Chemical diversity, medicinal potentialities, biosynthesis, and pharmacokinetics of anthraquinones and their congeners derived from marine fungi: a comprehensive update†

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Marine fungi receive excessive attention as prolific producers of structurally unique secondary metabolites, offering promising potential as substitutes or conjugates for current therapeutics, whereas existing research has only scratched the surface in terms of secondary metabolite diversity and potential industrial applications as only a small share of bioactive natural products have been identified from marine-derived fungi thus far. Anthraquinones derived from filamentous fungi are a distinct large group of polyketides containing compounds which feature a common 9,10-dioxoanthracene core, while their derivatives are...

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generated through enzymatic reactions such as methylation, oxidation, or dimerization to produce a large variety of anthraquinone derivatives. A considerable number of reported anthraquinones and their derivatives have shown significant biological activities as well as highly economical, commercial, and

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biomedical potentialities such as anticancer, antimicrobial, antioxidant, and anti-inflammatory activities. Accordingly, and in this context, this review comprehensively covers the state-of-art over 20 years of about 208 structurally diverse anthraquinones and their derivatives isolated from different species of marine-derived fungal genera along with their reported bioactivity wherever applicable. Also, in this manuscript, we will present in brief recent insights centred on their experimentally proved biosynthetic routes. Moreover, all reported compounds were extensively investigated for their in-silico drug-likeness and pharmacokinetics properties which intriguingly highlighted a list of 20 anthraquinone-containing compounds that could be considered as potential drug lead scaffolds.

1 Introduction

Throughout history, different natural sources have been used for treatment of diseases, and more recently as sources and valuable suppliers of biologically active compounds with diverse bioactivities that can be developed to be used in new drugs.\textsuperscript{1–6} Intriguingly, marine organisms and microorganisms were among the valuable sources of new natural products.\textsuperscript{2} Microbial secondary metabolites have been known for their chemical diversity and a broad range of bioactivities.\textsuperscript{5,6} Marine microorganisms are considered highly productive sources of physiologically active compounds including peptides, polyketides, terpenes, and alkaloids.\textsuperscript{6–10} Some marine-based compounds have been approved as drugs with different pharmacological uses,\textsuperscript{11,12} while several others are under different clinical trials before their approval as new drugs.\textsuperscript{11}

During the last few decades, numerous drug discovery programs focused on marine-derived microbial natural products due to their great potential for the production of structurally diverse biologically active secondary metabolites.\textsuperscript{11,14} Among the hot microbes responsible for the production of interesting compounds, fungi, served as the primary source for mining the first reported antibiotic, penicillin, whereas they are still one of the main sources for discovering novel bioactive compounds from different niches including the marine fungi which have high biological diversifications.\textsuperscript{13,16} Therefore, the bioactive secondary metabolites recovered from the marine-derived fungi have gained great interest as promising sources of therapeutics. Interestingly, more than a thousand compounds have been isolated from marine fungi with a wide range of bioactivities including antiviral, anticancer, and antibacterial activities.\textsuperscript{17} Even though only one bioactive compound, cyclosporine A, has been approved for clinical use in the market. This might be attributed to problems in the optimization methods or the screening approaches of natural product discovery.\textsuperscript{18}

Studying the marine-derived fungi has been started around two centuries ago when the first fungal species, Sphaeria posidoniae (Halothia posidoniae) was reported on a rhizome of the marine grass Posidonia oceanica \textit{in 1846}.\textsuperscript{19} Marine fungi have been isolated from different habitats including algae, mobile, and sessile invertebrates, sediments, marine mammals, and driftwood from different marine locations.\textsuperscript{20} Despite the importance of marine fungi as a promising source for novel bioactive secondary metabolites, marine fungi are still less investigated sources for natural product discovery programmes compared to other niches of fungi.\textsuperscript{18,21} Although the estimated number of fungal species on the earth is ranging from 1.5 to 5 million species, only around 1100 species have been exclusively isolated from the marine niche.\textsuperscript{18,28}

Marine-derived fungi produce various classes of different compounds with both chemical and biological diversities.\textsuperscript{22,23} For instance, they produce varieties of bioactive compounds such as terpenes, alkaloids, peptides, and polyketides.\textsuperscript{18} Polyketides have been reported in many previous studies as dominant natural products from marine filamentous fungi.\textsuperscript{24,25} They are a large group of complex chemical architectures such as anthraquinones, hydroxyanthraquinones, naphthoquinones, macrofides, flavonoids, polyenes, and tetracyclines. Around 700 anthraquinones and their derivatives have been reported from different natural sources, while anthraquinones are widely produced by marine filamentous fungi.\textsuperscript{26} Chemically, anthraquinones are a group of polyketides of the quinone family with a basic cyclic scaffold of three fused benzene rings including two ketone groups on the central 9, 10-carbons with different functional groups\textsuperscript{26} or by enzymatic reaction of the rings or the keto groups such as reduction, oxidation, dehydration or dimerization to result in a wide range of derivatives.\textsuperscript{27} Interestingly, many reported anthraquinones and their derivatives exhibited potent biological activities including antitumor, antibacterial, antifungal, antioxidant, and immunomodulatory bioactivities.\textsuperscript{16}

Drug-likeness and pharmacokinetics properties using SWISSADME online platform, which intriguingly highlighted a list of 20 anthraquinone containing compounds (ESI†) that could be considered as potential drug leads scaffolds. Such a massive connection between chemical spaces and bioactivities highlights the huge capacity of marine-derived fungi as an attractive biological source that is worth further exploitations with distinguished anticipations for the global pharmaceuticals industries.

Several interesting review articles have focused recently on the marine anthraquinones and their derivatives such as Fouillaud \textit{et al.} who reported the chemical diversity, specific bioactivities, biosynthetic pathways, biological sources, and the producing fungal genera of tens of marine-derived anthraquinones and their derivatives discovered before 2016.\textsuperscript{16} Also, another review by Masi and Evidente presented a comprehensive update of the bioactive fungal anthraquinones and analogues including the marine-derived anthraquinones produced via the acetate route over the period 1966–2020 with their sources, biosynthesis, biological activities, and industrial applications.\textsuperscript{28} Whereas Greco
et al. in their recent review critically described the marine-derived anthraquinones which showed anti-tumor activity as well as their mutagenic and genotoxic potentialities. Herein and as a part of our continuous program on pharmacologically active fungal natural products, we are presenting an extensive coverage over the period 2000–2020 for 208 anthraquinones and their derivatives, extensively reported from different marine-derived fungal genera such as Nigrospora, Aspergillus, Penicillium, Stemphylium, Alternaria, Eurotium, Trichoderma, Halorosellinia, and Fusarium. In addition, we reported here their different biological activities, drug-likeliness and pharmacokinetics properties wherever applicable, in addition to a general overview of their proposed biogenesis pathway. The investigation of in-silico drug-likeliness and pharmacokinetics properties of the marine-derived anthraquinones and their derivatives in this review could be advantageous in predicting the possibility of anthraquinones as drug candidates.

2 General biosynthetic pathway of anthraquinones

There have been extensive studies since the 1950s to determine the biosynthetic pathway of anthraquinones and the related natural products called xanthones. Feeding experiments using labelled acetates in fungi, first reported by Birch et al., showed that anthraquinone and xanthones are biosynthesized by polyketides. Genome sequencing and genetic transformation experiments have confirmed that the core structure of anthraquinones is synthesized in fungi by non-reducing polyketide synthase (nrPKS). This class of PKS share a common domain architecture which consists of an SAT (starter unit-ACP transacylase), KS (ketosynthase), AT (acyl transferase), PT (product template), and ACP (acyl carrier protein) (Fig. 1A). The biosynthesis of anthraquinones can be generalized using emodin (14) and endocrocin as examples (Fig. 1B). The nrPKS (MdpG) synthesize the polyketide, which is then cyclized with the loss of two water molecules by the PT domain. The polyketide is released by a metallo-hydrolase protein (MdpF) to obtain atrochrysone carboxylic acid, which can in most cases, undergo decarboxylation by a decarboxylase (MdpH1). This is followed by spontaneous dehydration and oxidation by an anthroneoxidase (MdpH2) to afford emodin (14). Some reports have also described that the final oxidation step could occur spontaneously. Further modification by tailoring proteins give rise to a huge diversity, these include methylation, dehydration, and dimerization.

Fig. 1 General biosynthetic pathway of anthraquinones in fungi. (A) domain architecture of the non-reducing polyketide synthase. (B) Biosynthetic pathways of the anthraquinones emodin (14) and endocrocin. The isotope labelling pattern is shown black bold lines and the polyketide starter unit is indicated in red.
3 Chemistry and medicinal potentialities of anthraquinones and their congeners derived from marine-derived fungi

In this manuscript, we provide extensive insights about chemical and biological investigations centered on anthraquinones and their derivatives exclusively derived from marine fungi. For the handling of this documentation, all isolated anthraquinones are classified and tabulated according to the marine fungal genera where they have been recovered along with their recorded biological potentialities whenever applicable.

