Review

Marine-Derived Penicillium Species as Producers of Cytotoxic Metabolites

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Abstract: Since the discovery of penicillin, Penicillium has become one of the most attractive fungal genera for the production of bioactive molecules. Marine-derived Penicillium has provided numerous excellent pharmaceutical leads over the past decades. In this review, we focused on the cytotoxic metabolites(* Cytotoxic potency was referred to five different levels in this review, extraordinary (IC\textsubscript{50}/LD\textsubscript{50}: <1 µM or 0.5 µg/mL); significant (IC\textsubscript{50}/LD\textsubscript{50}: 1~10 µM or 0.5~5 µg/mL); moderate (IC\textsubscript{50}/LD\textsubscript{50}: 10~30 µM or 5~15 µg/mL); mild (IC\textsubscript{50}/LD\textsubscript{50}: 30~50 µM or 15~25 µg/mL); weak (IC\textsubscript{50}/LD\textsubscript{50}: 50~100 µM or 25~50 µg/mL). The comparative potencies of positive controls were referred when they were available). produced by marine-derived Penicillium species, and on their cytotoxicity mechanisms, biosyntheses, and chemical syntheses.

Keywords: marine-derived Penicillium; natural products; cytotoxic metabolites; biosynthesis

1. Introduction

The oceans, which occupy more than 70% of the earth’s surface, undoubtedly support vast habitats and serve as prolific resources of various living organisms. Compared to terrestrial organisms, marine organisms often produce highly potent metabolites with unique structures to enable them to adapt to extremely challenging environments [1]. Developments and improvements made in biotechnology have led to a new era of bioprospecting for new marine products. Revolutionary target screening methods have improved the efficiency of drug discovery. In addition, leading edge genomics of biological symbiosis offer more opportunities to discover drug candidates and precursors. Marine endo zoic microorganisms represent a new frontier in the discovery of pharmaceutical agents [2]. In particular, marine-derived fungi are excellent producers of biologically active secondary metabolites. Since the isolation of the broad-spectrum antibiotic, cephalosporin C from the marine-derived fungus Acremonium chrysogenum, thousands of bioactive metabolites have been discovered and evaluated [3].

Cancer is the second leading cause of death. Lung, prostate, colorectal, and digestive tract cancer are commonly encountered in males, whereas breast, lung, and cervical cancer are the major causes of female death. Marine microorganisms produce limited amounts of highly efficient toxic substances to protect their hosts from enemies, and these substances have been investigated as potential anticancer drug precursors. In particular, marine-derived Penicillium species represent a new source of cytotoxic metabolites. In this review, we list all cytotoxic or antitumor secondary metabolites isolated from marine-derived Penicillium species and classify them into distinct chemical groups. In addition, we summarize the cytotoxicity mechanisms and proposed biosyntheses of these metabolites. Overall, more than 200 natural products and their synthetic analogues are included in this review.
2. Alkaloids

Cytochalasan alkaloids, characterized by a highly substituted perhydroisoindol-1-one fused to a macrocyclic ring, have been shown to possess potential cytotoxicity against diverse tumor cell lines [4,5]. Penochalasins, chaetoglobosins, and cytoglobosins are common classes of cytochalasan alkaloids. A series of cytochalasans, penochalasins A–J (1–10), chaetoglobosins A, C, E–G, O (11–16), and cytoglobosin C (17) (Figure 1) were isolated from the mangrove endophytic fungus P. chrysogenum [6] and from the marine alga Enteromorpha intestinalis [7,8]. Penochalasin A–H (1–8) and chaetoglobosins A, F, O (11, 14, 16) exhibited significant cytotoxic activity (ED\textsubscript{50} = 0.4, 0.3, 0.5, 3.2, 2.1, 1.8, 1.9, 2.8, 0.6, 0.9, and 2.4 μg/mL, respectively) against P388 lymphocytic leukemia cells. Moreover, chaetoglobosin A (11) reportedly induced apoptosis of chronic lymphocytic leukemia (CLL) cells by targeting the cytoskeleton. The underlying mechanisms involve the induction of cell-cycle arrest and the inhibition of membrane ruffling and cell migration; therefore, it was proposed as a novel drug for CLL [9].

Penochalasin I (9) exhibited significant cytotoxic activities against MDA-MB-435 (human breast cancer cell line) and SGC-7901 (human gastric cancer cell line) with IC\textsubscript{50} values of ~7 μM. Cytoglobosin C (17) showed potential cytotoxicity against both SGC-7901 and A549 (human lung adenocarcinoma) with IC\textsubscript{50} values of ~3–8 μM. Other cytochalasans, penochalasin J (10), chaetoglobosins C, E (12, 13), and chaetoglobosin G (15) showed moderate cytotoxicity against MDA-MB-435, SGC-7901, and A549 with IC\textsubscript{50} values in the range of 10–40 μM (epirubicin was used as a positive control with IC\textsubscript{50} values of 0.3–0.6 μM). A recent biosynthetic analysis showed that the fungal PKS-NRPS hybrid synthase, CheA, plays an essential role in cytochalasan formation [10].

Figure 1. Chemical structures of compounds 1–17.

Gliotoxin induces cellular immunosuppression and apoptosis [11], and its analogues are disulfur or polysulfur-containing mycotoxins that belong to a class of naturally occurring epipolythio piperazines (ETP). In 2012, the marine fungus Penicillium sp. JMF034, which was isolated from a deep sea sediment in Japan, was found to produce seven gliotoxin-related compounds, (bis(dethio)-10α-methylthio-3α-deoxy-3,3α-didehydrogliotoxin (18), 6-deoxy-5α,6-didehydrogliotoxin (19), bis(dethio) bis(methylthio)gliotoxin (20), bis(dethio)bis(methylthio)-5α,6-didehydrogliotoxin (21), 5α,6-didehydrogliotoxin (22), gliotoxin (23), and gliotoxin G (24) (Figure 2) [12], which potently killed P388 murine leukemia cells (IC\textsubscript{50} = 3.4, 0.058, 0.11, 0.11, 0.056, 0.024, and 0.020 μM, respectively). Because of their extraordinary cytotoxicity, gliotoxin analogues are considered as antitumor leads [13]. Dimeric ETPs were reported to inhibit histone methyltransferase (HMT); in addition, compounds (22–24) with disulfide or tetrasulfide bonds showed significant inhibitory
activities against HMT G9a (IC$_{50}$ = 2.6, 6.4, and 2.1 µM, respectively) rather than HMT SET7/9 (IC$_{50}$ > 100 µM). Gliotoxin G (24), isolated from the mangrove endophytic fungus P. brocae MA-231, was potently active against cisplatin-sensitive and resistant human ovarian cancer cell lines, A2780 and A2780 CisR, with IC$_{50}$ values of 664 and 661 nM, respectively (cisplatin was used as a positive control with IC$_{50}$ values of 1.67 and 12.63 µM, respectively) [14]. Compound 24 may be used as an anti-ovarian cancer agent, even in patients who are resistant to platinum compounds. Plausible hypotheses for the biosyntheses of ETPs have been previously reviewed [15].

![Chemical structures of compounds 18–24.](image)

Four new cytotoxic bisthiodiketopiperazines (brocazines A–F) (25–30) (Figure 3), which share molecular similarities with gliotoxin, were isolated from a fungal strain of P. brocae MA-231, collected from the marine mangrove Avicennia marina [16]. Their cytotoxicity was investigated in human prostate cancer (DU145), human cervical carcinoma (Hela), human hepatoma (HepG2), human breast carcinoma (MCF-7), human large-cell lung carcinoma (NCI-H460), SGC-790, human pancreatic cancer (SW1990), human colon carcinoma (SW480), and human glioma (U251) cell lines. Brocazines A, B, E, and F (25, 26, 29, and 30) exhibited significant cytotoxic effects against most of the cell lines tested with IC$_{50}$ values in the range of 0.89–9 µM (paclitaxel, cisplatin, cefitinib, doxorubicin, and gemcitabine were used as positive controls with IC$_{50}$ values of 1–11 µM). In contrast, brocazines C and D (27 and 28), which lack the α, β unsaturated ketone group, had much lower cytotoxicity (IC$_{50}$ > 20 µM), which suggests that the conjugated ketone system is crucial to the cytotoxic properties of bisthiodiketopiperazine analogues.

Two bisthiodiketopiperazines, pretrichodermamide C (31) and N-methylpretrichodermamide B (32) (also called adametizine B and A, respectively) (Figure 4), were isolated from a marine sponge-derived fungus (P. adametzioides AS-53) [17], a hyper saline lake-derived Penicillium sp. [18], and a marine algicolous fungus (Penicillium sp. KMM4672) [19]. All three studies showed that compound 32, which contains chlorine, exhibited significant cytotoxicity, wherein it reduced the viability of L5178Y mouse lymphoma cells, human prostate cancer 22Rv1 cells, PC-3 cells, LNCaP cells, and brine shrimps (IC$_{50}$ = 2, 0.51, 5.11, 1.76, and 4.8 µM, respectively; while kahalalide F, docetaxel, and colchicine were employed as positive controls with IC$_{50}$ values of 4.3, 0.013, 0.015, 0.004, and 8.1 µM, respectively). Furthermore, it was found active in hormone-resistant 22Rv1 cells at nanomolal concentrations. In contrast, metabolite 31 was completely inactive in all bioassays with IC$_{50}$ values > 100 µM. This remarkable difference in activity indicates that the halogen atom might improve the activity of the metabolite.
Roquefortine C (33) (Figure 5) is a potential neurotoxin that can activate P-glycoprotein and simultaneously inhibit P450-3A and other hemoproteins [20]. Roquefortine and meleagrin (38) analogues are considered biogenetically interrelated mycotoxins with promising cytotoxicity [21]. Recently, a series of roquefortine derivatives, roquefortines F–I (34–37), and meleagrin analogues, meleagrin analogues, meleagrin analogues, were isolated from the deep ocean sediment-derived fungus Penicillium sp. [22], and most of these compounds (34, 35, and 39–42) were active against A549, HL-60 (human promyelocytic leukemia), BEL-7402 (human hepatoma), and MOLT-4 (human acute T lymphoblastic leukemia) cancer cell lines. Meleagrin B (39) was the most cytotoxic against these four cell lines with IC50 values in the range of 1.5–7 μM; the other compounds had IC50 values in the range of 4–50 μM. Meleagrin (38) was also isolated from a deep sea sediment-derived fungus, P. commune SD-118, and was found to be cytotoxic in HepG2, NCI-H460, Hela, MDA-MB-231 (human breast cancer cells), and DU145 human cancer cell lines (IC50 = 12, 22, 20, 11, and 5 μg/mL, respectively; while fluorouracil was employed as a positive control with IC50 values of 14, 1, 14, 8, and 0.4 μg/mL, respectively) [23].

Penicimutanins A, B (43–45) and fructigenine A (46) (Figure 6) are structurally similar to roquefortines, and were first isolated from diethyl sulfate- or gentamicin-induced mutants of the marine-derived fungus P. purpurogenum G59 [24,25]. Mutation-based approaches can activate silent fungal gene clusters and afford more potent metabolites with unique structures. Compounds 44 and 45 are mutant cytotoxic products that showed potent activities against five human cancer cell lines: K562 (human chronic myelogenous leukemia), HL-60, Hela, BGC-823 (human gastric adenocarcinoma), and MCF-7 (IC50 values were 5–11 μM for 44 and 8–20 μM for 45). Compounds 43 and 46 also inhibited the proliferation of these cell lines (Inhibition Rate (IR)% = 22.6 and 20.8 (K562); 17.9 and 55.3 (HeLa); and 26.5 and 65.6% (MCF-7) at 100 μg/mL, respectively; while 5-fluorouracil was employed as a positive control with IR% of 48.5, 37.4, and 47.4 μg/mL at 100 μg/mL, respectively).
A concise enantioselective method for the total synthesis of (+)-11,11′-dideoxyverticillin A (47) and (+)-verticillin A (48) (Figure 7) in 1970, dimeric epidithiodiketopiperazine alkaloids have received much attention owing to their diverse biological activities and complex molecular structures [26,27]. In 1999, two additional dimeric epidithiodiketopiperazine alkaloids, (+)-11,11′-dideoxyverticillin A (49) and (+)-11′-deoxyverticillin A (50), were isolated from a marine alga-derived fungus Penicillium sp. and were found to exhibit extraordinary cytotoxicity against HCT-116 cells (human colon cancer) with IC_{50} of 30 ng/mL [28]. Chaetocin A (47) was the first compound reported to inhibit HMT, and to have specific effects on HMT SU(VAR)3-9 in vitro and in vivo [29]. (+)-11,11′-Dideoxyverticillin A (49), an alkaloid, exhibited diverse antitumor activities in vitro and in vivo [30]; in addition, it potently inhibited the phosphorylation of epidermal growth factor receptor in human breast cancer (MDA-MB-468) [31]. Movassaghi et al. used a concise enantioselective method for the total synthesis of (+)-11,11′-dideoxyverticillin A (49) in 2009 [32] based on mimicking the biosynthetic pathway; in addition, they used this approach to synthesize various dimeric epidithiodiketopiperazines [33].

![Figure 5. Chemical structures of compounds 33–42.](image1)

![Figure 6. Chemical structures of compounds 44–46.](image2)
Seven cytotoxic indole diterpene alkaloids, penitrems A,B (51–52), D–F (53–55), paspaline (58), and emindole SB (59) (Figure 8) were isolated from a marine Penicillium sp. KBr-induced mutation of this fungus produced two bromo-substituted indole alkaloids, 6-bromopenitrems B and E (56–57) [34]. Compounds (51–59) showed potent antiproliferative (IC_{50} = 5–20 \mu M for MCF-7; 8–30 \mu M for MDA-MB-231), anti-migratory (IC_{50} = 7–35 \mu M for MDA-MB-231) and anti-invasive properties (IR\% = 10–75\% at 15 \mu M) against human breast cancer cells. In addition, penitrems A, B, and E (51–52, 54) were evaluated in 60 human tumor cell lines as a part of the Development Therapeutics Program of the National Cancer Institute (NCI60). Penitrem B (52) exhibited the strongest mean growth inhibitory effect in the 60 human cancer cells (IR\% = 41.05\% at 10 \mu M) and was considered a potential selective inhibitory agent for leukemia cells. The nematode Caenorhabditis elegans was used to assess the brain’s Maxi-K (BK) channel inhibitory activity and toxicity in vivo [35,36]. Penitrem A (51) and 6-bromopenitretem E (57) displayed BK channel inhibition, comparable to that of a knockout strain. A pharmacophore study on the effects of the penitrem skeleton on the antiproliferative activity against MCF-7 cells indicated that less structural complexity of the penitrems, paspaline (58), and emindole SB (59) better maintained the molecular alignment and pharmacophoric features. Penitrem A (51) was also considered a neurotoxin that antagonizes BK channels [37].

Another large family of indole alkaloid mycotoxins, comprising communesins A–D (60–63) (Figure 9), was isolated from marine-derived Penicillium sp. from a marine alga [38], marine sponge [39], and marine sediment [40]. Communesin B (61) (also called nomofungin) was more cytotoxic to P388 lymphocytic leukemia cells (ED_{50} = 0.45 \mu g/mL) than communesin A (60) (ED_{50} = 3.5 \mu g/mL).
The antiproliferative activity of communesins B–D (61–63) was further evaluated in six lymphocytic leukemia cell lines (U-937, THP-1, NAMALWA, L-428, MOLT-3, and SUP-B15). They steadily and effectively inhibited the proliferation of five of these cell lines with ED$_{50}$ values ranging from 7 to 16 µg/mL; however, they were inactive in L-428 cells. The total synthesis of communesin B (61) was previously reported [41].

![Figure 9. Chemical structures of compounds 60–63.](image)

Four new cytotoxic prenylated indole alkaloid derivatives, penioxamide (64) [42], 13-O-prenyl-26-hydroxyverruculogen (65) [43], and penipalines B and C (66–67) (Figure 10) [44], were isolated from marine mangrove-derived *P. oxalicum* EN-201, marine sediment-derived *P. brefeldianum* SD-273, and marine sediment-derived *P. panum* SD-44, respectively. Metabolites 64–65 showed significant lethality in brine shrimps with LD$_{50}$ values of 5.6 and 9.4 µM, respectively (colchicine was employed as a positive control with an LD$_{50}$ value of 7.8 µM). Metabolites 66–67 induced moderate cytotoxicity against A549 (IC$_{50}$ = 20.44 and 21.54 µM, respectively) and HCT-116 cell lines (IC$_{50}$ = 14.88 and 18.54 µM, respectively).

![Figure 10. Chemical structures of compounds 64–67.](image)

In addition, three 1,4-diazepane derivatives, terretriones A, C, and D (68–70) (Figure 11), obtained from marine sponge-derived *P. vinaceum* [45] and marine tunicate-derived *Penicillium* sp. CYE-87 [46], moderately inhibited the migratory activity of MDA-MB-231 cells with IC$_{50}$ values of 17.7, 17.6, and 16.5 µM, respectively (Z-4-ethylthio-phenylmethylene hydantoin was used as a positive control with an IC$_{50}$ value of 43.4 µM). These findings indicate that terretriones might be potential anti-metastatic breast cancer candidates.
Six tetramic acid derivatives, penicillenols A1, A2, B1, B2, D1, and D2 (71–76) (Figure 12), were isolated from a marine sediment-derived fungus *P. citrinum*. Penicillenol B2 (74) exhibited the strongest cytotoxic activity against A-375 human malignant melanoma cell line (IC$_{50}$ = 0.97 µg/mL), whereas the IC$_{50}$ values of compounds 71–73 were 3.2, 13.8, and 2.8 µg/mL, respectively [47,48]. Penicillenols D1 and D2 (75–76) showed moderate cytotoxicity against A549 cells with IC$_{50}$ values of 17.2 and 12.1 µg/mL, respectively. However, penicillenols A1 and B1 (71, 73) showed significant cytotoxicity in HL-60 cells (IC$_{50}$ = 0.76 and 3.2 µM, respectively) [49]. A novel tetramic acid derivative, penicitrinine A (77), which contains a citrinin-like group, was isolated [50]. The combination of two cytotoxic fragments in this metabolite might contribute to its extensive antiproliferative activity in diverse tumor cell lines, particularly A-375 cells. Penicitrinine A (77) not only induced A-375 cell apoptosis by upregulating Bax and downregulating Bcl-2, but also inhibited A-375 cell metastatic activity by suppressing matrix metalloproteinase 9 (MMP-9) and promoting the expression of its specific inhibitor, tissue inhibitor of metalloproteinases-1 (TIMP-1). These findings suggest that penicitrinine A (77) is a potential lead compound.

