2020). More and more researchers are pinning their hopes for developing new drugs on the discovery of secondary metabolites from marine fungi. This article reviews the literature on deep-sea fungal active substances during the years 2020-2022 and describes 184 new compounds first reported from marine sources in 47 papers. In this review, compounds are classified into several broad categories based on their structure. This review also summarizes the biological activities of these compounds and the source of bacteria.

2 Nitrogen-containing compounds

2.1 Peptides

Cyclopeptides simplicilliumtides N and O (**1** and **2**) were isolated from the extract of the fermented mycelium of the deep-sea-derived *Simplicillium obclavatum* EIODSF 020. The configurations of **1** and **2** were determined by the advanced Marfeys method. Compounds **1** and **2** showed strong antifungal activity against *Alternaria solani* and *Colletotricum asianum* with MIC values of 0.195-6.250 μg/disc (Firmansyah et al., 2022). Indole diketopiperazine alkaloids chevalinulins A (**3**) and B (**4**) were obtained from *Aspergillus chevalieri* CS-122 (Yan et al., 2022) and displayed proangiogenic activity in transgenic zebrafish model at the concentrations of 40 and 80 μg/mL. Deep-sea-derived fungus *Aspergillus* sp. FS445 afforded aspechinulins A-D (**5**-**8**). Compounds **6** and **7** inhibit the production of NO at 20-90 μM (Liu et al., 2022b). A study of *Mycosphaerella* sp. SCSIO z05 led to the identification of a new iron (III) chelator, mycosphazine A (**9**), which was active against *Bacillus amyloliquefaciens* with a rate of about 249% at a concentration of 100 μg/mL (Huang et al., 2020). Western Atlantic deep-sea fungus *Penicillium chrysogenum* SCSIO 07007 yielded indolyl diketopiperazine, penilline C (**10**) (Han et al., 2020).

2.2 Alkaloids

Investigation of *Aspergillus sydowii* MCCC 3A00324 fermented broth afforded acremolin D (**11**), which was cytotoxic toward K562, Hela-S3, A549, HepG2, and K562 cell lines at the concentration of 20 μM (Niu et al., 2022). Investigation of a South China Sea-derived fungus, *Curvularia verruculosa*, led to the discovery of

vercytochalasins A (**12**) and B (**13**). Compound **12** exhibited angiotensin-I-converting enzyme inhibitory activity whereas **13** showed potent inhibitory activity against aquatic pathogenic bacteria Vibrio anguillarum, V. harveyi, and V. parahaemolyticus with MIC values 32, 8, and 4 μg/mL, respectively (the MIC values of positive control chloromycetin were 0.5, 1, and 2 μg/mL, respectively) (Hu et al., 2023). Fermentation of *Aspergillus puniceus* SCSIO z021 isolated from deep-sea sediment collected in Okinawa Trough yielded puniceusine O (**14**) and (±)-puniceusine P (**15**) (Liu et al., 2022a). A new quinoline alkaloid (**16**) was separated from *Aspergillus* sp. SCSIO06786 (Pang et al., 2020). *Phomopsis lithocarpus* FS508 yielded isoindolinone lactam lithocarlactam A (**17**), which was isolated from a deep-sea sediment sample collected at a depth of 3606 m in the Indian Ocean (Hu et al., 2022a). One new iron (III) chelator of coprogen-type siderophore mycosphamide A (**18**) was separated from a culture of *Mycosphaerella* sp. SCSIO z059 from deep-sea sediment from Okinawa Trough (Huang et al., 2020).

Three new usnic acid derivatives ochuscins C-E (**19**-**21**) were separated from *Ochroconis* sp. FS449, which was isolated from the sediment collected from the Indian Ocean (Chen et al., 2020d). Compounds **19** and **20** showed inhibitory activities against acetylcholinesterase with the IC_{50} values ranging from 49 to 80 μM (Chen et al., 2020d). A new paraherquamide, aculeaquamide A (**22**), was discovered from *Aspergillus aculeatinus* WHF0198 (Wu et al., 2022a). Diphenazine derivatives phenazostatins E-J (**23**-**28**) were separated from *Cystobasidium laryngis*, a strain isolated from deep-sea sediment collected from the Indian Ocean Ridge (Lee et al., 2022). Compound **28** was active against NUGC-3 with an IC_{50} of 7.7 nM. Verruculoid A (**29**), 12-nor-cytochalasin F (**30**), 22-methoxycytochalasin B6 (**31**), 19-hydroxycytochalasin B (**32**), and 20-deoxycytochalasin B (**33**) were obtained from *Curvularia verruculosa* CS-129, among which **29** showed anti-infective activity against *Escherichia coli* with an MIC of 2 μg/mL. Compound **32** was cytotoxic against MCF-7, HCT-116, and HepG-2, with IC_{50} values ranging from 5.2 to 12 μM (Hu et al., 2021). A study on the *Aspergillus* sp. derived from a *Sinularia* sp. soft coral resulted in (±)-17hydroxybrevianamide N (**34**) and (±)-N1-methyl-17-hydroxybrevianamide N (**35**) (Hu et al., 2021). The pyridone alkaloid arthpyrone L (**36**) was separated from the *Arthrinium* sp, and showed antiproliferative effects toward human A549, MG63, U2OS, MCF-7, and MDA-MB-231 cells (Zhang et al., 2021).

3 Polyketides

Three new hybrid sorbicillinoids, bisorbicillchaetones A-C(**37**-**39**), were discovered from *Penicillium* sp. SCSIO06868. Compounds **37** and **38** showed inhibitory activity towards NO production in LPS-activated RAW264.7, with IC_{50} values of 80.3 ± 3.6 μM and 38.4 ± 3.3 μM, respectively (Pang et al., 2022). *Purpureocillium* sp. SCSIO 06693 produced (E)-2-(8,9-dihydroxy-6,8-dimethyldec-4-en2-yl)-methylfuran-3(2H)-one (**40**), which inhibits the pancreatic lipase enzyme at 50 μg/mL (Song et al., 2022).