3.1 Anthraquinones isolated from Nigrospora sp.

Ten anthraquinones or their derivatives 1–10 were reported from the marine-derived fungus Nigrospora sp. Nigrodiquinone A (1) was isolated for the first time as a new hydroanthraquinone dimer from the zoanthid-derived fungus Nigrospora sp.17 Another four anthraquinone derivatives namely 4a-epi-9α-methoxydihydrodeoxybostrycin (2), 10-deoxybostrycin (3), 3,5,8-trihydroxy-7-methoxy-2-methyl-anthracene-9,10-dione (4), and austrocortirubin (5) were reported from both sea anemone-derived and zoanthid-derived fungus Nigrospora sp.,17 while austrocortirubin (5) was also recorded from the sea fan-derived fungus Fusarium sp.,19 and the mangrove endophytic fungi Guignardia sp.20 and Halorosellinia sp.21 Although nigrodiquinone A (1) showed no antiviral or antibacterial activities,17 compounds 4 and 5 displayed mild antiviral activity with IC₅₀ values of 93.7 μM against coxsackievirus and 74.0 μM against the respiratory syncytial virus (RSV), respectively.

Notably, compounds 2 and 3 showed potent antibacterial activity against both the Gram-positive bacteria, Staphylococcus aureus and Micrococcus tetragenus and the Gram-negative bacteria, Escherichia coli (E. coli), Vibrio anguillarum (V. anguillarum), and V. parahemolyticus. Compound 3 displayed MIC of equal to or less than 2.5 μM against all tested bacteria, whereas compound 2 exhibited MIC of equal to or less than 2.5 μM against all tested bacteria except V. anguillarum and V. parahemolyticus against which it showed MIC value of 25.0 μM.28 In addition, compound 3 showed potent cytotoxic activity against the human lung cancer cell line, A-549 with an IC₅₀ value of 4.56 μM,29 while austrocortirubin (5) displayed an IC₅₀ value of 6.3 μM against the human breast adenocarcinoma cells, MCF-7.39

Further anthraquinone derivatives 6–10 were previously isolated from the sea anemone-derived fungus Nigrospora sp.38 Also, some of these anthraquinone derivatives have been isolated from other marine fungal species such as Fusarium sp. PSU-F14 from which compounds 6–8 and 10 were recovered,39 while compounds 7, 8 and 10 were also isolated from the marine-derived fungus Aspergillus sp.42

Compounds 6–10 exhibited different interesting biological activities. For instance, nigrosporin B (6) displayed modest antimycobacterial activity,43 phytoxic activity,44 and potent antibacterial and cytotoxic activity.38 Also, 4-deoxybostrycin (9) showed modest anti-mycobacterial activity,42 potent antibacterial activity,42 and moderate antitumor activity.45 Nigrosporin B (6) and 4-deoxybostrycin (9) displayed potent antibacterial activity against both the Gram-positive bacteria, Bacillus subtilis (B. subtilis), B. cereus, Staphylococcus albus (S. albus), S. aureus, and Micrococcus tetragenus and the Gram-negative bacteria E. coli, V. anguillarum, and V. parahemolyticus with MIC values equal to or less than 2.5 and 3.12 μM, respectively.38 Moreover, both compounds exhibited modest anti-mycobacterial activity against several mycobacterial species including two multidrug-resistant Mycobacterium tuberculosis (M. tuberculosis) with MIC values of less than 30.0 μg mL⁻¹.41

Fig. 2 Chemical structures of compounds 1–10.
An additional example of anthraquinones isolated from _Nigrospora_ sp. with multiple bioactivities is tetrahydrobostrycin (8) which exhibited moderate to high antibacterial activity against the Gram-positive bacteria, _B. subtilis_ and _B. cereus_ (MIC values of 2.5 μM), _S. aureus_ and _Micrococcus luteus_ (MIC values of 2.5 μM), and _Micrococcus tetragenus_ (MIC value of 1.25 μM). Compound 8 also displayed good antibacterial activity against the Gram-negative bacteria _E. coli_ (MIC value of 6.25 μM), _V. anguillarum_ (MIC value of 1.56 μM), and _V. parahemolyticus_ (MIC value of 12.5 μM). Additionally, it exhibited potent activity against _M. tuberculosis_ with a MIC value of 12.50 μg mL⁻¹ and was also active as antimalarial agent against _Plasmodium falciparum_ with an IC₅₀ value of 7.94 μg mL⁻¹ (Fig. 2).

Fig. 3 Chemical structures of compounds 11–44.
3.2. Anthraquinones isolated from *Aspergillus* sp.

*Aspergillus* was the richest source of marine anthraquinones and their derivatives among all marine-derived fungi with 73 reported compounds including the previously mentioned 7, 8, and 10 as well as other seventy anthraquinones 11–80. For instance, thirteen compounds 11–23 were isolated from the marine-derived fungus *Aspergillus glaucus* (*A. glaucus*). Aspergiolide A (11), which features a naphtho[1,2,3-de]chromene-2,7-dione skeleton was isolated as a novel anthraquinone derivative from the marine-derived fungus *A. glaucus*. Aspergiolide B (12) was isolated from *A. glaucus* as a new analogue for aspergiolide A (11). Aspergiolides A and B (11 and 12) exhibited potent cytotoxic activities against both adenocarcinoma human alveolar basal epithelial cell line, A-549 with IC₅₀ values of 0.13 and 0.24 μM and human leukemia cell line, HL-60 with IC₅₀ values of 0.28 and 0.51 μM, respectively, indicating that methylation of one hydroxyl group in aspergiolide A (11) to be a methoxy group in aspergiolide B (12) slightly affected the cytotoxicity of aspergiolide A.

Physcion (13) was also isolated from other species of *Aspergillus* such as *A. glaucus*, *A. wentii*, and the halotolerant *A. glaucus* as a new analogue for aspergiolide A (11). Aspergiolides A and B (11 and 12) exhibited potent cytotoxic activities against both adenocarcinoma human alveolar basal epithelial cell line, A-549 with IC₅₀ values of 0.13 and 0.24 μM and human leukemia cell line, HL-60 with IC₅₀ values of 0.28 and 0.51 μM, respectively, indicating that methylation of one hydroxyl group in aspergiolide A (11) to be a methoxy group in aspergiolide B (12) slightly affected the cytotoxicity of aspergiolide A.

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variecolor\(^2\) besides the marine-derived fungus Microsporum sp.\(^3\). Physcion (13) displayed a wide array of biological activities including cytotoxic activity against human cervical carcinoma HeLa cells,\(^4\) moderate antifungal activity against Trichophyton mentagrophytes with a MIC value of 25.0 μg mL\(^{-1}\) and weak antifungal activity against both C. albicans and Cryptococcus neoformans with MIC value of 50.0 μg mL\(^{-1}\).\(^5\) It also exhibited weak free radical scavenging activity against 1,1-diphenyl-2-picrylhydrazyl (DPPH) with an IC\(_{50}\) value of 99.4 μg mL\(^{-1}\).\(^6\)

Furthermore, emodin (14) which was reported from the marine-derived fungus A. glaucus, was also recovered from many other marine fungal species such as Penicillium citrinum (P. citrinum),\(^7\) Trichoderma aureoviride (T. aureoviride),\(^8\) Monodictys sp.,\(^9\) Gliocladium sp.,\(^10\) Paecilomyces sp.,\(^11\) Eurotium rubrum (Eu. rubrum)\(^12\) and A. versicolor.\(^13\) Emodin (14) showed moderate antibacterial against Pseudomonas putida with a MIC value of 25.0 μM\(^14\) and significant anti-mycobacterial activity against M. tuberculosis with a MIC value of 12.5 μg mL\(^{-1}\) and modest antifungal activity against Candida albicans (C. albicans) with an IC\(_{50}\) value of 11.0 μg mL\(^{-1}\).\(^15\) Noteworthy, it showed potent cytotoxic activity against both oral human epidermoid carcinoma cell line, KB and human breast cancer cell line, MCF7 with IC\(_{50}\) values of 0.88 and 2.8 μg mL\(^{-1}\), respectively.\(^16\)

Further anthraquinones 17 and 18, and 20 which were isolated from both A. glaucus\(^17\) and the halotolerant A. variecolor,\(^18\) showed variable bioactivities. Questin (17) and catenarin (18) exhibited DPPH radical scavenging activity\(^19\) and potent antibacterial activity against Brevibacillus brevis with a MIC value of 1.0 μg mL\(^{-1}\),\(^20\) respectively, while (+)-variecolorquinone A (20) displayed positive cytotoxicity against the human hepatocellular carcinoma cell line, BEL-7402, mouse lymphoma cell line, P388, human leukemia cell line, HL-60, and adenocarcinoma human alveolar basal epithelial cells, A-549 with IC\(_{50}\) values of 114.0, 266.0, 309.0, and 3.0 μM, respectively.\(^21\)

Notably, the known anthraquinone dimer 21, as well as two new isomers of anthraquinone dimer 22 and 23, were also isolated from A. glaucus.\(^22\) However, compound 21 was not evaluated for any relevant bioactivity, the trans isomer of emodiphycosin bianthrone (22) showed good cytotoxicity against the cell lines; A-549 and HL-60 with IC\(_{50}\) values of 9.2 and 7.8 μM, respectively. On the other hand, its cis isomer 23 was less active as its IC\(_{50}\) values were 14.2 and 44.0 μM, respectively,\(^23\) suggesting that isomerization has affected the cytotoxicity of compound 22.

