marine drugs

MDPI

*Review*

# Deep-Sea Fungi Could Be the New Arsenal for Bioactive Molecules

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Received: 28 November 2019; Accepted: 17 December 2019; Published: 20 December 2019


**Abstract:** Growing microbial resistance to existing drugs and the search for new natural products of pharmaceutical importance have forced researchers to investigate unexplored environments, such as extreme ecosystems. The deep-sea (>1000 m below water surface) has a variety of extreme environments, such as deep-sea sediments, hydrothermal vents, and deep-sea cold region, which are considered to be new arsenals of natural products. Organisms living in the extreme environments of the deep-sea encounter harsh conditions, such as high salinity, extreme pH, absence of sun light, low temperature and oxygen, high hydrostatic pressure, and low availability of growth nutrients. The production of secondary metabolites is one of the strategies these organisms use to survive in such harsh conditions. Fungi growing in such extreme environments produce unique secondary metabolites for defense and communication, some of which also have clinical significance. Despite being the producer of many important bioactive molecules, deep-sea fungi have not been explored thoroughly. Here, we made a brief review of the structure, biological activity, and distribution of secondary metabolites produced by deep-sea fungi in the last five years.

**Keywords:** deep-sea; extreme; ecosystem; fungi; bioactive compounds; secondary metabolites

## 1. Deep-Sea Fungi: A Novel Source of Bioactive Molecules

Antibiotics and antifungal drugs are the most commonly used drugs in the world, but their role in treating human diseases has been greatly reduced due to the development of pathogen resistance against these drugs. Scientists are now looking for new, untapped and renewable resources for the isolation of novel compounds to with clinical importance. Despite the fact that the ocean provides habitats to a huge number of microbes, both fungi and bacteria for thousands of years, the microbes of these extreme ecosystems and their potential for new drug discovery have not yet been fully realized due to methodological and technical limitations. Fungi are the most diverse and abundant eukaryotic organisms on the planet, and their presence in all possible extreme ecosystems make them an ideal source for investigations of new drug development. Scientists are interested in the extraction of novel and unique natural products, having clinical importance, from different organisms living in the extreme environments. In addition to terrestrial extreme environments, the ocean could also be considered a good reservoir of bioactive metabolites [1–4]. Fungi living in the deep-sea environments are known to produce novel bioactive compounds. Although, it is not fully understood why the fungi living in the extreme environments produce unique and novel products, it is assumed that fungal genome has evolved to make necessary adjustments in order to sustain life in such harsh conditions and might be involved in chemical defense and communication [5].

The ocean is considered to be one of the most diverse ecosystems. Compared to terrestrial and coastal ecosystems, the deep-sea (water depths below 1000 m) has a variety of extreme environments,

such as temperatures ranging from 0 to 400 °C, lack of light and oxygen, high hydrostatic pressure up to 400 atm, and limited supply of nutrient substrates, making these habitats extremely difficult for life [6,7]. In order to inhabit such extreme ecosystems, organisms should have the potential to adjust to these conditions with different mechanism, such as regulating temperature, pH, and solute concentration, as well as the production of biomolecules to control DNA, protein, and lipid damage. This may be why microorganisms growing in these environments produce special metabolites.

Previously, drug investigators mainly considered bacteria, especially actinomycetes, as an important source of antifungal and antibacterial drugs. Cephalosporin C was the first compound derived from the marine fungus *Cephalosporium* sp. in 1949. After that, a number of important drugs— for instance, polyketide griseofulvin, terpenoid fusidic acid, cephalosporins, etc.—have been isolated from the marine fungi. Despite being the source of such important products, deep-sea fungi have not received full attention [8]. With the increasing demand for new drugs, scientists are now looking for new and unexplored resources for bioactive compounds, and the deep-sea consists of some extreme ecosystems that are worth exploring for new metabolites. Studies about isolating new bioactive molecules from marine environments are growing at an increasing rate, and hundreds of new compounds are reported every year; for instance, in 2017, a total of 448 new compounds were reported [9].

In this review, we present an overview of all those new and important bioactive metabolites isolated from deep-sea fungi during the last five years. We include only those molecules which were extracted from the deep-sea fungi associated with some kind of extreme environments, irrespective of its isolation from terrestrial counterparts, while all those compounds were excluded which were isolated from marine fungi and were not associated with extreme environments. This review will benefit all those who are interested in extreme-marine-environment fungi and their bioactive molecules. For more detailed information about other important secondary metabolites extracted from marine fungi, one should refer to our previous review papers [10–12].

## 2. Bioactive Compounds from Deep-Sea Fungi

According to the literature survey, we found 151 novel bioactive compounds isolated from marine fungi extracted from different extreme environments in the last five years. The majority of these compounds were isolated from two fungal genera i.e., *Penicillium* (63, 41.2% of the total compounds) and *Aspergillus* (43, 28.1% of the total compounds). Table 1 lists the detail of these compounds, which fall into different categories according to their structure.

### *2.1. Polyketide Compounds*

Twenty-four polyketide compounds (**1**–**24**; Figure 1) with important biological activities were isolated from fungi extracted from different deep-sea environments. Among them, compounds **1** and **2** were isolated from *Penicillium* spp., which showed antibiotic activity (MIC of 32 µg/mL against *Bacillus subtilis*) and nuclear factor NF-kB inhibition activity, respectively [13,14]. Compounds **3**–**11** were from *Aspergillus* sp. 16-02-1, which exhibited cytotoxicity (with a 10%–80% inhibition rate at 100 µg/mL against various cancer cell lines i.e., K562, HL-60, HeLa, and BGC-823) [15]. Similarly, compounds **12**–**24** were isolated from the species belonging to *Ascomycetes*, *Engyodontium*, and *Lindgomycetaceae*, out of which compounds **12**–**13** and **23**–**24** showed strong antibiotic activities against *Bacillus subtilis*, *Acinetobacter baumannii*, *Escherichia coli*, *Staphylococcus aureus*, *Enterococcus faecalis*, *Staphylococcus epidermidis*, and *Propionibacterium acnes*, while compounds **14**–**22** exhibited strong cytotoxic activity ($IC_{50}$ 4.9 µM) against U937 cells (Table 1) [16–18].