Quinolinone and quinazolinone alkaloids have unique pharmacophores that allow their binding to multiple sites with high affinity; moreover, they possess various biological properties [51]. Some cytotoxic quinolinone (78–82) and quinazolinone alkaloids (83–85) (Figure 13) were isolated from marine-derived members of the *Penicillium* genus, such as *P. janczewskii*, *Penicillium* sp. ghq208, *P. oxalicum* 0312F1, *P. chrysogenum* EN-118, and *P. commune* SD-118 [23]. 2-quinolinone metabolites (78–79) exhibited IR% values of 50–60% at 10 µg/mL. Interestingly, compound 80, which has an additional prenyl chain, showed significant cytotoxicity against MDA-MB-231 and HT-29 (human colon carcinoma) cell lines with IR% values of 92–96% at 10 µg/mL [52]. In addition, a 4-quinolinone derivative (82) exhibited significant cytotoxicity against the human lung cancer cell line 95-D
Both compounds 81 and 82 exhibited similar cytotoxicity (IC₅₀ = 11.3 and 13.2 µM, respectively) against HepG2 cells [53,54]. However quinazolinone derivatives (83–85) showed only moderate cytotoxicity (compound 83, IC₅₀ = 20 µg/mL in SW1990 cell line; compound 84, IC₅₀ = 8 µg/mL in DU145, A549, and Hela cell lines; and compound 85, IR% = 35–40 at 200 µg/mL in SGC-7901 and BEL-7404 cell lines) [55,56].

In an ongoing study that aims to produce new active metabolites from P. paneum SD-44 (a deep sea sediment-derived fungus) using culture variations, three amidine anthranilic acid analogues (86–88) and one triazole anthranilic acid derivative, penipanoid A (89) (Figure 14), were obtained after culture in malt and rice medium, respectively. Compounds 86 and 87 strongly inhibited RKO human colon cancer cell viability (IC₅₀ = 8.4 and 9.7 µM, respectively). In addition, compound 88 was cytotoxic to Hela cells (IC₅₀ = 6.6 µM) [57], whereas compound 89 with a triazole group only weakly inhibited SMMC-7721 cell viability (human hepatocarcinoma) (IC₅₀ = 54.2 µM) while fluorouracil was used as a positive control for three cell lines with IC₅₀ values of 25.0, 14.5, and 13.0 µM, respectively [58].

An azaphilone analogue, bis-sclerotioramin (90) (Figure 15), obtained from a marine mangrove endophytic fungus, Penicillium 303#, was found to possess moderate cytotoxicity against MDA-MB-435...
cell line (IC$_{50}$ = 7.13 µg/mL), while epirubicin was used as a positive control with an IC$_{50}$ value of 0.325 µg/mL [59]. Another novel alkaloid, the sorbicilin-derived sorbicillactone A (91), was first isolated from a Mediterranean sponge-derived fungus, P. chrysogenum. Sorbicillactone A (91) exhibited a selective antileukemic activity in L5178Y cells (murine leukemic lymphoblast) with an IC$_{50}$ of 2.2 µg/mL, as well as in other tumor cell lines (IC$_{50}$ > 10 µg/mL). The biosynthesis of sorbicillactone A (91) was investigated using $^{13}$C-labeled precursor feeding experiments, which showed that the its skeleton was derived from acetate, alanine, and methionine [60]. Furthermore, a new strategy for the large-scale biotechnological production of sorbicilin-derived alkaloids was developed for preclinical screening and a structure-activity relationship (SAR) study [61]. In addition, a 4-oxoquinoline derivative, brocaeloid B (92), isolated from the mangrove endophytic fungus P. brocae, showed mild lethality against brine shrimps with an LD$_{50}$ value of 87.6 µM [62]. Li et al. cultured the marine mangrove fungus P. varibile with the DNA methyltransferase inhibitor 5-azacytidine to identify novel responsive molecules by gene silencing. A highly modified fatty acid amide, varitatin A (93), exhibited a selective antileukemic activity in L5178Y cells (murine leukemic lymphoblast) with an IC$_{50}$ values in the range of 3–12 µM, respectively) and A549 (IC$_{50}$ = 82.8, 5.2, and 12.2 µM) [17].

Figure 15. Chemical structures of compounds 90–95.
3. Terpenes, Meroterpenes, and Steroids

The genus *Penicillium* is a well-known producer of eremophilane-type sesquiterpenes with phytotoxic, mycotoxic, and phytohormonic activities [68,69]. Chemical investigation of an Antarctic deep sea-derived fungus, *Penicillium* sp. PR19 N-1, yielded three new cytotoxic eremophilane-type sesquiterpenes (96–98) (Figure 16), which were moderately cytotoxic to HL-60 (IC$_{50} = 45.8$, 28.3, and 11.8 µM, respectively) and A549 (IC$_{50} = 82.8$, 5.2, and 12.2 µM, respectively) cancer cell lines [70,71]. Three other eremophilane-type sesquiterpenes (99–101) were isolated from a sea mud-derived fungus, *Penicillium* sp. BL 27-2. Of these, compound 99 was the most cytotoxic to P388, A549, HL-60, and BEL-7402 cell lines (IC$_{50} = 0.073, 0.096, 0.065, \text{and } 4.59$ µM, respectively), whereas compounds 100 and 101 had IC$_{50}$ values in the range of 3–12 µM [72]. These results suggest that the epoxide ring is essential for the cytotoxicity of eremophilane-type sesquiterpenes and that the presence of an acetyl group enhances the cytotoxicity. A new acorane sesquiterpene, adametacorenol B (102), isolated from a marine sponge-derived fungus, *P. ademetzioides* AS-53, displayed selective cytotoxicity against NCI-H466 cell lines (IC$_{50} = 5$ µM), compared to its cytotoxicity against the other 13 tumor cell lines tested (A549, DU145, HeLa, HepG2, Huh-7 (human hepatocarcinoma), L02 (human hepatocarcinoma), LM3 (murine breast cancer), MA (mouse Leydig tumor), MCF-7, SGC-7901, SW1990, SW480, and U251) (IC$_{50} > 10$ µM) [17].

![Chemical structures of compounds 96–102.](image)

The deep sea sediment-derived fungus *Penicillium* sp. was reported to be a good source of cytotoxic diterpenes. Six tetracyclic diterpenes, conidiogenones B–G (103–108) (Figure 17), exhibited cytotoxicity against HL-60, A549, BEL-7402, and MOLT-4 cell lines. Conidiogenone C (104) was potently cytotoxic against HL-60 and BEL-7402 cells with IC$_{50}$ values of 0.038 and 0.97 µM, respectively; however, it was not cytotoxic against A549 and MOLT-4 cell lines at 50 µM. Other conidiogenones (103, 105–108) had moderate cytotoxicity with IC$_{50}$ values ranging from 1 to 50 µM [22]. The spiroditerpenes, breviones I and A (109–110) were also obtained from this fungus and showed cytotoxicity comparable to that of cisplatin (the positive control) against MCF-7 cells (IC$_{50} = 7.44$ and 28.4 µM, respectively, versus 8.04 µM for cisplatin) [73].

Although several marine-derived steroids have been isolated, few have been found to be bioactive. A cytotoxic polyoxygenated steroid, penicisteroide A (111) (Figure 18), was isolated from a marine alga-derived fungus, *P. chrysogenum* QEN-24S. Penicisteroide A (111) displayed moderate cytotoxicity against Hela, SW1990, and NCI-H460 cell lines with IC$_{50}$ values of 15, 31, and 40 µg/mL, respectively [74]. Three other polyoxygenated steroids (112–114) and two epidioxygenated steroids (115–116) were isolated from the marine moss-derived fungus *Penicillium* sp. These steroids moderately inhibited HepG2 cell line growth (IC$_{50}$ values = 10.4, 15.6, 20.7, 16.8, and 21.3 µg/mL, respectively) [75]. In addition, an epidioxygenated steroid (117), produced by a sea squirt-derived fungus, *P. stoloniferum* QY2-10, was cytotoxic to P388 cells with an IC$_{50}$ of 4.07 µM [76]. Moreover, a marine *Penicillium* sp. fungus collected from the inner tissues of an unidentified sponge is reportedly the source.
of two epimeric steroids (118–119) and two cytotoxic steroids of a new class, dankasterone A (120) and B (121). Dankasterone A (120) was more effective than the positive control, adriamycin (IC$_{50}$ = 0.98 µM) against HL-60, Hela, and K562 cancer cell lines with IC$_{50}$ values of 0.78, 4.11, and 7.57 µM, respectively. Compounds 118–119 and 121 also significantly inhibited K562 cell growth (IC$_{50}$ = 4.38, 5.54, and 7.89 µM, respectively) [77].

Meroterpenes are widely distributed in the marine environment, particularly in brown algae and microorganisms. Terpene-quinone and -hydroquinone are the major bioactive members because they produce reactive oxygen species (ROS) [78]. Three quinone- and hydroquinone-type meroterpenes (122–124) (Figure 19) were isolated from a marine-derived *Penicillium* sp. Compounds 122 and 123 exhibited extensive cytotoxicity against five cancer cell lines (A549, SKOV-3 (human ovary adenocarcinoma), SKMel-2 (human skin cancer), XF498 (human CNS cancer), and HCT15 (human colon cancer)) with IC$_{50}$ values in the range of 3–10 µg/mL, whereas compound 124 had IC$_{50}$ values ranging from 20 to 40 µg/mL (doxorubicin was used as a positive control with IC$_{50}$ values of 0.02–0.8 µg/mL). These results suggest that the quinone form tends to be less cytotoxic [79]. Penicillone A (125), isolated from marine-derived *Penicillium* sp. F11., contains a carboxylic acid group instead of the isoprenyl tail, which resulted in mild cytotoxicity against fibrosarcoma (HT1080) and human nasopharyngeal carcinoma (Cne2) cell lines (IC$_{50}$ = 45.8 and 46.2 µM, respectively) [80].

Two sesquiterpene α-pyrones, phenylpyrropenes E and F (126–127) (Figure 20), were isolated from the marine-derived fungus *P. concentricum* ZLQ-69 and displayed moderate and selective cytotoxicity against MGC-803 cells (human gastric cancer) with IC$_{50}$ values of 19.1 and 13.6 µM, respectively (doxorubicin was used as a positive control with an IC$_{50}$ value of 0.37 µM) [81]. Furthermore, the marine sediment-derived fungus *Penicillium* sp. F446 yielded two new sesquiterpene γ-pyrene-type meroterpenes, penicillipyrene A and B (128–129), which were moderately cytotoxic against A549 cells (IC$_{50}$ = 15 and 17 µM, respectively, while doxorubicin was used as a positive control with

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**Figure 17. Chemical structures of compounds 103–110.**

**Figure 18. Chemical structures of compounds 111–121.**
were semi-synthesized in an SAR study, which showed that chlorohydrin and C6 substituents were crucial for cytotoxic activities. Furthermore, ligerin (132), a natural chlorinated merosesquiterpene related to fumagillin, was obtained from a marine-derived Penicillium sp., and showed selective in vitro antiproliferative activity against osteosarcoma cell lines (IC\textsubscript{50} = 117 nM against POS1 cells, which is 20 times greater than the IC\textsubscript{50} in other cancer cell lines), while doxorubicin was used as a positive control with IC\textsubscript{50} values of 0.2–0.6 μg/mL [84]. Ligerin analogues were semi-synthesized in an SAR study, which showed that chlorohydrin and C6 substituents were crucial for cytotoxic activities. Furthermore, ligerin (132) exhibited stronger cytotoxicity against human osteosarcoma SaOS2 and MG63 cancer cell lines. However, its cytotoxicity was less than that of TNP470 (a positive control and fumagillin analogue) [85].

![Chemical structures of compounds 122–125.](image1)

**Figure 19.** Chemical structures of compounds 122–125.

![Chemical structures of compounds 126–132.](image2)

**Figure 20.** Chemical structures of compounds 126–132.
4. Polyketides

Chromone derivatives are abundantly present in nature and are considered potential immunomodulatory, anticancer, and anti-inflammatory agents. Chromone scaffolds were reported to possess outstanding pharmacological properties [86]. A Chinese research group recently isolated four dihydrothiophene-condensed chromones, oxalicumones D, E (133–134) and A, B (135–136) (Figure 21) from a marine gorgonian-derived fungus, P. oxalicum SCSGAF 0023. Similar to synthetic dihydrothiophene-condensed chromones (137–144), these four natural chromones (133–136) displayed significant cytotoxicity against eight carcinoma cell lines (human lung adenocarcinoma (H1975), human lymphoma (U937), K562, BGC823, MOLT-4, MCF-7, HL-60, and Huh-7) (IC\textsubscript{50} < 10 \textmu M). Of these, oxalicumone A (135) was the most cytotoxic against MOLT-4 cell line (IC\textsubscript{50} = 0.30 \textmu M). An SAR study showed that the 2,3-dihydrothiophene unit was crucial for activity and that the presence of 1-OH and absolute configuration at C-6 contributed to cytotoxicity [87,88]. Subsequent pharmacological studies showed that oxalicumone A (135) inhibited leukemia cell growth and induced apoptosis, in part, via the induction of the endoplasmic reticulum stress pathway by upregulating calnexin and Bax and activating unfolded protein response [89]. Another study found that oxalicumone A (135) could induce oxidative stress injury in the mitochondria, and thus promote human renal epithelial cell death [90]. Chromosulfine (145), a novel cyclopentachromone sulfide which is structurally similar to dihydrothiophene-condensed chromones, was isolated from a neomycin-resistant mutant of the marine-derived fungus P. purpurogenum G59, and showed selective cytotoxicity against HL-60 cancer cell line (IC\textsubscript{50} = 16.7 \textmu M) [91]. Secalonic acid F (146), a chiral dimeric tetrahydroxanthone, was first isolated from Aspergillus sp. before discovering that the deep sea sediment-derived fungus Penicillium sp. F11 is a good source of this compound. Compound 146 induced HL-60 cell apoptosis by modulating the Rho GDP dissociation inhibitor 2 pathway [92]. Recent studies showed that secalonic acid F (146) could induce apoptosis by activating caspase 3 and 9 through the mitochondrial pathway in hepatocellular carcinoma, wherein it was found to be more effective than 5-fluorouracil [93]. Furthermore, a flavone, namely penimethavone A (147), obtained from a gorgonian-derived fungus, P. chrysogenum, exhibited selective cytotoxicity against Hela and rhabdomyosarcoma cell lines (IC\textsubscript{50} = 8.41 and 8.18 \textmu M, respectively) while adriamycin was used as a positive control with IC\textsubscript{50} values of 0.43 and 0.09 \textmu M, respectively [94].

Figure 21. Chemical structures of compounds 133–147.

Coumarin derivatives of the chromone isomers (148–150) (Figure 22) were also isolated from the deep sea sediment-derived fungus (P. chrysogenum SCSIO 41001), a marine sponge-derived fungus Penicillium sp., and a mangrove endophytic fungus (Penicillium sp. ZH16), respectively. The dimeric
isocoumarin, bipenicillisorin (148), displayed significant cytotoxicity against K562, A549, and Huh-7 cell lines (IC\(_{50}\) = 6.78, 6.94, and 2.59 \(\mu\)M, respectively), while taxol was used as a positive control with IC\(_{50}\) values of 3.44, 2.61, and 14.70 nM, respectively [95]. The dihydroisocoumarin monocerin (149) exhibited significant cytotoxicity against L5178Y cells (a murine lymphoma cell line) with an IC\(_{50}\) value of 8.4 \(\mu\)M (kahalalide F was used as a positive control with an IC\(_{50}\) value of 4.3 \(\mu\)M) [96]. Moreover, furanocoumarin (150) showed moderate cytotoxicity against human nasopharyngeal carcinoma (KB and KBv200) cell lines (IC\(_{50}\) = 5 and 10 \(\mu\)g/mL, respectively) [97].
Other fungal azaphilone polyketides include comazaphilones D–F (161–163) (Figure 24), pinophilins A, B, and Sch 725680 (164–166), which were isolated from a marine sediment-derived fungus, *P. commune* QSD-17 (comazaphilones D–F), and a marine seaweed-derived *P. pinophilum* Hedgcock (pinophilins A-B and Sch 725680). Comazaphilones D–F (161–163) showed selective but weak cytotoxicity against SW1990 cell line (IC$_{50}$ = 51, 26, and 53 μM, respectively), while fluorouracil was used as a positive control with an IC$_{50}$ value of 120 μM [109]. Azaphilone derivatives (164–166) were suggested to suppress cancer cell proliferation by inhibiting DNA replication via the inhibition of mammalian DNA polymerases A, B, and Y [110].

*Penicillium* sp. strain OUPS-79, which is derived from the marine alga *Enteromorpha intestinalis*, yielded various cytotoxic polyketides, including penostatins A–C, E–I (167–169, 171–175) (Figure 25) [111,112]. They were found to be significantly cytotoxic to P388 lymphocytic leukemia cells (ED$_{50}$ = 0.8, 1.2, 1.0, 0.9, 1.4, 0.5, 0.8, and 1.2 μg/mL, respectively). However, penostatin D (170) exhibited moderate cytotoxicity (ED$_{50}$ = 11.0 μg/mL), which may be attributed to the absence of the cyclic conjugated enone system. Moreover, penostatin C (169) exhibited significant cytotoxicity in seven of the 36 cell lines tested with ED$_{50}$ values ranging from 1 to 2 μg/mL. Recent studies have shown that penostatins A–C (167–169) may be tyrosine phosphatase 1B (PTP1B) inhibitors, which can be used to treat type II diabetes and other associated metabolic diseases (IC$_{50}$ = 15.87, 33.65, and 0.37 μM, respectively), while sodium orthovanadate was used as a positive control with an IC$_{50}$
value of 0.65 μM [113]. The total synthesis of penostatins A, B, and F (167, 168, 172) was previously reported [114,115].