Additional thirty anthraquinones 24–54 have been isolated from the marine-derived fungus A. versicolor. Two new anthraquinone dimers 24 and 25 besides three other known closely related anthraquinone derivatives 26–28 were isolated from the marine-derived fungus A. versicolor.\(^24\) Averatin (26) and its derivative 1’-O-methyl-averatin (27) were also isolated earlier from the marine-derived fungus P. purpureogenum G59 ref. 65 and Aspergillus sp. SCSIO F063,\(^25\) whereas averuquin (28) was formerly reported from the marine-derived fungus Aspergillus sp. SCSIO F063.\(^26\)

Compounds 24 and 25 showed selective antibacterial activity against the Gram-positive bacterium, S. aureus using the disk diffusion method at a concentration of 30.0 μg per well,\(^27\) whereas the same study revealed that compound 24 had a selective cytotoxic activity against human CNS cancer cells, XF-498 with an IC\(_{50}\) value of 22.39 μg mL\(^{-1}\).\(^28\) In addition, averantin (26) and its derivative 1’-O-methyl-averantin (27) displayed a weak antitumor activity against the bone marrow cancer cell line, K562 at a concentration of 100.0 μg mL\(^{-1}\).\(^29\) Another study mentioned that compound 27 exhibited modest cytotoxic activity against the human glioblastoma SF-268, human breast adenocarcinoma MCF-7 and human large-cell lung carcinoma NCI-H460 cell lines with IC\(_{50}\) values ranging from 33.59 to 44.22 μM, whilst compounds 26 and 28 displayed weak to moderate cytotoxic activity against MCF-7 with IC\(_{50}\) values of 45.47 and 29.69 μM, respectively.\(^30\) Also, compounds 26 and 27 displayed potent antioxidant activity, whereas compound 28 exhibited weak antioxidant activity in terms of antioxidant capacity compared to Trolox\(^31\) suggesting that the presence of oxygen in the side chain of the anthraquinones may play role in their antioxidant activity.

Additionally, compound 26 displayed promising antibacterial activity against different strains of the Gram-positive bacteria, Streptococcus pyogenes (Str. pyogenes) and S. aureus with MIC values of equal to or less than 3.13 μg mL\(^{-1}\), while its 1’-O-methylated derivative, 27 showed weaker antibacterial activity as it was only active against one strain of Str. pyogenes with a MIC value of 6.25 μg mL\(^{-1}\) with no activity against the other strain of Str. pyogenes or any strain of S. aureus up to a concentration of 12.5 μg mL\(^{-1}\),\(^32\) indicating that O-methylation at position 1 greatly affected the antibacterial activity of averantin (26).

Compound 29 which is another derivative of averantin (26) was isolated from another marine-derived fungus A. versicolor EN-7.\(^33\) Compound 29 showed weak antibacterial activity against only E. coli at a concentration of 20.0 μg per disk with no activity against S. aureus,\(^34\) suggesting that the O,O’-dimethylation of averantin (26) decreased its antibacterial activity against the Gram-positive bacteria.

The aflatoxin, averufin (30) and its O-methylated derivatives 6-O-methyl-averufin (31) and 6,8-O’,O’-dimethyl-averufin (32) were also isolated from different strains of the marine-derived fungus A. versicolor,\(^35\) whereas averufin (30) was also isolated from other species of Aspergillus such as A. niger\(^36\) and A. nidulans.\(^37\) Averufin (30) exhibited different bioactivities including potent antioxidant activity in terms of Trolox equivalent antioxidant capacity,\(^38\) weak cytotoxic activity,\(^39\) and moderate inhibitory activity against the multiplication of Tobacco Mosaic virus,\(^40\) in addition to weak antibacterial activity against the Gram-positive Str. pyogenes and S. aureus with MIC values equal to or less than 12.5 μg mL\(^{-1}\).\(^41\) On the other hand, neither 6-O-methyl-averufin (31) nor 6,8-O’,O’-dimethyl-averufin (32) showed any antimicrobial activity or anti-neuroinflammatory effect,\(^42\) respectively.

Moreover, further eight bioactive compounds 33–40 were also isolated from the marine-derived funguses A. versicolor\(^43\) including versicolorin B (33), averufanin (35) nidurufin (37), and versicinol (39) as well as their derivatives 1’-hydroxyversicinol B (34), noraverufanin (36), 6,8-O’,O’-dimethylnidurufin (38) and 6,8-O’,O’-dimethyl-versicinol (40), respectively.
respectively. Both versicolorin B (33) and its hydroxyl derivative, 1'-hydroxyversicolorin B (34) showed potent antioxidant activity as they displayed antioxidant capacity approximately equivalent to Trolox,67 while an old study revealed that 1'-hydroxyversicolorin B (34) (UCT1072M1) had potent cytoxicity against the human colon adenocarcinoma, HeLa S3 and the human lung giant cell carcinoma, Lu-65 with IC50 values of 2.1 and 2.2 μM, respectively.74

Indeed, averufanin (35) displayed a good antioxidant activity in terms of antioxidant capacity to Trolox,67 and weak activity against both acyl-CoA: cholesterol acyltransferase type 1 and 2 in the cell-based assay with IC50 values of 28.0 and 12.0 μM, respectively,75 whereas noraverufanin (36) exhibited a weak HIV latency–reversal activity with reactivation of 43.3% at concentration of 10.0 μM.75 Nidurufin (37) which has been also isolated from the marine fungus A. niger76 as well as P. purpurogenum G59,65 showed weak antitumor activity against the bone marrow cancer cell line, K562 with an inhibition rate percentage of 25.5% at a concentration of 100.0 μg mL−165 and moderate antioxidant capacity with 0.62 as Trolox equivalent as antioxidant.67

Another previous study showed that nidurufin (37) had exhibited strong anticancer activity against the A-549 cells, the human ovarian cancer cells, SK-OV-3, the human skin cancer cells, SK-MEL-2, the human CNS cancer cells, XF-498, and the human colon cancer HCT-15 with IC50 values of 1.83, 3.39, 3.16, 1.78, and 2.2 μg mL−1 beside good antibacterial activity against different strains of the Gram-positive bacteria Str. pyogenes and S. aureus with MIC values of equal to or less than 3.13 μg mL−1.8a

Compound 38 (6,8-O,O'-dimethyl-nidurufin), showed weak antibacterial activity against the Gram-positive S. aureus as well as the Gram-negative E. coli with inhibition zones of 7 and 6.5 mm, respectively using the disk diffusion method at a concentration of 20.0 μg per disk,69 suggesting that the new derivatization by O,O'-dimethylation in position 6 and 8 in this compound had affected the antibacterial activity of the parent metabolite, nidurufin (37) which showed better antibacterial activity when tested against the Gram-positive bacteria as discussed above.

Versiconol (39) exhibited weak anticancer activity against the A-549 cells, the SK-OV-3 cells, the SK-MEL-2 cells, the XF-498 cells, and the HCT-15 cells with IC50 values of 20.45, 15.29, 15.86, 23.73, and 19.2 μg mL−1, respectively,8a whilst its O,O'-dimethylated derivative, 6,8-O,O'-dimethyl-versiconol (40) showed selective weak antibacterial activity against S. aureus with inhibition zones of 6.5 mm using disk diffusion method at a concentration of 20.0 μg per disk when tested against both S. aureus and E. coli.69

Other bioactive compounds isolated from the marine fungus A. versicolor were compounds 41 and 42, 47 and 48, and 50–54.59,69,76 1-methyl-emodin (41) which is an O-methylated derivative of emodin (14) and both were isolated from A. versicolor,79 exhibited better cytotoxic activity than emodin (14) itself against human epidermoid carcinoma cell line, KBV200 with an IC50 value of 190.81 μM,49 although 41 did not show any cytotoxicity against the human leukemia cell line, CCRF-CEM and some other solid tumors including the human lung H-125, human colon HCT-116, and human liver Hep-G2 cells.76 On the other hand, compound 41 showed less inhibitory activity against Hepatitis C virus (HCV) protease than its parent 14 with IC50 values of 40.2 and 22.5 μg mL−1, respectively.76 The same study showed that the new metabolite from A. versicolor, isorhodoptilometrin-1-methyl-ether (42) displayed moderate antibacterial activity against B. cereus, S. subtilis, and S. aureus at a concentration of 50.0 μg per disk and mild selective cytotoxicity against the Hep-G2 cell line.76