Two new polyketides fischerins A (**41**) and B (**42**) were obtained from *Aspergillus fischeri* FS452, among which **42** showed cytotoxicity against A549, HepG-2, MCF-7, and SF-268 ranging from 7 to 10 μM (Liu et al., 2021). *Aspergillus puniceus* SCSIO z021 produced three new metabolites, (±)-puniceusone A (**43**), (±)-2,3-dihydroxypropyl 6-ethyl-2,4-dihydroxy3-methylbenzoate (**44**), and (5-ethyl-3-hydroxy-2-methyl) phenyl-b-D-glucoside (**45**)(Liu et al., 2022a). Phomalichenones E-G (**46**-**48**) were isolated from *Alternaria* sp. MCCC 3A00467, and **47** showed cytotoxic activity against U266 cells (Zhong et al., 2022). Two new macrolides cyclopiumolides A (**49**) and B (**50**) with a spiculisporic acidic moiety were isolated from *Penicillium cyclopium* SD-413 and showed cytotoxicity against TE-1, FaDu, and SF126 cells with IC_{50} values ranging from 5.86-17.05 μM (Li et al., 2022). A study of *Paraconiothyrium hawaiiense* FS482 resulted in the identification of hawatides A-G (**51**-**57**). Compound **54** inhibited the production of NO and cytotoxicity against HepG-2, A549, SF-268, and MCD-7 cell lines (Chen et al., 2021b). *Ochroconis* sp. FS449 yielded a series of usnic acid derivatives ochuscins A(**58**), B (**59**), F(**60**), and G (**61**), of which compounds **59** and **61** inhibited the action of acetylcholinesterase (Chen et al., 2020d). Lithocaldehydes A (**62**) and B (**63**), were isolated from *Phomopsis lithocarpus* FS508, which displayed antifungal and antibacterial activity at micromolar levels (Liu et al., 2020).

A series of polyketides asperochratides A-J (**64**-**73**) were produced by *Aspergillus ochraceus*, and compounds **68**-**71** displayed cytotoxicity toward BV-2 cells (Zou et al., 2020). Cultivation of *Penicillium chrysogenum* SCSIO 07007 produced new α-pyrone derivatives chrysopyrones A and B (**74** and **75**) which inhibit human protein tyrosine phosphatases (Han et al., 2020). A chemical investigation of a culture extract of *Phomopsis tersa* FS441 led to the discovery of chlorinated azaphilones tersaphilones A-E (**76**-**80**). Compounds **79**-**80** demonstrated cytotoxicity against cancer cell lines A549, MCF-7, and SF-268 (Chen et al., 2021a). Spiromastol L-N (**81**-**83**) and spiromastixin (**84**) were isolated from an extract of *Spiromastix* sp. SCSIO F190, which displayed inhibitory activity against methicillin-resistant bacterial strains of *Staphylococcus aureus*, *Enterococcus faecalis* ATCC 29212, and *Bacillus subtilis* BS01 (Cai et al., 2023).

Steckwaic acids A-D (**85**-**88**), 11-ketotanzawaic acid D (**89**), 6,15-dihydroxytanzawaic acid M (**90**), (15*R*)-methoxytanzawaic acid M (**91**), 15*S*-methoxytanzawaic acid M (**92**), 8-hydroxytanzawaic acid M (**93**), and 8-hydroxytanzawaic acid B (**94**) were obtained from *Penicillium steckii* AS-324, which was isolated from *Acanthogorgiidae* sp. coral in the Western Pacific Ocean. Compounds **85**, **89**, and **93** displayed antibacterial activity with *Vibrio anguillarum*, *Micrococcus luteus*, and *Pseudomonas aeruginosa* (Hu et al., 2022b). Peniterphenyls A-C (**95**-**97**) was discovered in *Penicillium* sp. SCSIO4103, which displayed activity against HSV-1/2 with EC_{50} values in the range of 1.4 ± 0.6 to 9.3 ± 3.7 μM (Chen et al., 2021c). Penithoketone (**98**) and penithochromones A-L (**99**-**109**) were produced by *Penicillium thomii* YPGA3. Compound **98** displayed cytotoxicity against MCF-7, MDA-MB-468, C4-2B, and C4-2B/ENZR (Li et al., 2020). *Aspergillus terreus* CC-S06-18 afforded a dihydrobenzofuran-phenyl acrylate hybrid compound, aspeterreurone A (**110**), which displayed cytotoxic activities against cell lines BGC823, MGC803, HGC27, and AGS and inhibited the STAT3 phosphorylation (Wang et al., 2020).

Hypoxone A (**111**), 4,8-dimethoxy-1-naphthol (**112**), and 1'-hydroxy-4',8,8'-trimethoxy[2,2']binaphthalenyl-1,4-dione (**113**)

were produced by the fungus *Hypoxylon rubiginosum* FS521, and were cytotoxic against the tumor cell lines SF-268, MCF-7, HepG-2, and A549 (Zhang et al., 2020). The dibenzodioxocinone canescenin A (**114**) produced by the *Penicillium canescens* SCSIO z053 showed weak antibacterial and antibiofilm activities toward *Bascillus amyloliquefaciens* and *Pseudomonas aeruginosa* (Dasanayaka et al., 2020). Two phenols, insphenol A (**115**) and acetylpeniciphenol (**116**), were isolated from the cold sea-derived *Aspergillus insuetus* SD-512. Compound **116** inhibited *Edwardsiella tarda*, *Vibrio alginolyticus*, and *Vibrio vulnificus* (Chi et al., 2021a).

4 Terpenoid

4.1 Terpenoid exclude steroids

Chemical analysis of *Paraconiothyrium hawaiiense* FS482 isolated from the sediment of the Indian Ocean afforded four cyclized diterpenoids hawanoids A-D (**117**-**120**), which displayed inhibitory activities against PAF-induced platelet aggregation (Chen et al., 2023). *Penicillium polonicum* CS-252 yielded new verrucosidin derivatives poloncosidins G-K (**121**–**125**). **121** was active against aquatic (*Micrococcus luteus*, *Edwardsiella ictarda*) and human pathogenic (*Pseudomonas aeruginosa* and *Escherichia coli*) bacteria (Li et al., 2023). A fermentation broth of *Aspergillus* sp. SCSIO06786 afforded sesquiterpene derivatives compound **126**-**127** and compound **128** (Pang et al., 2020). Photeroids A (**129**) and B (**130**), two structurally fascinating meroterpenoids, together with phomeroids A (**132**) and B (**132**), were isolated from the deep-sea-derived fungus *Phomopsis tersa* FS441, which showed strong cytotoxicity (Chen et al., 2020b; Chen et al., 2020c);. Phenolic bisabolanes Asperbisabolanes A-N (**133**-**149**), were purified from *Aspergillus sydowii* MCCC 3A0032. Compound **138** exhibited inhibitory activity against NO secretion in LPS-activated BV-2 microglia cells. Compound **144** also showed anti-inflammatory activity (Niu et al., 2020). Asperal acids A-E (**150**-**154**) were produced by *Aspergillus alabamensis* and showed diverse antimicrobial activity. For example, **153** displayed antimicrobial activity against *Triticum aestivum L.* and **150**-**153** and **155** showed antimicrobial activities against *Staphylococcus aureus*, *Bacillus subtilis*, *Penicillium italicum*, *Fusarium graminearum*, and *Fusarium oxysporum* (Hu et al., 2022c).