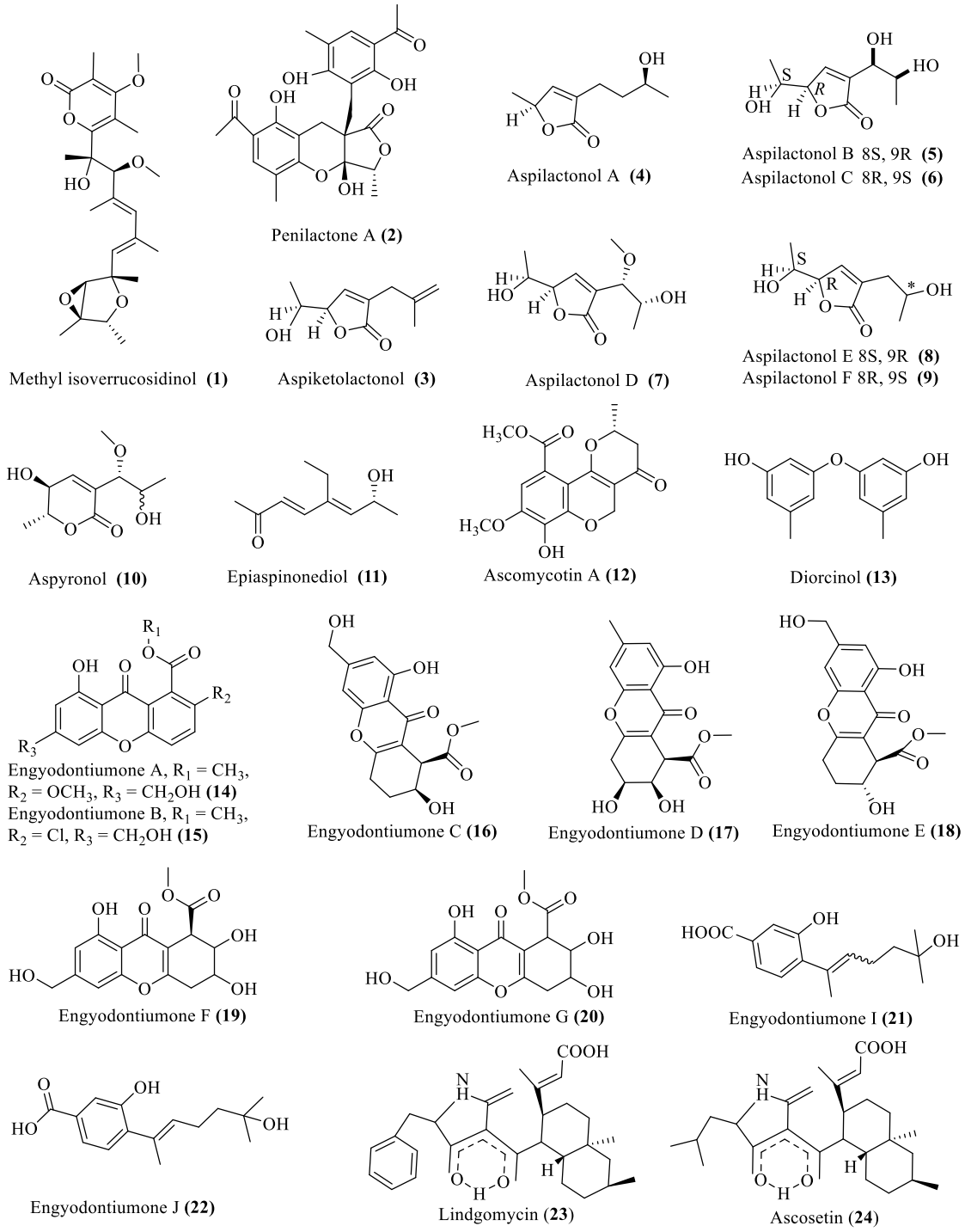



**Figure 1.** Structures of polyketide secondary metabolites obtained from deep-sea fungi.

## 2.2. Nitrogen-Containing Compounds

Twenty-four novel alkaloid-bioactive compounds (**25**–**48**; Figure 2) have been reported from deep-sea fungi since 2013, out of which compounds **25**–**40** were isolated from *Penicillium* spp., and showed cytotoxic activities against BV2 cell ($IC_{50}$ of 27–45 μg/mL), brine shrimp ($IC_{50}$ of 14.1 to 38.5 μg/mL), SMMC-7721 ($IC_{50}$ of 54.2 μM), BEL-7402 (($IC_{50}$ of 17.5 μM), and BEL-7402 ($IC_{50}$ of 19.8 μM) [19–21]. Compounds **41**–**46** were identified from *Aspergillus* spp., in which compounds **41** and **45**–**46** displayed antibiotic activity (MIC of 30 to 40 μg/mL) against BCG, *Candida albicans*, *Bacillus subtilis*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Bacillus cereus*, *Klebsiella pneumoniae*, and *Escherichia coli*,

while compounds **47** and **48** were extracted from other genera and showed antimicrobial activity (MIC between 16 and 64 μg/mL against *Escherichia coli*, *Aeromonas hydrophila*, *Micrococcus luteus*, *Staphylococcus aureus*, *Vibrio anguillarum*, *Vibrio harveyi*, and *Vibrio parahaemolyticus*) and cytotoxic activity against human cervical carcinoma HeLa, respectively [22–26].

