Review

Potential Pharmacological Resources: Natural Bioactive Compounds from Marine-Derived Fungi

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Abstract: In recent years, a considerable number of structurally unique metabolites with biological and pharmacological activities have been isolated from the marine-derived fungi, such as polyketides, alkaloids, peptides, lactones, terpenoids and steroids. Some of these compounds have anticancer, antibacterial, antifungal, antiviral, anti-inflammatory, antioxidant, antibiotic and cytotoxic properties. This review partially summarizes the new bioactive compounds from marine-derived fungi with classification according to the sources of fungi and their biological activities. Those fungi found from 2014 to the present are discussed.

Keywords: marine-derived fungi; fungal metabolites; bioactive compounds; natural products

1. Introduction

The oceans, which cover more than 70% of the earth’s surface and more than 95% of the earth’s biosphere, harbor various marine organisms. Because of the special physical and chemical conditions in the marine environment, almost every class of marine organism displays a variety of molecules with structurally unique features. However, unlike the long historical medical uses of terrestrial plants, marine organisms have a shorter history in pharmacological application [1]. In recent years, a significant number of novel metabolites with pharmacological potential have been discovered from marine organisms, such as polyketides, alkaloids, peptides, proteins, lipids, shikimates, glycosides, isoprenoids and hybrids, which exhibit biological activity including anticancer, antitumor, antiproliferative, antimicrotubule, cytotoxic, photo protective, as well as antibiotic and antifouling properties [2]. Among them, marine microorganisms, such as bacteria, actinomycetes, fungi and cyanobacteria have attracted more attention as potential lead compound producers. In comparison to marine invertebrates, they are a renewable and a reproducible source, as they can be cultured and can even be envisaged as amazing microbial factories for natural products [3].

Previously, scientists always focused on actinomycetes for their abilities to produce antibiotics. In fact, many fungal metabolites in the pharmaceutical market indicates the potential of microorganisms as valuable sources of lead drugs, e.g., the antibiotic polyketide griseofulvin (Likuden M®), the antibacterial terpenoid fusidic acid (Fucidine®), semi-synthetic or synthetic penicillins and cephalosporins, macrolides, statins as well as the ergot alkaloids such as ergotamine (Ergo-Kranit®) [4]. In 1949, the first secondary metabolite isolated from a marine-derived fungal strain, famous cephalosporin C, was produced by a culture of a Cephalosporium sp. isolated from the Sardinian coast. However, this was a more or less accidental discovery.

Despite the discovery of such important drug from marine fungi, the number of bioactive natural products originated from marine fungi increased extremely slowly. It is only from the late 1980s that researchers have focused on marine-derived fungi. In fact, marine-derived fungi are very important sources for novel bioactive secondary metabolites that could potentially be used as...
drugs. Blunt et al., mentioned that marine-derived fungi have a greater proportion of marine natural compounds with more desirable oral-bioavailability and physico-chemical properties with molecular weight (MW) < 400 and clogP (calculated octanol-water logP) < 4 [5]. Compounds that meet these criteria can suggest the optimum combinations for potential pharmaceuticals [5]. Currently, thousands of structurally unique and biologically active compounds have been reported from marine fungi.

According to a classical definition, marine fungi are divided into obligate marine fungi and facultative marine fungi [6]. In fact, marine fungi often live as symbionts in algae, mangrove, coral, sea anemone, starfish, sea urchin, seagrass, and, especially, sponges. Collection of marine fungi usually requires the collection of the host or supporting material (e.g., algae, marine invertebrates, sediment or water, and even driftwood). Herein, a neutral term “marine-derived fungi” was used, which includes any fungal strain obtained from marine environment using cultivation techniques with “marine” media, which do not differentiate between facultative marine strains and contaminants from terrestrial habitats.

The aim of this review is to give an overview on secondary metabolites from marine-derived fungi and their biological activities, focusing on the period from 2014 to the present. In similar published reviews, assignments of a given metabolite to a certain category were generally based on structural considerations. It is obvious that classifications of the enormous structural diversity of marine fungal-derived metabolites are different in various literature reports, which only represents the authors’ personal judgments. In this article, these metabolites were classified according to the sources of marine fungi.

2. Metabolites from Marine-Derived Fungi

2.1. Marine Animals

2.1.1. Sponge

Two new 4-hydroxy-2-pyridone alkaloids, arthpyrones (1–2), were isolated from the fungus Arthrinium arundinis ZSDS1-F3, which obtained from sponge (Xisha Islands, China). Compounds 1 and 2 had significant in vitro cytotoxicities against the K562, A549, Huh-7, H1975, MCF-7, U937, BGC823, HL60, Hela and MOLT-4 cell lines, with IC50 values ranging from 0.24 to 45 μM. Furthermore, compound 2 displayed significant AchE inhibitory activity (IC50 = 0.81 μM), whereas compound 1 showed modest activity (IC50 = 47 μM) (Figure 1) [7].

![Figure 1. Structures of compounds 1–2.](image)

Chemical examination of the solid culture of the endophytic fungus Stachybotrys chartarum isolated from the sponge Niphates recondita (Weizhou Island in Beibuwan Bay, Guangxi Province of China) resulted in the isolation of seven new phenylspirodrimanes, named chartarilactams (3–9). Compounds 3–9 exhibited potent lipid-lowering effects in HepG2 cells in a dose of 10 μM (Figure 2) [8].
The extract of a strain of *Aspergillus versicolor* MF359 (from the sponge of *Hymeniacidon perleve*, Bohai Sea, China) yielded one new secondary metabolites, named 5-methoxydihydrosterolgmatocystin (10). Compound 10 showed potent activity against *Staphylococcus aureus* (*S. aureus*) and *Bacillus subtilis* (*B. subtilis*) with MIC values of 12.5 and 3.125 μg/mL, respectively (Figure 3) [9].

The fungus *Diaporthaceae* sp. PSU-SP2/4 from marine sponge (Trang city, Thailand) generated a new pentacyclic cytochalasin (diaporthalasin, 11). Compound 11 displayed potent antibacterial activity against both *S. aureus* and methicillin-resistant *S. aureus* (MRSA) with equal MIC values of 2 μg/mL (Figure 3) [10].