Phomactin diterpenes neocucurbols A-D (**156**-**159**) produced by marine fungus *Neocucurbitaria unguis-hominis* FS685 has a structurally complex polycyclic ring system, while neocucurbols E-H **(160**-**163)** has a tricyclic ring system (Cai et al., 2020). *Aspergillus insuetus* SD-512 collected cold seep sediments produced new ophiobolin sesterterpenoids: (6*R*)-16,17,21,21-*O*-tetrahydroophiobolin G (**164**), (6*R*)-16,17-dihydroophiobolin H (**165**), (5*S*, 6*S*)-16,17-dihydroophiobolin H (**166**), and three phthalide derivatives farnesylemefuranones D-F (**167**-**169**). Compounds **166** and **167**-**169** had a broad spectrum of antibacterial activity against a panel of pathogenic bacteria including *Escherichia coli* QDIO-1, *Pseudomonas aeruginosa* QDIO-2, *Aeromonas hydrophilia* QDIO-10, *Edwardsiella tarda* QDIO-8, *Vibrio alginolyticus* QDIO-7, *V. anguillarum* QDIO-9, *V. parahemolyticus* QDIO-5, and *V. vulnificus* QDIO-4 (Chi et al., 2020). Pyran-3,5-dione derivative, canescenin B (**170**), was isolated from *Penicillium canescens* SCSIO z053, and showed weak antibacterial and antibiofilm activities toward *Bascillus amyloliquefaciens* and *Pseudomonas aeruginosa* at 100 μM (Dasanayaka et al., 2020).

4.2 Steroids

Punicesterones A-G (**171**-**177**) were discovered from *Aspergillus puniceus* SCSIO z021. **172** and **173** displayed antibacterial activity and the ability to reduce triglyceride production (Huang et al., 2022). A new steroidal compound, solitumergosterol A (**178**), was isolated from *Penicillium solitum* MCCC 3A00215; **178** exhibited anticancer activity against MB231 (He et al., 2021). A culture of *Phomopsis tersa* FS441 produced phosteoid A (**179**) (Chen et al., 2020a). A marine-derived fungus, *Aspergillus unguis* IV17-109, produced aspersterols A-D (**180**-**183**). Compound **180** showed growth inhibition against six cancer cell lines. Compounds **181**-**183** displayed anti-inflammatory activity as well (Cao et al., 2022). The steroid 7b,8b-epoxy-(22*E*,24*R*)-24-methylcholesta-4,22-diene-3,6-dione (**184**), was isolated from the fungus *Aspergillus penicillioides* SD-311. Compound **184** showed antibacterial activity against *Vibrio anguillarum* with an MIC value of 32 μg/mL (Chi et al., 2021b).

5 Discussion and prospect

In summary, we reported 184 new compounds derived from 46 deep-sea-associated fungi during 2020-2022 (Table 1). The categories of the 184 new compounds discovered during the review period is shown in the following Figures 1, 2. In the past three years, researchers have discovered 80 polyketides, 68 terpenoids, and 36 Nitrogen-containing compounds (Figure 1). It can be hypothesized that the content of polyketides and terpenoids in the metabolites of deep-sea fungi is higher than that of Nitrogen-containing compounds, but it remains to be verified. According to the biological activity profile of these new compounds (Figure 1), only 70 new compounds have detected biological activity. Of the 70

TABLE 1 The detailed information of the 175 new compounds from the deep-sea-associated fungi.

Compound	Producing Strain	Environment Source	Bioactivity	Ref.
1-2	Simplicillium obclavatum EIODSF 020	the East Indian Ocean	Antifungal	(Firmansyah et al., 2022)
3-4	Aspergillus chevalieri CS-122	the South China Sea	Vivo proangiogenic	(Yan et al., 2022)

(Continued)