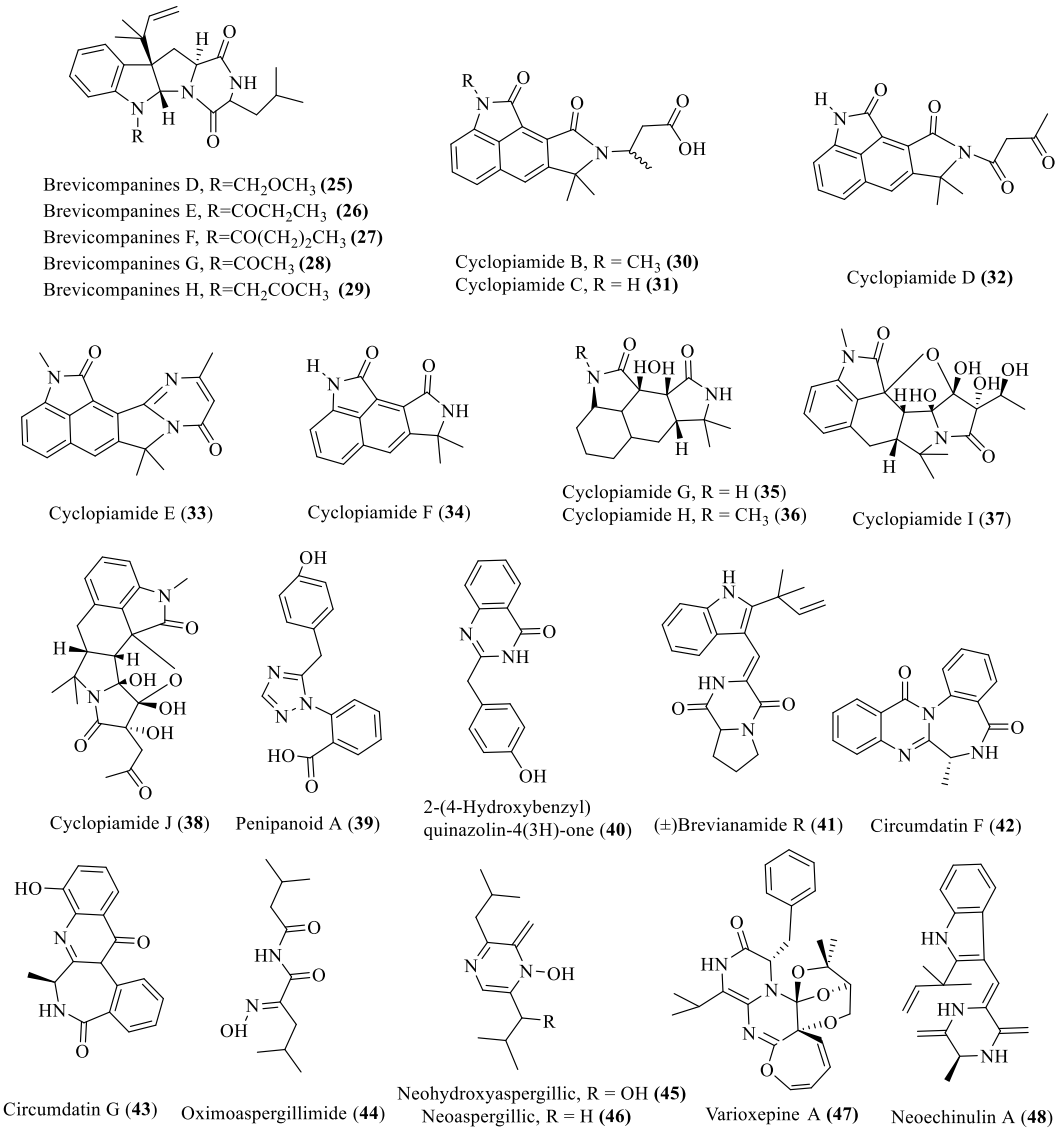



**Figure 2.** Bioactive alkaloid compounds isolated from deep-sea fungi.

## 2.3. Polypeptides

Twenty-two polypeptides with novel structures (**49–70**; Figure 3) were reported from fungi inhabiting different marine environments during 2013–2019. Compounds **49** and **50** were isolated from *Penicillium canescens* and displayed antibiotic activity against *Bacillus amyloliquefaciens* and *Pseudomonas aeruginosa* at 100 μM, while compounds **51–55** were extracted from *Aspergillus* spp., in which **51–54** showed cytotoxic activity ($IC_{50}$ of 15–25 μg/mL) against HepG2, SMMC-7721, Bel-7402, and human glioma U87 cell lines, while compound **55** showed inhibitory effects ($IC_{50}$ value of 5.11 μmol/L) against *Mycobacterium tuberculosis* protein tyrosine phosphatase B (MptpB) [27–30]. However, compounds **56–64**, which were obtained from *Simplicillium obclavatum*, and **65–70**, obtained from *Trichoderma asperellum*, displayed cytotoxicity ($IC_{50}$ of 39.4–100 μM) against human leukemia HL-60 and K562 cell lines and antibiotic activity ($IC_{50}$ of 39.4–100 μM) against Gram-positive bacteria

(e.g., *Bacillus amyloliquefaciens*, *Staphylococcus aureus*) and Gram-negative bacteria (e.g., *Pseudomonas aeruginosa* and *Escherichia coli*), respectively [28,31].