A new chevalone derivative, named chevalone E (12), was isolated from the ethyl acetate extract of the undescribed marine sponge-associated fungus *Aspergillus similanensis* KUFA 0013, which was collected from the Similan Islands, Phang Nga Province, Southern Thailand. Compound 12 was found to show synergism with the antibiotic oxacillin against methicillin-resistant *S. aureus* (Figure 3) [11].

Xylarianaphthol-1 (13), a new dinaphthofuran derivative, was isolated from an Indonesian marine sponge-derived fungus of order *Xylariales* on the guidance of a bioassay using the transfected human osteosarcoma MG63 cells (MG63<sub>hE3</sub>). Compound 13 activated p21 promoter stably transfected in MG63 cells with dose-dependent pattern. Expression of p21 protein in the wild-type MG63 cells was also promoted by xylarianaphthol-1 treatment, indicating compound 13 was expected to contribute to cancer prevention or treatment (Figure 3) [12].

A new polyketide with a new carbon skeleton, lindgomycin (14), was extracted from mycelia and culture broth of different Lindgomycetaceae strains, which were isolated from a sponge of the Kiel Fjord in the Baltic Sea (Germany) and from the Antarctic. Compound 14 showed antibiotic activities with IC<sub>50</sub> value of 5.1 ± 0.2 μM against MRSA (Figure 3) [13].
2.1.2. Coral

The fungus *Aspergillus terreus* SCSGAF0162 was isolated from gorgonian corals *Echinogorgia aurantiaca* (the South China Sea). Three lactones including three territrem derivatives (15–17) and a butyrolactone derivative (18) were isolated from the fungus under solid-state fermentation of rice. Among them, compounds 15 and 16 showed strong inhibitory activity against acetylcholinesterase with IC50 values of 4.2 ± 0.6 and 4.5 ± 0.6 μM, respectively. This was the first report that compounds 17 and 18 had evident antiviral activity towards HSV-1, with IC50 values of 16.4 ± 0.6 and 21.8 ± 0.8 μg·mL⁻¹, respectively. Moreover, compound 15 had obvious antifouling activity with EC50 values of 12.9 ± 0.5 μg·mL⁻¹ toward barnacle *Balanus amphitrite* larvae (Figure 4) [14].

![Figure 4. Structures of compounds 15–18.](image)

Two new dihydrothiophene-condensed chromones, oxalicumones (19–20) were isolated from a culture broth of the marine gorgonian-associated fungus *Penicillium oxalicum* SCSGAF 0023. Compounds 19 and 20 showed significant cytotoxicity against several carcinoma cell lines with IC50 less than 10 μM (Figure 5) [15].

![Figure 5. Structures of compounds 19–20.](image)

The fungal strain *Nigrospora oryzae* SCSGAF 0111 (from marine gorgonian *Verrucella umbraculum*, South China Sea) yielded two new citrinins, nigrospins B and C (21–22). Compounds 21–22 showed weak antifungal activity against *Aspergillus versicolor* with inhibition zone of 8 cm at 50 μg/paper disc, with a positive control thiram of 8 cm at 5 μg/paper disc (Figure 6) [16].

Two nucleoside derivatives (23–24) were isolated from the fungus *Aspergillus versicolor* which was derived from the gorgonian *Dichotella gemmacea* in the South China Sea. Compounds 23/24 (a mixture of compound 23:compound 24 at a ratio of 7:10) exhibited selective antibacterial activity against *Staphylococcus epidermidis* with an MIC value of 12.5 μM (Figure 6) [17].

![Figure 6. Structures of compounds 21–24.](image)
Two new sulfur-containing benzofuran derivatives, eurothiocin A and B (25 and 26) were isolated from the fungus *Eurotium rubrum* SH-823 which was obtained from a *Sarcophyton* sp. soft coral in the South China Sea. The compounds (25 and 26) shared a methyl thiolester moiety, which was quite rare in natural secondary metabolites. Both of them exhibited more potent inhibitory effects against *α*-glucosidase activity than acarbose, which was the clinical *α*-glucosidase inhibitor. Further mechanistic analysis demonstrated that both of them exhibited competitive inhibition characteristics (Figure 7) [18].

*Chondrostereum* sp. was isolated from the inner tissue of a soft coral *Sarcophyton tortuosum*, which was collected from the Hainan Sanya National Coral Reef Reserve, China. When this fungus was cultured in a liquid medium containing glycerol as the carbon source, a new metabolite, chondrosterin 27 was obtained. Compound 27 exhibited potent cytotoxic activities against the cancer cell lines CNE-1 and CNE-2 with the IC₅₀ values of 1.32 and 0.56 μM (Figure 7) [19].

![Figure 7. Structures of compounds 25–29.](image)

A steroid derivative, compound 28 was isolated from the fermentation broth of a gorgonian-derived *Aspergillus* sp. fungus. The fungus was isolated from the inner part of the fresh gorgonian *M. abnormalis*, which was collected from the Xisha Islands coral reef of the South China Sea. Compound 28 inhibited the larval settlement of barnacle *Balanus amphitrite* with EC₅₀ 18.40 ± 2.0 μg/mL (Figure 7) [20].

A new diphenyl ether derivative, talaromycin A (29) was isolated from a gorgonian-derived fungus, *Talaromyces* sp. The fungal strain was isolated from a piece of fresh tissue from the inner part of the gorgonian *Subergorgia suberosa*, collected from the Weizhou coral reef in the South China Sea. Compound 29 showed potent antifouling activities against the larval settlement of the barnacle *Balanus amphitrite* with the EC₅₀ value 2.8 ± 0.2 μg/mL (Figure 7) [21].

2.1.3. Starfish

Liang et al. [22] investigated the influence on secondary metabolites with variety of cultivation parameters of marine fungus, *Neosartorya pseudofischeri*, which was isolated from the inner tissue of starfish *Acanthaster planci*. Glycerol-peptone-yeast extract (GlyPY) and glucose-peptone-yeast extract (GluPY) media were applied to culture this fungus. A novel gliotoxin (30) was produced with GluPY medium. Compound 30 displayed significant inhibitory activities against three multidrug-resistant bacteria, *S. aureus* (ATCC29213), MRSA (R3708) and *Escherichia coli* (*E. coli*) (ATCC25922), as well as cytotoxicities against some cell lines including human embryonic kidney (HEK) 293 cell line and human colon cancer cell lines, HCT-116 and RKO (a poorly differentiated colon carcinoma cell line) (Figure 8).