Additionally, 1-hydroxy-2-methyl-anthraquinone (47) and its novel dimethoxy derivative; 2-(dimethoxy methyl)-1-hydroxy-9,10-anthraquinone (48) were evaluated for their antibacterial activity against two strains of methicillin-resistant S. aureus (MRSA) (CGMCC 1.12409 and ATCC 43300) and three strains of Vibrio (V. rotiferianus, V. vulnificus, and V. campbellii). Noteworthy, the dimethoxy derivative 48 was highly active against the MRSA strains showing MIC values of 7.8 and 3.9 μg mL−1, respectively, and was moderately active against the Vibrio strains with MIC values ranging from 15.6 to 62.5 μg mL−1.79 The same study mentioned that a molecular docking study was conducted to explain the cause behind this antimicrobial activity revealing the least binding energy of compound 48 with both AmpC β-lactamase and topoisomerase IV (Topo IV).59 On the other hand, its parent compound 47 displayed potent larvicidal activity against the larvae of Aedes aegypti with an IC50 value of 1.8 μg mL−1.77

Moreover, another anthraquinone derivative, damnacanthal (50) which was reported from A. versicolor25 showed strong larvicidal activity against the larvae of Aedes aegypti with an IC50 value of 7.4 μg mL−177 and weak antibacterial activity against some strains of MRSA and Vibrio with MIC values ranging from 31.3 to 125.0 μg mL−1.79 Similarly, xanthopurpurin (51) showed weak antibacterial properties against some strains of MRSA and Vibrio with the same MIC range of damnacanthal (50).59 Also, compound 51 previously showed strong antiplatelet aggregation activity via inhibition of collagen-induced aggregation.78 In addition, a chemically related rubiadin (52) showed a strong inhibitory activity on the formation of advanced glycation end products with an IC50 value of 179.31 μM.79 Notably, its hydroxylated derivative; 6-hydroxyrubiadin (53) displayed potent inhibitory activity on phosphatase of regenerating liver-3 with an IC50 value of 1.3 μg mL−1 causing inhibition of migration of phosphatase of regenerating liver-3 expressed tumor cells with no cytotoxicity.80

Additional four derivatives 55–58 were isolated from the marine-derived fungus A. wentii.80,81 Wentiquinone C (55) showed no free radical scavenging activity up to a concentration of 1000.0 μg mL−149 whereas compounds 56–58 were not tested for any relevant bioactivity.81

Further derivatives including compounds 59–64 were isolated from the halotolerant fungus A. variicolor,96 while compounds 65–67 were reported from A. nidulans.74 Compounds 59 and 60 exhibited potent DPPH radical scavenging activity (antioxidant activity) with IC50 values of 6.0 and 11.0 μM, respectively79 suggesting that the O-methylation of eurolitone (59), slightly affected its antioxidant activity. Interestingly, Questinol (62) which was also isolated from the marine-derived fungi
**Talaromyces stipitatus** KUFA 0208 \(^{82}\) and **Eu. amstelodami**, \(^{81}\) displayed significant anti-inflammatory activity via different mechanisms including inhibition of both nitric oxide and prostaglandin E2 production and, inhibition of the production of some inflammatory cytokines such as interleukin-1β, IL-10, IL-6, and tumor necrosis factor-α. Compound 62 also showed slight inhibitory activity against cyclooxygenase-2 (COX-2) expression at a concentration of 200.0 μM.\(^{86}\) In addition, compound 62 exhibited potent anti-obesity activity with a 60% reduction in the stained lipids with an IC\(_{50}\) value of 0.95 μM, while the chemically related compound, fallacinol (63) showed no significant anti-obesity activity.\(^{82}\) Interestingly, versicolorin C (65) displayed selective potent antibacterial activity against both *E. coli* and *V. parahaemolyticus* with a MIC value of 1.0 μg mL\(^{-1}\) and, against *V. anguillarum* and *Edwardsiella ictaluri* with MIC values of 4.0 and 8.0 μg mL\(^{-1}\), respectively, whilst the closely related congener isoversicolorin C (66) displayed selective potent antibacterial activity against both *V. alginolyticus* and *Edwardsiella ictaluri* with MIC values of 1.0 and 4.0 μg mL\(^{-1}\), respectively.\(^{73}\) Further, twelve anthraquinones including three non-halogenated ones 68–70, seven new chlorinated anthraquinone derivatives 71–77, and two new brominated anthraquinone derivatives 78 and 79 were isolated from the marine-derived fungus *Aspergillus sp.* SCSIO F063,\(^{66}\) in addition to compound 80 which was reported from another marine-derived fungus *Aspergillus sp.* SF-6796.\(^{72}\) Compounds 68–70 are chemically related to each other and are derivatives of averantin (26) which was isolated in the same study as a metabolite from *Aspergillus sp.* SCSIO F063,\(^{66}\) while it was isolated earlier from the marine-derived fungus *A. versicolor*.\(^{74}\) Averantin-1'-butyl-ether (70) exhibited weak cytotoxicity against SF-268 and MCF-7 cell lines with IC\(_{50}\) values of 47.19 and 40.47 μM, respectively, revealing slightly better cytotoxicity than its parent; averantin (26) which only showed activity against the MCF-7 cell line with an IC\(_{50}\) value of 45.47 μM,\(^{66}\) suggesting that the structural modification in 70 has improved its bioactivity. By contrast, neither compound 68 nor 69 displayed any cytotoxicity against all tested human cell lines including NCI-H460, SF-268, and MCF-7 ref. 66 indicating that O-methylation of averantin (26) in compounds 68 and 69 may negatively influence their cytotoxicity. It is noteworthy that the chlorinated anthraquinone derivative, 72 exhibited potent cytotoxicity against NCI–H460, SF-268, and MCF-7 cells with IC\(_{50}\) values of 7.42, 7.11, and 6.64 μM, respectively. While 71 showed weak cytotoxicity against only the MCF-7 cell line with an IC\(_{50}\) value of 36.41 μM, 73 displayed better cytotoxic activity against the three cell lines; NCI–H460, SF-268, and MCF-7 with IC\(_{50}\) values of 37.19, 34.06 and 26.09 μM, respectively.\(^{66}\) The other chlorinated anthraquinones, 75 and 77 demonstrated weak to modest cytotoxic activity against only the MCF-7 cell line with IC\(_{50}\) values of 49.53 and 24.38 μM, respectively. The same study revealed that from the two isolated brominated anthraquinones, only 78 displayed modest cytotoxicity against NCI–H460, SF-268, and MCF-7 cell lines with IC\(_{50}\) values of 18.91, 24.69, and 25.62 μM, respectively.\(^{66}\) Furthermore, another bioactive derivative of averantin (26) isolated from *Aspergillus sp.* is 6,8,1'-O,O',O'-trimethyl-averantin (80) which showed an anti-neuroinflammatory effect via different mechanisms including suppression of the overproduction of many pro-inflammatory mediators including COX-2, prostaglandin E2, and nitric oxide in lipopolysaccharide-activated BV2 microglial cells\(^{75}\) (Fig. 3 and 4).

### 3.3. Anthraquinones from *Penicillium sp.*

Furthermore, eighteen compounds 81–98 besides the previously reported compounds 14, 17, 26, 27, and 37 were isolated from different species of the marine-derived fungus *Penicillium*. Indeed, penicillanthranin A (81) and B (82) which are anthraquinone-citrinin derivatives, as well as chrysophanol (83) and ω-hydroxyemodin (84), were isolated from the marine fungu *P. citrinum* PSU-F51.\(^{83}\) Penicillanthranin A (81) and chrysophanol (83) exhibited selective antibacterial activity against the Gram-positive *S. aureus* ATCC25923 with MIC value of 16.0 μg mL\(^{-1}\) for both compounds and MRSA SK1 with MIC values of 16.0 and 64.0 μg mL\(^{-1}\), respectively, while compounds 82 and 84 were not screened for their antimicrobial activity in the same study.\(^{81}\) Interestingly, some earlier studies revealed that ω-hydroxyemodin (84) showed moderate activity against MRSA SK1 and mild activity against *S. aureus* ATCC 25592 with MIC values of 32.0 and 200.0 μg mL\(^{-1}\), respectively,\(^{54}\) in addition to good anti- mycobacterial activity against *M. tuberculosis* H37Ra with a MIC value of 12.5 μg mL\(^{-1}\).\(^{84}\) It also showed potent cytotoxicity against the human oral epidermoid carcinoma KB cells with an IC\(_{50}\) value of 4.5 μg mL\(^{-1}\), and weak cytotoxic activity against both the human breast cancer cells, MCF7 and the human lung carcinoma cells, NCI–H187 with IC\(_{50}\) values of 22.0 and 39.0 μg mL\(^{-1}\), respectively.\(^{81}\) In contrast, penicillanthranin A (81) showed selective cytotoxicity to the KB cell lines with an IC\(_{50}\) value of 30.0 μg mL\(^{-1}\).\(^{54}\)