Fungal phenolic polyketides have diverse biological activities and unique structures [116]. A weak DNA topoisomerase I inhibitor, compound (176) (Figure 26), was obtained from the marine sediment-derived *P. oxalicum* HSY05 [117], whereas a racemic mixture (177–178) was obtained from the co-cultivation of marine mangrove-derived *Penicillium* sp. WC-29-5 and *Streptomyces fradiae* 007. Compounds 177–178 displayed significant cytotoxicity against H1975 cell lines (IC50 = 3.97 and 5.73 μM, respectively). Moreover, compound 178 exhibited cytotoxicity against HL-60 cells (IC50 = 3.73 μM) [118]. Using a bioinformatics tool, Marine Halogenated Compound Analysis (MeHaloCoA), three halogenated bioactive metabolites, (+)-5-chlorogriseofulvin (179) as well as griseophenones I and G (180–181), were isolated from a marine-derived *P. canescens*. They inhibited the growth of KB cells at a concentration of 0.6 μM (IR% = 49, 58, and 47%, respectively) [119]. Furthermore, one benzophenone, iso-monodictyphenone (182), and two diphenyl ether derivatives, penikellides A and B (183–184), were isolated from a mangrove endogenous fungus, *Penicillium* sp. MA-37. These three metabolites exhibited moderate brine shrimp lethality (LD50 = 25.3, 14.2, and 39.2 μM, respectively), while colchicine was used as a positive control with an LD50 value of 1.22 μM [120]. Penicillide (185), a multifunctional metabolite produced by a marine sediment-derived *Penicillium* sp. strain, was shown to be an acyl-CoA cholesterol acyltransferase (ACAT) [121], nonpeptide calpain inhibitor [122], and oxytocin antagonist [123]. Furthermore, compound 185 was found to exhibit cytotoxic, antibiotic, and plant growth inhibitory properties. Recently, two marine fungi, *P. pinophilum* (derived from a gorgonian) and *Penicillium* sp. ZLN29 (derived from a sediment), were found to produce penicillide (185) and penicillide derivatives (186–187) that exhibited potent cytotoxicity against HepG2 cell line (IC50 = 9.7 and 9.9 μM for 185–186, respectively); moreover, compound 187 showed additional cytotoxicity against Hela cell line (IC50 = 6.1 μM) [124,125]. Two anthraquinone derivatives, nidurufin (188) and averantin (189), isolated from a marine sediment-derived fungus, *P. flavidorsum* SHK1-27, were cytotoxic against K562 cell line (IC50 = 12.6 and 27.7 μM, respectively), while adriamycin was used as a positive control with an IC50 value of 1.5 μM. Nidurufin (188) was suggested to induce cell cycle arrest at the G2/M transition in a time-dependent manner [126]. The total synthesis of (±)-nidurufin (188), an aflatoxin precursor, was previously described [127].
Members of the sorbicillinoid family are hexaketide metabolites isolated from various fungi. In 2005, Zhu et al. found two sorbicillin analogues (benzoquinone (190–191)), two bisvertinolones (192–193), and three bridged bicyclic bisorbicillinoids (194–196) (Figure 27) in a marine sediment-derived fungus, *P. terrestre*. Dihydrobisvertinolone (192) and trichodimerol (196) demonstrated the strongest cytotoxic effects (IC$_{50}$ = 0.52 μM in A549, IC$_{50}$ = 0.33 μM in P388, respectively), while etoposide was used as a positive control with IC$_{50}$ values of 1.4 and 0.064 μM, respectively [128,129]. The preliminary SAR showed that an intact sorbyl side chain played a decisive role [130]. Further investigation of this strain yielded two additional chlorinated sorbicillinoids (197–198). Interestingly, the configuration at C-19 was found to largely determine the cytotoxicity, wherein chloctanspirone A (197) (R configuration) was 4-fold more active than chloctanspirone B (198) (S configuration) in HL-60 and A549 cancer cell lines [131].

Macrolides represent a well-known class of antibiotics, and curvularin (200) (Figure 28) is a heat shock protein (HSP90) inhibitor [132]. (10E, 15S)-10,11-Dehydrocurvularin (199) was isolated from
marine sponge-derived *Penicillium* sp. DRF2 and *Curvularia* sp. It exhibited significant cytotoxicity with mean IC\textsubscript{50} values ranging from 0.28 to 6 μM in 14 different solid tumors (36 tumor cell lines) [133,134]. *Penicillium* fungi are also a good source of tanzawaic acid polyketides, which exhibit antibiotic resistance [135], as well as anti-inflammatory [136] and cytotoxic activities. Tanzawaic acid P (201), isolated from a marine-derived fungus, *Penicillium* sp. CF07370, was selectively toxic to U937 cancer cells via the activation of the mitochondrial apoptotic pathway [137]. Computational ligand-protein-DNA binding analysis revealed that tanzawaic acid D (202), isolated from *P. steckii*, effectively and selectively bound to the transcription factor, forkhead box O1 (FOXO1), which can regulate epidermal growth factor receptor (EGFR) signaling, suppress cell cycle progression, and stabilize the conformation of FOXO1-DNA [138].

![Figure 28. Chemical structures of compounds 199–202.](image1)

5. Lipopeptides

Fellutamides A and B (210–211) (Figure 29) were the first cytotoxic lipopeptides isolated from fish-derived *P. fellutanum* [139]. Compounds 210 and 211 exhibited significant cytotoxicity against murine leukemia P388 (IC\textsubscript{50} = 0.2 and 0.1 μg/mL, respectively), L1210 (IC\textsubscript{50} = 0.8 and 0.7 μg/mL, respectively), and KB cells (IC\textsubscript{50} = 0.5 and 0.7 μg/mL, respectively). Recently, seven new similar lipopeptides, penicimutalides A–G (203–209) and fellutamides B and C (211–212) were isolated from a diethyl sulfate-induced mutant of the marine fungus, *P. purpurogenum* G59 [140]. They were cytotoxic against five human cancer cell lines (K562, HL-60, Hela, BGC-823, and MCF-7). Compounds 203–209 and 212 exhibited weak cytotoxicity (IR% = 10–50% at 100 μg/mL, while 5-fluorouracil as a positive control with the IR% of 37–50% at 100 μg/mL). However, fellutamide B (211) with a C-terminal aldehyde group was more potent with IC\textsubscript{50} values that ranged from 20 to 80 μg/mL, which indicated that the C-terminal aldehyde group improves the cytotoxicity.

![Figure 29. Chemical structures of compounds 203–212.](image2)
6. Miscellaneous Compounds

Polyphenol derivatives are the most abundant fungal secondary metabolites. Unsurprisingly, marine Penicillium sp. is a good source of polyphenol derivatives. Two trimeric peniphenylanes A, B (213–214) and three dimeric peniphenylanes D, F, G (215–217) (Figure 30) were isolated from the deep sea sediment-derived fungus, P. fellutanum HDN14-323. Peniphenylane D (215) displayed more potent and extensive cytotoxicity with IC50 values in the range of 9–30 μM in three cancer cell lines (Hela, HL-60, and HCT-116), while doxorubicin was used as a positive control with the IC50 values of 0.2, 0.6, and 0.2 μM, respectively [141]. The marine sediment-derived fungus, P. terrestre was found to produce several gentisyl alcohol derivatives, including trimeric terrestrol A (225) and dimeric terrestrols B–H (218–224), which were found to be cytotoxic against HL-60, MOLT-4, BEL-7402, and A549 cancer cell lines with IC50 values in the range of 5–65 μM [142]. Interestingly, the marine mangrove endogenous P. expansum 091006 yielded four novel cytotoxic phenolic bisabolane sesquiterpenoids (expansols A–C; E (226–229)) with IC50 values of 15.7, 5.4, 18.2, and 20.8 μM, respectively, in HL-60 cells. In addition, expansol B (227) showed significant cytotoxicity against A549 cells (IC50 = 1.9 μM), while etoposide was used as a positive control with IC50 values of 0.042 and 0.63 μM for two cell lines, respectively [143,144].

Figure 30. Chemical structures of compounds 230–233.

Patulin (230) (Figure 31) is a mycotoxin commonly found in rotting fruits, and is used as a potassium-uptake inhibitor or inducer of ion flux across cell membranes. An alga-derived Penicillium sp. was found to produce patulin (230) along with (+)-epiepoxydon (231), both of which exhibited extraordinary cytotoxic effects in P388 cells (IC50 = 0.06 and 0.2 μg/mL, respectively). Furthermore, (+)-epiepoxydon (231) had significant cytotoxicity against seven other cancer cell lines with IC50 values in the range of 0.3–1.5 μg/mL [111]. The isobenzofurannone derivative (232) isolated from a mangrove endophytic Penicillium sp. displayed moderate cytotoxicity against KB and KBV200 cells (IC50 = 6 and 10 μg/mL, respectively) [145], whereas the penicillic acid (233), isolated from marine-derived Penicillium strain, exhibited moderate cytotoxicity against POS1, AT6-1(murine prostatic carcinoma), and L929 (murine fibroblasts) cell lines (IC50 = 7.8, 29.4, and 12.9 μM, respectively), while doxorubicin was used as a positive control with IC50 values of 0.04–2 μM [84].
7. Conclusions

The rapid development of marine biotechnology and ever increasing needs of industrial applications resulted in the emergence of marine natural products as alternative drug sources in the early 1990s [146]. Marine-associated microorganisms are sensitive to culture conditions; therefore, strains living in extremely competitive environments tend to provide high potency leads (compound 154 in this review inhibited OVCAR-3 cell line at nanomolar concentrations). Furthermore, the activation of silent gene clusters may activate new biosynthetic pathways that produce compounds with novel structure, which provide equally valid leads (compounds 44 and 45, which have unique skeletons, had cytotoxic effects in the five cancer cell lines with IC50 values of ~10 μM). Interestingly, the halogenation of compound 31, which was completely inactive, produces compound 32, which exhibited a much greater potency (compound 32 had significant cytotoxicity in 22Rv1 cells at nanomolar levels) [147].

The genus Penicillium has been explored for antitumor leads in recent years [148]. However, the marine ecological diversity of this genus offers more opportunities for drug discovery. This review includes more than 200 cytotoxic or antitumor compounds isolated from marine Penicillium fungus and chemically synthesized analogues. Of these, the major metabolites are alkaloids, particularly diketopiperazine alkaloids and indole alkaloids (Appendix A, Table A1). Cytochalasan alkaloids, which are indole alkaloids, constitute a large class of mycotoxins that exhibit significant cytotoxicity against P388 cells (IC50 < 1 μg/mL). Furthermore, a series of diketopiperazine alkaloids, gliotoxin analogues, and roquefortine analogues with remarkable cytotoxicity at nanomolar levels are potential anticancer leads. Terpenoid metabolites appear to be more effective against cancer cell lines than steroids; in particular, compounds 99, 104, and 132 were effective at nanomolar levels. Furthermore, citrinins (chromone analogues) and their derivatives, which are polyketide mycotoxins, possess excellent cytotoxic activities. Penostatins (cytotoxic polyketides) are cytotoxic to P388 cells with IC50 values of ~1 μg/mL. With the exception of 210 and 211, lipopeptides exhibited moderate cytotoxicity. In addition, the Penicillium genus can produce polyphenolic compounds (terrestrols) with pronounced cytotoxicity.

Although our review includes most of the cytotoxic metabolites described in the literature, more compounds are yet to be identified in marine Penicillium sp. Different marine hosts and environments can also affect the biosynthesis of metabolites by endozooic fungi. Notably, over 99% of the symbiotic microorganisms cannot be cultured. Further investigations may utilize metagenome libraries of the host organisms to identify more metabolites produced by symbiotic microorganisms [149]. Additionally, further studies are needed to explore the functional mechanisms of the bioactive compounds and to optimize their production.

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Conflicts of Interest: The authors have no conflict of interest to declare.
## Appendix A

**Table A1.** Secondary metabolites from *Penicillium* strain of marine origin. Items are listed according to the metabolite numbers used in this review.

| Metabolites       | Producing Stain         | Environment Source | Type               | Cell Lines/Brine Shrimp | IC$_{50}$, LD$_{50}$, or IR (%) | Target                                                                 | References |
|-------------------|-------------------------|--------------------|--------------------|-------------------------|-------------------------------|----------------------------------------------------------------------------|------------|
| Penochalasin A (1) | *Penicillium* sp.       | Marine alga        | Indole alkaloid    | P388                    | 0.4 µg/mL                     | Cell-cycle arrest induction, membrane ruffling inhibition, and cell migration | [8]        |
| Penochalasin B (2) | *Penicillium* sp.       | Marine alga        | Indole alkaloid    | P388                    | 0.3 µg/mL                     | Cell-cycle arrest induction, membrane ruffling inhibition, and cell migration | [8]        |
| Penochalasin C (3) | *Penicillium* sp.       | Marine alga        | Indole alkaloid    | P388                    | 0.5 µg/mL                     | Cell-cycle arrest induction, membrane ruffling inhibition, and cell migration | [8]        |
| Penochalasin D (4) | *Penicillium* sp.       | Marine alga        | Indole alkaloid    | P388                    | 3.2 µg/mL                     | Cell-cycle arrest induction, membrane ruffling inhibition, and cell migration | [7]        |
| Penochalasin E (5) | *Penicillium* sp.       | Marine alga        | Indole alkaloid    | P388                    | 2.1 µg/mL                     | Cell-cycle arrest induction, membrane ruffling inhibition, and cell migration | [7]        |
| Penochalasin F (6) | *Penicillium* sp.       | Marine alga        | Indole alkaloid    | P388                    | 1.8 µg/mL                     | Cell-cycle arrest induction, membrane ruffling inhibition, and cell migration | [7]        |
| Penochalasin G (7) | *Penicillium* sp.       | Marine alga        | Indole alkaloid    | P388                    | 1.9 µg/mL                     | Cell-cycle arrest induction, membrane ruffling inhibition, and cell migration | [7]        |
| Penochalasin H (8) | *Penicillium* sp.       | Marine alga        | Indole alkaloid    | P388                    | 2.8 µg/mL                     | Cell-cycle arrest induction, membrane ruffling inhibition, and cell migration | [7]        |
| Penochalasin I (9) | *P. chrysogenum* V11    | Mangrove           | Indole alkaloid    | MDA-MB-435, SGC-7901, A549 | (7.55, 7.32, 16.13) µM       | Cell-cycle arrest induction, membrane ruffling inhibition, and cell migration | [6]        |
| Penochalasin J (10)| *P. chrysogenum* V11    | Mangrove           | Indole alkaloid    | MDA-MB-435, SGC-7901, A549 | (36.68, 37.70, 35.93) µM     | Cell-cycle arrest induction, membrane ruffling inhibition, and cell migration | [6]        |
| Chaetoglobosin A (11) | *P. chrysogenum* V11  | Mangrove           | Indole alkaloid    | P388, MDA-MB-435, SGC-7901, A549 | 0.6 µg/mL, (37.56, 7.84, 6.56) µM | Cell-cycle arrest induction, membrane ruffling inhibition, and cell migration | [6,8,9]  |
| Chaetoglobosin C (12) | *P. chrysogenum* V11  | Mangrove           | Indole alkaloid    | MDA-MB-435, SGC-7901, A549 | (19.97, 15.36, 17.82) µM     | Cell-cycle arrest induction, membrane ruffling inhibition, and cell migration | [6]        |
| Chaetoglobosin E (13) | *P. chrysogenum* V11  | Mangrove           | Indole alkaloid    | MDA-MB-435, SGC-7901, A549 | 36.63 µM                     | Cell-cycle arrest induction, membrane ruffling inhibition, and cell migration | [6]        |
| Chaetoglobosin F (14) | *P. chrysogenum* V11  | Mangrove           | Indole alkaloid    | P388, MDA-MB-435, SGC-7901, A549 | 0.9 µg/mL, (37.77, 26.53, 27.72) µM | Cell-cycle arrest induction, membrane ruffling inhibition, and cell migration | [6,8]  |
| Chaetoglobosin G (15) | *P. chrysogenum* V11  | Mangrove           | Indole alkaloid    | MDA-MB-435, SGC-7901, A549 | (38.77, 25.86, 27.63) µM     | Cell-cycle arrest induction, membrane ruffling inhibition, and cell migration | [6]        |
| Chaetoglobosin O (16) | *Penicillium* sp.       | Marine alga        | Indole alkaloid    | P388                    | 2.4 µg/mL                     | Cell-cycle arrest induction, membrane ruffling inhibition, and cell migration | [7]        |
| Cytophlobosin C (17) | *P. chrysogenum* V11  | Mangrove           | Indole alkaloid    | MDA-MB-435, SGC-7901, A549 | (12.58, 8.15, 3.35) µM       | Cell-cycle arrest induction, membrane ruffling inhibition, and cell migration | [6]        |
| 18                | *Penicillium* sp. JMF034| Deep sea sediment  | Diketopiperazine   | P388                    | 3.4 µM                        | Cell-cycle arrest induction, membrane ruffling inhibition, and cell migration | [12]      |
Table A1. Cont.