A novel isobenzofuranone derivative, pseudaboydins A (31) was isolated from the marine fungus, *Pseudallescheria boydii*, associated with the starfish, *Acanthaster planci*. Compound 31 showed moderate...
cytotoxic activity against HONE1, SUNE1 and GLC82 with IC₅₀ values of 37.1, 46.5 and 87.2 μM, respectively (Figure 8) [23].

![Figure 8. Structures of compounds 30-31.](image)

2.1.4. Bryozoan

Three new cyclohexadepsipeptides of the isaridin class including isaridin G (32), desmethylisaridin G (33), and desmethylisharidin C1 (34) were isolated and identified from the marine bryozoan-derived fungus Beauveria felina EN-135. Compounds 32–34 showed inhibitory activity against E. coli with MIC values of 64, 64, and 8 μg/mL, respectively. This is the first report on antibacterial activities of the isaridins (Figure 9) [24].

Bioassay-guided fractionation of a culture extract of Beauveria felina EN-135, an entomopathogenic fungus isolated from an unidentified marine bryozoan, led to the isolation of a new cyclodepsipeptide, iso-isaridin D (35); two new O-containing heterocyclic compounds felinones A and B (36 and 37). Compound 35 exhibited potent lethality against brine shrimp (Artemia salina), with LD₃₀ values of 26.58 μM, notably stronger than that of the positive control colchicine, while compounds 36 and 37 possessed weak activity. Only compound 37 showed inhibitory activity (MIC value of 32 μg/mL) higher than that of the chloramphenicol control (MIC value of 4 μg/mL) against Pseudomonas aeruginosa (Figure 9) [25].

![Figure 9. Structures of compounds 32-37.](image)

2.1.5. Sea Urchin

The Penicillium sp. SF-6013 was isolated from the sea urchin Brisaster latifrons, which was collected from the Sea of Okhotsk. Chemical investigation of strain SF-6013 resulted in the discovery of a new tanzawaic acid derivative, 2E,4Z-tanzawaic acid D (38). Screening for anti-inflammatory effects in lipopolysaccharide (LPS)-activated microglial BV-2 cells indicated that compound 38 inhibited the production of nitric oxide (NO) with IC₅₀ values of 37.8 μM (Figure 10) [26].

2.1.6. Fish

Two new rubrolides, rubrolides R (39) and S (40), were isolated from the fermentation broth of the marine-derived fungus Aspergillus terreus OUCMDZ-1925, which was isolated from the viscera of C. haematocheilus grown in the waters of the Yellow River Delta. Compound 39 showed comparable or
superior antioxidation against ABTS radicals to those of trolox and ascorbic acid with an IC$_{50}$ value of 1.33 μM. Compound 40 showed comparable or superior anti-influenza A (H1N1) virus activity to that of ribavirin with an IC$_{50}$ value of 87.1 μM. Compounds 39 and 40 showed weak cytotoxicity against the K562 cell line with IC$_{50}$ values of 12.8 and 10.9 μM, respectively, while were inactive against the A549, HL-60, Hela and HCT-116 cell lines (Figure 10) [27].

2.1.7. Prawn

The fungal strain, *Aspergillus flavus* OUCMDZ-2205, was obtained from the prawn, *Panaeus vannamei*, from the Lianyungang sea area, Jiangsu Province of China. Two new indole-diterpenoids (41 and 42) were isolated from the fermentation broth of the fungus. Compound 41 exhibited antibacterial activity against *S. aureus* with a MIC value of 20.5 μM and showed PKC-beta inhibition with an IC$_{50}$ value of 15.6 μM. Both 41 and 42 could arrest the A549 cell cycle in the S phase at a concentration of 10 μM (Figure 11) [28].

2.1.8. Others

The marine-derived fungus *Eurotium amstelodami* was isolated from an unidentified marine animal collected from the Sungsan coast in Jeju Island, Korea. An anthraquinone derivative, questinol (43) was successfully isolated from the broth extract of the fungus for the first time. Questinol (43) did not exhibit cytotoxicity in LPS-stimulated RAW 264.7 cells up to 200 μM while could significantly inhibit NO and PGE$_2$ production at indicated concentrations. Furthermore, it could inhibit the production of pro-inflammatory cytokines, including IL-1β, TNF-α, and IL-6 and suppress the expression level of iNOS in a dose-dependent manner through the western blot analysis. All these results suggest that questinol might be selected as a promising agent for the prevention and therapy of inflammatory disease (Figure 11) [29].

A novel aspochalasin, 20-β-methylthio-aspochalasin Q (named as aspochalasin V, 44) was isolated from culture broth of *Aspergillus* sp., which was obtained in the gut of a marine isopod *Ligia oceanica* (Dinghai in Zhoushan, Zhejiang Province of China). This is the first report about methylthio-substituted aspochalasin derivative. Apochalasin V showed moderate cytotoxic activity against the prostate cancer PC3 cell line and HCT116 cell line with IC$_{50}$ values of 30.4 and 39.2 μM, respectively (Figure 11) [30].

Two new cerebrosides, penicillosides A (45) and B (46) were isolated from the marine-derived fungus *Penicillium* species, which were gained from the Red Sea tunicate, *Didemnum* species in the Mangrove. Penicilloside A displayed antifungal activity against *Candida albicans* while penicilloside B illustrated antibacterial activities against *S. aureus* and *E. coli*. Additionally, both compounds showed weak activity against HeLa cells (Figure 11) [31].

![Figure 10. Structures of compounds 38–40.](image-url)
2.2. Mangrove

Six new compounds with polyketide decalin ring, peaurantigroseols A–F (47–52), were isolated from the fermentation products of mangrove endophytic fungus *Penicillium aurantiogriseum* 328#, which was collected from the bark of *Hibiscus tiliaeus* in the Qi’ao Mangrove Nature Reserve of Guangdong Province, China. Compounds 47–52, showed low inhibitory activity against human aldose reductase (at a concentration of 50 μM), the corresponding value of percent inhibitions were 16%, 6%, 31%, 22%, 26%, 2%, respectively (Figure 12) [32].