Another bioactive metabolite, 2-acetoxy-7-chlorocitroterosine (85) which was first recovered from a mangrove-derived fungus *P. citrinum* HL-5126 ref. 84 demonstrated moderate antibacterial activity against *S. aureus* and significant activity against *V. parahaemolyticus* with MIC values of 22.8 and 10.0 μg mL\(^{-1}\), respectively,\(^{84}\) suggesting that such modification in its structure by acetylation, chlorination, and O-methylation of ω-hydroxyemodin (84) resulted in significant improvement in its anti-bacterial activity. Further anthraquinone derivatives discovered from the marine fungus *P. oxalicum*, including citreoresein-3-O-sulphate (86), emodin-3-O-sulphate (87), and aloe-emodin (88) were not tested for any relevant activity.\(^{85}\) However, other previous studies revealed that aloe-emodin (88) displayed modest antimalarial activity against *Plasmodium falciparum* (MRC-2) with an EC\(_{50}\) value of 22.0 μg mL\(^{-1}\) and weak anti-microbial activity against the Gram-positive bacteria, *S. aureus*, *S. epidermidis*, *B. cereus*, *S. subtilis*, and *Micrococcus kristinae*, and the Gram-negative bacteria, *E. coli*, *Enterobacter aerogenes*, *Proteus vulgaris*, and *Shigella sonnei* with MIC values ranging from 62.5 to 250.0 μg mL\(^{-1}\).\(^{87}\)

Additional ten bioactive compounds including eight newly isolated anthraquinone–amino acid conjugates, namely emodacinamide A–H \(^{89–96}\) along with the previously isolated anthraquinone derivatives; emodic acid (97) and 2-chloro-1,3,8-trihydroxy-6 (hydroxymethyl)-anthracene-9,10 dione (98), were isolated from the marine fungus *Penicillium* sp. SCSIO sof101.\(^{88}\)
Emodacidamides A–H (89–96) displayed immunomodulatory activity with inhibitory activity against IL-2 production from Jurkat cells. Intriguingly, emodacidamides A (89), C (91), and E (93) showed potent IL-2 inhibitory activity with IC₅₀ values of 4.1, 5.1, and 5.4 μM, respectively. Meanwhile, emodic acid (97) showed no remarkable inhibition of IL-2 secretion at a concentration of 20.0 μM, indicating that amino acid conjugation with the anthraquinone derivatives enhanced their inhibitory effect on IL-2 secretion.

On the other side, emodic acid (97) which was previously isolated from the marine endophytic fungus Eu. rubrum, 38 evoked potent inhibition of p56lk tyrosine kinase with an IC₅₀ value of 1.07 μg mL⁻¹. In addition, compound 97 demonstrated a potent inhibitory effect on both the tyrosine kinase domain of the epidermal growth factor receptor and protein tyrosine kinase p59fyn with IC₅₀ values of 0.078 and 0.080 μg mL⁻¹, respectively without any noted cytotoxicity on human foreskin fibroblast (99) (Fig. 5).

### 3.4. Anthraquinones from Stemphylium sp.

The marine-derived fungus Stemphylium is another good source of the bioactive anthraquinones with thirty-two recovered compounds 99–130. A group of twenty-five anthraquinones derivatives 99–123 were reported from a mangrove-derived fungus Stemphylium sp. 33231 ref. 90 including the bioactive altersolanol A, B, C (99, 101, 104) and L (105) as well as their derivatives dihydroaltersolanol A (100), tetrahydroaltersolanol B (102), 2-O-acetylatersolanol B (103).

Altersolanol A (99) showed selective antimicrobial activity against S. aureus, E. coli, B. subtilis, and Micrococcus tetragenus with MIC values of 2.07, 4.1, 4.1, and 8.2 μM, respectively, whereas altersolanol B (101) displayed similar antibacterial activity against S. aureus, E. coli and B. subtilis as well as the Gram-positive bacterium, Kocuria rhizophila with MIC values of 7.8 μM for all strains. The same study revealed that altersolanol C (104) had a narrow spectrum of activity against only B. subtilis with a MIC value of 8.8 μM, while altersolanol L (105) had no antibacterial activity against the tested strains. In the contrast, another recent study demonstrated that altersolanol L (105) had a modest antifungal activity against P. italicum and Rhizoctonia solani with MIC values of 35.0 and 50.0 μg mL⁻¹, respectively.

Additionally, a recent study showed that both altersolanol A (99) and B (101) had strong cytotoxicity against MCF-7 and HCT-116 cell lines with IC₅₀ values of 7.21, 1.3 μM for altersolanol A (99) and, 9.0, 3.5 μM for altersolanol B (101), respectively. By contrast, dihydroaltersolanol A (100) did not show any antibacterial activity or cytotoxicity when tested against various microbes and cell lines, suggesting that the derivatization of its parent altersolanol A (99) into dihydroaltersolanol A (100) lead to a significant change in its biological activities.
Furthermore, ampelanol (107), macrosporin (108) and its sulphate derivative, macrosporin-7-O-sulphate (109), in addition to its glycosidic derivative, macrosporin 7-O-(6′-acetyl)-α-D-glucopyranoside (110), as well as auxarthrol C (111), were also recovered from the marine fungus Stemphylium sp. 33 231.90 Ampelanol (107) displayed moderate cytotoxicity against the murine lymphoma cell line, LS178Y,94 whereas macrosporin (108) exhibited significant antibacterial activity against Micrococcus tetragenus, E. coli, and S. aureus with MIC values of 4.6, 4.6, and 9.2 μM, respectively.96 On the other hand, both derivatives of macrosporin (108), macrosporin-7-O-sulphate (109) and macrosporin 7-O-(6′-acetyl)-α-D-glucopyranoside (110) displayed no antibacterial activity against the same indicator strains up to a concentration of 10.0 μM,99 indicating that these modifications in the chemical structure of macrosporin (108) have greatly affected its antibacterial activity. Additionally, macrosporin (108) was shown to have potent antifungal activity against Fusarium oxysporum (F. oxysporum) with a MIC value of 3.75 μg mL⁻¹ and modest antifungal activity against Colletotrichum musae, F. graminearum, P. italicum, and Colletotrichum gloeosporioides with MIC values ranging from 3.0 to 60.0 μg mL⁻¹.94 Noteworthy, compound 110 demonstrated a remarkable brine shrimp lethality using Artemia salina with an LD₅₀ value of 10.0 μM,90 while the parent compound 108, and its derivative 109 showed no lethality in the same study99 suggesting that brine shrimp lethality might be dependent on acetylation and/or glycosylation of this compound. Also, the same study revealed that auxarthrol C (111) displayed selective antibacterial activity against only the Gram-negative organism, E. coli with a MIC value of 9.8 μM with no notable cytotoxicity or brine shrimp lethal effect.99

Moreover, other bioactive anthraquinone dimers including alterporriols B-E (113–116), N (117), Q (118), U (121), and V (122) were also isolated from the same fungus Stemphylium sp. 33 231.90 The anthraquinone dimers, alterporriols B-E (113–116) displayed positive antibacterial activity, whereas alterporriol A (112) did not show either antibacterial or cytotoxic activity.99 Alterporriol B (113) showed a narrow spectrum of antimicrobial activity against B. cereus with a MIC value of 7.9 μM, whereas alterporriol C (114) showed selective antibacterial activity against S. albus with a MIC value of 8.9 μM. Interestingly, alterporriol D (115) exhibited notable antibacterial activity against both S. aureus and E. coli and with MIC values of 5.0 and 7.5 μM, respectively, while alterporriol E (116) displayed potent antimicrobial activity against both B. cereus and E. coli with MIC values of 2.5 and 5.0 μM, respectively.99 The same study demonstrated that alterporriol Q (118) and R (119) showed no antimicrobial activity against various tested microbes up to a concentration of 10.0 μM.99 This finding was confirmed in another study which showed that both compounds did not display any antibacterial activity against different Gram-positive bacteria as well as E. coli from the Gram-negative bacteria up to a concentration of 20.0 μM.93 However, alterporriol Q (118) exhibited strong antiviral activity against the porcine reproductive and respiratory syndrome virus with a MIC value of 22.0 μM, whereas alterporriol R (119) showed no antiviral activity.93 Also, the same study revealed that alterporriol C (114) had a modest antiviral activity with a MIC value of 39.0 μM.99 In addition, the other anthraquinone dimers, alterporriol U (121) and V (122) exhibited a narrow spectrum of antibacterial bioactivity against the Gram-positive bacterium, B. cereus with MIC values of 8.3 and 8.1 μM, respectively.99

Further anthraquinone dimers including alterporriol N (117), F (124), G (125), Z1 (126), Z2 (127), and Z3 (128) were also isolated recently from another marine fungus Stemphylium sp. FJJ006.95 They showed neither antimicrobial activity against the Gram-positive and Gram-negative bacterial strains up to a concentration of 128.0 μg mL⁻¹ nor antitumor activity against a panel of cancer cell lines with an IC₅₀ value higher than 20.0 μM. Also, they did not show bioactivity against the microbial enzymes, isocitrate lyase, and sortase A with an IC₅₀ value of more than 145.0 μM. However, the same study revealed that alterporriols N (117), F, G, and Z₁–Z₃ (124–127) had anti-inflammatory activity through their capability of suppressing the lipopolysaccharide-induced nitric oxide production in the murine macrophages RAW 264.7 cells with IC₅₀ values of 8.4, 9.6, 10.7, 11.6, and 16.1 μM, respectively, whereas alterporriol Z₂ (128) did not display any anti-inflammatory activity.95 On the other hand, another previous study demonstrated the potent cytotoxicity of alterporriol F (124) against the HeLa and KB human cell lines with IC₅₀ values of 6.5 and 7.0 μg mL⁻¹, respectively.99 In addition, alterporriol N (117) was presented in another study as a weak antimicrobial agent with a narrow spectrum of activity against only the Gram-positive bacteria, Enterococcus faecalis, MRSA, and Str. pneumoniae with MIC values of 15.63, 62.5, and 125.0 μg mL⁻¹, respectively, while the same study revealed that alterporriol G (125) had a moderate cytotoxicity against the mouse cancer cell line, L5178Y99 (Fig. 6 and 7).