TABLE 1 Continued

Compound	Producing Strain	Environment Source	Bioactivity	Ref.
5-8	Aspergillus *sp.* FS445	Indian Ocean	NO production inhibitory (**6** and **7**)	(Liu et al., 2022b)
9	Mycosphaerella sp. SCSIO z059	Okinawa Trough	Biofilm formation promotion	(Huang et al., 2020)
10	Penicillium chrysogenum SCSIO 07007	the Western Atlantic		(Han et al., 2020)
11	Aspergillus sydowii MCCC 3A00324	the South Atlantic Ocean	Cytotoxic	(Niu et al., 2022)
12-13	Curvularia verruculosa	the South China Sea	AngiotensinI-converting enzyme (ACE) inhibitory (**12**) and antibacterial activity (**13**).	(Hu et al., 2023)
14-15	Aspergillus puniceus SCSIO z021	Okinawa Trough		(Liu et al., 2022a)
16	Aspergillus sp. SCSIO06786	Indian Ocean		(Pang et al., 2020)
17	Phomopsis lithocarpus FS508	Indian Ocean		(Hu et al., 2022a)
18	Mycosphaerella sp. SCSIO z059	Okinawa Trough		(Huang et al., 2020)
19-21	Ochroconis sp. FS449	Indian Ocean	Acetylcholinesterase inhibitory (**19** and **20**)	(Chen et al., 2020d)
22	Aspergillus aculeatinus WHF0198	the South China Sea		(Wu et al., 2022a)
23-28	Cystobasidium laryngis	Indian Ocean Ridge	Cytotoxic (**28**)	(Lee et al., 2022)
29-33	Curvularia verruculosa CS-129	the South China Sea.	*Escherichia coli* inhibitory (**29**) and cytotoxic (**32**)	(Hu et al., 2021)
34-35	*Aspergillus* sp. *fungus*	the South China Sea		(Xu et al., 2021)
36	*Arthrinium* sp.	the South China Sea	Cytotoxic (**36**)	(Zhang et al., 2021)
37-39	Penicillium sp. SCSIO06868	Indian Ocean	NO production inhibitory (**37** and **38**)	(Pang et al., 2022)
40	Purpureocillium sp. SCSIO 06693	Western Pacific	PL enzyme inhibitory (**40**)	(Song et al., 2022)
41-42	Aspergillus fischeri FS452	Indian Ocean sludge	Cytotoxic (**42**)	(Liu et al., 2021)
43-45	Aspergillus puniceus SCSIO z021	Okinawa Trough		(Liu et al., 2022a)
46-48	Alternaria sp. MCCC 3A00467	Pacific Ocean	Cytotoxic (**47**)	(Zhong et al., 2022)
49-50	Penicillium cyclopium SD-413	the East China Sea	Cytotoxic	(Li et al., 2022)
51-57	Paraconiothyrium hawaiiense FS482.	Indian Ocean sediments	NO production inhibitory and cytotoxic (**54**)	(Chen et al., 2021b)
58-61	Ochroconis sp. FS449	Indian Ocean	Acetylcholinesterase inhibitory (**59** and **61**)	(Chen et al., 2020d)
62-63	Phomopsis lithocarpus FS508	Indian Ocean	Antifungal	(Liu et al., 2020)
64-73	Aspergillus ochraceus	the Northeastern Pacific	Cytotoxic (**68**–**71**)	(Zou et al., 2020)
75-75	Penicillium chrysogenum SCSIO 07007	the Western Atlantic	PTP1B inhibitory (**74** and **75**)	(Han et al., 2020)

(Continued)

TABLE 1 Continued

Compound	Producing Strain	Environment Source	Bioactivity	Ref.
76-80	Phomopsis tersa FS441	Indian Ocean	Cytotoxic	(Chen et al., 2021a)
81-84	Spiromastix sp. SCSIO F190	the Northern South China Sea	Anti-bacteria	(Cai et al., 2023)
85-94	Penicillium steckii AS-324	the Western Pacific Ocean	Anti-bacteria (**85**, **89**, and **93**)	(Hu et al., 2022b)
95-97	Penicillium sp. SCSIO41030	the South China Sea		(Chen et al., 2021c)
98-109	Penicillium thomii YPGA3	the Yap Trench (West Pacific Ocean)		(Li et al., 2020)
110	Aspergillus terreus CC-S06-18	Seawater samples	Cytotoxic	(Wang et al., 2020)
111-113	*Hypoxylon rubiginosum* FS521	the South China Sea		(Zhang et al., 2020)
114	*Penicillium canescens* SCSIO z053	Okinawa Trough	Antibacterial and antibiofilm	(Dasanayaka et al., 2020)
115-116	*Aspergillus insuetus* SD-512	the South China Sea	Antibacterial (**86**)	(Chi et al., 2021a)
117-120	Paraconiothyrium hawaiiense FS482	Indian Ocean	PAF-induced platelet aggregation inhibitory	(Chen et al., 2023)
121-125	Penicillium polonicum CS-252	the East China Sea		(Li et al., 2023)
126-128	Aspergillus sp. SCSIO06786	Indian Ocean		(Pang et al., 2020)
129-130	Phomopsis tersa FS441	Indian Ocean	Cytotoxic	(Chen et al., 2020c)
131-132	Phomopsis tersa FS441	Indian Ocean		(Chen et al., 2020b)
133-149	Aspergillus sydowii MCCC 3A00324	the South Atlantic Ocean	NO secretion inhibitory (**138**, **144**, and **148**)	(Niu et al., 2020)
150-155	Aspergillus alabamensis	Dongzhai Port, Hainan Island, People's Republic of China.	Antimicrobial (**150**-**153** and **155**)	(Hu et al., 2022c)
156-163	*Neocucurbitaria unguis-hominis* FS685	the northern South China Sea		(Cai et al., 2020)
164-169	Aspergillus insuetus SD-512	the northeastern South China Sea	Antibacterial (**166** and **167**-**169**)	(Chi et al., 2020)
170	*Penicillium canescens* SCSIO z053	Okinawa Trough	Antibacterial and antibiofilm	(Dasanayaka et al., 2020)
171-177	Aspergillus puniceus SCSIO z021	Okinawa Trough	Reducing triglyceride and antibacterial (**172** and **173**)	(Huang et al., 2022)
178	Penicillium solitum MCCC 3A00215	the Northwest Atlantic Ocean	Cytotoxic (**178**)	(He et al., 2021)
179	Phomopsis tersa FS441	Indian Ocean		(Chen et al., 2020a)
180-183	Aspergillus unguis IV17-109	Indian Ocean	Cytotoxic (**180**) and anti-inflammatory (**181**-**183**)	(Cao et al., 2022)
184	*Aspergillus penicillioides* SD-311	the South China Sea	Antibacterial (**184**)	(Chi et al., 2021b)

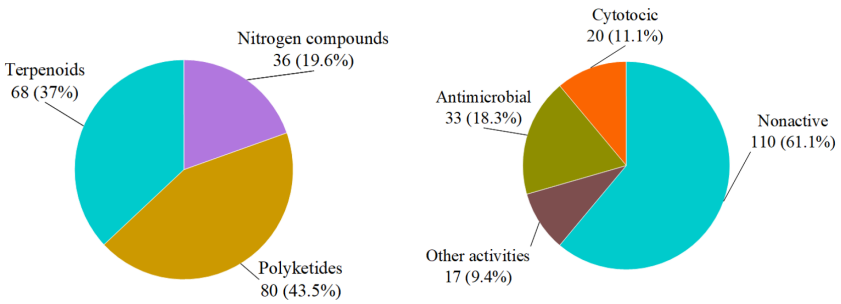

FIGURE 1
Structural and bioactive categories of deep-sea-associated fungi natural products (left: structures, right: bioactivities).