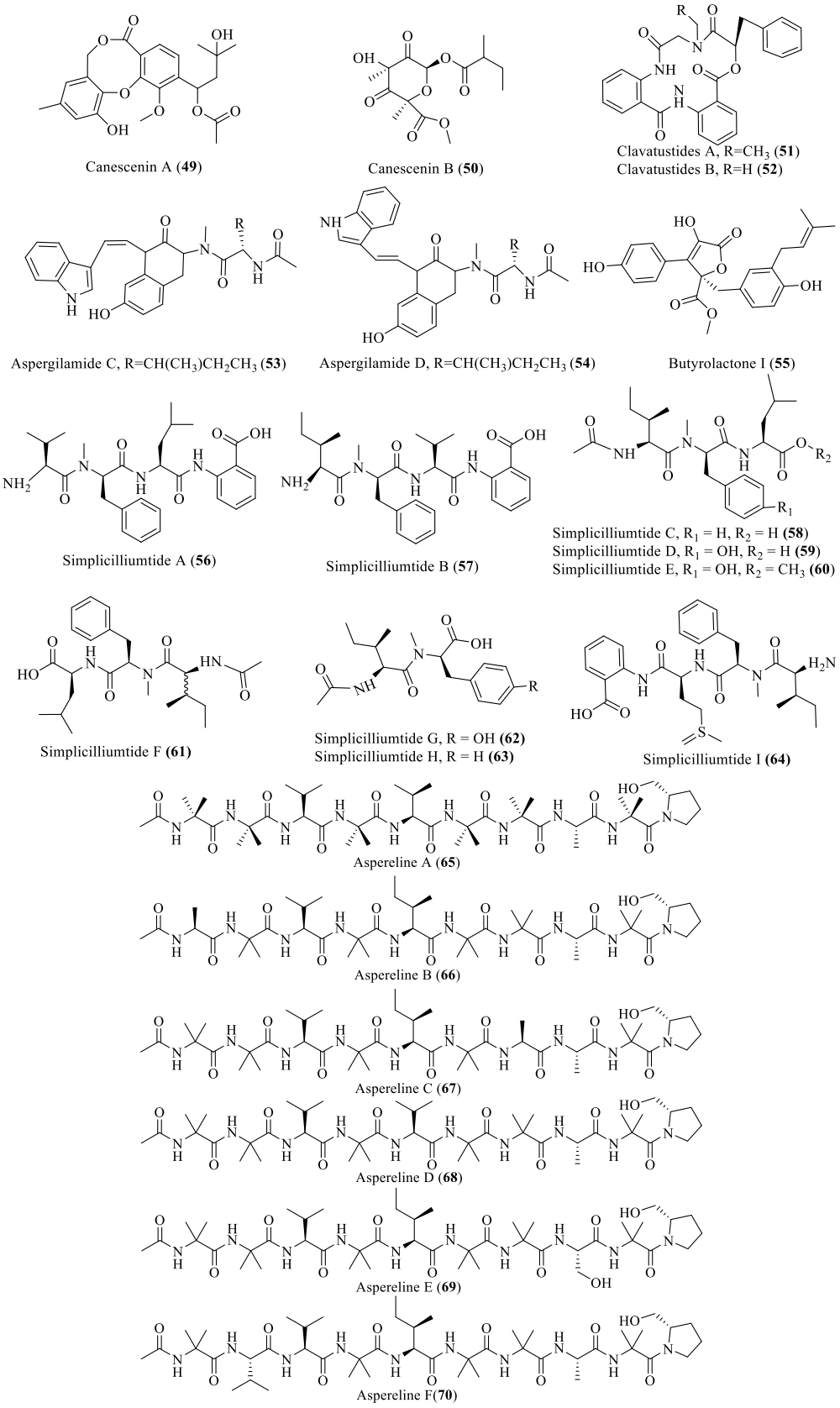
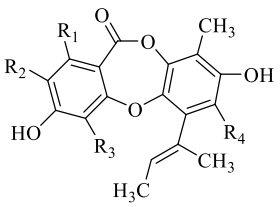
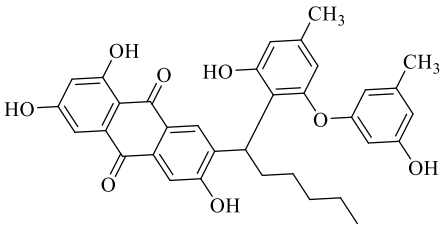



**Figure 3.** Bioactive polypeptides isolated from deep-sea fungi.

### 2.4. Ester and Phenolic Derivatives

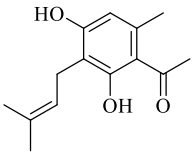
Six new ester derivatives (**71–76**; Figure 4) were extracted from *Aspergillus ungui* NKH-007 and showed inhibition of sterol O-acyltransferase (SOAT) enzymes in Chinese hamster ovary (CHO) cells and are thus considered to be good candidates for an anti-atherosclerotic agent [32]. Five new phenolic compounds (**77–81**; Figure 4) isolated from *Penicillium* sp. and *Aspergillus versicolor* showed potent activity against *Staphylococcus aureus* and *Bacillus subtilis*, with MIC values of 2–8 μg/mL [33,34]. However, compounds **78–81** expressed antiviral activity toward HSV-1, with $EC_{50}$ values of 3.12–6.25 μM [34].



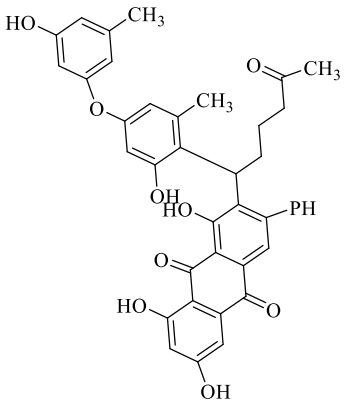


Asperigilol G **(78)**

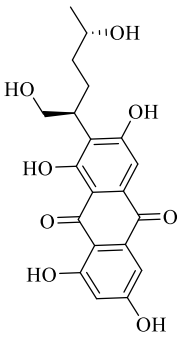
7-Chlorofolipastatin, $R_1$=$CH(CH_3)CH(CH_3)$,$R_2$=H, $R_3$=$CH_3$, $R_4$=Cl **(71)**
Folipostatin, $R_1$=$CH(CH_3)CH(CH_3)$,$R_2$=H, $R_3$=$CH_3$, $R_4$=H **(72)**
Unguinol, $R_1$=$CH_3$,$R_2$=H, $R_3$=$CH_3$, $R_4$=H **(73)**
2-Chlorounginol, $R_1$=$CH_3$,$R_2$=Cl, $R_3$=$CH_3$, $R_4$=H **(74)**
2,7-Dichloroung, $R_1$=$CH_3$,$R_2$=Cl, $R_3$=$CH_3$, $R_4$=Cl **(75)**
Nornidulin, $CH_3$, R1=$CH_3$, $R_2$=Cl, $R_3$=Cl, $R_4$=Cl **(76)**



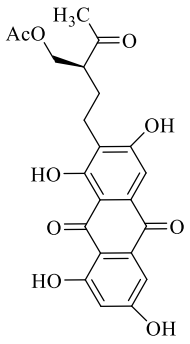
Pestalotionol **(77)**



Aspergilol H **(79)**



Aspergilol I **(80)**



Coccoquinone A **(81)**

**Figure 4.** Ester and phenolic derivatives obtained from deep-sea fungi.

### 2.5. Piperazine Derivatives

Fourteen new piperazine derivatives (**82–95**; Figure 5) reported from marine fungi during the last five years. These derivatives were isolated from genera of *Penicillium*, *Aspergillus*, and *Dichotomomyces* collected from deep-sea sediments. Compounds **82–84** showed strong cytotoxicity with $IC_{50}$ of 1.7 and 2 μM against K562 and mouse lymphoma cell line, respectively; similarly, compounds **91–95** also showed strong cytotoxic activity [35–37]. Compounds **85–89** showed antibacterial activity against *Staphylococcus aureus* with the MIC values of 6.25–12.5 μg/mL [21]. The new compound **90** also showed stronger inhibition activity against α-glucosidase with $IC_{50}$ value of 138 μM [37].