| Metabolites                              | Producing Stain          | Environment Source   | Type              | Cell Lines/Brine Shrimp | IC$_{50}$, LD$_{50}$, or IR (%) | Target                                | References |
|------------------------------------------|--------------------------|----------------------|-------------------|-------------------------|----------------------------------|---------------------------------------|------------|
|                                          | Penicillium sp. JMF034   | Deep sea sediment    | Diketopiperazine  | P388                    | 0.058 µM (IC$_{50} = 55$ µM)     | HMT G9a (IC$_{30} = 58$ µM)           | [12]       |
|                                          | 20 Penicillium sp. JMF034| Deep sea sediment    | Diketopiperazine  | P388                    | 0.11 µM                          | HMT G9a (IC$_{30} = 2.6$ µM)          | [12]       |
|                                          | 21 Penicillium sp. JMF034| Deep sea sediment    | Diketopiperazine  | P388                    | 0.11 µM                          | HMT G9a (IC$_{30} = 2.6$ µM)          | [12]       |
|                                          | 22 Penicillium sp. JMF034| Deep sea sediment    | Diketopiperazine  | P388                    | 0.056 µM                          | HMT G9a (IC$_{30} = 2.6$ µM)          | [12]       |
| Gliotoxin (23)                           | Penicillium sp. JMF034   | Deep sea sediment    | Diketopiperazine  | P388                    | 0.024 µM                          | HMT G9a (IC$_{30} = 2.6$ µM)          | [12,13]   |
| Gliotoxin G (24)                         | Penicillium sp. JMF034   | Deep sea sediment    | Diketopiperazine  | P388                    | 0.02 µM (0.664, 0.661) µM          | HMT G9a (IC$_{30} = 2.1$ µM)          | [12,14]   |
| Brozazine A (25)                         | P. brocae MA-231         | Mangrove             | Diketopiperazine  | Du145, Hela, HepG2, MCF-7, NCI-H460, SGC-7901, SW1990, SW480, U251 | (4.2, 6.8, 6.4, 5.5, 4.9, 2.6, 6.0, 2.0, 5.2) µM | [16] |
| Brozazine B (26)                         | P. brocae MA-231         | Mangrove             | Diketopiperazine  | Du145, Hela, HepG2, MCF-7, NCI-H460, SGC-7901, SW1990, SW480, U251 | (3.6, 5.3, 5.5, 6.1, 4.0, 2.4, 6.4, 1.2, 3.5) µM | [16] |
| Brozazine E (29)                         | P. brocae MA-231         | Mangrove             | Diketopiperazine  | Du145, Hela, HepG2, MCF-7, NCI-H460, SGC-7901, SW1990, SW480, U251 | (11.2, 4.3, 5.6, 9.0, 12.4, 3.3, 2.1, 6.1) µM | [16] |
| Brozazine F (30)                         | P. brocae MA-231         | Mangrove             | Diketopiperazine  | Du145, Hela, HepG2, MCF-7, NCI-H460, SGC-7901, SW1990, SW480, U251 | (1.7, 6.9, 2.9, 3.0, 0.89, 8.0, 5.9, 5.3) µM | [16] |
| N-methylpretrichodermaide B/adametizines A (32) | Penicillium sp. | Marine sponge/sediment/alga | Diketopiperazine | Artemia salina | 4.8 µM                          | [17–19] |

The table continues with more entries for various metabolites and their characteristics.
| Metabolites          | Producing Stain | Environment Source | Type          | Cell Lines/Brine Shrimp | IC$_{50}$, LD$_{50}$, or IR (%) | Target                                                                                      | References |
|---------------------|-----------------|--------------------|---------------|------------------------|---------------------------------|---------------------------------------------------------------------------------------------|------------|
| Roquefortine C (33) | *Penicillium* sp.| Deep sea sediment  | Diketopiperazine | A549, HL-60, BEL-7402, MOLT-4 | (14.0, 33.6, 13.0, 21.2) µM | Activate P-glycoprotein and inhibit P450-3A and other haemoproteins                         | [20,22]   |
| Roquefortine F (34) | *Penicillium* sp.| Deep sea sediment  | Diketopiperazine | A549, HL-60            | (42.5, 36.6) µM               |                                                                                             | [22]       |
| Roquefortine G (35) | *Penicillium* sp.| Deep sea sediment  | Diketopiperazine | A549, HL-60            | (14.0, 33.6, 13.0, 21.2) µM |                                                                                             | [22]       |
| Meleagrin (38)      | *Penicillium* sp.| Deep sea sediment  | Indole alkaloid  | A549, HL-60 Hepg2, NCI-H460, Hela, DU145, MDA-MB-231, | (19.9, 7.4) µM (12.0, 22.0, 20.0, 11.0, 5.0) µg/mL | Arrest the cell cycle through G$_2$/M phase Inhibitor of tubulin polymerization             | [21–23]   |
| Meleagrin B (39)    | *Penicillium* sp.| Deep sea sediment  | Indole alkaloid  | A549, HL-60 Hepg2, NCI-H460, Hela, DU145, MDA-MB-231, | (2.7, 6.7, 1.8, 2.9) µM       |                                                                                             | [21,22]   |
| Meleagrin C (40)    | *Penicillium* sp.| Deep sea sediment  | Indole alkaloid  | A549, BEL-7402, MOLT-4 | (9.9, 10.0, 4.7) µM            |                                                                                             | [22]       |
| Meleagrin D (41)    | *Penicillium* sp.| Deep sea sediment  | Indole alkaloid  | A549                   | 32.2 µM                        |                                                                                             | [21]       |
| Meleagrin E (42)    | *Penicillium* sp.| Deep sea sediment  | Indole alkaloid  | A549                   | 55.9 µM                        |                                                                                             | [21]       |
| Penicimutanin (43)  | Mutant *P. purpurogenum* G59 | Marine soil        | Diketopiperazine | K562, Hela, MCF-7     | IR% (100 µg/mL): 22.6%, 17.9%, 26.3% |                                                                                             | [24]       |
| Penicimutanin A (44) | Mutant *P. purpurogenum* G59 | Marine soil        | Diketopiperazine | K562, HL-60, Hela, BGC-823, MCF-7 | (11.4, 5.4, 9.5, 8.0, 5.4) µM |                                                                                             | [24]       |
| Penicimutanin B (45) | Mutant *P. purpurogenum* G59 | Marine soil        | Diketopiperazine | K562, HL-60, Hela, BGC-823, MCF-7 | (19.9, 12.1, 17.7, 16.6, 8.0) µM |                                                                                             | [24]       |
| Fructigenine A (46) | Mutant *P. purpurogenum* G59 | Marine soil        | Diketopiperazine | K562, Hela, MCF-7, BGC-823 | IR% (100 µg/mL): 20.8%, 55.3%, 65.6%, 34.8% |                                                                                             | [24,25]   |
| 11,11′-dideoxyverticillin A (49) | *Penicillium* sp. | Marine alga        | Diketopiperazine | HCT-116               | 30 ng/mL | Induce G$_2$/M arrest through p38 MAPK pathway; Epidermal growth factor receptor tyrosine kinase inhibitor | [26,30,31] |
| Metabolites          | Producing Stain          | Environment Source | Type           | Cell Lines/Brine Shrimp | IC<sub>50</sub>, LD<sub>50</sub>, or IR (%) | Target                        | References |
|----------------------|--------------------------|--------------------|----------------|-------------------------|------------------------------------------|--------------------------------|------------|
| 11'-deoxyverticillin A (50) | *Penicillium* sp.       | Marine alga        | Diketopiperazine | MCF, MDA-MB-231         | IC<sub>50</sub> 30 ng/mL               |                                | [28]       |
| Penitrem A (51)      | *P. commune* isolate GS20 | Sponge/Sediment    | Indole alkaloid  | MCF-7, MDA-MB-231       | IC<sub>50</sub> 11.9, 9.8 µM, LD<sub>50</sub> 8.7 µM, IR% (15 µM) > 75% | BK channel inhibitor          | [34]       |
| Penitrem B (52)      | *P. commune* isolate GS20 | Sponge/Sediment    | Indole alkaloid  | MCF-7, MDA-MB-231       | IC<sub>50</sub> 5.5, 13.7 µM, LD<sub>50</sub> 10.3 µM |                                | [34]       |
| Penitrem D (53)      | *P. commune* isolate GS20 | Sponge/Sediment    | Indole alkaloid  | MCF-7, MDA-MB-231       | IC<sub>50</sub> 8.3, 29.7 µM, LD<sub>50</sub> 9.2 µM |                                | [34]       |
| Penitrem E (54)      | *P. commune* isolate GS20 | Sponge/Sediment    | Indole alkaloid  | MCF-7, MDA-MB-231       | IC<sub>50</sub> 17.5, 25.4 µM, LD<sub>50</sub> 20.3 µM |                                | [34]       |
| Penitrem F (55)      | *P. commune* isolate GS20 | Sponge/Sediment    | Indole alkaloid  | MCF-7, MDA-MB-231       | IC<sub>50</sub> 15.0, 13.8 µM, LD<sub>50</sub> 35.0 µM |                                | [34]       |
| 6-bromopenitrem B (56) | *P. commune* isolate GS20 | Sponge/Sediment    | Indole alkaloid  | MCF-7, MDA-MB-231       | IC<sub>50</sub> 19.3, 18.8 µM, LD<sub>50</sub> 30.3 µM, IR% (15 µM) > 40% |                                | [34]       |
| 6-bromopenitrem E (57) | *P. commune* isolate GS20 | Sponge/Sediment    | Indole alkaloid  | MCF-7, MDA-MB-231       | IC<sub>50</sub> 16.7, 8.5 µM, LD<sub>50</sub> 9.6 µM | BK channel inhibitor          | [34]       |
| Emnidole SB (59)     | *P. commune* isolate GS20 | Sponge/Sediment    | Indole alkaloid  | MCF-7, MDA-MB-231       | IC<sub>50</sub> 10.1, 21.3 µM, LD<sub>50</sub> 19.0 µM |                                | [34,37]   |
| Metabolites         | Producing Stain                  | Environment Source          | Type               | Cell Lines/Brine Shrimp               | IC<sub>50</sub>, LD<sub>50</sub>, or IR (%)                      | Target              | References |
|---------------------|----------------------------------|-----------------------------|--------------------|--------------------------------------|---------------------------------------------------------------|---------------------|------------|
| Communesin A (60)   | *Penicillium* sp.                | Marine alga/Sediment        | Indole alkaloid    | P388                                 | 3.5 µg/mL                                                     |                    | [38,40]   |
| Communesin B (61)   | *Penicillium* sp.                | Marine alga/Sponge/Sediment | Indole alkaloid    | P388, U-937, THP-1, NAMALWA, MOLT-3, SUP-B15 | (0.45, 10.4, 11.4, 9.9, 8.1, 7.2) µg/mL                      |                    | [38–40]   |
| Communesin C (62)   | *Penicillium* sp.                | Marine sponge               | Indole alkaloid    | U-937, THP-1, NAMALWA, MOLT-3, SUP-B15 | (11.3, 13.1, 8.2, 8.6, 10.8) µg/mL                             |                    | [39]      |
| Communesin D (63)   | *Penicillium* sp.                | Marine sponge               | Indole alkaloid    | U-937, THP-1, NAMALWA, MOLT-3, SUP-B15 | (13.1, 16.2, 14.6, 9.9, 9.0) µg/mL                             |                    | [39]      |
| Penioxamide (64)    | *P. oxalicum* EN-201             | Mangrove                    | Indole alkaloid    | A. salina                           | 5.6 µM                                                       |                    | [42]      |
|                    | *P. brefeldianum* SD-273         | Marine sediment             | Indole alkaloid    | A. salina                           | 9.4 µM                                                       |                    | [43]      |
| Penipaline B (66)   | *P. paneum* SD-44                | Marine sediment             | Indole alkaloid    | A549, HCT-116                        | (20.44, 14.88) µM                                             |                    | [44]      |
| Penipaline C (67)   | *P. paneum* SD-44                | Marine sediment             | Indole alkaloid    | A549, HCT-116                        | (21.54, 18.54) µM                                             |                    | [44]      |
| Terretrione A (68)  | *P. vinaceum*                    | Marine sponge               | 1,4-diazepane alkaloid | MDA-MB-231                       | 17.7 µM                                                      |                    | [45]      |
| Terretrione C (69)  | *Penicillium* sp. CYE-87         | Marine tunicate             | 1,4-diazepane alkaloid | MDA-MB-231                       | 17.6 µM                                                      |                    | [46]      |
| Terretrione D (70)  | *Penicillium* sp. CYE-87         | Marine tunicate             | 1,4-diazepane alkaloid | MDA-MB-231                       | 16.5 µM                                                      |                    | [46]      |
| Penicillenol A1 (71)| *Penicillium* sp. GQ-7/*P. citrinum* | Mangrove/Marine sediment      | Pyrrolidinone alkaloid | A-375, HL-60, A549, BEL-7402, P388 | 3.2 µg/mL (0.76, 23.8, 13.03, 8.85) µM                       |                    | [47,49]   |
| Penicillenol A2 (72)| *Penicillium* sp. GQ-7/*P. citrinum* | Mangrove/Marine sediment      | Pyrrolidinone alkaloid | A-375, HL-60                       | 13.8 µg/mL                                                   |                    | [47,49]   |
| Penicillenol B1 (73)| *Penicillium* sp. GQ-7/*P. citrinum* | Mangrove/Marine sediment      | Pyrrolidinone alkaloid | A-375, HL-60                       | 2.8 µg/mL                                                   |                    | [47,49]   |
| Penicillenol B2 (74)| *Penicillium* sp. GQ-7/*P. citrinum* | Mangrove/Marine sediment      | Pyrrolidinone alkaloid | A-375, HL-60                       | 0.97 µg/mL                                                   |                    | [47,49]   |
| Penicillenol D1 (75)| *P. citrinum*                    | Marine sediment             | Pyrrolidinone alkaloid | A549, HL-60                      | (17.2, 18.5) µg/mL                                          |                    | [48]      |
| Penicillenol D2 (76)| *P. citrinum*                    | Marine sediment             | Pyrrolidinone alkaloid | A549, HL-60                      | (12.1, 14.5) µg/mL                                          |                    | [48]      |
| Metabolites                | Producing Stain | Environment Source | Type                  | Cell Lines/Brine Shrimp | IC$_{50}$, LD$_{50}$, or IR (%) | Target                              | References |
|---------------------------|----------------|-------------------|-----------------------|-------------------------|--------------------------------|----------------------------------|------------|
| Penitrinine A (77)        | *P. citrinum*  | Marine sediment   | Pyrrolidinone alkaloid| A-375, SPC-A1, HGC-27   | (20.12, 28.67, 29.49) µM        | Upregulate Bax, downregulate Bcl-2, suppress MMP-9 and TIMP-1 | [50]       |
| 78                        | *P. janczewskii*| Sea water         | Quinolinone           | MDA-MB-231, DU-145, SKOV-3, HT-29, A549, CAKI-1, SK-MEL-2, K562 | IR % (10 µg/mL) = 20–50%        |                                   | [52]       |
| 79                        | *P. janczewskii*| Sea water         | Quinolinone           | MDA-MB-231, DU-145, SKOV-3, HT-29, A549, CAKI-1, SK-MEL-2, K562 | IR % (10 µg/mL) = 30–90%        |                                   | [52]       |
| 80                        | *P. janczewskii*| Sea water         | Quinolinone           | MDA-MB-231, DU-145, SKOV-3, HT-29 | IR % (10 µg/mL) = 91.6%, 69.2%, 79.8%, 96.0% |                                   | [52]       |
| 81                        | *Penicillium* sp. ghq208/*Penicillium* sp. | Marine sediment/Mangrove | Quinolinone           | 95-D, HepG2             | (0.57, 6.5) µg/mL               |                                   | [53,54]    |
| 82                        | *Penicillium* sp. ghq208 | Marine sediment   | Quinolinone           | HepG2                   | 13.2 µM                         |                                   | [55]       |
| 83                        | *P. commune* SD-118 | Deep sea sediment | Quinazolinone         | SW1990                  | 20 µg/mL                        |                                   | [23]       |
| 84                        | *P. chrysogenum* EN-118 | Marine alga      | Quinazolinone         | DU145, A549, Hela       | 8 µg/mL                         |                                   | [56]       |
| 85                        | *P. oxalicum* 0312F1 | Marine (not clear) | Quinazolinone         | SGC-7901, BEL-7404     | IR % (200 µg/mL) = 30–40%       |                                   | [57]       |
| Penipacid A (86)           | *P. paneum* SD-44 | Deep sea sediment | Amidine alkaloid      | RKO                     | 8.4 µM                          |                                   | [58]       |
| Penipacid E (87)           | *P. paneum* SD-44 | Deep sea sediment | Amidine alkaloid      | RKO                     | 9.7 µM                          |                                   | [58]       |
| 88                        | *P. paneum* SD-44 | Deep sea sediment | Imine alkaloid        | Hela                    | 6.6 µM                          |                                   | [58]       |
| Penipanoid A (89)          | *P. paneum* SD-44 | Deep sea sediment | Triazole alkaloid     | SMMC-7721               | 54.2 µM                         |                                   | [58]       |
| Bis-sclerotiorammin (90)   | *Penicillium* 303# | Mangrove          | Azaphilone alkaloid   | MDA-MB-231              | 7.13 µM                         |                                   | [59]       |
| Sorbicillactone (91)       | *P. chrysogenum* | Marine sponge     | Miscellaneous Alkaloid | LS178Y                  | 2.2 µg/mL                       | Selective anti-leukemic           | [60]       |
| Metabolites                  | Producing Stain | Environment Source | Type                | Cell Lines/Brine Shrimp | IC_{50}, LD_{50}, or IR (%) | Target                                                                 | References |
|------------------------------|-----------------|--------------------|---------------------|-------------------------|-----------------------------|------------------------------------------------------------------------|------------|
| Brocaeloid B (92)            | *P. brocae*     | Mangrove           | Miscellaneous Alkaloid | *A. salina*             | 36.7 μM                     |                                                                                                                                 | [62]       |
| Varitatin (93)               | Mutant *P. variabile* | Mangrove           | Amide alkaloid       | HCT-116                 | 2.8 μM                      | IR%(1 μM) = 50% and 40% (PDGFR-β and ErbB4)                             | [63]       |
| 18-hydroxydecaturin B (94)   | *P. oxalicum*   | EN-201             | Pyridinyl-α-pyrene alkaloid | *A. salina*             | 2.3 μM                      | Inhibit MEK/ERK pathway and activate class II PI3K/Beclin 1 pathway     | [42]       |
| Xantocillin X (95)           | *P. commune*    | SD-118             | Isocyanide alkaloid  | MCF-7, HepG2, NCI-H460, Hela, DU145, MDA-MB-231 | (12, 7, 10, 10, 8) μg/mL   | Inhibit MEK/ERK pathway and activate class II PI3K/Beclin 1 pathway     | [23, 67]  |
| 96 Penicillium sp. PR19 N-1  | Marine sludge   | Sesquiterpene      | HL-60, A549          | (45.8, 82.8) μM         | NCI-H446                    | 5.0 μM                                                                 | [70]       |
| 97 Penicillium sp. PR19 N-1  | Marine sludge   | Sesquiterpene      | HL-60, A549          | (28.3, 5.2) μM          | NCI-H446                    | 5.0 μM                                                                 | [70]       |
| 99 Penicillium sp. PR19 N-1  | Marine sludge   | Sesquiterpene      | HL-60, A549          | (11.8, 12.2) μM         | NCI-H446                    | 5.0 μM                                                                 | [71]       |
| 100 Penicillium sp. BL 27-2  | Sea mud         | Sesquiterpene      | P388, A549, HL-60, BEL-7402 | (0.073, 0.096, 0.065, 4.59) μM | NCI-H446                    | 5.0 μM                                                                 | [72]       |
| Sporogen-AO 1 (100)          | Penicillium sp. | BL 27-2            | Sea mud              | P388, A549, HL-60, BEL-7402 | (10.1, 8.81, 10.4, 5.7) μM | NCI-H446                    | 5.0 μM                                                                 | [72]       |
| 101 Penicillium sp. BL 27-2  | Sea mud         | Sesquiterpene      | P388, A549, HL-60, BEL-7402 | (8.71, 3.51, 7.75, 11.8) μM | NCI-H446                    | 5.0 μM                                                                 | [72]       |
| Adametacorenol B (102)       | *P. adametzioides* | AS-53              | Marine sponge        | NCI-H446                | 5.0 μM                      | NCI-H446                    | 5.0 μM                                                                 | [17]       |
| Conidiogenone B (103)        | Penicillium sp. | Deep sea sediment  | Diterpene           | A549, HL-60             | (40.3, 28.2) μM             | NCI-H446                    | 5.0 μM                                                                 | [22]       |
| Conidiogenone C (104)        | Penicillium sp. | Deep sea sediment  | Diterpene           | A549, HL-60, BEL-7402   | (0.038, 0.97) μM            | NCI-H446                    | 5.0 μM                                                                 | [22]       |
| Conidiogenone D (105)        | Penicillium sp. | Deep sea sediment  | Diterpene           | A549, HL-60, BEL-7402   | (9.3, 5.3, 11.7, 21.1) μM   | NCI-H446                    | 5.0 μM                                                                 | [22]       |
| Conidiogenone E (106)        | Penicillium sp. | Deep sea sediment  | Diterpene           | A549, HL-60, MOLT-4     | (15.1, 8.5, 25.8) μM        | NCI-H446                    | 5.0 μM                                                                 | [22]       |
| Conidiogenone F (107)        | Penicillium sp. | Deep sea sediment  | Diterpene           | A549, HL-60, BEL-7402   | (42.2, 17.8, 17.1) μM       | NCI-H446                    | 5.0 μM                                                                 | [22]       |
Table A1. Cont.