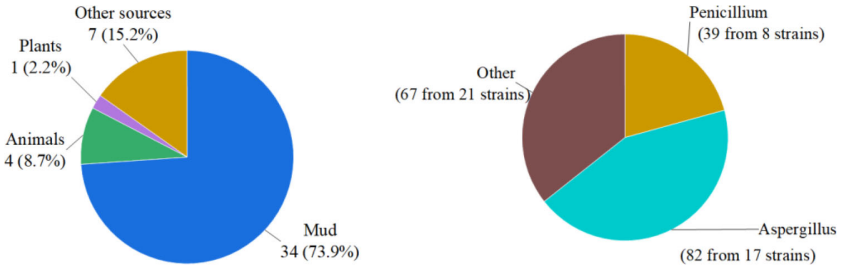

FIGURE 2
Source categories of deep-sea-associated fungi and their natural products (left: environmental samples, right: microbial origin).

active new compounds, 20 were associated with cytotoxicity. Almost half of the compounds have anti-infective activity. Meanwhile, 11 compounds have shown enzyme inhibitory activity, and a few have anti-inflammatory activity. These activities will lead the research culture to develop new drug leads for crucial diseases like cancer. Analysis from the environmental source of strains (Figure 2) suggested that mud was the main source of the deep-sea fungi, contributing 34 out of all 46 strains. Analysis of the microbial origin of these compounds found that *Aspergillus* fungi were the main contributors to these new compounds, contributing a total of 82 new compounds derived from 17 different strains. In terms of culture medium (Figure 3), 36 out of 46 strains were cultured using the rice medium and 10 strains using liquid culture medium. All of these media are rich in nutrients and differ significantly from the oligotrophic environment in the deep sea. No habitat-based cultivation strategies according to the deep-sea environmental factors, such as low oxygen and high pressure, were explored and applied to activate the silent gene cluster of deep-

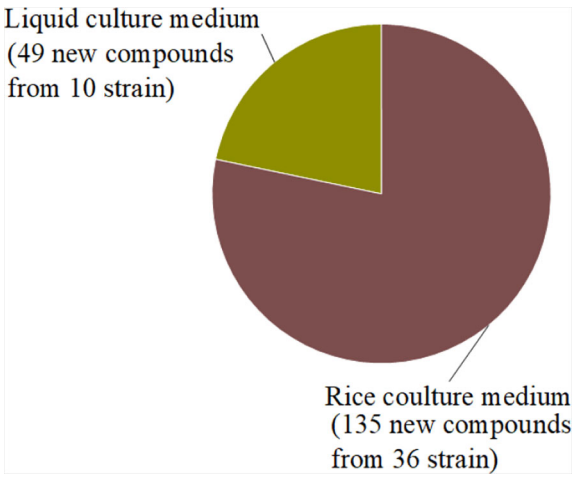

FIGURE 3
Culture medium categories of the deep-sea-associated fungi.

sea fungi, although these strategies have been successfully applied to other deep-sea microorganisms.

In summary, these structurally novel active compounds reveal an astonishing unique secondary metabolic system of deep-sea fungi. However, deep-sea fungi are still a special resource with infinite potential of biologically active and structurally new compounds that has not been fully recognized, explored, and utilized. In the cultivation of deep-sea fungi, it is necessary to try to activate their silent gene clusters using the deep-sea habitat-simulating strategy, so as to further tap their secondary metabolic potential. This requires the joint efforts of researchers dedicating their efforts to deep-sea-derived fungi.

Author contributions

ZW drafted the manuscript. MQ reviewed and corrected the manuscript. CW, YW, and FK conceived, guided, and revised. QW revised the manuscript. All authors have read and agreed to the published version of the manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

Almaliti, J., and Gerwick, W. H. (2023). Methods in marine natural product drug discovery: what's new? *Expert Opin. Drug Discovery* 18, 687–691. doi: 10.1080/17460441.2023.2214360

Ameri, A. (2014). Marine microbial natural products. *Jundishapur J. Natural Pharm. Prod.* 9, e24716. doi: 10.17795/jjnpp-24716

Bhakuni, D. S., and Rawat, D. S. (2005). *Bioactive marine natural products* (New Delhi, India: Anamaya Publishers).

Blayney, D. W., Bazhenova, L., Lloyd, G. K., Huang, L., and Mohanlal, R. (2016). Plinabulin, a novel small molecule that ameliorates chemotherapy-induced neutropenia, is administered on the same day of chemotherapy and has anticancer efficacy. *Blood: Amer Soc. Hematol.* 128, 2508–2508. doi: 10.1182/blood.V128.22.2508.2508

Cai, C. L., Chen, Y. Y., Zhou, L., Gong, N. Y., Zhang, H., Sun, C. L., et al. (2023). Antimicrobial polyketides from the marine-derived fungus spiromastix sp. SCSIO F190. *J. Nat. Prod.* 86, 589–595. doi: 10.1021/acs.jnatprod.2c00900

Cai, S. Y., He, J. L., Bai, K. K., Niu, S. W., and Hong, B. H. (2020). Secondary metabolites of deep-sea fungi and their biological activities: research advances. *J. Int. Pharm. Res.* 1674-0440, 12–1033-15. doi: 10.13220/j.cnki.jipr.2020.12.003

Cao, V. A., Kwon, J. H., Kang, J. S., Lee, H. S., Heo, C. S., and Shin, H. J. (2022). Aspersterols a-d, ergostane-type sterols with an unusual unsaturated side chain from the deep-Sea-Derived fungus *Aspergillus unguis*. *J. Nat. Prod.* 85, 2177–2183. doi: 10.1021/acs.jnatprod.2c00398

Chen, S. S., Chen, Y. C., Li, S. N., Liu, H. X., Li, D. L., Liu, Z. M., et al. (2021b). Hawatides a-G, new polyketides from the deep-sea-derived fungus *Paraconiothyrium hawaiiense* FS482. *Tetrahedron* 93, 132303. doi: 10.1016/j.tet.2021.132303

Chen, S. C., Liu, Z. M., Chen, Y. C., Tan, H. B., Liu, H. X., and Zhang, W. M. (2021a). Tersaphilones a-e, cytotoxic chlorinated azaphilones from the deep-sea-derived fungus *Phomopsis tersa* FS441. *Tetrahedron* 78, 131806. doi: 10.1016/j.tet.2020.131806