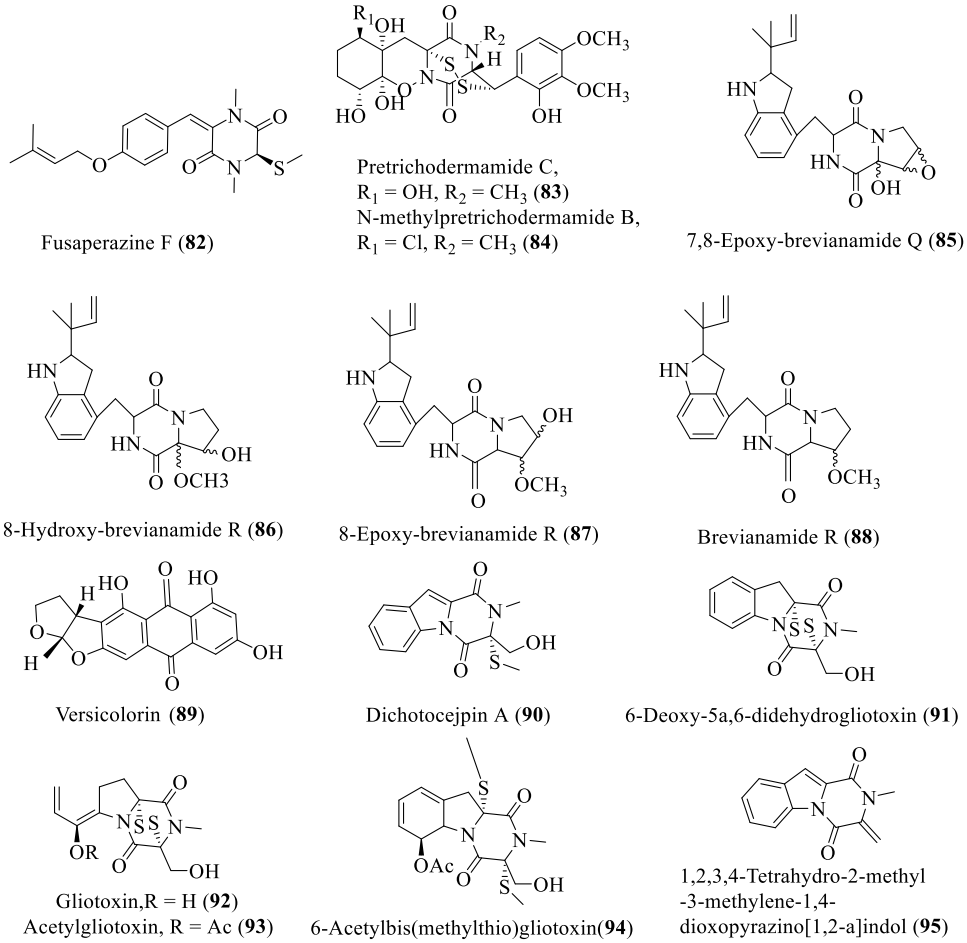



**Figure 5.** Piperazine derivatives isolated from deep-sea fungi.

## *2.6. Terpenoid Compounds*

Thirty-six new and important bioactive terpenoids (**96–131**; Figure 6) have been isolated from marine fungi extracted from the deep-sea sediments since 2013. Compounds **96–113** were isolated from *Penicillium* spp., while compounds **114–131** were extracted from *Aspergillus* spp. Breviones (**96–99**), isolated from the deepest sediment-derived fungus *Penicillium* sp. (5115 m depth), displayed diverse activities, such as cytotoxicity against HeLa, MCF-7, and A549 cells with $IC_{50}$ values of 7.44 to 32.5 μM, respectively, and growth inhibition of HIV-1 with $EC_{50}$ value of 14.7 μM against C8166 cells [22,38]. Compounds **100–110** showed antibiotic and inhibition activities against silkworm, while 20-nor-isopimarane diterpenoids, including aspewentins (**114–118**), asperethers (**121–125**), asperoloids (**119–120**), and compounds **130** and **131**, showed cytotoxic activities [33,39–45]. However, the spirocyclic diterpenes (**111–113)** exhibited strong anti-allergic effect with 18% inhibition at 20 μg/mL [46]. Interestingly, four new compounds (**126–129**) were extracted from hydrothermal vent-derived *Aspergillus sydowii*, through activation of a new pathway for secondary metabolite production by the addition of a 5-azacytidine (a DNA methyltransferase inhibitor). These compounds showed anti-inflammatory and antidiabetic activities and are thus the first secondary metabolites isolated from fungi which have both antidiabetic and anti-inflammatory activities [47].