| Metabolites                  | Producing Stain          | Environment Source | Type       | Cell Lines/Brine Shrimp                     | IC$_{50}$, LD$_{50}$, or IR (%)          | Target References |
|------------------------------|--------------------------|--------------------|------------|--------------------------------------------|-------------------------------------------|-------------------|
| Conidiogenone G (108)        | *Penicillium* sp.        | Deep sea sediment  | Diterpene  | A549, HL-60, BEL-7402, MOLT-4              | (8.3, 1.1, 43.2, 4.7) µM                  | [22]              |
| Brevione I (109)             | *Penicillium* sp.        | Deep sea sediment  | Diterpene  | MCF-7                                      | 7.44 µM                                   | [73]              |
| Brevione A (110)             | *Penicillium* sp.        | Deep sea sediment  | Diterpene  | MCF-7                                      | 28.4 µM                                   | [73]              |
| Penicisteroid A (111)        | *P. chrysogenum* QEN-24S| Marine alga        | Steroid    | Hela, SW1990, NCI-H460                    | (15, 31, 40) µg/mL                       | [74]              |
| 112                          | *Penicillium* sp.        | Marine moss        | Steroid    | HepG2                                      | 10.4 µg/mL                                | [75]              |
| 113                          | *Penicillium* sp.        | Marine moss        | Steroid    | HepG2                                      | 15.6 µg/mL                                | [75]              |
| 114                          | *Penicillium* sp.        | Marine moss        | Steroid    | HepG2                                      | 20.7 µg/mL                                | [75]              |
| 115                          | *Penicillium* sp.        | Marine moss        | Steroid    | HepG2                                      | 16.8 µg/mL                                | [75]              |
| 116                          | *Penicillium* sp.        | Marine moss        | Steroid    | HepG2                                      | 21.3 µg/mL                                | [75]              |
| 117                          | *P. stoloniferum* QY2-10 | Sea squirt         | Steroid    | P388                                       | 4.07 µM                                   | [76]              |
| 118                          | *Penicillium* sp.        | Marine sponge      | Steroid    | K562                                       | 5.54 µM                                   | [77]              |
| 119                          | *Penicillium* sp.        | Marine sponge      | Steroid    | K562                                       | 4.38 µM                                   | [77]              |
| Dankasterone A (120)         | *Penicillium* sp.        | Marine sponge      | Steroid    | HL-60, Hela, K562                          | (0.78, 4.11, 7.57) µM                     | [77]              |
| Dankasterone B (121)         | *Penicillium* sp.        | Marine sponge      | Steroid    | HL-60, Hela, K562                          | (3.25, 4.74, 7.89) µM                     | [77]              |
| 7-deacetoxyyanuthone (122)   | *Penicillium* sp.        | Marine (not clear) | Meroterpene| A549, SKOV-3, SKMEL-2, XF498, HCT-15       | (7.74, 6.35, 3.86, 10.04, 10.07) µg/mL    | [79]              |
| Farnesyibenzenediol (123)    | *Penicillium* sp.        | Marine (not clear) | Meroterpene| A549, SKOV-3, SKMEL-2, XF498, HCT-15       | (4.73, 5.31, 4.80, 5.94, 6.11) µg/mL      | [79]              |
| Farnesylquinone (124)        | *Penicillium* sp.        | Marine (not clear) | Meroterpene| A549, SKOV-3, SKMEL-2, XF498, HCT-15       | (25.44, 37.29, 18.41, 38.07, 42.56) µg/mL| [79]              |
| Penicillone A (125)          | *Penicillium* sp. F11    | Marine (not clear) | Meroterpene| HT1080, C6w2                               | (45.8, 46.2) µM                           | [80]              |
| Phenylpyropene E (126)       | *P. concentricum* ZLQ-69 | Sea water          | Sesquiterpene| MGC-803                                    | 19.1 µM                                   | [81]              |
| Metabolites         | Producing Stain       | Environment Source | Type           | Cell Lines/Brine Shrimp | IC<sub>50</sub>, LD<sub>50</sub>, or IR (%) | Target                                      | References |
|---------------------|-----------------------|--------------------|----------------|-------------------------|---------------------------------------------|---------------------------------------------|------------|
| Phenylpyropene F    | *P. concentricum* ZLQ-69 | Sea water          | Sesquiterpene  | MGC-803                 | 13.6 µM                                     |                                             | [81]       |
| Penicillipyrone A   | *Penicillium* sp. F446 | Marine sediment    | Sesquiterpene  | K562, A549              | (28, 15) µM                                 |                                             | [82]       |
| Penicillipyrone B   | *Penicillium* sp. F446 | Marine sediment    | Sesquiterpene  | K562, A549              | (50, 17) µM                                 |                                             | [82]       |
| 130 Penicillium 303# | Mangrove              | Meroterpene        |                | MDA-MB-435, HepG2, HCT-116, A549 | (34.25, 24.56, 33.72, 37.82) µg/mL          |                                             | [59]       |
| 131 Penicillium 303# | Mangrove              | Meroterpene        |                | MDA-MB-435, HepG2, HCT-116, A549 | (31.32, 23.87, 29.19, 34.08) µg/mL          |                                             | [59]       |
| Ligerin (132)       | *Penicillium* sp.     | Sea water          | Merosesquiterpene | POS1, SaOS2, MG63     | (117/78, 137, 1459) nM                      |                                             | [84,85]    |
| Oxalicumone D       | *P. oxalicum* SCSGAF 0023 | Marine gorgonian   | Chromone       | BGC823, MOLT-4          | (10.10, 5.74) µM                            |                                             | [87]       |
| Oxalicumone E       | *P. oxalicum* SCSGAF 0023 | Marine gorgonian   | Chromone       | H1975, U937, K5652, BGC823, MOLT-4, MCF-7, HL-60, Huh-7 | (5.45, 4.16, 8.80, 1.96, 1.36, 4.32, 2.96, 6.33) µM |                                             | [87]       |
| Oxalicumone A       | *P. oxalicum* SCSGAF 0023 | Marine gorgonian   | Chromone       | H1975, U937, K5652, BGC823, MOLT-4, MCF-7, HL-60, Huh-7, A375, A549, Hela, HepG2, SW-620, L-02 | (10.38, 2.35, 4.53, 4.89, 0.30, 11.30, 2.55, 9.49, 11.7, 41.9, 46.2, 77.8, 22.6, 99.0) µM |                                             | [87,88]    |
| Oxalicumone B       | *P. oxalicum* SCSGAF 0023 | Marine gorgonian   | Chromone       | U937, MOLT-4, HL-60, A375, Hela, SW-620 | (5.00, 2.30, 6.41, 27.8, 60.9, 40.6) µM |                                             | [87,88]    |
| Chromosulfine       | Mutant *P. purpurogenum* G59 | Marine (not clear) | Chromone       | K562, HL-60, BGC-823, Hela, MCF-7 | (60.8, 16.7, 73.8, 75.4, 59.2) µM |                                             | [91]       |
| Secalonic acid F    | *Penicillium* sp.     | Deep sea sediment  | Xanthone       | HL-60                   |                                             | Modulate Rho GDP dissociation inhibitor 2 Activate caspase 3 and caspase 9 | [92,93]    |
| Penimethavone A     | *P. chrysogenum*      | Marine gorgonian   | Flavone        | Hela, rhabdomyosarcoma  | (8.41, 8.18) µM                            |                                             | [94]       |
| Bipenicillisorin    | *P. chrysogenum* SCSIO 41001 | Deep sea sediment  | Coumarin       | K562, A549, Huh-7      | (6.78, 6.94, 2.59) µM |                                             | [95]       |
Table A1. Cont.

| Metabolites              | Producing Stain | Environment Source | Type                  | Cell Lines/Brine Shrimp | IC_{50}, LD_{50}, or IR (%) | Target                                                                 | References |
|--------------------------|-----------------|--------------------|-----------------------|-------------------------|-----------------------------|------------------------------------------------------------------------|------------|
| Monocerin (149)          | *Penicillium* sp.| Marine sponge      | Coumarin              | L5178Y                  | 8.4 µM                      |                                                                        | [96]       |
|                          |                 |                    |                       |                         |                             |                                                                        |            |
| 150                      | *Penicillium* sp.| Mangrove           | Coumarin              | KB, KBv200              | (5, 10) µg/mL               | Inhibit respiration complex III                                        | [97]       |
| Citrinin (151)           | *Penicillium* sp| Marine sponge      | Azaphilone polyketide | KB, KBv200              | (5, 10) µg/mL               | Inhibit respiration complex III                                        | [99,101]  |
| Penicitrinol L (152)     | *P. citrinum*   | Marine sediment    | Azaphilone polyketide | SW-620                  | 25.6 µM                     |                                                                        | [48]       |
| Penicitrinol M (153)     | *P. citrinum*   | Marine sediment    | Azaphilone polyketide | SW-620                  | 20.9 µM                     |                                                                        | [48]       |
| Berkelic acid (154)      | *Penicillium* sp.| Acid mine lake     | Azaphilone polyketide | OVCAR-3 (in NCI60)      | 91 nM                       | Inhibit MMP-3 (IC_{50} = 1.87 µM) Inhibit caspase 1 (IC_{50} = 98 µM) | [102]      |
| Sargassopenilline C (155)| *P. thomii*     | Marine alga        | Azaphilone polyketide |                         |                             | Inhibit the oncogenic nuclear factor AP-1 (IC_{50} = 15 µM)            | [104]      |
| Sculezonone A (156)      | *Penicillium* sp.| Marine sponge      | Azaphilone polyketide |                         |                             | Inhibit both DNA polymerases (α and β)                                 | [105]      |
| Sculezonone B (157)      | *Penicillium* sp.| Marine sponge      | Azaphilone polyketide |                         |                             | Inhibit both DNA polymerases (α and β)                                 | [105]      |
| Dicitrinone B (158)      | *P. citrinum*   | Marine sediment    | Azaphilone polyketide |                         |                             | Induce apoptosis through ROS-related caspase pathway                   | [106]      |
| Perinadine A (159)       | *P. citrinum*   | Marine fish        | Azaphilone polyketide | L1210                   | 20 µg/mL                    |                                                                        | [107]      |
| Herqueiazole (160)       | *Penicillium* sp| Marine sediment    | Azaphilone polyketide | A549                    | 67.3 µM                     |                                                                        | [108]      |
| Comazaphilone D (161)    | *P. commune* QSD-17 | Marine sediment | Azaphilone polyketide | SW1990                  | 51 µM                       |                                                                        | [109]      |
| Comazaphilone E (162)    | *P. commune* QSD-17 | Marine sediment | Azaphilone polyketide | SW1990                  | 26 µM                       |                                                                        | [109]      |
### Table A1. Cont.

| Metabolites        | Producing Stain          | Environment Source | Type                     | Cell Lines/Brine Shrimp       | IC<sub>50</sub>, LD<sub>50</sub>, or IR (%) | Target                                                                 | References |
|--------------------|--------------------------|--------------------|--------------------------|-----------------------------|------------------------------------------|-----------------------------------------------------------|------------|
| Comazaphilone F    | *P. commune* QSD-17      | Marine sediment    | Azaphilone polyketide    | SW1990                      | 53 µM                                    | Inhibit the mammalian DNA polymerases A, B, Y family       | [109]      |
| Pinophilin A       | *P. pinophilum* Hedgcok  | Marine seaweed     | Azaphilone polyketide    | A549, BALL-1, HCT-116, Hela, NUGC-3 | (52.5, 50.2, 51.3, 55.6, 54.7) µM       | Inhibit the mammalian DNA polymerases A, B, Y family       | [110]      |
| Pinophilin B       | *P. pinophilum* Hedgcok  | Marine seaweed     | Azaphilone polyketide    | A549, BALL-1, HCT-116, Hela, NUGC-3 | (93.1, 90.4, 92.5, 99.0, 96.8) µM       | Inhibit the mammalian DNA polymerases A, B, Y family       | [110]      |
| Sch 725680 (166)   | *P. pinophilum* Hedgcok  | Marine seaweed     | Azaphilone polyketide    | A549, BALL-1, HCT-116, Hela, NUGC-3 | (65.7, 62.0, 64.6, 68.8, 66.4) µM       | Inhibit the mammalian DNA polymerases A, B, Y family       | [110]      |
| Penostatin A       | *Penicillium sp.* OUPS-79 | Marine alga        | Polyketide               | P388                         | 0.8 µg/mL                                | PTP1B inhibitor (IC<sub>50</sub> = 15.87 µM)                 | [111,113] |
| Penostatin B       | *Penicillium sp.* OUPS-79 | Marine alga        | Polyketide               | P388                         | 1.2 µg/mL                                | PTP1B inhibitor (IC<sub>50</sub> = 33.65 µM)                 | [111,113] |
| Penostatin C       | *Penicillium sp.* OUPS-79 | Marine alga        | Polyketide               | P388, BSY-1, MCF-7, HCC2998, NCI-H522, DMS114, OVCAR-3, MKN1 | (1.0, 2.0, 1.6, 2.0, 2.5, 1.9, 2.4, 1.7) µg/mL | PTP1B inhibitor (IC<sub>50</sub> = 0.37 µM)                 | [111,113] |
| Penostatin D       | *Penicillium sp.* OUPS-79 | Marine alga        | Polyketide               | P388                         | 11.0 µg/mL                               |                                                           | [111]      |
| Penostatin E       | *Penicillium sp.* OUPS-79 | Marine alga        | Polyketide               | P388                         | 0.9 µg/mL                                |                                                           | [111]      |
| Penostatin F       | *Penicillium sp.* OUPS-79 | Marine alga        | Polyketide               | P388                         | 1.4 µg/mL                                |                                                           | [112]      |
| Penostatin G       | *Penicillium sp.* OUPS-79 | Marine alga        | Polyketide               | P388                         | 0.5 µg/mL                                |                                                           | [112]      |
| Penostatin H       | *Penicillium sp.* OUPS-79 | Marine alga        | Polyketide               | P388                         | 0.8 µg/mL                                |                                                           | [112]      |
| Penostatin I       | *Penicillium sp.* OUPS-79 | Marine alga        | Polyketide               | P388                         | 1.2 µg/mL                                |                                                           | [112]      |
Table A1. Cont.

| Metabolites | Producing Stain | Environment Source | Type | Cell Lines/Brine Shrimp | IC$_{50}$, LD$_{50}$, or IR (%) | Target | References |
|-------------|-----------------|--------------------|------|-------------------------|-------------------------------|--------|------------|
| 176         | *P. oxalicum* HSY05 | Marine sediment | Phenolic polyketide | DNA topoisomerase 1 inhibitor | [117] |
| 177         | Co-cultured *Penicillium* sp. WC-29-5 | Mangrove | Phenolic polyketide | H1975 | 3.97 µM | [118] |
| 178         | Co-cultured *Penicillium* sp. WC-29-5 | Mangrove | Phenolic polyketide | H1975, HL-60 | (5.73, 3.73) µM | [118] |
| (+)-5-chlorogriseofulvin (179) | *P. canescens* MMS460 | Sea water | Phenolic polyketide | KB | IR% (0.6 µM) = 49% | [119] |
| Griseophenone I (180) | *P. canescens* MMS460 | Sea water | Phenolic polyketide | KB | IR% (0.6 µM) = 58% | [119] |
| Griseophenone G (181) | *P. canescens* MMS460 | Sea water | Phenolic polyketide | KB | IR% (0.6 µM) = 47% | [119] |
| Iso-monodictyphenone (182) | *Penicillium* sp. MA-37 | Mangrove | Phenolic polyketide | *A. salina* | 25.3 µM | [120] |
| Penikellide A (183) | *Penicillium* sp. MA-37 | Mangrove | Phenolic polyketide | *A. salina* | 14.2 µM | [120] |
| Penikellide B (184) | *Penicillium* sp. MA-37 | Mangrove | Phenolic polyketide | *A. salina* | 39.2 µM | [120] |
| Penicilide (185) | *Penicillium* sp. ZLN29 | Marine sediment | Phenolic polyketide | HepG2 | (6.7/9.7, 7.8) µM | ACAT and nonpeptide calpain inhibitor | [121,122,124,125] |
| Prepenicilide (186) | *Penicillium* sp. ZLN29 | Marine sediment | Phenolic polyketide | HepG2, RD | 9.9 µM | [124] |
| Hydroxypenicilide (187) | *P. pinophilum* | Marine gorgonian | Phenolic polyketide | Hela | 6.1 µM | [125] |
| Nidurufin (188) | *P. flavidorsum* SHK1-27 | Marine sediment | Anthraquinone | K562 | 12.6 µM | Induce cell cycle arrest at G$_2$/M transition | [126] |
| Averantin (189) | *P. flavidorsum* SHK1-27 | Marine sediment | Anthraquinone | K562 | 12.6 µM | [126] |
| 190         | *P. terrestre* | Marine sediment | Polyketide | A549, P388 | (5.3, 15.7) µM | [128] |
### Table A1. Cont.