Chen, S. C., Liu, Z. M., Chen, Y. C., Tan, H. B., Zhu, S., Liu, H. X., et al. (2020a). Phosteoid a, a highly oxygenated norsteroid from the deep-sea-derived fungus *Phomopsis tersa* FS441. *Tetrahedron Lett.* 61, 151555. doi: 10.1016/j.tetlet.2019.151555

Chen, S. S., Liu, H. X., Li, S. N., Chen, Y. C., Ye, W., Li, H. H., et al. (2023). Hawanoids a-e, unprecedented diterpenoids with PAF-induced platelet aggregation inhibitory activities from the deep-sea-derived fungus *Paraconiothyrium hawaiiense*. *Chin. Chem. Lett.* 34, 107513. doi: 10.1016/j.cclet.2022.05.027

Chen, S. C., Liu, Z. M., Tan, H. B., Chen, Y. C., Li, S. N., Li, H. H., et al. (2020b). Phomeroids a and b: two novel cytotoxic meroterpenoids from the deep-sea-derived fungus *Phomopsis tersa* FS441. *Organic Chem. Frontiers.* 7, 557–562. doi: 10.1039/C9QO01365B

Chen, S. C., Liu, Z. M., Tan, H. B., Chen, Y. C., Zhu, S., Liu, H. X., et al. (2020c). Photeroids a and b, unique phenol-sesquiterpene meroterpenoids from the deep-sea-derived fungus *Phomopsis tersa*. *Org. Biomol. Chem.* 18, 642–645. doi: 10.1039/c9ob02625h

Chen, S. S., Liu, H. X., Ye, W., Li, S. N., Li, D. L., Liu, Z. M., et al. (2020d). Ochuscins a-G, highly oxygenated usnic acid derivatives from the deep-sea-derived fungus *Ochroconis* sp. FS449. *Tetrahedron* 76, 131066. doi: 10.1016/j.tet.2020.131066

Chen, W. H., Zhang, J. W., Qi, X., Zhao, K., Pang, X. Y., Lin, X. P., et al. (2021c). P-terphenyls as anti-HSV-1/2 agents from a deep-Sea-Derived penicillium sp. *J. Nat. Prod.* 84, 2822–2831. doi: 10.1021/acs.jnatprod.1c00400

Chi, L. P., Li, X. M., Wan, Y. P., Li, Y. H., Li, X., and Wang, B. G. (2021a). Two new phenol derivatives from the cold seep-derived fungus *Aspergillus insuetus* SD-512. *Chem. Biodivers.* 18, e2100512. doi: 10.1002/cbdv.202100512

Chi, L. P., Li, X. M., Wan, Y. P., Li, X., and Wang, B. G. (2020). Ophiobolin sesterterpenoids and farnesylated phthalide derivatives from the deep Sea cold-Seep-Derived fungus *Aspergillus insuetus* SD-512. *J. Nat. Prod.* 83, 3652–3660. doi: 10.1021/acs.jnatprod.0c00860

Chi, L. P., Yang, S. Q., Li, X. M., Li, X. D., Wang, B. G., and Li, X. (2021b). A new steroid with 7β, 8β-epoxidation from the deep sea-derived fungus *Aspergillus penicillioides* SD-311. *J. Asian Nat. PROD Res.* 23, 884–891. doi: 10.1080/10286020.2020.1791096

Dasanayaka, S. A. H. K., Nong, X. H., Liang, X., Liang, J. Q., Amin, M., and Qi, S. H. (2020). New dibenzodioxocinone and pyran-3, 5-dione derivatives from the deep-sea-derived fungus *Penicillium canescens* SCSIO z053. *J. Asian Nat. PROD Res.* 22, 338–345. doi: 10.1080/10286020.2019.1575819

Debbab, A., Aly, A. H., Lin, W. H., and Proksch, P. (2010). Bioactive compounds from marine bacteria and fungi. *Microbial. Biotechnol.* 3, 544–563. doi: 10.1111/j.1751-7915.2010.00179.x

Firmansyah, K., Xiao, L., and Qi, S. H. (2022). Bioassay-guided isolation of antifungal cyclopeptides from the deep-sea-derived fungus *Simplicillium obclavatum* EIODSF 020. *Phytochem. Letters.* 48, 1874–3900. doi: 10.1016/j.phytol.2022.01.017

Gerwick, W. H., and Moore, B. S. (2012). Lessons from the past and charting the future of marine natural products drug discovery and chemical biology. *Chem. Biol.* 19, 85–98. doi: 10.1016/j.chembiol.2011.12.014

Gozari, M., Alborz, M., El-Seedi, H. R., and Jassbi, A. R. (2020). Chemistry, biosynthesis, and biological activity of terpenoids and meroterpenoids in bacteria and fungi isolated from different marine habitats. *Eur. J. Med. Chem.* 210, 112957. doi: 10.1016/j.ejmech.2020.112957

Han, W. R., Cai, J., Zhong, W. M., Xu, G. M., Wang, F. Z., Tian, X. P., et al. (2020). Protein tyrosine phosphatase 1B (PTP1B) inhibitors from the deep-sea fungus *Penicillium chrysogenum* SCSIO 07007. *Bioorg. Chem.* 96, 103646. doi: 10.1016/j.bioorg.2020.103646

He, Z. H., Xie, C. L., Hao, Y. J., Xu, L., Wang, C. F., Hu, M. Y., et al. (2021). Solitumergosterol a, a unique 6/6/6/6/5 steroid from the deep-sea-derived *Penicillium solitum* MCCC 3A00215. *Org. Biomol. Chem.* 19, 9369–9372. doi: 10.1039/d1ob01392k

Hu, X. Y., Li, X. M., Wang, B. G., and Meng, L. H. (2022b). Tanzawaic acid derivatives: fungal polyketides from the deep-Sea coral-derived endozoic *Penicillium steckii* AS-324. *J. Nat. Prod.* 85, 1398–1406. doi: 10.1021/acs.jnatprod.2c00211

Hu, X. Y., Li, X. M., Yang, S. Q., Li, X., Wang, B. G., and Meng, L. H. (2023). Vercytochalasins a and b: two unprecedented biosynthetically related cytochalasins from the deep-sea-sourced endozoic fungus *Curvularia verruculosa*. *Chin. Chem. Lett.* 34, 107516. doi: 10.1016/j.cclet.2022.05.030