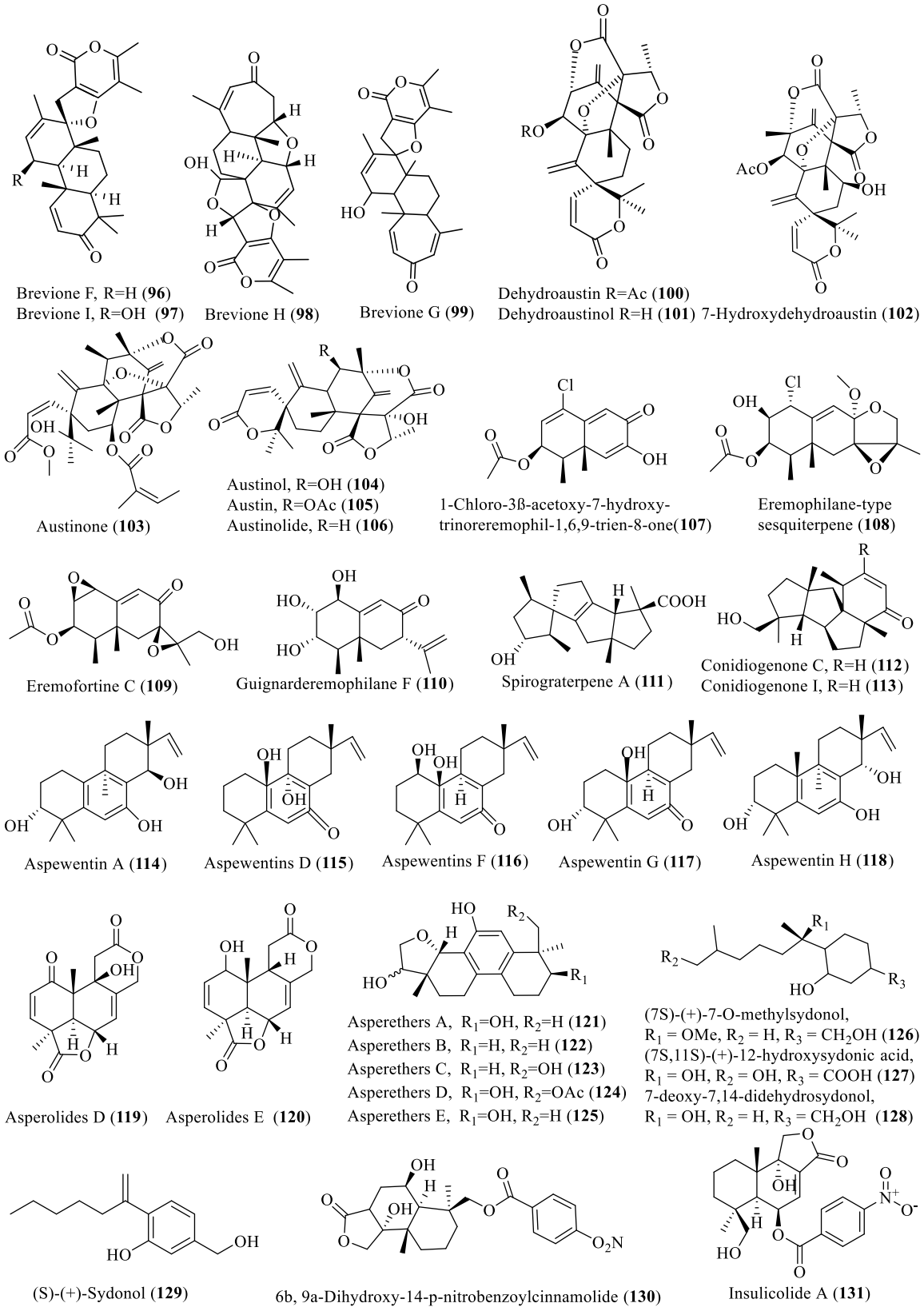



**Figure 6.** Structures of terpenoid secondary metabolites obtained from deep-sea fungi.

## 2.7. Other Unrelated Compounds

Twenty secondary metabolites with different structures were isolated from deep-sea fungi, mainly from *Penicillium* spp. and *Aspergillus* spp. (**132–151**; Figure 7). Penipacids A–F (**134–139**),

polyoxygenated sterol (**132**), dicitrinone B (**133**) and butanolide A (**140**), which were isolated from deep-sea sediments-derived *Penicillium* spp., showed cytotoxic activities against RKO, MCF-7, PTP1B and A375 cancer cell lines with $IC_{50}$ values of 8.4–28.4 μM [38,42,48,49]. Similarly, four isocoumarins, penicillisocoumarin A–D (**147**–**150**), and an isocoumarins aspergillumarin B (**151**) were also isolated from *Penicillium* which showed weak antibacterial activities [33]. Four antibiotic cyclopenin derivatives compounds (**141**–**144**) and a series of antitumor wentilactones (**145**,**146**) were isolated from *Aspergillus* spp. [50,51].