| Metabolites | Producing Stain                      | Environment Source | Type         | Cell Lines/Brine Shrimp | IC₅₀, LD₅₀, or IR (%) | Target                                              | References |
|-------------|--------------------------------------|--------------------|--------------|-------------------------|-----------------------|-----------------------------------------------------|------------|
| 191         | *P. terrestre*                        | Marine sediment    | Polyketide   | A549, P388              | (7.6, 10.5) µM        |                                                     | [128]      |
| Dihydrobisvertinolone (192) | *P. terrestre*                        | Marine sediment    | Polyketide   | A549, P388              | (0.52, 1.7) µM        |                                                     | [128]      |
| 193         | *P. terrestre*                        | Marine sediment    | Polyketide   | A549                    | 1.4 µM                |                                                     | [128]      |
| 194         | *P. terrestre*                        | Marine sediment    | Polyketide   | A549, P388              | (2.1, 2.8) µM         |                                                     | [129]      |
| 195         | *P. terrestre*                        | Marine sediment    | Polyketide   | A549, P388              | (4.3, 8.8) µM         |                                                     | [129]      |
| Trichodimero (196) | *P. terrestre*                        | Marine sediment    | Polyketide   | A549, P388              | (4.7, 0.33) µM        |                                                     | [129]      |
| Chloctanspirone A (197) | *P. terrestre*                        | Marine sediment    | Polyketide   | HL-60, A549             | (9.2, 39.7) µM        |                                                     | [131]      |
| Chloctanspirone B (198)  | *P. terrestre*                        | Marine sediment    | Polyketide   | HL-60                   | 37.8 µM               |                                                     | [131]      |
| (10E,15E)-10,11-Dehydrocurvularin (199) | *Penicillium* sp. DRF2              | Marine sponge      | Macrolide    | 36 tumor cell lines     | 0.28~6 µM             |                                                     | [133,134] |
| Curvularin (200) | *Penicillium* sp. DRF2              | Marine sponge      | Macrolide    | HSP90 inhibitor         |                       |                                                     | [132]      |
| Tanzawaic acid P (201) | *Penicillium* sp. CF07370            | Marine sediment    | Polyketide   | Jurkat, K562, Raji      | (28.6, 30.2, 20.3) µM| Active the mitochondrial apoptotic pathway           | [137]      |
| Tanzawaic acid D (202) | *P. steckii*                        | Marine (not clear) | Polyketide   | K562, HL-60, K562, Raji | 10~40%                | Bind to the FOXO1 which regulates EGFR signaling and stabilizes the FOXO1-DNA conformation | [138]      |
| Penicimutamide A (203) | Mutant *P. purpurogenum* G59        | Marine soil        | Lipopeptide  | K562, HL-60, Hela, BGC-823, MCF-7 | IR% (100 µg/mL) = 10~40% |                                                     | [140]      |
| Penicimutamide B (204) | Mutant *P. purpurogenum* G59        | Marine soil        | Lipopeptide  | K562, HL-60, Hela, BGC-823, MCF-7 | IR% (100 µg/mL) = 25~40% |                                                     | [140]      |
| Penicimutamide C (205) | Mutant *P. purpurogenum* G59        | Marine soil        | Lipopeptide  | K562, HL-60, Hela, BGC-823, MCF-7 | IR% (100 µg/mL) = 10~40% |                                                     | [140]      |
| Penicimutamide D (206) | Mutant *P. purpurogenum* G59        | Marine soil        | Lipopeptide  | K562, HL-60, Hela, BGC-823, MCF-7 | IR% (100 µg/mL) = 20~40% |                                                     | [140]      |
### Table A1. Cont.

| Metabolites       | Producing Stain                     | Environment Source | Type       | Cell Lines/Brine Shrimp | IC<sub>50</sub>, LD<sub>50</sub>, or IR (%) | Target                          | References |
|-------------------|-------------------------------------|--------------------|------------|-------------------------|---------------------------------------------|----------------------------------|------------|
| Penicimutamide E  | Mutant <i>P. purpurogenum</i> G59   | Marine soil        | Lipopeptide| K562, HL-60, Hela, BGC-823, MCF-7 | IR% (100 µg/mL) = 10–45%                 | [140]                            |            |
| Penicimutamide F  | Mutant <i>P. purpurogenum</i> G59   | Marine soil        | Lipopeptide| K562, HL-60, Hela, BGC-823, MCF-7 | IR% (100 µg/mL) = 10–50%                 | [140]                            |            |
| Penicimutamide G  | Mutant <i>P. purpurogenum</i> G59   | Marine soil        | Lipopeptide| K562, HL-60, Hela, BGC-823, MCF-7 | IR% (100 µg/mL) = 10–20%                 | [140]                            |            |
| Fellutamide A     | <i>P. jellatum</i>                  | Marine fish        | Lipopeptide| P388, L1210             | (0.2, 0.8) µg/mL                          | [139]                            |            |
| Fellutamide B     | <i>P. jellatum</i>                  | Marine fish        | Lipopeptide| P388, L1210             | (0.1, 0.7) µg/mL                          | [139]                            |            |
| Fellutamide C     | Mutant <i>P. purpurogenum</i> G59   | Marine soil        | Lipopeptide| K562, HL-60, Hela, BGC-823, MCF-7 | IR% (100 µg/mL) = 30–50%                 | [140]                            |            |
| Peniphenylane A   | <i>P. jellatum</i> HDN14-323        | Deep sea sediment  | Polyphenol  | Hela                    | 14.5 µM                                    | [141]                            |            |
| Peniphenylane B   | <i>P. jellatum</i> HDN14-323        | Deep sea sediment  | Polyphenol  | Hela, HCT-116           | (11.4, 15.8) µM                           | [141]                            |            |
| Peniphenylane D   | <i>P. jellatum</i> HDN14-323        | Deep sea sediment  | Polyphenol  | Hela, HL-60, HCT-116    | (9.3, 18.2, 31.7) µM                       | [141]                            |            |
| Peniphenylane F   | <i>P. jellatum</i> HDN14-323        | Deep sea sediment  | Polyphenol  | Hela                    | 29.3 µM                                    | [141]                            |            |
| Peniphenylane G   | <i>P. jellatum</i> HDN14-323        | Deep sea sediment  | Polyphenol  | Hela, HL-60, HCT-116    | (16.6, 23.2, 24.7) µM                      | [141]                            |            |
| Terrestol B       | <i>P. terrestre</i>                | Marine sediment    | Polyphenol  | HL-60, MOLT-4, A549, BEL-7402 | (6.1, 5.8, 18.3, 62.3) µM                 | [142]                            |            |
| Terrestol C       | <i>P. terrestre</i>                | Marine sediment    | Polyphenol  | HL-60, MOLT-4, A549, BEL-7402 | (5.5, 5.6, 18.2, 57.3) µM                 | [142]                            |            |
| Terrestol D       | <i>P. terrestre</i>                | Marine sediment    | Polyphenol  | HL-60, MOLT-4, A549, BEL-7402 | (5.3, 5.5, 14.3, 38.5) µM                 | [142]                            |            |
| Terrestol E       | <i>P. terrestre</i>                | Marine sediment    | Polyphenol  | HL-60, MOLT-4, A549, BEL-7402 | (54.7, 6.4, 9.6, 59.0) µM                 | [142]                            |            |
Table A1. Cont.

| Metabolites          | Producing Stain | Environment Source | Type     | Cell Lines/Brine Shrimp | IC_{50}, LD_{50}, or IR (%) | Target Description                                                                 | References |
|----------------------|-----------------|--------------------|----------|-------------------------|-----------------------------|-----------------------------------------------------------------------------------|------------|
| Terrestol F (222)    | *P. terrestre*   | Marine sediment    | Polyphenol | HL-60, MOLT-4, A549, BEL-7402 | (55.0, 58.1, 13.8, 63.2) µM |                                                                                  | [142]      |
| Terrestol G (223)    | *P. terrestre*   | Marine sediment    | Polyphenol | HL-60, MOLT-4, A549, BEL-7402 | (5.1, 6.5, 5.7, 6.0) µM     |                                                                                  | [142]      |
| Terrestol H (224)    | *P. terrestre*   | Marine sediment    | Polyphenol | HL-60, MOLT-4, A549, BEL-7402 | (6.3, 5.8, 33.8, 61.9) µM   |                                                                                  | [142]      |
| Terrestol A (225)    | *P. terrestre*   | Marine sediment    | Polyphenol | HL-60, MOLT-4, A549, BEL-7402 | (33.3, 5.5, 23.5, 57.0) µM  |                                                                                  | [142]      |
| Expansol A (226)     | *P. expansum*    | Mangrove           | Polyphenol | HL-60                   | 15.7 µM                     |                                                                                  | [143]      |
| Expansol B (227)     | *P. expansum*    | Mangrove           | Polyphenol | HL-60, A549             | (5.4, 1.9) µM               |                                                                                  | [143,144]  |
| Expansol C (228)     | *P. expansum*    | Mangrove           | Polyphenol | HL-60                   | 18.2 µM                     |                                                                                  | [143]      |
| Expansol E (229)     | *P. expansum*    | Mangrove           | Polyphenol | HL-60                   | 20.8 µM                     |                                                                                  | [143]      |
| Patulin (230)        | *Penicillium sp.*| Marine alga        | Other     | P388, BSY-1, MCF-7, HCC2998, NCI-H522, DMS114, OVCAR-3, MKN1 | (0.06, 0.34, 0.65, 1.54, 0.30, 0.57, 0.37, 0.39) µg/mL | Potassium-uptake inhibitor / Ion flux across cell membranes inducer | [111]      |
| (+)-Epiepoxydon (231)| *Penicillium sp.*| Marine alga        | Other     | P388                    | 0.2 µg/mL                   |                                                                                  | [111]      |
| 232                  | *Penicillium sp.*| Mangrove           | Other     | KB, KBv200               | (6, 10) µg/mL               |                                                                                  | [145]      |
| Penicillic acid (233)| *Penicillium sp.*| Sea water          | Other     | POS1, AT6-1, L299       | (7.8, 29.4, 12.9) µM        |                                                                                  | [84]       |
References

1. Lindequist, U. Marine-Derived Pharmaceuticals—Challenges and Opportunities. Biomol. Ther. 2016, 24, 561–571. [CrossRef] [PubMed]

2. Wang, H.; Hong, J.; Yin, J.; Moon, H.R.; Liu, Y.; Wei, X.; Oh, D.-C.; Jung, J.H. Dimeric Octaketide Spiroketalts from the Jellyfish-Derived Fungus Paecilomyces variotii J08NF-1. J. Nat. Prod. 2015, 78, 2832–2836. [CrossRef] [PubMed]

3. Lee, Y.M.; Kim, M.J.; Li, H.; Zhang, P.; Bao, B.; Lee, K.J.; Jung, J.H. Marine-derived Aspergillus species as a source of bioactive secondary metabolites. Mar. Biotechnol. 2013, 15, 499–519. [CrossRef] [PubMed]

4. Ding, G.; Song, Y.C.; Chen, J.R.; Xu, C.; Ge, H.M.; Wang, X.T.; Tan, R.X. Chaetoglobosin, a cytochalasan alkaloid from endophytic Chaetomium globosum IFB-E019. J. Nat. Prod. 2006, 69, 302–304. [CrossRef] [PubMed]

5. Zhang, J.; Ge, H.M.; Jiao, R.H.; Li, J.; Peng, H.; Wang, Y.R.; Wu, J.H.; Song, Y.C.; Tan, R.X. Cytotoxic chaetoglobosins from the endophyte Chaetomium globosum. Planta Med. 2010, 76, 1910–1914. [CrossRef] [PubMed]

6. Huang, S.; Chen, H.; Li, W.; Zhu, X.; Ding, W.; Li, C. Bioactive Chaetoglobosins from the Mangrove Endophytic Fungus Penicillium chrysogenum. Mar. Drugs 2016, 14, 172. [CrossRef] [PubMed]

7. Iwamoto, C.; Yamada, T.; Ito, Y.; Minoura, K.; Numata, A. Cytotoxic cytochalasans from a Penicillium species separated from a marine alga. Tetrahedron 2001, 57, 2997–3004. [CrossRef]

8. Numata, A.; Takahashi, C.; Ito, Y.; Minoura, K.; Yamada, T.; Matsuda, C.; Nomoto, K. Penochalasins, a novel class of cytotoxic cytochalasans from a Penicillium species separated from a marine alga: Structure determination and solution conformation. J. Chem. Soc. Perkin 1 1996, 3, 239–245. [CrossRef]

9. Knudsen, P.B.; Hanna, B.; Ohl, S.; Sellner, L.; Zenz, T.; Dohner, H.; Stilgenbauer, S.; Larsen, T.O.; Lichter, P.; Seiffert, M. Chaetoglobosin A preferentially induces apoptosis in chronic lymphocytic leukemia cells by targeting the cytoskeleton. Leukemia 2014, 28, 1289–1298. [CrossRef] [PubMed]

10. Schümann, J.; Hertweck, C. Molecular basis of cytochalasan biosynthesis in fungi: Gene cluster analysis and evidence for the involvement of a PKS-NRPS hybrid synthase by RNA silencing. J. Am. Chem. Soc. 2007, 129, 9564–9565. [CrossRef] [PubMed]

11. McDougall, J. Antiviral action of gliotoxin. Arch. Viro 1969, 27, 255–267. [CrossRef]

12. Sun, Y.; Takada, K.; Takemoto, Y.; Yoshida, M.; Nogi, Y.; Okada, S.; Matsunaga, S. Gliotoxin analogues from a marine-derived fungus, Penicillium sp., and their cytotoxic and histone methyltransferase inhibitory activities. J. Nat. Prod. 2011, 75, 111–114. [CrossRef] [PubMed]

13. Vigushin, D.; Mirsaidi, N.; Brooke, G.; Sun, C.; Pace, P.; Inman, L.; Moody, C.; Coombes, R. Gliotoxin is a dual inhibitor of farnesyltransferase and geranylgeranyltransferase I with antitumor activity against breast cancer in vivo. Med. Oncol. 2004, 21, 21–30. [CrossRef]

14. Meng, L.-H.; Wang, C.-Y.; M.; Li, X.-M.; Hu, X.-Y.; Kassack, M.U.; Kurtán, T.; Wang, B.-G. Three Diketopiperazine Alkaloids with Spirocyclic Skeletons and One Bisthiodiketopiperazine Derivative from the Mangrove-Derived Endophytic Fungus Penicillium brocae MA-231. Org. Lett. 2016, 18, 5304–5307. [CrossRef] [PubMed]

15. Jiang, C.-S.; Guo, Y.-W. Epipolythiodioxopiperazines from fungi: Chemistry and bioactivities. Mini Rev. Med. Chem. 2011, 11, 728–745. [CrossRef] [PubMed]

16. Meng, L.-H.; Li, X.-M.; Lv, C.-T.; Huang, C.-G.; Wang, B.-G. Brocazines A–F, cytotoxic bisthiodiketopiperazine derivatives from Penicillium brocae MA-231, an endophytic fungus derived from the marine mangrove plant Avicennia marina. J. Nat. Prod. 2014, 77, 1921–1927. [CrossRef] [PubMed]

17. Liu, Y.; Li, X.-M.; Meng, L.-H.; Jiang, W.-L.; Xu, G.-M.; Huang, C.-G.; Wang, B.-G. Bisthiodiketopiperazines and acorane sesquiiterpenes produced by the marine-derived fungus Penicillium admetzioides AS-53 on different culture media. J. Nat. Prod. 2015, 78, 1294–1299. [CrossRef] [PubMed]

18. Orfali, R.S.; Aly, A.H.; Ebrahim, W.; Abdel-Aziz, M.S.; Müller, W.E.; Lin, W.; Daletos, G.; Proksch, P. Pretrichodermande C and N-methylpretrichodermande B, two new cytotoxic epidithiodiketopiperazines from hyper saline lake derived Penicillium sp. Phytochem. Lett. 2015, 11, 168–172. [CrossRef]

19. Yurchenko, A.N.; Smetanina, O.F.; Ivanets, E.V.; Kalinovsky, A.I.; Khudyakova, Y.V.; Kirichuk, N.N.; Popov, R.S.; Bokemeyer, C.; Von Amsberg, G.; Chingizova, E.A. Pretrichodermandes D–F from a Marine Algicolous Fungus Penicillium sp. KMM 4672. Mar. Drugs 2016, 14, 122. [CrossRef] [PubMed]
20. Aninat, C.; Andre, F.; Delaforge, M. Oxidative metabolism by P450 and function coupling to efflux systems: Modulation of mycotoxin toxicity. Food Addit. Contam. 2005, 22, 361–368. [CrossRef] [PubMed]

21. Du, L.; Feng, T.; Zhao, B.; Li, D.; Cai, S.; Zhu, T.; Wang, F.; Xiao, X.; Gu, Q. Alkaloids from a deep ocean sediment-derived fungus 

22. Du, L.; Li, D.; Zhu, T.; Cai, S.; Wang, F.; Xiao, X.; Gu, Q. New alkaloids and diterpenes from a deep ocean sediment derived fungus 