![Figure 11. Structures of compounds 41–46.](image1)

![Figure 12. Structures of compounds 47–52.](image2)

Aspergifuranone (53), isocoumarin derivatives (±) 54 were separated from the mangrove endophytic fungus *Aspergillus* sp. 16-5B, which was isolated from the leaves of *Sonneratia apetala* from Dongzhaihang Mangrove National Nature Reserve in Hainan Island, China. Both of them were evaluated for their α-glucosidase inhibitory activities, and compound 53 showed significant inhibitory activity with IC$_{50}$ value of 9.05 ± 0.60 μM. Kinetic analysis showed that compound 53 was a noncompetitive inhibitor of α-glucosidase. Compound 54 exhibited moderate inhibitory activities, with IC$_{50}$ value of 90.4 ± 2.9 μM (Figure 13) [33].

A new alkaloid, brocaeloid B (55), containing C-2 reversed prenylation, was isolated from cultures of *Penicillium brocae* MA-192, an endophytic fungus obtained from the fresh leaves of the marine mangrove plant *Avicennia marina* in Hainan island, China. Compound 55 showed lethality against brine shrimp (*Artemia salina*) with an LD$_{50}$ value of 36.7 μM (Figure 13) [34].

The fungus *Phoma* sp. OUCMDZ-1847, which was isolated from a mangrove fruit sample of *Kandelia candel* (Wenchang, Hainan Province, China), generated a new thiodiketopiperazine, named
phomazines B (56). Compound 56 showed cytotoxicity against the MGC-803 cell line with IC_{50} value of 8.5 \mu M (Figure 13) [35].

Four new disulfide-bridged diketopiperazine derivatives, brocazines (57–60) were isolated from *Penicillium brocae* MA-231, a fungus obtained from the fresh tissue of the marine mangrove plant *Avicennia marina* that was collected at Hainan Island, China. Compounds 57–60 showed cytotoxic activities against nine tumor cell lines, including Du145, HepG2, HeLa, NCI-H460, MCF-7, SGC-7901, SW1990, U251 and SW480, with IC_{50} values ranging from 0.89 to 9.0 \mu M (Figure 13) [36].

![Figure 13. Structures of compounds 53–60.](image)

A new isochroman, (3R,4S)-3,4-dihydro-8-hydroxy-4-methoxy-3-methylisocoumarin (61), was isolated from the marine fungus *Phomopsis* sp. (No. Gx-4), which was obtained from the mangrove sediment of ZhuHai, Guangdong, China. Primary bioassays and preliminary pharmacological tests indicated that compound 61 could accelerate the growth of subintestinal vessel plexus (SIV) branches markedly (Figure 14) [37].

*Penicillium brocae* MA-231, an endophytic fungus, was obtained from the fresh tissue of the marine mangrove plant *Avicennia marina*. After investigation, five new sulfide diketopiperazine derivatives, namely, penicbrocazines A–E (62–66) were isolated and identified. In the antimicrobial experiments, compounds 63–65 showed activity against *S. aureus*, with MIC values of 32.0, 0.25 and 8.0 \mu g/mL, respectively. Compound 64 also showed activity against *Micrococcus luteus* with MIC value of 0.25 \mu g/mL. Moreover, compounds 63, 65 and 66 implied activity against plant pathogen *Gaeumannomyces graminis* with MIC values of 0.25, 8.0, and 0.25 \mu g/mL, respectively (Figure 14) [38].
Two new biogenetically related compounds (67–68) have been isolated from a fungus *Penicillium dipodomyicola* HN4-3A from mangrove of South China Sea. Compounds 67 and 68 showed strong inhibitory activity against *Mycobacterium tuberculosis* protein tyrosine phosphatase B (MptpB) with IC$_{50}$ values of 0.16 ± 0.02 µM and 1.37 ± 0.05 µM, respectively (Figure 15) [39].

Investigation of the marine mangrove-derived fungal strain *Penicillium* sp. MA-37 resulted in the isolation of one new benzophenone, *iso*-monodictyphenone (69) and two new diphenyl ether derivatives penikellides A (70) and B (71). Compounds 69–71 exhibited brine shrimp lethality, with LD$_{50}$ values of 25.3, 14.2 and 39.2 µM, respectively, while the positive control colchicine had LD$_{50}$ value of 1.22 µM. Compound 69 showed antibacterial activity against *Aeromonas hydrophilia* with MIC 8 µg/mL, while the positive control, chloromycetin exhibited a MIC of 4 µg/mL (Figure 15) [40].

A new naphthalene derivative, vaccinal A (72), was isolated from *Pestalotiopsis vaccinii* (cgmcc3.9199) endogenous with the mangrove plant *Kandelia candel* (L.) Druce (Rhizophoraceae). Compound 72 exhibited *in vitro* anti-enterovirus 71 (EV71) with IC$_{50}$ value of 19.2 µM and potent COX-2 inhibitory activity with IC$_{50}$ value of 1.8 µM (Figure 16) [41].

The fungus *Astrocytis* sp. BCC 22166 was isolated from a mangrove palm, Nypa, at Hat Khanom-Mu Ko Thale Tai National Park, Nakhon Si Thammarat Province of Thailand. Two new compounds, phthalide 73, dihydrosisoumarin 74 were separated from the fungus. Compound 73 exhibited antibacterial activity against *Bacillus cereus* (IC$_{50}$ = 12.5 µg/mL), while compound 74 showed cytotoxicity to KB and Vero cells with values of IC$_{50}$ 22.6 and 48.2 µg/mL respectively (Figure 16) [42].
A new aromatic amine, pestalamine A (75) was isolated from mangrove-derived endophytic fungus *Pestalotiopsis vaccinii* that was isolated from a branch of *Kandelia candel* (L.) Druce (*Rhizophoraceae*), a usual vivarpous mangrove species in coastal and estuarine areas of southern China. Pestalamine A (75) showed moderate cytotoxicities against human cancer cell lines (MCF-7, HeLa, and HepG2) with IC50 values of 40.3, 22.0, and 32.8 μM, respectively (Figure 16) [43].