3.5. Anthraquinones from Alternaria sp.
A list of twenty anthraquinones was isolated earlier from different species of Alternaria including the previously mentioned compounds, 100–102, 104, 105, 107, 108, and 114 as well as twelve anthraquinone derivatives, 131–142. Two bioactive bi-anthraquinones, named alterporriol K (131) and L (132) were isolated from the marine endophytic fungus Alternaria sp. ZJ9-6B ref. 98 and displayed moderate cytotoxic activity against the human breast cancer cells, MCF-7 and MDA-MB-435 with IC₅₀ values of [29.11 and 26.97 μM] for alterporriol K (131) and [20.04 and 13.11 μM] for alterporriol L (132), respectively, while alterporriol M (133) was not evaluated for any biological activity in this study.99

Further compounds including alterporriol O (134) and P (135) were isolated from the marine-derived Aspergillus sp. ZJ-2008003. Only alterporriol P (135) exhibited significant cytotoxicity against the human prostate cancer cell line, PC3, colon cancer cell line, HCT-116, liver hepatoma cell lines, Hep-G2 and Hep-3B in addition to the breast cancer cell line, MCF-7/ADR with IC₅₀ values of 6.4, 8.6, 20.0, 21.0, and 23.0 μM, respectively. Unlike, alterporriol O (134) did not demonstrate any bioactivity when it was evaluated for its cytotoxicity, antibacterial activity, and antiviral activities.93
Additional anthraquinones, tetrahydroaltersolanols C–F (136–139) were also isolated from the marine-derived Alternaria sp. ZJ-2008003. Only tetrahydroaltersolanol C (136) displayed moderate antiviral activity against the porcine reproductive and respiratory syndrome virus with an IC\textsubscript{50} value of 65.0 μM.

More anthraquinone derivatives (140–142) were reported recently from the marine fungus Alternaria tenuissima DFFSC013. Anthrininone A (140) demonstrated selective protein tyrosine phosphatase inhibitory effect on indoleamine 2,3 dioxygenase 1 enzyme with an IC\textsubscript{50} value of 32.3 μM as well as the stimulatory effect on the intracellular levels of calcium in HEK293 cells at a concentration of 10.0 μM. Anthraniumones A and B (143 and 144) were reported earlier as new hydroxyanthraquinones from the marine fungus T. harzianum XS-20090075. They showed neither DNA Topo I inhibitory activity nor anti-acetylcholinesterase activity. The same study revealed that phomarin (145), ω-hydroxydigitoemodin (146), pachybasin (147), and (+)-2’S-isorhodoptilometrin (148) isolated also from T. harzianum XS-20090075, displayed a weak anti-acetylcholinesterase activity at a concentration of 100.0 μM.

Interestingly, pachybasin (147) also demonstrated potent cytotoxic activity against the human cancer cell lines, KB and KBv200 with IC\textsubscript{50} values of 3.17 and 3.21 μM, respectively. In addition, its derivative, ω-hydroxyypachybasin (149) as well as (+)-2’S-isorhodoptilometrin (148) exhibited moderate or good cytotoxicity against Hep-G2 and HeLa cancer cell lines showing IC\textsubscript{50} values of [9.39 and 22.6 μM] for ω-hydroxyypachybasin (149) and [2.10 and 8.59 μM] for (+)-2’S-isorhodoptilometrin (148), respectively. On the other hand, compound 141 did not show a noticeable stimulatory effect on the intracellular levels of calcium in HEK293 cells at a concentration of 10.0 μM ref. 99 (Fig. 8).

### 3.6. Anthraquinones from Trichoderma sp.

Trichoderma sp. is another prolific anthraquinones producer from which the previously discussed compounds 14, 83, and 84 were isolated as well as the anthraquinone derivatives, 143–155. Harzianumones A and B (143 and 144) were reported earlier as new hydroxyanthraquinones from the marine fungus T. harzianum XS-20090075. They showed neither DNA Topo I inhibitory activity nor anti-acetylcholinesterase activity. The same study demonstrated that compound 148 isolated from the marine-derived fungus T. aureoviride PSU-F95 showed good antibacterial activity against MRSA with a MIC value of 16.0 μg mL\textsuperscript{-1}. Similarly, coniothranthraquinone 1 (150) displayed significant antibacterial activity against MRSA and S. aureus with MIC values of 8.0 and 16 μg mL\textsuperscript{-1}, respectively. In the contrast, trichodermaquinone (151) which was also isolated from the marine fungus T. aureoviride PSU-F95 demonstrated very weak antibacterial activity against MRSA with a MIC value of 200.0 μg mL\textsuperscript{-1}. However, compounds 152 and 153 which...
were recovered also from the marine fungus *T. aureoviride* PSU-F95, both were not evaluated for any bioactivity in this study.  

Additionally, coniothyrinone A (154) and lentisone (155) were previously isolated from another marine fungus, *Trichoderma* sp., and exhibited potent antibacterial activity against the Gram-negative bacteria, *V. parahaemolyticus*, *V. anguillarum*, and *Pseudomonas putida* with MIC values of [6.25, 1.56, 3.13 \( \mu \text{M} \)] for coniothyrinone A (154) and [12.5, 1.56, 6.25 \( \mu \text{M} \)] for lentisone (155), respectively (Fig. 9).

### 3.7. Anthraquinones from *Eurotium* sp.

Seventeen anthraquinones and their derivatives were reported from species of the marine fungus *Eurotium*, including the previously mentioned compounds 14, 15, 18–20, 60, 62, 97, and 154 in addition to other eight congeners, 156–163. Compound 9-dehydroxyeurotinone (156) and its O-methyl derivative, 2-O-methyl-9-dehydroxyeurotinone (157) as well as its glycosidic derivative, 2-O-methyl-4-O-(\( \alpha \)-D-ribofuranosyl)-9-dehydroxyeurotinone (158) were isolated from the marine-derived fungus *Eu.*
rubrum. The parent compound, 9-dehydroxyeurotinone (156) exhibited weak antibacterial activity against the Gram-negative bacterium, *E. coli* showing a 7 mm zone of inhibition using 100.0 μg per disk. Also, it displayed selective cytotoxic activity against the human cholangiocarcinoma cells, SW1990 with an IC<sub>50</sub> value of 25.0 μg mL<sup>-1</sup>. Another study revealed that compounds 157–159 had positive antioxidant activity through free radical scavenging activity against DPPH.

Furthermore, the same study showed that eurorubrin (160) demonstrated a potent free radical scavenging activity with an IC<sub>50</sub> value of 44.0 μM with better antioxidant activity than the standard antioxidant, butylated hydroxytoluene which had an IC<sub>50</sub> value of 82.6 μM. Interestingly, 3-O-(α-D-ribofuranosyl)-questin (159) and eurorubrin (160) were re-isolated also from the marine endophytic fungus *Eu. cristatum* EN 220. They displayed modest antibacterial activity against the Gram-negative bacterium, *E. coli* with MIC values of 32.0 and 64.0 μg mL<sup>-1</sup>, respectively. Notably, 3-O-(α-D-ribofuranosyl)questinol (161) which is an alcoholic derivative of the bioactive compound, 3-O-(α-D-ribofuranosyl)questin (159) showed no antibacterial activity against *E. coli* suggesting that this hydroxylation leads to loss of the antimicrobial activity.

Furthermore, asperflavin ribofuranoside (162) which was isolated earlier from the marine fungus *Eu. cristatum* EN 220 ref. 101 and the marine-derived fungus *Microsporum* sp., was reported as a potent free radical scavenging agent with an IC<sub>50</sub>
value of 14.2 μM with better antioxidant activity than the standard antioxidant, ascorbic acid which had an IC_{50} value of 20.0 μM. Also, it exhibited modest antibacterial activity against both MRSA and the multidrug-resistant S. aureus with MIC values of 50.0 and 50.0 μg mL^{-1}, respectively. Moreover, rubrumol (163) was reported as a new anthraquinone derivative from the saline-alkali endophytic fungus Eu. rubrum with relaxation activity on Topo I with an IC_{50} value of 23.0 μM (Fig. 10).