Hu, X. Y., Wang, C. Y., Li, X. M., Yang, S. Q., Li, X., Wang, B. G., et al. (2021). Cytochalasin derivatives from the endozoic *Curvularia verruculosa* CS-129, a fungus isolated from the deep-Sea squat lobster *Shinkaia crosnieri* living in the cold seep environment. *J. Nat. Prod.* 84, 3122–3130. doi: 10.1021/acs.jnatprod.1c00907

Hu, J. H., Wang, N. Y., Liu, H. X., Li, S. N., Liu, Z. M., Zhang, W. M., et al. (2022a). Secondary metabolites from a deep-sea derived fungal strain of *Phomopsis lithocarpus* FS508. *Nat. Prod Res.* 27, 1–8. doi: 10.1080/14786419.2022.2044810

Hu, Z. B., Zhu, Y. J., Chen, J., Chen, J. J., Li, C. Y., Gao, Z. Z., et al. (2022c). Sesquiterpenoids with phytotoxic and antifungal activities from a pathogenic fungus aspergillus alabamensis. *J. Agric. Food Chem.* 70, 12065–12073. doi: 10.1021/acs.jafc.2c05703

Huang, Z. H., Liang, X., Gu, Q., Ma, X., and Qi, S. H. (2022). Punicesterones a-G, polyhydroxylated mycoecdysteroids from the deep-sea-derived fungus *Aspergillus puniceus* SCSIO z021. *Phytochemistry* 205, 113511. doi: 10.1016/j.phytochem.2022.113511

Huang, Z. H., Liang, X., and Qi, S. H. (2020). A new iron(III) chelator of coprogen-type siderophore from the deep-sea-derived fungus *Mycosphaerella* sp. SCSIO z059. *Chin. J. Nat. Med.* 18, 243–249. doi: 10.1016/S1875-5364(20)30029-7

Jensen, P. R., and Fenical, W. (1994). Strategies for the discovery of secondary metabolites from marine bacteria: ecological perspective. *Annu. Rev. Microbiol.* 48, 559–584. doi: 10.1146/annurev.mi.48.100194.003015

Jimenez, J. T., Sturdikova, M., and Sturdik, E. (2009). Natural products of marine origin and their perspective in the discovery of new anticancer drugs. *Acta Chimica Slovaca.* 2, 63–74.

Kobayashi, S., and Yuki, R. (1954). On the specificity of kidney catalase activity in salmonid fishes. *Bull. Faculty Fish. Hokkaido University* 5, 137–148.

Lee, H. S., Kang, J. S., Cho, D. Y., Choi, D. K., and Shin, H. J. (2022). Isolation, structure determination, and semisynthesis of diphenazine compounds from a deep-Sea-Derived strain of the fungus *Cystobasidium laryngis* and their biological activities. *J. Nat. Prod.* 85, 857–865. doi: 10.1021/acs.jnatprod.1c00985

Li, H. H., Du, X. Y., Chen, C. Y., Qi, J. F., and Wang, Y. (2021). Current research on natural products and biological activities of *Aspergillus* fungi from marine sources. *Pharm. Inform.* 10, 92. doi: 10.12677/pi.2021.103013

Li, Q., Xu, W., Fan, R. Z., Zhang, J., Li, Y. L., Wang, X. W., et al. (2020). Penithoketone and penithochromones a-l, polyketides from the deep-Sea-Derived fungus *Penicillium thomii* YPGA3. *J. Nat. Prod.* 83, 2679–2685. doi: 10.1021/acs.jnatprod.0c00571

Li, Y. H., Yang, S. Q., Li, X. M., Li, X., Wang, B. G., and Li, H. L. (2022). Cyclopiumolides a and b, unusual 13-membered macrolides from the deep sea-sourced fungus *Penicillium cyclopium* SD-413 with antiproliferative activities. *Bioorg. Chem.* 128, 106104. doi: 10.1016/j.bioorg.2022.106104

Li, Y. H., Yang, S. Q., Li, X. M., Li, X., Wang, B. G., and Li, H. L. (2023). Five new verrucosidin derivatives from *Penicillium polonicum*, deep-sea cold-seep sediment isolated fungus. *Fitoterapia* 165, 105387. doi: 10.1016/j.fitote.2022.105387

Liao, M. L., Zhang, S., Zhang, G. Y., Chu, Y. M., Somero, G. N., and Dong, Y. w. (2017). Heat-resistant cytosolic malate dehydrogenases (cMDHs) of thermophilic intertidal snails (genusEchinolittorina): protein underpinnings of tolerance to body temperatures reaching 55°C. *J. Exp. Biol.* 220, 2066–2075. doi: 10.1242/jeb.156935

Liu, Z. M., Chen, Y. C., Li, S. N., Hu, C. Y., Liu, H. X., and Zhang, W. M. (2022b). Indole diketopiperazine alkaloids from the deep-sea-derived fungus aspergillus sp. FS445. *Nat. Prod Res.* 36, 5213–5221. doi: 10.1080/14786419.2021.1925271

Liu, Z. M., Li, S. N., Chen, Y. C., Li, M. Q., Liu, H. X., and Zhang, W. M. (2021). Cytotoxic polyketides from the deep-sea-derived fungus *Aspergillus fischeri* FS452. *Nat. Prod Res.* 36, 5701–5707. doi: 10.1080/14786419.2021.2015595

Liu, C. M., Liang, X., Yao, F. H., and Qi, S. (2022a). Five new aromatic polyketides and isoquinoline alkaloids from the deep-sea-derived fungus *Aspergillus puniceus* SCSIO z021. *Tetrahedron* 126, 133067. doi: 10.1016/j.tet.2022.133067

Liu, H. B., Liu, Z. M., Li, H. H., Tan, H. B., Zhang, Q. B., Li, D. L., et al. (2020). Lithocaldehydes a and b, polyketides from the deep sea-derived fungus *Phomopsis lithocarpus* FS508. *Org. Biomol. Chem.* 18, 7326–7329. doi: 10.1039/d0ob01674h