![Structures of compounds 72–75.](image)

A new aromatic butyrolactone, flavipesins A (76), was isolated from marine-derived endophytic fungus *Aspergillus flavipes*. All8. This was isolated from the inner leaves of mangrove plant *Acanthus ilicifolius* (Daya Bay, Shenzhen City, Guangdong Province, China). Compound 76 displayed significant antibacterial activity against *S. aureus* (MIC = 8.0 μg/mL) and *B. subtillis* (MIC = 0.25 μg/mL). Compound 76 also showed the unique antibiofilm activity of decreasing the number of living cells embed in the biofilm matrix from 390.6 to 97.7 μg/mL (p < 0.01). This indicates that compound 76 could penetrate the biofilm matrix and kill the living bacteria inside mature *S. aureus* biofilm (Figure 17) [44].

A new prenylated phenol vaccinol I (77) was isolated from endogenous fungi *Pestalotiopsis vaccinii* (cgmcc3.9199) of mangrove plant *Kandelia candel* (L.) Druce (*Rhizophoraceae*). Compound 77 exhibited potent COX-2 inhibitory activity (IC50 = 16.8 μM) (Figure 17) [45].

Penicibilaenes A (78) and B (79), two sesquiterpenes possessing a tricyclo[6.3.1.01,5] dodecane skeleton, were characterized from *Penicillium bilaiae MA-267*, a fungus obtained from the rhizospheric soil of the mangrove plant *Lumnitzeraceae racemosa*. Both of them exhibited selective activity against the plant pathogenic fungus *Colletotrichum gloeosporioides* (MIC = 1.0 and 0.125 μg/mL, respectively) (Figure 17) [46].

Three new resveratrol derivatives, resveratrodehydes A–C (80–82), were isolated from the mangrove endophytic fungus *Alternaria* sp. R6. All compounds showed broad-spectrum inhibitory activities against human breast MDA-MB-435, human liver HepG2, and human colon HCT-116 by MTT assay (IC50 < 50 μM). Especially, compounds 80 and 81 both exhibited marked cytotoxic activities against HCT-116 and MDA-MB-435 cell lines (IC50 < 10 μM). Additionally, compounds 80 and 82 showed moderate antioxidant effect by DPPH radical scavenging assay (Figure 17) [47].

![Structures of compounds 76–82.](image)

The strategy that co-cultivation of two mangrove fungi, *Phomopsis* sp. K38 and *Alternaria* sp. E33 (Leizhou Peninsula, Guangdong Province, China) in a single confined environment generated
new active natural products, including three new cyclic tetrapeptides, cyclo(Ø-Pro-L-Tyr-L-Pro-L-Tyr) (83), cyclo(Gly-L-Phe-L-Pro-L-Tyr) (84) and cyclo(L-leucyl-trans-4-hydroxy-L-proyl-D-leucyl-trans-4-hydroxy-L-proline) (85). Compounds 83–85 showed moderate to high antifungal activities (Candida albicans, Gaeumannomyces graminis, Rhizoctonia cerealis, Helminthosporium sativum and Fusarium graminearum) as compared with the positive control (Figure 18) [48,49].

![Figure 18. Structures of compounds 83–85.](image1)

2.3. Sediment

*Penicillium chrysogenum* PJX-17, which was separated from marine sediment (South China Sea) generated two novel sorbicillinoids combining a bicyclo[2.2.2] octane with a 2-methoxyphenol moiety, sorbatechols A (86) and B (87) respectively. Compounds 86 and 87 exhibited activities against influenza virus A (H1N1), with IC₅₀ values of 85 and 113 μM, respectively (Figure 19) [50].

The fungal strain *Penicillium* sp. F446, which was isolated from marine sediments at the depth of 25 m collected from Geomun-do (Island), Korea, generated a novel meroterpenoid, penicillipyrones B (88). Compound 88 showed significant induction of quinone reductase (Figure 19) [51].

![Figure 19. Structures of compounds 86–88.](image2)

An epidithiodiketopiperazine, N-methyl-pretrichodermamide B (89) was isolated from the fungus *Penicillium* sp. WN-11-1-3-1-2, derived from the sediment of a hyper saline lake located at Wadi El-Natrun in Egypt, 80 km northwest of Cairo. Compound 89 showed pronounced cytotoxicity against the murine lymphoma L5178Y mouse lymphoma cell line, IC₅₀ = 2 μM (Figure 20) [52].

One new polyketide (90) was isolated from the lipophilic extract of the marine-derived fungus *Isaria felina* KMM 4639 from marine sediments at a depth of 10 m (South China Sea, coast of Vietnam). Compound 90 exhibited cytotoxicity against HL-60 and THP-1 cell lines with IC₅₀ values of 4.3 and 37.4 μM, respectively (Figure 20) [53].

One new indole diketopiperazine peroxide, 13-O-prenyl-26-hydroxyverruculogen (91), was isolated and identified from the culture extract of the marine sediment-derived fungus *Penicillium brefeldianum* SD-273. Compound 91 showed potent lethality against brine shrimp (*Artemia salina*), with LD₅₀ value of 9.44 μM, comparing with the positive control colchicine (LD₅₀ = 99.0 μM) (Figure 20) [54].
Fungus *Spicaria elegans* KLA03 was derived from marine sediments collected in Jiaozhou Bay, China. Eleganketal A (92), a naturally occurring aromatic polyketide possessing a rare highly oxygenated spiro[isobenzofuran-1,3′-isochroman] ring system, was isolated from the fungus by culturing it in a modified mannitol-based medium. The synthetic (+)-92a and its separated enantiomers showed no cytotoxicity against HL-60 and K562 cells (IC$_{50}$ > 50 µM). Only compound (−)-92a exhibited activity against the influenza A H1N1 virus with an IC$_{50}$ = 149 µM (Figure 21) [55].

Two novel tetracyclic oxindole alkaloids, speradines G (93) and H (94), were isolated from the marine-derived fungus *Aspergillus oryzae*, isolated from marine sediments (Langqi Island, Fujian, China). This is the first report on cyclopiazonic acid (CPA)-type alkaloids with a hexacyclic skeleton. The compounds 93–94 showed unconspicuous cytotoxic effects on the Hela, HL-60 and K562 cell lines, IC$_{50}$ values larger than 30 µg/mL (Figure 21) [56].