### 3.8. Anthraquinones from Fusarium sp.

Twelve anthraquinone derivatives were isolated earlier from different species of the marine-derived fungus Fusarium sp. including the previously discussed compounds 5-8 and 10 along with other structurally related compounds 164–170. Although both nigrosporin A (164) and fusaranthraquinone (165) were recovered from the marine-derived fungus Fusarium sp. PSU-F14, only nigrosporin A (164) displayed promising inhibitory activity against photosynthesis and weak antibacterial activity against B. subtilis showing an inhibition zone of 14 mm at 200 ppm, whereas fusaranthraquinone (165) did not demonstrate any antibacterial activity when it was tested against both S. aureus and MRSA. Interestingly, additional bioactive fusaquinons A–C (166–168) were reported from the marine fungus Fusarium sp. ZH-210 and displayed weak cytotoxic activity against MCF-7, KB, and KBv200 cell lines with IC_{50} values of more than 50.0 μM.

It is noteworthy that nigrosporin A (164) and fusaquinon A (166) were also evaluated in another study for their antimalarial, anti-mycobacterial, antibacterial, and cytotoxic activity. Both compounds showed no antimalarial, antibacterial, or anti-mycobacterial activity, whereas they showed selective cytotoxicity. Nigrosporin A (164) displayed weak cytotoxic activity against the MCF-7 cell line with an IC_{50} value of 110.36 μM and good cytotoxicity against the NCI–H187 cell line with an IC_{50} value of 13.69 μM, while fusaquinon A (166) exhibited weak cytotoxicity against both human cancer cells, MCF-7, and monkey kidney cells, Vero cells with IC_{50} values of 84.38 and 44.46 μM, respectively. Also, fusaquinon A (166) displayed potent cytotoxicity against the NCI–H187 cell line with an IC_{50} value of 7.32 μM. Another bioactive anthraquinone derivative isolated from the mangrove-derived fungus Fusarium sp. ZZP60 was 6,8-dimethoxy-1-methyl-2-(3-oxobutyl)anthracene-9,10-dione (169). Notably, it demonstrated moderate cytotoxicity against Hep2 and Hep-G2 cells with IC_{50} values of 16.00 and 23.00, respectively (Fig. 11).

### 3.9. Anthraquinones from Engyodontium album

Six compounds 171–176 out of seven anthraquinone derivatives 171–177 isolated from the marine-derived fungus Engyodontium

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**Fig. 10** Chemical structures of compounds 156–163.

**Fig. 11** Chemical structures of compounds 164–170.
album LF069 were bioactive, while the anthraquinone derivative, Engyodontochone D (177) was not tested for any relevant biological activity. It is noteworthy that compounds 171–173 exhibited diverse bioactivities including antibacterial, antifungal, and cytotoxic activity. They demonstrated better antibacterial activity against S. epidermidis and MRSA than chloramphenicol with an IC\textsubscript{50} values of [0.19 and 0.17 \mu M] for engyodontochone A (171), [0.21 and 0.25 \mu M] for JBIR-99 (172), and [0.22 and 0.24 \mu M] for engyodontochone B (173), respectively. On the other hand, they displayed weak to modest antifungal activity against the fungi, C. albicans, and T. rubrum with IC\textsubscript{50} values ranging from 4.3 to 13.5 \mu M. Additionally, compounds 171–173 exhibited moderate cytotoxicity against the mouse fibroblasts cell line, NIH-3T3 with IC\textsubscript{50} values of 11.0, 13.2, and 14.4 \mu M, respectively.

In addition, engyodontochone C (174) in the same study showed a good selective bioactivity against S. epidermidis and MRSA with IC\textsubscript{50} values of 1.80 and 2.39 \mu M, respectively. In addition, it displayed weak cytotoxic activity against the cell line, NIH-3T3 with an IC\textsubscript{50} value of 34.3 \mu M, whereas it did not show any antifungal activity against either, C. albicans or T. rubrum up to a concentration of 100.0 \mu M. Similarly, engyodontochone F (175) demonstrated promising selective antibacterial activity against both S. epidermidis and MRSA with IC\textsubscript{50} values of 3.41 and 3.13 \mu M, respectively although it exhibited weak selective antifungal activity against T. rubrum with an IC\textsubscript{50} value of 73.4 \mu M. In the contrast, engyodontochone E (176) has only showed potent antibacterial activity against S. epidermidis and MRSA with IC\textsubscript{50} values of 6.77 and 6.74 \mu M, respectively with no antifungal or cytotoxic activity up to a concentration of 100.0 and 50.0 \mu M, respectively (Fig. 12).

### 3.10. Anthraquinones from Sporendonema casei

Seven bioactive anthraquinones named 4-dehydroxyltersolanol A (178) and auxarthrols D–H (179–183) along with the previously discussed altersolanol B (101) were recovered from the marine fungus, *Sporendonema casei* HDN16-802. Interestingly, 4-dehydrosysylersolanol A (178) exhibited the best antibacterial activity among this group of anthraquinones against *M. phlei*, *B. subtilis*, *Pseudomonas aeruginosa*, *V. parahaemolyticus*, and *Proteus* sp. with MIC values ranging from 25.0 to 50.0 \mu M. However, its parent altersolanol A (99) demonstrated potent antibacterial activity against *S. aureus*, *E. coli*, *B. subtilis*, and *Micrococcus tetragenus* with MIC values of 2.07, 4.1, 4.1, and 8.2 \mu M, suggesting that its dehydroxylation might lead to a decrease in its antimicrobial activity.

In the contrast, auxarthrol E (180) and H (183) showed no antimicrobial activity against different indicator strains. However, auxarthrol F (181) only displayed very weak activity against *M. phlei*, *B. subtilis*, *Pseudomonas aeruginosa*, and *Proteus* sp. with a MIC value of 200.0 \mu M. Both auxarthrol D (179) and G (182) demonstrated a broad spectrum of antibacterial activity against *M. phlei*, *B. subtilis*, *Pseudomonas aeruginosa*, *V. parahaemolyticus*, and *Proteus* sp. with MIC values ranging from 25.0 to 100.0 \mu M, whereas compound 182 displayed very weak antifungal activity against *C. albicans* with a MIC value of 200.0 \mu M. Moreover, only compounds 179 and 181 were evaluated for their cytotoxicity against different cancer cell lines in the same study revealing modest cytotoxic activity against several cell lines. Compound 179 exhibited a selective cytotoxic effect on seven cell lines including HL-60, HCT-116, MGC-803, MDA-MB-231, SH-SY5Y, PC-3, and BEL-7402 with IC\textsubscript{50} values ranging from 7.5 to 22.9 \mu M. In the contrast, compound 181 displayed a broad spectrum of cytotoxicity against the eleven tested cancer cell lines in this study with IC\textsubscript{50} values ranging from 4.5 to 22.2 \mu M. In addition, all compounds 178–183 showed significant anticoagulant activity, meanwhile, they did not show any antimycobacterial activity (Fig. 13).

### 3.11. Anthraquinones from other marine fungi

A considerable number of anthraquinones and their derivatives were isolated from other marine-derived fungi including compounds 184–208. Compounds 184–192, as well as previously discussed anthraquinone derivatives, 5, 41, 83, and 147, were reported from the mangrove endophytes, *Halorosellinia* sp. No. 1403 and *Guignardia* sp. No. 4382. Eight compounds from them, 184–191 showed weak cytotoxic activity, while 192...
displayed no cytotoxicity up to a concentration of 500.0 μM. It is noteworthy that compounds 184–188 exhibited weak cytotoxicity against both tested cancer cell lines, KB and KBv200 with IC₅₀ values ranging from 34.64 to 243.69 μM, whereas compounds 189–191 demonstrated a narrow spectrum of activity against only KBv200 cell line with IC₅₀ values of 72.60, 185.68, and 301.47 μM, respectively. The best cytotoxicity was recorded for 1,3-dihydroxy-6-methoxy-8-methyl-anthracene-9,10-dione (187) which displayed activity against both KB and KBv200 cells with IC₅₀ values of 38.05 and 34.64 μM, respectively.48

Interestingly, SZ-685C (193) was isolated as a novel anthraquinone derivative from the marine endophytic fungus Halorosellinia sp. No. 1403 with anticancer potential.108–110 It was demonstrated that SZ-685C (193) had anticancer activity against the rat pituitary adenoma (MMQ) and human non-functioning pituitary adenoma cell lines with IC₅₀ values of 14.51 and 18.76 μM, respectively, while it had an IC₅₀ value of 56.09 μM against the normal cell line, rat pituitary cells.108 Another study revealed similar results of its cytotoxic activity against the MMQ and normal rat pituitary cell lines with IC₅₀ values of 13.2 and 49.1 μM, respectively.110 Also, it showed good cytotoxicity against both human MCF-7 and MCF-7/ADR cancer cell lines with IC₅₀ values of 7.38 and 4.17 μM, respectively.109