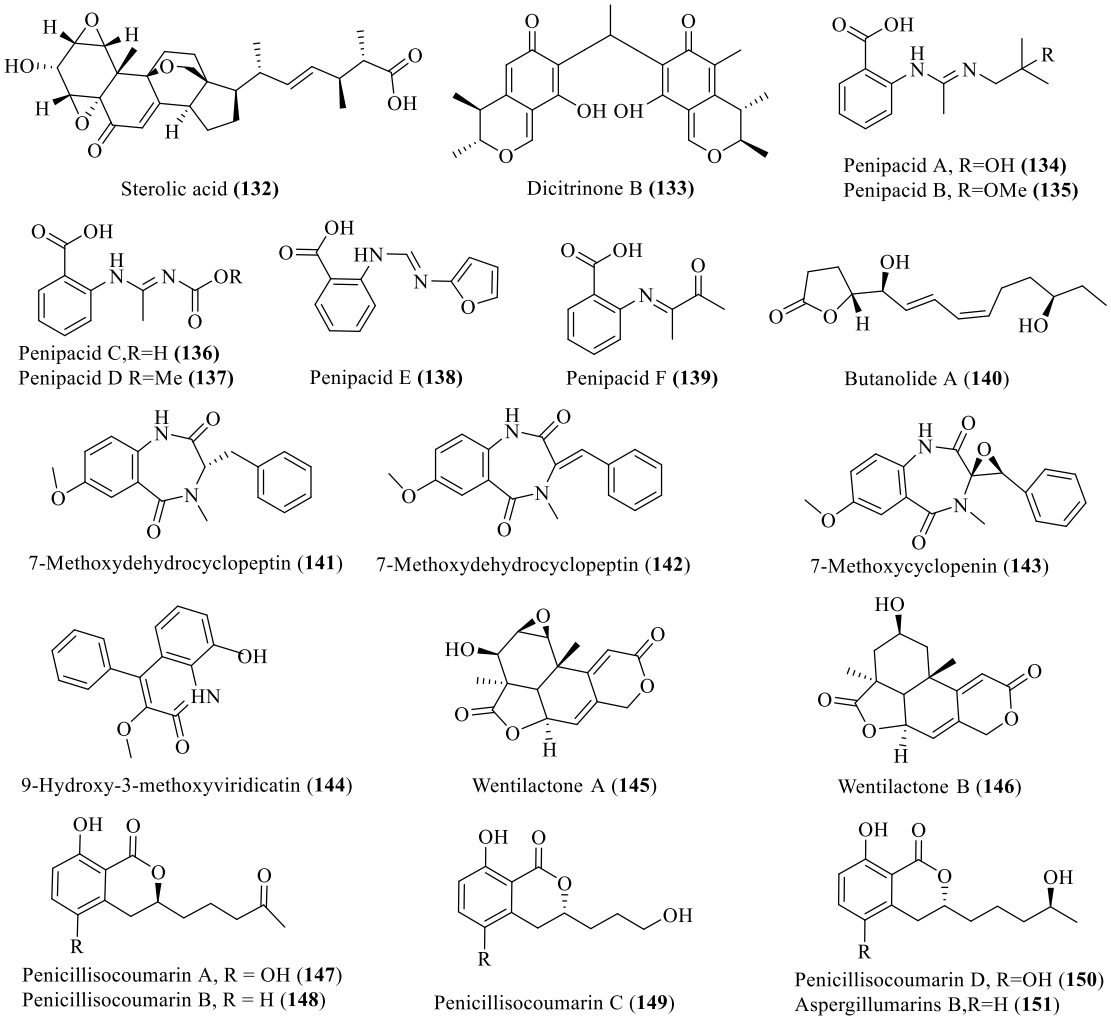



**Figure 7.** Bioactive metabolites derived from deep-sea fungi.

**Table 1.** Secondary metabolites extracted from deep-sea fungi during 2013–2019.

| Metabolites | Fungal Species | Source | Location | Depth (m) * | Bioactivity | Ref. |
|---|---|---|---|---|---|---|
| | | **Polyketide** | | | | |
| Methyl-isoverrucosidinol **(1)** | *Penicillium* sp. Y-50-10 | Sulfur-rich Sediment | hydrothermal vent, Taiwan | _ | Antibiotic | [13] |
| Penilactone A **(2)** | *Penicillium crustosum* PRB-2 | Sediment | Prydz Bay, Antarctica | 526 | NF-kB inhibition | [14] |
| Aspiketolactonol **(3)**<br>Aspilactonols A–F **(4-9)**<br>Aspyronol **(10)**<br>Epiaspinonediol **(11)** | *Aspergillus* sp. 16-02-1 | Hydrothermal vent water | Lau Basin, Southwest Pacific Ocean, | 2255 | Cytotoxic | [15] |
| Ascomycotin A **(12)**<br>Diorcinol **(13)** | *Ascomycota* sp. Ind19F07 | Sediment | Indian Ocean | 3614 | Antibiotic | [16] |
| Engyodontiumones A–J **(14-22)** | *Engyodontium album* DFFSCS021 | Sediment | South China Sea | 3739 | Cytotoxic | [18] |
| Lindgomycin **(23)**<br>Ascosetin **(24)** | *Lindgomycetaceae* strains KF970 and LF327 | Sediment | Greenland Sea, Baltic Sea | 3650 | Antibiotic | [17] |
| | | **Nitrogen-containing compounds** | | | | |
| Brevicompanines D–H **(25-29)** | *Penicillium* sp. F1 | Sediment | _ | 5080 | LPS-induced inflammation | [22] |
| Cyclopiamide B–J **(30-38)** | *Penicillium commune* DFFSCS026 | Sediment | South China Sea | 3563 | Cytotoxic | [24] |
| Penipanoid A **(39)**<br>Quinazolinone **(40)** | *Penicillium paneum* SD-44 | Sediment | South China Sea | 201 | Cytotoxic | [23] |
| (±) Brevianamide R **(41)** | *Aspergillus* versicolor MF180151 | Sediment | Bohai Sea, China | _ | Antibacterial | [21] |
| Circumdatin F and G **(42-43)** | *Aspergillus westerdijkiae* SCSIO 05233 | Sediment | South China Sea | 4593 | Cytotoxic | [20] |
| Oximoaspergillimide **(44)**<br>Neohydroxyaspergillic **(45)**<br>Neoaspergillic **(46)** | *Aspergillus* sp. (CF07002) | Water | Pacific Ocean off the coast of Panama | | Cytotoxic<br>Antibiotic | [19] |
| Varioxepine A **(47)** | *Paecilomyces variotii* EN-291 | Deep sea water | _ | _ | Antibiotic | [26] |
| Neoechinulin A **(48)** | *Microsporum* sp. (MFS-YL) | Red alga | Guryongpo, Korea | _ | Cytotoxic | [25] |
| | | **Polypeptide** | | | | |
| Canescenin A and B **(49-50)** | *Penicillium canescens* SCSIO z053 | Water | East China Sea | 2013 | Antibacterial | [27] |
| Clavatustide A and B **(51-52)** | *Aspergillus clavatus* C2WU | Hydrothermal vent crab | Taiwan Kueishantao | _ | Cytotoxic | [29] |
| Aspergillamides C and D **(53-54)**<br>Butyrolactone I **(55)** | *Aspergillus terreus* SCSIO 41008 | Sponge | Guangdong, China | _ | Cytotoxic<br>Antibiotic | [30] |
| Simplicilliumtides A–I **(56-64)** | *Simplicillium obclavatum* EIODSF 020 | Sediment | East Indian Ocean | 4571 | Cytotoxic | [31] |
| Asperelines A–F **(65-70)** | *Trichoderma asperellum* | Sediment | Antarctic Penguin Island | _ | Antibiotic | [28] |

**Table 1.** *Cont.*

| Metabolites | Fungal Species | Source | Location | Depth (m) * | Bioactivity | Ref. |
|---|---|---|---|---|---|---|
| **Esters** | | | | | | |
| 7-chlorofolipastatin **(71)**<br>Folipostatin B **(72)**<br>Unguinol **(73)**<br>2-chlorounginol **(74)**<br>2,7-dichlorounguinol **(75)**<br>Nornidulin **(76)** | *Aspergillus ungui* NKH-007 | Sediment | Suruga Bay, Japan | _ | Anti-atherosclerotic<br>Cytotoxic<br>Antibiotic | [32] |
| **Phenolic** | | | | | | |
| Pestalotionol **(77)** | *Penicillium* sp. Y-5-2 | Hydrothermal vent water | Kueishantao off Taiwan | _ | Antibiotic | [33] |
| Aspergilol G–I **(78-80)**<br>Coccoquinone A **(81)** | *Aspergillus versicolor* SCSIO 41502 | Sediment | South China Sea | 2326 | Anti-HSV-1<br>Antioxidant<br>Antifouling | [34] |
| **Piperazine** | | | | | | |
| Fusaperazine F **(82)** | *Penicillium crustosum* HDN153086 | Sediment | Prydz Bay, Antarctica | _ | Cytotoxic | [35] |
| N-methyl-pretrichodermamide B **(83)**<br>Pretrichodermamide C **(84)** | *Penicillium* sp. (WN-11-1-3-1-2) | Hypersaline sediment | Wadi El-Natrun, Egypt | _ | Cytotoxic | [36] |
| (±) 7,8-epoxy-brevianamide Q **(85)**<br>(±) 8-hydroxy-brevianamide R **(86)**<br>(±) 8-epihydroxy-brevianamide R **(87)**<br>Brevianamide R **(88)**<br>Versicolorin B **(89)** | *Aspergillus versicolor* MF180151 | Sediment | Bohai Sea, China | _ | Antibiotic | [21] |
| Dichotocejpins A **(90)**<br>6-deoxy-5a,6-didehydrogliotoxin **(91)**<br>Gliotoxin **(92)**<br>Acetylgliotoxin **(93)**<br>6-acetylbis(methylthio)-gliotoxin **(94)**<br>1,2,3,4-tetrahydro-2-methyl-3-methylene-1,4-dioxopyrazino [1,2-a] indole **(95)** | *Dichotomomyces cejpii* FS110 | Sediment | South China Sea | 3941 | α-Glucosidase inhibition<br>Cytotoxic | [37] |
| **Terpenoid** | | | | | | |
| Brevione F–I **(96-99)** | *Penicillium* sp. (MCCC 3A00005) | Sediment | Pacific Ocean | 5115 | Cytotoxic<br>HIV-1 inhibition | [22,38] |
| Dehydroaustin **(100)**<br>Dehydroaustinol **(101)**<br>7-hydroxydehydroaustin **(102)**<br>Austinone **(103)**<br>Austinol **(104)**<br>Austin **(105)**<br>Austinolide **(106)** | *Penicillium* sp. Y-5-2 | Hydrothermal vent water | Kueishantao off Taiwan | 8 | Antibacterial<br>Anti-insectal | [33] |