23. Shang, Z.; Li, X.; Meng, L.; Li, C.; Gao, S.; Huang, C.; Wang, B. Chemical profile of the secondary metabolites produced by a deep sea sediment-derived fungus 

24. Fang, S.-M.; Wu, C.-J.; Li, C.-W.; Cui, C.-B. A practical strategy to discover new antitumor compounds by activating silent metabolite production in fungi by diethyl sulphate mutagenesis. Mar. Drugs 2014, 12, 1788–1814. [CrossRef] [PubMed]

25. Chai, Y.-J.; Cui, C.-B.; Li, C.-W.; Wu, C.-J.; Tian, C.-K.; Hua, W. Activation of the dormant secondary metabolite production by introducing gentamicin-resistance in a marine-derived 

26. Hauser, D.; Weber, H.; Sigg, H. Isolation and configuration of Chaetocin. Helv. Chim. Acta 1970, 53, 1061–1073. [CrossRef] [PubMed]

27. Katagiri, K.; Sato, K.; Hayakawa, S.; Matsushima, T.; Minato, H. Verticillin A, a new anti-biotic from 

28. Son, B.; Jensen, P.; Kauffman, C.; Penicillium commune produced by a deep sea sediment-derived fungus 

29. Greiner, D.; Bonaldi, T.; Eskeland, R.; Roemer, E.; Imhof, A. Identification of a specific inhibitor of the histone methyltransferase SU (VAR) 3-9. Nat. Chem. Biol. 2005, 1, 143–145. [CrossRef] [PubMed]

30. Chen, Y.; Miao, Z.-H.; Zhao, W.-M.; Ding, J. The p38 pathway is synergized by p38 MAPK signaling to mediate 11,11′-dideoxyverticillin-induced G2/M arrest. FEBS Lett. 2005, 579, 3683–3690. [CrossRef] [PubMed]

31. Zhang, Y.-X.; Chen, Y.; Guo, X.-N.; Zhang, X.-W.; Zhao, W.-M.; Zhong, L.; Zhou, J.; Xi, Y.; Lin, L.-P.; Ding, J. 11,11′-dideoxy-verticillin: A natural compound possessing growth factor receptor tyrosine kinase-inhibitory effect with anti-tumor activity. Anti-Cancer Drugs 2005, 16, 515–524. [CrossRef] [PubMed]

32. Kim, J.; Ashenhurst, J.A.; Movassaghi, M. Total synthesis of (+)-11,11′-dideoxyverticillin A. Science 2009, 324, 238–241. [CrossRef] [PubMed]

33. Kim, J.; Movassaghi, M. Biogenetically-inspired total synthesis of epidithiodiketopiperazines and related alkaloids. Acc. Chem. Res. 2015, 48, 1159–1171. [CrossRef] [PubMed]

34. Sallam, A.A.; Houssen, W.E.; Gissendanner, C.R.; Orabi, K.Y.; Foudah, A.I.; El Sayed, K.A. Bioguided discovery and pharmaphore modeling of the mycotoxic indole diterpene alkaloids penitrems as breast cancer proliferation, migration, and invasion inhibitors. MedChemComm 2013, 4, 1360–1369. [CrossRef] [PubMed]

35. Sings, H.; Singh, S. Tremorgenic and nontremorgenic 2,3-fused indole diterpenoids. Alkaloids Chem. Biol. 2003, 60, 51–163. [PubMed]

36. Saikia, S.; Nicholson, M.J.; Young, C.; Parker, E.J.; Scott, B. The genetic basis for indole-diterpene chemical diversity in filamentous fungi. Mycol. Res. 2008, 112, 184–199. [CrossRef] [PubMed]

37. Cavanagh, J.; Holton, J.; Nolan, C.; Ray, D.; Naik, J.; Mantle, P. The effects of the tremorgenic mycotoxin penitrem A on the rat cerebellum. Vet. Pathol. 1998, 35, 53–63. [CrossRef] [PubMed]

38. Numata, A.; Takahashi, C.; Ito, Y.; Takada, T.; Kawai, K.; Usami, Y.; Matsumura, E.; Imachi, M.; Ito, T.; Hasegawa, T. Communesins, cytotoxic metabolites of a fungus isolated from a marine alga. Tetrahedron Lett. 1998, 39, 2333–2338. [CrossRef]

39. Jadulco, R.; Edrada, R.A.; Ebel, R.; Berg, A.; Schaumann, K.; Wray, V.; Steube, K.; Proksch, P. New Communesin Derivatives from the Fungus Penicillium sp. Derived from the Mediterranean Sponge Axinella v errucosa. J. Nat. Prod. 2004, 67, 78–81. [CrossRef] [PubMed]

40. Vansteelandt, M.; Kerzaon, I.; Blanchet, E.; Tankoua, O.F.; Du Pont, T.R.; Joubert, Y.; Monteau, F.; Le Bizec, B.; Frisvad, J.C.; Pouchus, Y.F. Patulin and secondary metabolite production by marine-derived Penicillium strains. Fungal Biol. 2012, 116, 954–961. [CrossRef] [PubMed]
41. Crawley, S.L.; Funk, R.L. A synthetic approach to nomofungin/communesin B. Org. Lett. 2003, 5, 3169–3171. [CrossRef] [PubMed]

42. Zhang, P.; Li, X.-M.; Liu, H.; Li, X.; Wang, B.-G. Two new alkaloids from Penicillium oxalicum EN-201, an endophytic fungus derived from the marine mangrove plant Rhizophora stylosa. Phytochem. Lett. 2015, 13, 160–164. [CrossRef]

43. An, C.-Y.; Li, X.-M.; Li, C.-S.; Xu, G.-M.; Wang, B.-G. Prenylated indoleketopiperazine peroxides and related homologues from the marine sediment-derived fungus Penicillium brefeldianum SD-273. Mar. Drugs 2014, 12, 746–756. [CrossRef] [PubMed]

44. Li, C.S.; Li, X.M.; An, C.Y.; Li, X.-M.; Gao, S.-S.; Cui, C.-M.; Sun, H.-F.; Wang, B.-G. Triazole and dihydroimidazole derivatives from deep sea sediment-derived fungus Penicillium paneum SD-44. Helv. Chim. Acta 2014, 97, 1440–1444. [CrossRef]

45. Shaala, L.A.; Youssef, D.T. Identification and bioactivity of compounds from the fungus Penicillium sp. CYE-87 isolated from a marine tunicate. Mar. Drugs 2015, 13, 1698–1709. [CrossRef] [PubMed]

46. Chen, L.; Zhou, T.; Zhao, Y.-Y. Four new penicitrinols and two new penicillenols from the marine-derived fungus Penicillium citrinum. Heterocycles 2012, 85, 413–419. [CrossRef]

47. Chen, L.; Zhou, T.; Zhao, Y.-Y. Four new penicitrinols and two new penicillenols from the marine-derived fungus Penicillium citrinum. Heterocycles 2015, 91, 1007–1016. [CrossRef]

48. Lin, Z.-J.; Lu, Z.-Y.; Zhu, T.-J.; Fang, Y.-C.; Gu, Q.-Q.; Zhu, W.-M. Penicillenols from Penicillium sp. GQ-7, an endophytic fungus associated with Aegiceras corniculatum. Chem. Pharm. Bull. 2008, 56, 217–221. [CrossRef] [PubMed]

49. Liu, Q.-Y.; Zhou, T.; Zhao, Y.-Y.; Chen, L.; Gong, M.-W.; Xia, Q.-W.; Ying, M.-G.; Zheng, Q.-H.; Zhang, Q.-Q. Antitumor effects and related mechanisms of penicitrinine A, a novel alkaloid with a unique spiro skeleton from the marine fungus Penicillium citrinum. Mar. Drugs 2015, 13, 4733–4753. [CrossRef] [PubMed]

50. Jafari, E.; Khajouei, M.R.; Hassanzadeh, F.; Hakimelahi, G.H.; Khodarahmi, G.A. Quinazolinone and quinazo-line derivatives: Recent structures with potent antimicrobial and cytotoxic activities. Res. Pharm. Sci. 2016, 11, 1–14. [PubMed]

51. He, J.; Lion, U.; Sattler, I.; Gollmick, F.A.; Grabley, S.; Cai, J.; Meiners, M.; Schünke, H.; Schaumann, K.; Dechert, U. Diastereomeric Quinolinone Alkaloids from the Marine-Derived Fungus Penicillium j anczewskii. J. Nat. Prod. 2005, 68, 1397–1399. [CrossRef] [PubMed]

52. Gao, H.; Zhang, L.; Zhu, T.; Gu, Q.; Li, D. Unusual pyrrolyl 4-quinolinone alkaloids from the marine-derived fungus Penicillium sp. ghq208. Chem. Pharm. Bull. 2012, 60, 1458–1460. [CrossRef] [PubMed]

53. Shao, C.-L.; Wang, C.-Y.; Gu, Y.-C.; Wei, M.-Y.; Pan, J.-H.; Deng, D.-S.; She, Z.-G.; Lin, Y.-C. Penicinoline, a new pyrrolyl 4-quinolinone alkaloid with an unprecedented ring system from an endophytic fungus Penicillium sp. Bioorg. Med. Chem. Lett. 2010, 20, 3284–3286. [CrossRef] [PubMed]

54. Shen, S.; Li, W.; Wang, J. A novel and other bioactive secondary metabolites from a marine fungus Penicillium oxalicum 0312f1. J. Nat. Prod. Rep. 2013, 27, 2286–2291. [CrossRef] [PubMed]

55. An, C.Y.; Li, X.M.; Li, C.S.; Gao, S.S.; Shang, Z.; Wang, B.G. Triazoles and Other N-Containing Metabolites from the Marine-Derived Endophytic Fungus Penicillium chrysogenum EN-118. Helv. Chim. Acta 2013, 96, 682–687. [CrossRef]

56. Li, C.-S.; Li, X.-M.; Gao, S.-S.; Lu, Y.-H.; Wang, B.-G. Cytotoxic anthranilic acid derivatives from deep sea sediment-derived fungus Penicillium paneum SD-44. Mar. Drugs 2013, 11, 3068–3076. [CrossRef] [PubMed]

57. Li, C.-S.; An, C.-Y.; Li, X.-M.; Gao, S.-S.; Cui, C.-M.; Sun, H.-F.; Wang, B.-G. Triazole and dihydroimidazolone alkaloids from the marine sediment-derived fungus Penicillium paneum SD-44. J. Nat. Prod. 2011, 74, 1331–1334. [CrossRef] [PubMed]

58. Li, J.; Yang, X.; Lin, Y.; Yuan, J.; Lu, Y.; Zuo, X.; Li, J.; Li, M.; Lin, Y.; He, J. Meroterpenes and azaphilones from marine mangrove endophytic fungus Penicillium 303. Fitoterapia 2014, 97, 241–246. [CrossRef] [PubMed]

59. Bringmann, G.; Lang, G.; Gulder, T.A.; Tsuruta, H.; Mühlbacher, J.; Maksimenka, K.; Steffens, S.; Schaumann, K.; Stöhr, R.; Wiese, J. The first sorbicillinoid alkaloids, the antileukemic sorbicillactones A and B, from a sponge-derived Penicillium chrysogenum strain. Tetrahedron 2005, 61, 7252–7265. [CrossRef]

60. Bringmann, G.; Gulder, T.A.; Lang, G.; Schmitt, S.; Stöhr, R.; Wiese, J.; Nagel, K.; Imhoff, J.F. Large-scale biotechnological production of the antileukemic marine natural product sorbicillactone A. Mar. Drugs 2007, 5, 23–30. [CrossRef] [PubMed]
62. Zhang, P.; Meng, L.H.; Mándi, A.; Kurtán, T.; Li, X.M.; Liu, Y.; Li, X.; Li, C.S.; Wang, B.G. Brocaeloids A–C, 4-Oxoquinoline and Indole Alkaloids with C-2 Reversed Prenylation from the Mangrove-Derived Endophytic Fungus Penicillium broace. Eur. J. Org. Chem. 2014, 2014, 4029–4036. [CrossRef] [PubMed]

63. He, X.; Zhang, Z.; Chen, Y.; Che, Q.; Zhu, T.; Gu, Q.; Li, D. Varitatin A, a Highly Modified Fatty Acid Amide from Penicillium variabile Cultured with a DNA Methyltransferase Inhibitor. J. Nat. Prod. 2015, 78, 2841–2845. [CrossRef] [PubMed]

64. Zhang, Y.; Li, C.; Swenson, D.C.; Gloer, J.B.; Wicklow, D.T.; Dowd, P.F. Novel antiinsectan oxalicine alkaloids from two undescribed fungicolous Penicillium spp. Org. Lett. 2003, 5, 773–776. [CrossRef] [PubMed]

65. Takatsuki, A.; Suzuki, S.; Ando, K.; Tamura, G.; Arima, K. New antiviral antibiotics; xanthocillin X mono-and dimethylether, and methoxy-xanthocillin X dimethylether. I: Isolation and characterization. J. Antibiot. 1968, 21, 671–675. [CrossRef] [PubMed]

66. Rothe, W. Vorläufige Mitteilung über eine neues Antibiotikum. Pharmazie 1950, 5, 190.

67. Zhao, Y.; Chen, H.; Shang, Z.; Jiao, B.; Yuan, B.; Sun, W.; Wang, B.; Miao, M.; Huang, C. SD118-xanthocillin X (1), a novel marine extract from Penicillium commune, induces autophagy through the inhibition of the MEK/ERK pathway. Mar. Drugs 2012, 10, 1345–1359. [CrossRef] [PubMed]

68. Sugawara, F.; Hallock, Y.; Bunkers, G.; Kenfield, D.; Strobel, G.; Yoshida, S. Phytoactive eremophilanes produced by the weed pathogen Drechslera gigantea. Biosci. Biotechnol. Biochem. 1993, 57, 236–239. [CrossRef] [PubMed]

69. Tirilly, Y.; Kloosterman, J.; Sipmä, G.; Ketenes-Van den Bosch, J.J. A fungitoxic sesquiterpene from Hansfordia pulvinata. Phytochemistry 1983, 22, 2082–2083. [CrossRef]

70. Lin, A.; Wu, G.; Gu, Q.; Zhu, T.; Li, D. New eremophilane-type sesquiterpenes from an Antarctic deep sea derived fungus, Penicillium sp. PR19 N-1. Arch. Pharm. Res. 2014, 37, 839–844. [CrossRef] [PubMed]

71. Wu, G.; Lin, A.; Gu, Q.; Zhu, T.; Li, D. Four new chloro-eremophilane sesquiterpenes from an Antarctic deep sea derived fungus, Penicillium sp. PR19N-1. Mar. Drugs 2013, 11, 1399–1408. [CrossRef] [PubMed]

72. Huang, Y.F.; Qiao, L.; Lv, A.L.; Pei, Y.H.; Tian, L. Eremophilane sesquiterpenes from the marine fungus Penicillium sp. BL27-2. Chin. Chem. Lett. 2008, 19, 562–564. [CrossRef]

73. Li, Y.; Ye, D.; Shao, Z.; Cui, C.; Che, Y. A steroid and spiroditerpenoids from a Penicillium sp. isolated from a deep sea sediment sample. Mar. Drugs 2012, 10, 497–508. [CrossRef] [PubMed]

74. Gao, S.-S.; Li, X.-M.; Li, C.-S.; Proksch, P.; Wang, B.-G. Penicisteroids A and B, antifungal and cytotoxic polyoxygenated steroids from the marine alga-derived endophytic fungus Penicillium chrysogenum QEN-245. Bioorg. Med. Chem. Lett. 2011, 21, 2894–2897. [CrossRef] [PubMed]

75. Sun, Y.; Tian, L.; Huang, J.; Li, W.; Pei, Y.-H. Cytotoxic sterols from marine-derived fungus Penicillium sp. Nat. Prod. Rep. 2006, 20, 381–384. [CrossRef] [PubMed]

76. Xin, Z.-H.; Zhu, T.-J.; Wang, W.-L.; Du, L.; Fang, Y.-C.; Gu, Q.-Q.; Zhu, W.-M. Isocoumarin derivatives from the sea squirt-derived fungus Penicillium stoloniferum QY2-10 and the halotolerant fungus Penicillium notatum B-52. Arch. Pharm. Res. 2007, 30, 816–819. [CrossRef] [PubMed]

77. Qi, J.; Shao, C.-L.; Liu, M.; Qi, X.; Wang, C.-Y. Bioactive steroids from a marine-derived fungus Penicillium sp. from the South China Sea. Chem. Nat. Compos. 2014, 3, 568–570. [CrossRef]

78. Menna, M.; Imperatore, C.; D’Aniello, F.; Aiello, A. Meroterpenes from marine invertebrates: Structures, occurrence, and ecological implications. Mar. Drugs 2013, 11, 1602–1643. [CrossRef] [PubMed]

79. Li, X.; Choi, H.D.; Kang, J.S.; Lee, C.-O.; Son, B.W. New polyoxygenated farnesylcyclohexenones, deacetoxyjanuthone A and its hydro derivative from the marine-derived fungus Penicillium sp. J. Nat. Prod. 2003, 66, 1499–1500. [CrossRef] [PubMed]

80. Zhuang, P.; Fang, X.-Y.; Yi, Z.-W.; Qiu, Y.-K.; Wu, Z. Two new compounds from marine-derived fungus Penicillium sp. F11. J. Asian Nat. Prod. Res. 2012, 14, 197–203. [CrossRef] [PubMed]

81. Ding, Z.; Zhang, L.; Fu, J.; Che, Q.; Li, D.; Gu, Q.; Zhu, T. Phenylpyropenes E and F: New meroterpenes from the marine-derived fungus Penicillium concentricum ZLQ-69. J. Antibiot. 2015, 68, 748–751. [CrossRef] [PubMed]

82. Liao, L.; Lee, J.-H.; You, M.; Choi, T.J.; Park, W.; Lee, S.K.; Oh, D.-C.; Oh, K.-B.; Shin, J. Penicillipyropenes A and B, meroterpenoids from a marine-derived Penicillium sp. fungus. J. Nat. Prod. 2014, 77, 406–410. [CrossRef] [PubMed]