One new cyclic peptide, psychrophilins (95), possessing a rare amide linkage between the carboxylic acid in anthranilic acid (ATA) and the nitrogen from an indole moiety, was obtained from the culture of the marine-derived fungus *Aspergillus versicolor* ZLN-60, isolated from the mud (depth, 20 m) of the Yellow Sea. Compound 95 showed potent lipid-lowering effects at a dose of 10 µM as assessed by Oil Red O staining (Figure 22) [57].

Two new prenylated indole alkaloids, including a β-carboline, penipalines B (96), and one indole carbaldehyde derivative, penipaline C (97), were obtained from the deep-sea-sediment derived fungus *Penicillium paneum* SD-44 cultured in a 500-L bioreactor. Compounds 96 and 97 showed potent cytotoxic activities against two tumor cell lines, A-549 and HCT-116. The IC$_{50}$ values of compounds 96 and 97 against HCT-116 were 14.88 and 18.54 µM, while those against A-549 were 20.44 and 21.54 µM, respectively (Figure 22) [58].

The fungal strain *Aspergillus versicolor* HDN08-60, isolated from the sediments in the South China Sea, was fermented on liquid culture (60 L) for 30 days and extracted three times with ETOAc. A novel versicamide H (98) was obtained. Compound 98 exhibited moderate activity against HL-60 cells (IC$_{50}$ = 8.7 µM) and selective PTK inhibitory activities in further investigation with target screening (Figure 22) [59].
Penicillium purpurogenum cyclonerodiol analogues, a 3,4-
new compounds by activating silent fungal metabolic pathways.
23) penicimutanin (102). Compounds 99–101 inhibited several human cancer cell lines (K562, HL-60, HeLa, BGC-823, and MCF-7) with IC₅₀ values lower than 20 μM, compound 102 also inhibited the cell lines to some extent [60]. In addition, three new C25 steroids (103–105) with an unusual bicyclo[4.4.1]A/B ring with the Z-configuration of 20,22-double bond were isolated. All of them weakly inhibited several human cancer cell lines (K562, HL-60 and HeLa) to varying extents (Figure 23) [61]. Furthermore, seven new (106–112) lipopeptides were isolated from the extract of mutant, which showed weak cytotoxicity (Figure 23) [62]. These results provided the way to discover new compounds by activating silent fungal metabolic pathways.

Ascotricha sp. ZJ-M-5, is a fungus isolated from a mud sample, which was collected on a coastal beach in Fenghua County, Zhejiang Province, China. Chemical investigations were found to produce cyclonerodiol analogues, a 3,4-seco lanostane triterpenoid, and diketopiperazines in an eutrophic medium by the one strain-many compounds (OSMAC) analysis. Two new caryophyllene derivatives
(113–114) were produced in an oligotrophic medium, Czapek Dox broth with or without Mg$^{2+}$. (+)-6-O-Demethylpestalotiopsin A (113) and (+)-6-O-demethylpestalotiopsin C (114), which have a five-membered hemiacetal structural moiety, showed growth inhibitory abilities against K562 and HL-60 leukemia cell lines with the lowest GI$_{50}$ value of 6.9 ± 0.4 μM. This indicated that modification of the culture media was effective in the discovery of novel bioactive fungal secondary metabolites (Figure 24) [63].

The marine fungus *Cladosporium* sp. was isolated from a sediment sample collected from Yangshashan Bay, Ningbo, Zhejiang Province, China. Two new sulfur-containing diketopiperazines (DKPs), cladosporin A (115) and cladosporin B (116), were separated from the fungus by high-speed counter-current chromatography (HSCCC). Cytotoxic activity tests showed that compounds 115 and 116 exhibited moderate cytotoxic activities to HepG2 cell line, with values of IC$_{50}$ 21 and 42 μg/mL (Figure 24) [64].

![Figure 24. Structures of compounds 113–116.](image1)

A novel cyclic dipeptide, 14-hydroxy-cyclopeptine (117), was purified from a deep sea derived fungus SCS1OW2 identified as an *Aspergillus* sp. Fungus SCS1OW2 was isolated from deep marine sediment sample collected in the South China Sea at a depth of 2439 m. Compound 117 inhibited nitric oxide production with IC$_{50}$ value at 40.3 μg/mL in a lipopolysaccharide and recombinant mouse interferon-γ-activated macrophage-like cell line, RAW 264.7 (Figure 25) [65].

*Trichobotrys* (118–120), a class of new tetramic acid derivatives with a decalin ring, were characterized from the culture of *Trichobotrys effuse* DFFSCS021 derived from the deep sea sediment collected from the South China Sea. Compounds 118–120 exhibited significant selective cytotoxicity against human carcinoma KG-1a cell line with IC$_{50}$ values of 5.44, 8.97, and 6.16 μM, and obvious antiviral activity towards HSV-1 with IC$_{50}$ values of 3.08, 9.37, and 3.12 μM, respectively (Figure 25) [66].

![Figure 25. Structures of compounds 117–120.](image2)

2.4. *Alga*

The *Aspergillus ustus* cf-42 strain, which was obtained from the fresh tissue of the marine green alga *C. fragile* (Zhoushan Island, China), generated a new ergosteroid derivative, isocyathisterol (121). Compound 121 exhibited weak antibacterial activity against *S. aureus* and *E. coli* (inhibitory diameters of 5.7 and 6.7 mm, respectively) at 30 mg/disc (Figure 26) [67].
Five new polyketides (122–126) have been isolated from the lipophilic extracts of the marine-derived fungi *Penicillium thomii* and *Penicillium lividum* isolated from superficial mycobiotas of the brown alga *Sargassum miyabei* (Lazurnaya Bay, the Sea of Japan). Compound 123 was able to inhibit the transcriptional activity of the oncogenic nuclear factor AP-1 with IC$_{50}$ value of 15 µM after 12 h of treatment. Compound 125 exhibited cytotoxicity against splenocytes with a IC$_{50}$ value of 38 µM. It was shown that compounds 124 and 126 at a non-toxic concentration (10 µM) inhibited the adhesion of macrophages (30%–40% of inhibition). In addition, compounds 122 and 125 exhibited radical scavenging activity against DPPH with IC$_{50}$ values of 100 and 50 µM, respectively (Figure 26) [68].