**Table 1.** *Cont.*

| Metabolites | Fungal Species | Source | Location | Depth (m) * | Bioactivity | Ref. |
|---|---|---|---|---|---|---|
| 1-chloro-3β-acetoxy-7-hydroxytrinoreremophil-1,6,9-trien-8-one **(107)**<br>Eremophilane-type sesquiterpenes **(108)**<br>Eremofortine C **(109)** | *Penicillium* sp. PR19N-1 | Sediment | Prydz Bay, Antarctica | 526 | Cytotoxic | [40,41] |
| Guignarderemophilane F **(110)** | *Penicillium* sp. S-1-18 | Sediment | Antarctic | 1393 | Antibacterial | [42] |
| Spirograterpene A **(111)**<br>Conidiogenone C and I **(112-113)** | *Penicillium granulatum* MCCC 3A00475 | Water | Prydz Bay of Antarctica | 2284 | Antiallergic | [46] |
| Aspewentin A and D–H **(114-118)**<br>Asperethers A–E **(121-125)**<br>Asperolides D and E **(119-120)** | *Aspergillus wentii* SD-310 | Sediment | South China Sea | 2038 | Antimicrobial<br>Cytotoxic<br>Anti-inflammatory | [39,43,44] |
| (7S)-(+)7-O-methylsydonol **(126)**<br>(7S,11S)-(+)-12-hydroxysydonic acid **(127)**<br>7-deoxy-7,14-didehydrosydonol **(128)**<br>(S)-(+)-sydonol **(129)** | *Aspergillus sydowii* | Sediment | Hsinchu, Taiwan | _ | Anti-inflammatory | [47] |
| 6b,9a-dihydroxy-14-p-nitrobenzoylcinnamolide **(130)**<br>Insulicolide A **(131)** | *Aspergillus ochraceus* Jcma1F17 | Marine alga *Coelarthrum* sp. | South China Sea | _ | Antiviral<br>Cytotoxic | [45] |
| **Other compounds** | | | | | | |
| Sterolic acid **(132)** | *Penicillium* sp. MCCC 3A00005 | Sediment | East Pacific Ocean | 5115 | Cytotoxic | [38] |
| Dicitrinone B **(133)** | *Penicillium citrinum* | Sediment | Langqi Island, Fujian, China | _ | Antitumor | [49] |
| Penipacids A–F **(134-139)** | *Penicillium paneum* SD-44 | Sediment | South China Sea | _ | Cytotoxic | [48] |
| Butanolide A **(140)** | *Penicillium* sp. S-1-18 | Sediment | Antarctic seabed | 1393 | Cytotoxic | [42] |
| 7-Methoxycyclopeptin **(141)**<br>7-Methoxy dehydro cyclopeptin **(142)**<br>7-Methoxy cyclopenin **(143)**<br>9-Hydroxy-3-methoxyviridicatin **(144)** | *Aspergillus versicolor* XZ-4 | Hydrothermal vent crab | Kueishantao, Taiwan | | Antibiotic | [50] |
| Wentilactone A and B **(145-146)** | *Aspergillus dimorphicus* SD317 | Sediment | South China Sea | 2038 | Antitumor | [51] |
| Penicillisocoumarin A–D **(147-150)**<br>Aspergillumarins B **(151)** | *Penicillium* sp. Y-5-2 | Hydrothermal vent water | Kueishantao off Taiwan | 8 | Antibacterial | [33] |

* Depth represents water depth below the surface.

## 3. Conclusions and Perspective

The results of current studies indicate that the deep-sea extreme environmental fungi are one of the rich and unexploited sources of important medicinal lead compounds. Most of the fungi (e.g., *Penicillium* spp. and *Aspergillus* spp.) living in the extreme environments of the deep-sea have the potential to synthesize new bioactive compounds. However, the research on deep-sea fungi and their metabolites is very limited due to the difficulty of sampling and the limitation of culture technology. Thanks to the advances in genome technology and the implementation of the deep-sea drilling program, novel compounds with great biological activities are expected from these fungi in the near future. From the literature review, we can say these fungi from the extreme environments have the potential to produce clinically important natural products. The compounds we discussed in this review show strong bioactivities and might have the potential to be a future anticancer drug. Among them, terpenoid derivatives were the most important and abundant compound category which were mainly isolated from deep-sea derived *Penicillium* spp. and *Aspergillus* spp. This class of compounds showed strongest antibiotic and cytotoxic activities as compared to other classes of compounds and has the potential to be a future candidate for anticancer drugs, especially brevione, which was isolated from the deepest part of the sea and showed the strongest cytotoxic activity.

**Author Contributions:** Writing—original draft preparation, M.Z.u.A.; writing—review and editing, Y.-N.M., Y.-R.X. and C.-H.L. All authors have read and agreed to the published version of the manuscript.

**Funding:** This work was financially supported by the National Natural Science Foundation of China (General Program: 41773083, 41973073; Major Program: 91951121).

**Conflicts of Interest:** The authors declare that they have no competing interests.

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