Marmann, A., Aly, A. H., Lin, W., Wang, B., and Proksch, P. (2014). Co-Cultivation: a powerful emerging tool for enhancing the chemical diversity of microorganisms. *Mar. Drugs* 12, 1043–1065. doi: 10.3390/md12021043

Niu, S. W., Chen, Z. M., Pei, S. X., Shao, Z. Z., Zhang, G. Y., and Hong, B. H. (2022). Acremolin d, a new acremolin alkaloid from the deep-sea sediment-derived *Aspergillus sydowii* fungus. *Nat. Prod Res.* 36, 4936–4942. doi: 10.1080/14786419.2021.1913587

Niu, S. W., Yang, L. H., Zhang, G. Y., Chen, T. T., Hong, B. H., Pei, S. X., et al. (2020). Phenolic bisabolane and cuparene sesquiterpenoids with anti-inflammatory activities from the deep-sea-derived *Aspergillus sydowii* MCCC 3A00324 fungus. *Bioorg. Chem.* 105, 104420. doi: 10.1016/j.bioorg.2020.104420

Pang, X. Y., Lin, X. P., Zhou, X. F., Yang, B., Tian, X. P., Wang, J. F., et al. (2020). New quinoline alkaloid and bisabolane-type sesquiterpenoid derivatives from the deep-sea-derived fungus aspergillus sp. SCSIO06786. *Fitoterapia* 140, 104406. doi: 10.1016/j.fitote.2019.104406

Pang, X. Y., Wang, P., Liao, S. R., Zhou, X. F., Lin, X. P., Yang, B., et al. (2022). Three unusual hybrid sorbicillinoids with anti-inflammatory activities from the deep-sea derived fungus penicillium sp. SCSIO06868. *Phytochemistry* 202, 113311. doi: 10.1016/j.phytochem.2022.113311

Skinner, R. H. (1982). The interrelation of water quality, external parasites and gill pathology of some fishes from Biscayne Bay, Florida. *Fishery Bulletin*. 80. doi: 10.1577/1548-8446(1982)007<0020:EVOLMF>2.0.CO;2

Song, Y. Y., Song, M. M., Chen, W. H., Pang, X. Y., Wang, F. Z., Tian, X. P., et al. (2022). One new furanone analog from the deep-sea fungus purpureocillium sp. SCSIO 06693. *Nat. Prod Res.* 18, 1–7. doi: 10.1080/14786419.2022.2089671

Subramani, R., and Sipkema, D. (2019). Marine rare actinomycetes: a promising source of structurally diverse and unique novel natural products. *Mar. Drugs* 17, 249. doi: 10.3390/md17050249

Wang, W. Y., Yang, J., Liao, Y. Y., Cheng, G., Chen, J., Mo, S. W., et al. (2020). Aspeterreurone a, a cytotoxic dihydrobenzofuran-phenyl acrylate hybrid from the deep-Sea-Derived fungus *Aspergillus terreus* CC-S06-18. *J. Nat. Prod.* 83, 1998–2003. doi: 10.1021/acs.jnatprod.0c00189

Wu, J., Wang, F. Q., He, L. M., Zhou, S. Y., Wang, S. B., Jia, J., et al. (2022a). Aculeaquamide a, cytotoxic paraherquamide from the marine fungus *Aspergillus aculeatinus* WHUF0198. *Nat. Prod Res.* 36, 4388–4393. doi: 10.1080/14786419.2021.1998047

Wu, Y. Z., Zhang, H. M., An, F. F., and Zheng, Y. B. (2022b). Research progress on secondary metabolites of aspergillus versicolor from different habitats. *Natural Product Res. Dev.* 35, 342–352. doi: 10.16333/j.1001-6880.2023.2.018

Xu, W. F., Chao, R., Hai, Y., Guo, Y. Y., Wei, M. Y., Wang, C. Y., et al. (2021). 17-hydroxybrevianamide n and its N1-methyl derivative, quinazolinones from a soft-Coral-Derived aspergillus sp. fungus: 13S enantiomers as the true natural products. *J. Nat. Prod.* 84, 1353–1358. doi: 10.1021/acs.jnatprod.1c00098

Yan, L. H., Li, P. H., Li, X. M., Yang, S. Q., Liu, K. C., Wang, B. G., et al. (2022). Chevalinulins a and b, proangiogenic alkaloids with a Spiro[bicyclo[2.2.2]octane-diketopiperazine] skeleton from deep-Sea cold-Seep-Derived fungus *Aspergillus chevalieri* CS-122. *Org. Lett.* 24, 2684–2688. doi: 10.1021/acs.orglett.2c00781

Yin, Q. Z., Liu, X. W., Zhang, Z. J., Lei, H. X., and Wu, B. (2023). Chemistry and bioactivities of alkaloids isolated from marine fungi (covering 2016-2022). *Fitoterapia* 164, 105377. doi: 10.1016/j.fitote.2022.105377

Zhang, J., Chen, Y. C., Liu, Z. M., Guo, B. C., Gao, X. X., Liu, H. X., et al. (2020). Cytotoxic secondary metabolites from a Sea-derived fungal strain of *Hypoxylon rubiginosum* FS521. *Chin. J. Org. Chem.* 40, 1367. doi: 10.6023/cjoc201912012

Zhang, Y. Y., Li, M. R., Zhang, Q. Q., Wang, Z. Y., Li, X. X., Bao, J., et al. (2021). Arthpyrone l, a new pyridone alkaloid from a deep-Sea arthrinium sp., inhibits proliferation of MG63 osteosarcoma cells by inducing G0/G1 arrest and apoptosis. *Chem. Biodivers.*, 18, e2000639. doi: 10.1002/cbdv.202000639

Zhong, T. H., Zeng, X. M., Feng, S. B., Zhang, H. T., Zhang, Y. H., Luo, Z. H., et al. (2022). Three new phomalone derivatives from a deep-sea-derived fungus alternaria sp. MCCC 3A00467. *Nat. Prod Res.* 36, 414–418. doi: 10.1080/14786419.2020.1771706

Zou, Z. B., Zhang, G., Li, S. M., He, Z. H., Yan, Q. X., Lin, Y. K., et al. (2020). Asperochratides a-J, ten new polyketides from the deep-sea-derived *Aspergillus ochraceus*. *Bioorg. Chem.* 105, 104349. doi: 10.1016/j.bioorg.2020.104349