Figure 26. Structures of compounds 121–126.

Seven new astalide meroterpenoids (127–133) were isolated from the alga-derived fungi *Penicillium thomii* KMM 4645 and *Penicillium lividum* KMM 4663, which was isolated from superficial mycobiotas of the brown alga *Sargassum miyabei* (Lazurnaya Bay, the Sea of Japan). Compounds 127, 128, 132 and 133 could inhibit AP-1-dependent transcriptional activity in JB6 Cl41 cell lines at noncytotoxic concentrations. Compounds 127–133 exhibited significant inhibitory effects against endo-1,3-β-D-glucanase from a crystalline stalk of the marine mollusk *Pseudocardium sachalinensis* (Figure 27) [69].

Figure 27. Structures of compounds 127–133.

The fungal strain *Penicillium echinulatum* pt-4 was isolated from marine red alga *Chondrus ocellatus* that was collected from the coast of Pingtan Island, China. One new meroterpene, arisugacin K (134) was isolated from the culture of strain pt-4. Compound 134 showed inhibitory activity against *E. coli* with an inhibition diameter 8 mm at 30 µg/disk (Figure 28) [70].

A new nitrobenzoyl sesquiterpenoid, 6b,9a-dihydroxy-14-p-nitrobenzoylcinnamolide (135) was isolated from extracts of the culture of marine-derived fungus *Aspergillus ochraceus* Jma1F17, which was derived from a marine alga *Coelarthrum* sp. in Paracel Islands, South China Sea. Compound 135 displayed significant cytotoxicities against 10 cancer cell lines (K562, H1975, U937, Molt-4, BGC-823, HL60, MCF-7, A549, Hela, and Huh-7), with IC$_{50}$ values of 1.95 µM to 6.35 µM. In addition, compound 135 also showed antiviral activities against EV71 and H3N2 (Figure 28) [71].
A structurally unique 3H-oxepine-containing alkaloid, varioxepine A (136), characterized by a condensed 3,6,8-trioxabicyclo[3.2.1]octane motif, was isolated from the marine algal-derived endophytic fungus *Paecilomyces variotii*. Compound 136 was evaluated for antimicrobial activity against several human- and aqua-pathogenic bacteria (*Aeromonas hydrophila*, *S. aureus*, *Vibrio anguillarum*, *E. coli*, *Micrococcus luteus*, *Vibrio harveyi*, and *Vibrio parahaemolyticus*). The results revealed that compound 136 has diverse antibacterial activities with the MIC values ranging from 16 to 64 µg/mL. Furthermore, it inhibited plant pathogenic fungus *Fusarium graminearum*, with an MIC value of 4 µg/mL (Figure 28) [72].

![Figure 28. Structures of compounds 134–136.](image)

Two new butenolides, namely, butyrolactone IX (137) and aspulvinone O (138) were isolated from the marine-derived endophytic fungus *Paecilomyces variotii* from *Grateloupia turuturu*, a red alga collected from the coast of Qingdao, China. The isolated butenolides were tested for the activity against DPPH radicals and the results indicated that butyrolactone (137) possessed potent activity with IC₅₀ values 186.3 µM, while aspulvinone (138) showed significant activity with IC₅₀ value 11.6 µM. The author speculated that a larger conjugated aromatic system gave aspulvinone (138) more stronger DPPH radical scavenging activity than that of butyrolactone (137) (Figure 29) [73].

A new benzamide derivative (methyl 4-(3,4-dihydroxybenzamido) butanoate (139) was isolated from the marine brown alga-derived endophytic fungus *Aspergillus wentii* EN-48. Compound 139 showed significant scavenging activity against DPPH with IC₅₀ values of 5.2 µg/mL, which was significantly stronger than BHT (IC₅₀ = 36.9 µg/mL) (Figure 29) [74].

![Figure 29. Structures of compounds 137–139.](image)

Two new oxepine-containing diketopiperazine-type alkaloids, varioloids A and B (140 and 141), were isolated from the fungus *Paecilomyces variotii* EN-291, which was isolated from *Grateloupia turuturu*, a marine red algae collected from the coast of Qingdao, China. Compounds 140 and 141 exhibited potent activity against the plant pathogenic fungus *Fusarium graminearum* with MIC values of 8 and 4 µg/mL, respectively (Figure 30) [75].

A new eudesmane sesquiterpenoid, eudesma-4(15),7-diene-5,11-diol (142) has been isolated from the red alga * Laurencia obtusa*, which was collected off the Saudi Arabia Red Sea Coast at Jeddah. Both qualitative and quantitative antifungal assays revealed that compound 142 exhibited a good antifungal effect against *Candida albicans*, *Candida tropicalis*, *Aspergillus flavus* and *Aspergillus niger*; the MIC values were 2.92, 2.10, 2.92, 6.5 µg/mL, respectively (Figure 30) [76].
2.5. Sea Water

One unusual pyridone, trichodin A (143), was extracted from the marine fungus, Trichoderma sp. strain MFI106 isolated from the Greenland Seas. Compound 143 showed antibiotic activities against Staphylococcus epidermidis with IC50 value of 24 μM (Figure 31) [77].

The fungus Penicillium 303# was isolated from sea water, which was collected from Zhanjiang Mangrove National Nature Reserve in Guangdong Province, China. Three new metabolites (compounds 144–146) were isolated from the fungus fermentation medium. Those compounds showed weak to moderate cytotoxic activities against MDA-MB-435 (Figure 31) [78].

A marine strain Stachybotrys sp. MF347, which was isolated from a driftwood sample collected at Helgoland (North Sea, Germany), provided a novel spirocyclic drimane coupled by two drimane fragment building blocks 147. Compound 147 exhibited comparable antibacterial activities with chloramphenicol against the clinically relevant MRSA (Figure 32) [79].