83. Hanson, F.; Eble, T. An antiphage agent isolated from Aspergillus sp. J. Bacteriol. 1949, 58, 527–529. [PubMed]
84. Vansteelandt, M.; Blanchet, E.; Egorov, M.; Petit, F.; Toupet, L.; Bondon, A.; Monteau, F.; Le Bizec, B.; Thomas, O.P.; Pouchus, Y.F. Ligerin, an antiproliferative chlorinated sesquiterpenoid from a marine-derived *Penicillium* strain. *J. Nat. Prod.* 2013, 76, 297–301. [CrossRef] [PubMed]

85. Blanchet, E.; Vansteelandt, M.; Bot, R.L.; Egorov, M.; Guittion, Y.; Pouchus, Y.F.; Grovel, O. Synthesis and antiproliferative activity of ligerin and new fumagillin analogs against osteosarcoma. *Eur. J. Med. Chem.* 2014, 79, 244–250. [CrossRef] [PubMed]

86. Keri, R.S.; Budagumpi, S.; Pai, R.K.; Balakrishna, R.G. Chromones as a privileged scaffold in drug discovery: A review. *Eur. J. Med. Chem.* 2014, 87, 340–374. [CrossRef] [PubMed]

87. Bao, J.; Luo, J.-F.; Qin, X.-C.; Xu, X.-Y.; Zhang, X.-Y.; Tu, Z.-C.; Qi, S.-H. Dihydrothiophene-condensed chromones from a marine-derived fungus *Penicillium oxalicum* and their structure-bioactivity relationship. *Bioorg. Med. Chem. Lett.* 2014, 24, 2433–2436. [CrossRef] [PubMed]

88. Sun, Y.-L.; Bao, J.; Liu, K.-S.; Zhang, X.-Y.; He, F.; Wang, Y.-F.; Nong, X.-H.; Qi, S.-H. Cytotoxic dihydrothiophene-condensed chromones from the marine-derived fungus *Penicillium oxalicum*. *Planta Med.* 2013, 79, 1474–1479. [CrossRef] [PubMed]

89. Wang, J.; Wang, Q.-L.; Nong, X.-H.; Zhang, X.-Y.; Xu, X.-Y.; Qi, S.-H.; Wang, Y.-F. Oxalicumone A, a new dihydrothiophene-condensed sulfur chromone induces apoptosis in leukemia cells through endoplasmic reticulum stress pathway. *Eur. J. Pharmocol.* 2016, 783, 47–55. [CrossRef] [PubMed]

90. Shi, S.; Guo, K.; Wang, X.; Chen, H.; Min, J.; Qi, S.; Zhao, W.; Li, W. Toxicity study of oxalicumone A, derived from a marine-derived fungus *Penicillium oxalicum*, in cultured renal epithelial cells. *Mol. Med. Rep.* 2017, 15, 2611–2619. [CrossRef] [PubMed]

91. Yi, L.; Cui, C.-B.; Li, C.-W.; Peng, J.-X.; Gu, Q.-Q. Chromosulfine, a novel cyclopentachromone sulfide produced by a marine-derived fungus after introduction of neomycin resistance. *RSC Adv.* 2016, 6, 43975–43979. [CrossRef]

92. Li, N.; Yi, Z.; Wang, Y.; Zhang, Q.; Zhong, T.; Qiu, Y.; Wu, Z.; Tang, X. Differential proteomic analysis of HL60 cells treated with secalonic acid F reveals caspase 3-induced cleavage of Rho GDP dissociation inhibitor 2. *Oncol. Rep.* 2012, 28, 2016–2022. [CrossRef] [PubMed]

93. Gao, X.; Sun, H.; Liu, D.; Zhang, J.; Zhang, J.; Yan, M.; Pan, X. Secalonic acid-F inhibited cell growth more effectively than 5-fluorouracil on hepatocellular carcinoma in vitro and in vivo. *Neoplasma* 2017, 64, 344–350. [CrossRef] [PubMed]

94. Hou, X.-M.; Wang, C.-Y.; Gu, Y.-C.; Shao, C.-L. Penimethavone A, a flavone from a gorgonian-derived fungus *Penicillium chrysogenum*. *Nat. Prod. Rep.* 2016, 30, 2274–2277. [CrossRef] [PubMed]

95. Chen, S.; Wang, J.; Wang, Z.; Lin, X.; Zhao, B.; Kaliaperumal, K.; Liao, X.; Tu, Z.; Li, J.; Xu, S. Structurally diverse secondary metabolites from a deep sea-derived fungus *Penicillium chrysogenum* SCSIO 41001 and their biological evaluation. *Fitoterapia* 2017, 117, 71–78. [CrossRef] [PubMed]

96. Chen, H.; Aktas, N.; Konuklugil, B.; Mandi, A.; Daletos, G.; Lin, W.; Dai, H.; Kurtan, T.; Proksch, P. A new fusaricin analogue from *Penicillium* sp. isolated from the Mediterranean sponge *Ircinia onos*. *Tetrahedron Lett.* 2015, 56, 5317–5320. [CrossRef]

97. Huang, Z.; Yang, J.; Cai, X.; She, Z.; Lin, Y. A new furanocoumarin from the mangrove endophytic fungus *Penicillium* sp. (ZH16). *Nat. Prod. Rep.* 2012, 26, 1291–1295. [CrossRef] [PubMed]

98. Hetherington, A.C.; Raistrick, H. On the production and chemical constitution of a new yellow colouring matter, citrinin, produced from glucose by *Penicillium citrinum* Thom. *Philos. Trans. R. Soc. Lond.* 1931, 220, 269–295. [CrossRef]

99. Chagas, G.M.; Campello, A.P.; Klüppel, M.; Lúcia, W. Mechanism of citrinin-induced dysfunction of mitochondria. I. Effects on respiration, enzyme activities and membrane potential of renal cortical mitochondria. *J. Appl. Toxicol.* 1992, 12, 123–129. [CrossRef] [PubMed]

100. He, Y.; Cox, R.J. The molecular steps of citrinin biosynthesis in fungi. *Chem. Sci.* 2016, 7, 2119–2127. [CrossRef]

101. Subramani, R.; Kumar, R.; Prasad, P.; Aalbersberg, W. Cytotoxic and antibacterial substances against multi-drug resistant pathogens from marine sponge symbiont: Citrinin, a secondary metabolite of *Penicillium* sp. *Asian Pac. J. Trop. Biomed.* 2013, 3, 291–296. [CrossRef]
103. Wu, X.; Zhou, J.; Snider, B.B. Synthesis of (−)-Berkelic Acid. *Angew. Chem. Int. Ed.* 2009, 48, 1283–1286. [CrossRef] [PubMed]

104. Zhuravleva, O.I.; Sobolevskaya, M.P.; Afifyatullov, S.S.; Kirichuk, N.N.; Denisenko, V.A.; Dmitrenok, P.S.; Yurchenko, E.A.; Dysshlovoy, S.A. Sargassopenillines A–G, 6,6-spiroketals from the alga-derived fungi *Penicillium thomii* and *Penicillium lividum*. *Mar. Drugs* 2014, 12, 5930–5943. [CrossRef] [PubMed]

105. Perpelescu, M.; Kobayashi, J.I.; Furuta, M.; Ito, Y.; Izuta, S.; Takemura, M.; Suzuki, M.; Yoshida, S. Novel phalenelone derivatives from a marine-derived fungus exhibit distinct inhibition spectra against eukaryotic DNA polymerases. *Biochemistry* 2002, 41, 7610–7616. [CrossRef] [PubMed]

106. Chen, L.; Gong, M.-W.; Peng, Z.-F.; Zhou, T.; Ying, M.-G.; Zheng, Q.-H.; Liu, Q.-Y.; Zhang, Q.-Q. The marine fungal metabolite, dicitrinone B, induces A375 cell apoptosis through the ROS-related caspase pathway. *Mar. Drugs* 2014, 12, 1939–1958. [CrossRef] [PubMed]

107. Sasaki, M.; Tsuda, M.; Sekiguchi, M.; Mikami, Y.; Kobayashi, J.I. Perinadine A, a Novel Tetracyclic Alkaloid from Marine-Derived Fungus *Penicillium citrinum*. *Org. Lett.* 2005, 7, 4261–4264. [CrossRef] [PubMed]

108. Julianti, E.; Lee, J.-H.; Liao, L.; Park, W.; Park, S.; Oh, D.-C.; Oh, K.-B.; Shin, J. New polypolyketol metabolites from a marine-derived fungus *Penicillium sp.* *Org. Lett.* 2013, 15, 1286–1289. [CrossRef] [PubMed]

109. Gao, S.-S.; Li, X.-M.; Zhang, Y.; Li, C.-S.; Cui, C.-M.; Wang, B.-G. Comazaphilones A–F, azaphilone derivatives from the marine sediment-derived fungus *Penicillium commune* QSD-17. *J. Nat. Prod.* 2011, 74, 256–261. [CrossRef] [PubMed]

110. Myobatake, Y.; Takeuchi, T.; Karamochi, K.; Kuriyama, I.; Ishido, T.; Hirano, K.; Sugawara, F.; Yoshida, H.; Mizushima, Y. Pinophilins A and B, inhibitors of mammalian A-, B-, and Y-family DNA polymerases and human cancer cell proliferation. *J. Nat. Prod.* 2012, 75, 135–141. [CrossRef] [PubMed]

111. Iwamoto, C.; Minoura, K.; Oka, T.; Oh, H.; Hagishita, S.; Numata, A. Absolute stereostructures of novel cytotoxic metabolites, penostatins A–E, from a *Penicillium* species separated from an *Enteromorpha* alga. *Tetrahedron* 1999, 55, 14353–14368. [CrossRef] [PubMed]

112. Iwamoto, C.; Minoura, K.; Hagishita, S.; Nomoto, K.; Numata, A. Penostatins F–I, novel cytotoxic metabolites from a *Penicillium* species separated from an *Enteromorpha* marine alga. *J. Chem. Soc. Perkin 1* 1998, 3, 449–456. [CrossRef]

113. Chen, Y.-P.; Yang, C.-G.; Wei, P.-Y.; Li, L.; Luo, D.-Q.; Zheng, Z.-H.; Lu, X.-H. Penostatin derivatives, a novel kind of protein phosphatase 1B inhibitors isolated from solid cultures of the entomogenous fungus *Isaria tenue*. *Molecules* 2014, 19, 1663–1671. [CrossRef] [PubMed]

114. Snider, B.B.; Liu, T. Total Synthesis of (±)-Deoxypenostatin A. Approaches to the Syntheses of Penostatins A and B. *J. Org. Chem.* 2000, 65, 8490–8498. [CrossRef] [PubMed]

115. Barriault, L.; Ang, P.J.; Lavigne, R.M. Rapid Assembly of the Bicyclo [5.3.1] undecenone Core of Penostatin F: A Successive Diels-Alder/Claisen Reaction Strategy with an Efficient Stereochemical Relay. *Org. Lett.* 2004, 6, 1317–1319. [CrossRef] [PubMed]

116. Crawford, J.M.; Townsend, C.A. New insights into the formation of fungal aromatic polyketides. *Nat. Rev. Microbiol.* 2010, 8, 879–889. [CrossRef] [PubMed]

117. Liu, B.; Wang, H.-F.; Zhang, L.-H.; Liu, F.; He, F.-J.; Bai, J.; Hua, H.-M.; Chen, G.; Pei, Y.-H. New compound with DNA Topo I inhibitory activity purified from *Penicillium oxalicum* HSY05. *Nat. Prod. Rep.* 2015, 29, 2197–2202. [CrossRef] [PubMed]

118. Wang, Y.; Wang, L.; Zhuang, Y.; Kong, F.; Zhang, C.; Zhu, W. Phenolic polyketides from the co-cultivation of marine-derived *Penicillium* sp. WC-29–5 and *Streptomyces fradiae* 007. *Mar. Drugs* 2014, 12, 2079–2088. [CrossRef] [PubMed]

119. Rouiller, C.; Guittion, Y.; Valery, M.; Amand, S.; Prado, S.; Robiou du Pont, T.; Grovel, O.; Pouchus, Y.F. Automated detection of natural halogenated compounds from LC-MS profiles–Application to the isolation of bioactive chlorinated compounds from marine-derived fungi. *Anal. Chem.* 2016, 88, 9143–9150. [CrossRef] [PubMed]

120. Luo, H.; Li, X.-M.; Li, C.-S.; Wang, B.-G. Diphenyl ether and benzophenone derivatives from the marine mangrove-derived fungus *Penicillium* sp. MA-37. *Phytochem. Lett.* 2014, 9, 22–25. [CrossRef] [PubMed]

121. Nishida, H.; Tomoda, H.; Cao, J.; Araki, S.; Okuda, S.; Omura, S. Purpactins, new inhibitors of Acyl-CoA: Cholesterol acyltransferase produced by *Penicillium purpurogenum*. *J. Antibiot.* 1991, 44, 152–159. [CrossRef] [PubMed]
122. Chung, M.-C.; Lee, H.; Chun, H.; Kho, Y. Penicillide, a nonpeptide calpain inhibitor, produced by Penicillium sp. J. Microbiol. Biotechnol. 1998, 8, 188–190.

123. Zhao, D.-L.; Shao, C.-L.; Zhang, Q.; Wang, K.-L.; Shi, T.; Wang, C.-Y. Azaphilone and diphenyl ether derivatives from a gorgonian-derived strain of the fungus Penicillium pinophilum. J. Nat. Prod. 2015, 78, 2310–2314. [CrossRef] [PubMed]

124. Ren, H.; Liu, W.-W. Nidurufin as a new cell cycle inhibitor from marine-derived fungus Penicillium flavidorsum sp. ZLN29. Helv. Chim. Acta 2013, 96, 514–519. [CrossRef]

125. Harned, A.M.; Volp, K.A. The sorbicillinoid family of natural products: Isolation, biosynthesis, and synthetic studies. Nat. Prod. Rep. 2011, 28, 1790–1810. [CrossRef] [PubMed]

126. Li, D.; Chen, L.; Zhu, T.; Kurt, G.; O’Malley, G.J.; Murphy, R.A., Jr.; Cava, M.P. Aflatoxin precursors: Total synthesis of (+−)-averufin and (+−)-nidurufin. J. Org. Chem. 1985, 50, 5533–5537. [CrossRef]

127. Liu, W.; Gu, Q.; Zhu, W.; Cui, C.; Fan, G. Two new benzoquinone derivatives and two new bisorbicillinoids were isolated from a marine-derived fungus Penicillium terrestr. J. Antibiot. 2005, 58, 441–446. [CrossRef] [PubMed]

128. Liu, W.; Gu, Q.; Zhu, W.; Cui, C.; Fan, G. Dihydrotrichodimerol and tetrahydrotrichodimerol, two new bisorbicillinoids, from a marine-derived Penicillium terrestr. J. Antibiot. 2005, 58, 621–624. [CrossRef] [PubMed]

129. O’Malley, G.J.; Murphy, R.A., Jr.; Cava, M.P. Aflatoxin precursors: Total synthesis of (+−)-averufin and (+−)-nidurufin. J. Org. Chem. 1985, 50, 5533–5537. [CrossRef]

130. Cardoso-Martínez, F; José, M.; Díaz-Marrero, A.R.; Darias, J.; Cerella, C.; Diederich, M.; Cueto, M. Tanzawaic acids, a chemically novel set of bacterial conjugation inhibitors. PLoS ONE 2016, 11, e0148098. [CrossRef] [PubMed]

131. Shin, H.J.; Pil, G.B.; Heo, S.-J.; Lee, H.-S.; Lee, J.S.; Lee, Y.-J.; Lee, J.; Won, H.S. Anti-inflammatory activity of the activated production of silent metabolites in a marine-derived fungus by chemical mutagenesis strategy. Mar. Drugs 2017, 15, 329.

132. Chung, M.-C.; Lee, H.; Chun, H.; Kho, Y. Penicillide, a nonpeptide calpain inhibitor, produced by Penicillium sp. J. Microbiol. Biotechnol. 1998, 8, 188–190.
142. Chen, L.; Fang, Y.; Zhu, T.; Gu, Q.; Zhu, W. Gentisyl alcohol derivatives from the marine-derived fungus *Penicillium terrestre*. *J. Nat. Prod.* 2007, 71, 66–70. [CrossRef] [PubMed]

143. Wang, J.; Lu, Z.; Liu, P.; Wang, Y.; Li, J.; Hong, K.; Zhu, W. Cytotoxic Polyphenols from the Fungus *Penicillium expansum* 091 006 Endogenous with the Mangrove Plant *Excoecaria agallocha*. *Planta Med.* 2012, 78, 1861–1866. [CrossRef] [PubMed]

144. Lu, Z.; Zhu, H.; Fu, P.; Wang, Y.; Zhang, Z.; Lin, H.; Liu, P.; Zhuang, Y.; Hong, K.; Zhu, W. Cytotoxic polyphenols from the marine-derived fungus *Penicillium expansum*. *J. Nat. Prod.* 2010, 73, 911–914. [CrossRef]

145. Yang, J.; Huang, R.; Qiu, S.X.; She, Z.; Lin, Y. A new isobenzofuranone from the mangrove endophytic fungus *Penicillium* sp. (ZHS8). *Nat. Prod. Rep.* 2013, 27, 1902–1905. [CrossRef] [PubMed]

146. Kornprobst, J.-M.; La Barre, S. New Trends in Marine Natural Products. *J. Oceanogr. Mar. Res.* 2014, 2, 1000e109.

147. Zeng, Y.; Kamdem, R.S.; Orfali, R.S.; Dai, H.; Makhlofi, G.; Janiak, C.; Liu, Z.; Proksch, P. A new cyclohexapeptide, penitropeptide and a new polyketide, penitropone from the endophytic fungus *Penicillium tropicum*. *Tetrahedron Lett.* 2016, 57, 2998–3001. [CrossRef]

148. Koul, M.; Singh, S. *Penicillium* spp.: Prolific producer for harnessing cytotoxic secondary metabolites. *Anti-Cancer Drugs* 2017, 28, 11–30. [CrossRef] [PubMed]

149. Brady, S.F.; Simmons, L.; Kim, J.H.; Schmidt, E.W. Metagenomic approaches to natural products from free-living and symbiotic organisms. *Nat. Prod. Rep.* 2009, 26, 1488–1503. [CrossRef] [PubMed]

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