Penicilliumine (148), a new structure was isolated from the fermentation Penicillium commune 366606, a marine-derived fungus isolated from the sea water collected at Qingdao, China. Compound 148 was not cytotoxic against MCF-7, SMMC-7721, HL-60, A-549 and SW480 cells or no potent inhibiting the nitric oxide release. Compound (−)-148 and (+)-148 could inhibit the acetylcholinesterase activity by 18.7% (±0.26%) and 32.4% (±2.08%) at the concentration of 50 μM, respectively, compared with 43.6% (±2.12%) inhibition rate of the positive control tacrine (Figure 32) [80].

A strain of the fungus Penicillium chrysogenum was collected from sea water (10–25 m depth), off the North Sea coast, China. A new benzoic acid, 2-(2-hydroxypropanamido) benzoic acid (149), isolated from the fermentation broth of fungus, showed remarkable anti-inflammatory and analgesic activities but exhibited no ulcerogenic effect (Figure 32) [81].
2.6. Others

Racemic dinaphthalenone derivatives (±)-asperlone A (150) and (±)-asperlone B (151) were isolated from the cultures of *Aspergillus* sp. 16-5C from the leaves of *S. apetala*, which were collected in Hainan Island, China. Compounds 150 and 151 exhibited potent inhibitory effects against *Mycobacterium tuberculosis* protein tyrosine phosphatase B (MptPB) with IC\textsubscript{50} values of 4.24 ± 0.41, 4.32 ± 0.60 μM, respectively, which represent a new type of lead compounds for the development of new anti-tuberculosis drugs (Figure 33) [82].

A new polychlorinated triphenyl diether named microspeaerol (152) and a new naphthalene derivative named seimatorone (153), were isolated from the endophytic fungus *Microsphaeropsis* sp. and *Seimatosporium* sp., which were isolated from the halotolerant herbaceous plant *Salsola oppositifolia* from Playa del Íngles (Gomera, Spain). Preliminary studies revealed that compound 152 showed good antibacterial activities against *Bacillus Megaterium* and *E. coli*, and good antilagal and antifungal activities against *Chlorella fusca* and *Microbotryum violaceum*, respectively. On the other hand, compound 153 exhibited moderate antibacterial, antialgal, and antifungal activities (Figure 33) [83].

![Figure 33. Structures of compounds 150–153.](image)

3. Future Perspectives and Concluding Remarks

Based on the above literature, we can find that marine-derived *Aspergillus* and *Penicillium* are the most ubiquitous genera, probably because both of them are salt tolerant, fast growing and easily obtained. As seen in Figure 34, about 3/4 of all new compounds reported from marine fungi are derived from isolation from living matter, *i.e.* marine animals (30.1%) and marine plants (42.5%), while the remaining compounds are obtained from non-living sources, most notably sediments (22.9%). Within the individual groups, mangrove habitats (25.5%), alga (14.4%), and sponges (9.2%) are the predominant sources for fungal diversity. A newly emerging source is the deep sea. The extreme environment encountered in the form of low temperature, elevated hydrostatic pressure, absence of light, high concentrations of metals in hydrothermal vents and hypoxic conditions possibly produce structurally unique metabolites. Nevertheless, very few reports are related to this habitat because of scarcity of source. It is worth mentioning that an increasing number of Chinese scientists are engaging in this research field, mostly focusing on mangrove areas around South China Sea.

![Figure 34. New compounds from marine-derived fungi included in this review, divided by sources of the fungal strains.](image)
According to the structural types, of the 153 compounds included in this review, alkaloids (27.0%) and polyketides (25.7%) play a dominant role. Moreover, peptides, terpenes, lactone, and steroids are 13.8%, 9.9%, 3.9% and 3.3%, respectively (see Figure 35).

**Figure 35.** New compounds from marine-derived fungi included in this review, divided by structural types.

As illustrated in Figure 36, biological activities of these compounds are mainly focused in the areas of cytotoxicity (37.5%) and antimicrobial activity, including antibacterial activity (18.4%), antifungal activity (7.9%) and antiviral activity (7.2%). Furthermore, other selective activities include antioxidant, anti-inflammatory, antifouling, lipid-lowering activities, lethality against brine shrimp effects, etc.

**Figure 36.** Bioactive categories of new compounds from marine-derived fungi included in this review.

The oceans are the largest underexploited wealthy resource of potential drugs. Marine-derived fungi have provided a variety of potential pharmacological metabolites and thus represent a valuable resource of new drug candidates. In the period covered by the first review of this series, from the beginning until 2002, 272 new structures had been reported, in 2009 more than 200 was reached [2], and in 2012 and 2013, the numbers were 288 and 302, respectively [3,84]. Though bioactivities of secondary metabolites from marine fungi reveal interesting levels for a number of clinical relevant targets, they are not well represented in the pipelines of drugs and none of them currently is on the market. Only Plinabulin, a synthetic cyclic dipeptide analogue of halimide, which is isolated from a marine fungus species, is in phase II clinical trial for treatment of non-small cell lung cancer. Thus, there is still a long way to go [85].
First of all, many marine-derived fungal biosynthetic pathways are silent under common laboratory culture conditions, and activation of the silent pathways may enable access to new metabolites. One strain–many compounds (OSMAC) strategy, chemical epigenetic modification (e.g., using DNA methyltransferase inhibitor, 5-azacytidine, histone deacetylase inhibitors, suberoylanilide hydroxamic acid and sodium butyrate [60–62,86–88]), co-culture method [48], or gene level manipulations could be applied to access new secondary metabolites. Furthermore, as mentioned above, alterations of the culture conditions might lead to changes of the metabolic spectrum. The pharmaceutical industry should concentrate on how to appropriately maintain certain physico-chemical factors, viz., amount of oxygen available, optimum pH and temperature, avoiding variation of secondary metabolites.

What is more, a better understanding of the molecular basis of biosynthesis and regulation mechanisms will contribute to making better use of the enormous chemical potential of marine derived fungi, which depends on the continuous development of the new techniques [89,90].

In addition, beyond the current in vitro bioactivity examination, further in vivo and preclinical studies, as well as side effects examinations, are required to determine the bioactive compounds with potential therapeutic applications.

We believe that with the development of more automated and more affordable techniques for isolating and characterizing marine fungi bioactive metabolites, marine fungi will be promising sources for novel therapeutic agents that will be useful in controlling human diseases and protecting human health.

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