Additional anthraquinone derivatives, phomopsantheraquinone (194), and 1-hydroxy-3-methoxy-6-methyl-anthraquinone (195) were isolated from the marine-derived fungus Phomopsis sp. PSU-MA214, besides the previously mentioned compounds 102, 107, 108, and 136.111 Phomopsantheraquinone (194) demonstrated cytotoxicity against MCF-7 and KB cancer cell lines with an IC₅₀ value of 27.0 μg mL⁻¹ for both cell lines. Also, it exhibited moderate antibacterial activity against both MRSA and S. aureus with MIC values of 64.0 and 128.0 μg mL⁻¹, respectively. In the contrast, 1-hydroxy-3-methoxy-6-methyl-anthraquinone (195) neither showed antibacterial activity nor cytotoxicity.111

Further three anthraquinones, tetrahydroxanthraquinone (196), methoxy-tetrahydroxanthraquinone (197), and 1,2,3,6,8-pentahydroxy-7,8-(1 R)-1-methoxyethyl)-9,10-anthraquinone (198) along with previously mentioned noraverufanin (36), were recorded from the sponge-associated fungus Microsphaeropsis sp.112 All those anthraquinones showed a broad spectrum of protein kinases’ inhibitory activity against cyclin-dependent kinase 4 in complex with its activator cyclin D1, protein kinase C, and epidermal growth factor receptor with IC₅₀ values ranging from 18.5 to 54.0 μM.112

Moreover, the anthraquinone, lunatin (199), and the anthraquinone dimer, cytoskyrin A (200) were reported earlier from the sponge-associated fungus Curvularia lunata with positive antibacterial activity.113 Both compounds exhibited antibacterial activity against B. subtilis, S. aureus, and E. coli using the disk diffusion method at a concentration of 5.0 μg per disk. Meanwhile, they showed no antifungal activity against C. albicans up to a concentration of 10.0 μg per disk.113

Furthermore, rheoemodin (201), 2 [2’-bis-(7-methyl-1,4,5-trihydroxy-anthracene-9,10-dione) (202), as well as the previously discussed compounds 62, 63, and 84, were isolated earlier from another sponge-associated fungus Talaromyces stipitatus KUFA 0207.12 Rheoemodin (201) displayed no significant anti-obesity activity, whereas 2,2’-bis-(7-methyl-1,4,5-trihydroxy-anthracene-9,10-dione) (202) was not tested for any relevant activity.12

Additional two anthraquinones, 7-methoxymacrosporin (203) and 7-(γ,γ)-dimethyl-allyloxy-macrosporin (204) along with the previously discussed compounds 102, 105, 107 and 108, were isolated from the mangrove fungus, Phoma sp. L28.121 7-methoxymacrosporin (203) displayed weak antifungal activity against F. graminearum, F. oxysporum, P. italicum, Rhizoctonia solani, and Colletotrichum gloeosporioides with MIC values of 100.0, 100.0, 100.0, 150.0, and 200.0 μg mL⁻¹, respectively. Also, 7-(γ,γ)-dimethyl-allyloxy-macrosporin (204) demonstrated weak selective antifungal activity against F. graminearum, Rhizoctonia solani, and Colletotrichum gloeosporioides with MIC values of 80.0, 150.0, and 200.0 μg mL⁻¹, respectively.21 By comparing this weak antifungal activity of 203 and 204 to their parent macrosporin (108) which displayed potent antifungal activity against F. oxysporum and modest antifungal activity against Colletotrichum musae, F. graminearum, P. italicum, and Colletotrichum gloeosporioides,21 we can conclude that the structural modifications in both 203 and 204 have greatly affected their bioactivity.

Four additional bioactive anthraquinone derivatives were reported from the marine-derived fungus Monodictys sp. including the previously discussed compounds 14, 83, and 147.
as well as monodictyquinone A ([205]). Compound 205 displayed promising antimicrobial activity against *B. subtilis*, *E. coli*, and *C. albicans* showing zones of inhibition with a diameter of 15.0, 15.0, and 11.0 mm, respectively at a concentration of 10.0 μg per disk.\(^5\)

Two other anthraquinone derivatives, 1,3,6-trihydroxy-7-(1-hydroxyethyl) anthracene-9,10-dione ([206]) and phaseolorin I ([207]) were isolated earlier from the marine-derived fungi, *Cladosporium* sp. HNWSW-1 ref. 114 and *Diaporthe phaseolorum* FS431,\(^115\) respectively. Phaseolorin I ([207]) was inactive when it was tested for its cytotoxicity against the cell lines, MCF-7, Hep-G2, A549, and SF-268,\(^115\) whereas compound 206 did not demonstrate cytotoxicity against the cell lines, BEL-7042, HeLa, and K562 as well as the human papillomavirus-related endocervical adenocarcinoma SGC-7901 cell lines.\(^114\) However, anthraquinone 206 exhibited α-glycosidase inhibitory activity with an IC\(_{50}\) value of 49.3 μM compared to the standard agent, acarbose which had an IC\(_{50}\) value of 275.7 μM.\(^114\)

Finally, 6,8-O,O\(^2\)-dimethyl-averufanin (208) which is a derivative of the bioactive anthraquinone derivative, averufanin (35) was previously reported from the unidentified marine endophytic fungus ZSUH-36 as well as the previously mentioned compounds 27, 30, 32 and 33, 40, 43, and 80.\(^116\) Compound 208 demonstrated weak antifungal activity against the phytopathogenic fungi, *Botrytis cinerea* and *Magnaporthe oryzae* with MIC values of 50.0 and 100.0 μM, respectively.\(^117\) Also, it displayed good phytotoxicity on the hypocotyls of radish seedlings at a concentration of 100.0 μM with an inhibition rate of 30.6% compared to 28.1% for the standard, glyphosate\(^117\) (Fig. 14).

### 4 Drug likeness and pharmacokinetics of marine anthraquinones

Altogether, 208 anthraquinones and their derivatives were characterized from 20 marine-derived fungal genera. These include *Nigrospora*, *Aspergillus*, *Penicillium*, *Stemphylium*, and *Alternaria*, among others. The identified anthraquinones revealed diverse biological and pharmacological activities including anticancer, antiviral, antimicrobial, antioxidant, and anti-inflammatory activities. Here, we attempted to highlight their potential as drug candidates via exploring their drug-likeness using several molecular descriptors including several drug-likeness rules (Muegge, Ghose, Veber, Egan, and Lipinski). Surprisingly, 133 anthraquinones satisfied all parameters of the
Fig. 15  Distribution of molecular weight ($M_{\text{wt}}$), fraction of sp$^3$ carbons (FCsp$^3$), number of rotatable bonds (RB), topological polar surface area (TPSA), lipophilicity ($\log P$), solubility ($\log S$) according to the species. Comparison between the values of FCsp$^3$ and $M_{\text{wt}}$, $\log P$ and $M_{\text{wt}}$, TPSA and $M_{\text{wt}}$, $\log S$ and $M_{\text{wt}}$, $\log P$ and $\log S$, and $\log S$ and TPSA. NIG: Nigrospora sp., ASP: Aspergillus sp., PEN: Penicillium sp., STE: Stemphylium sp., ALT: Alternaria sp., TRI: Trichoderma sp., EUR: Eurotium sp., FUS: Fusarium sp., ENG: Engyodontium album, SPO: Sporendonema casei, and OTH: other marine fungi.
Table 1  Anthraquinones and their derivatives isolated from different species of marine-derived fungi with their sources and biological activities. MF = Molecular formula.

| Compound MF | Name | Bioactivity | Source | Ref. |
|-------------|------|-------------|--------|------|
| 1 C31H32O12 | Nigrodiquinone A | Displayed no antibacterial or antiviral activity | Zoanthid-derived fungus Nigrospora sp. | 37 |
| 2 C17H22O7 | 4a-epi-9-methoxydihydrodeoxybostrycin | Antibacterial activity | Zoanthid-derived fungus Nigrospora sp. and sea anemone-derived fungus Nigrospora sp. | 37 and 38 |
| 3 C16H16O7 | 10-Deoxybostrycin | Antibacterial and cytotoxic activities | Zoanthid-derived fungus Nigrospora sp. and sea anemone-derived fungus Nigrospora sp. | 37 and 38 |
| 4 C16H12O6 | 3,5,8-Trihydroxy-7-methoxy-2-methyl-anthracene-9,10-dione | Antiviral activity | Zoanthid-derived fungus Nigrospora sp. and sea anemone-derived fungus Nigrospora sp. | 37 and 38 |
| 5 C16H12O5 | Austrocortirubin | Antiviral and cytotoxic activities | Zoanthid-derived fungus Nigrospora sp., mangrove endophytic fungi Halorosellinia sp. (no. 1403), and Gigartina sp. (no. 4382), sea anemone-derived fungus Nigrospora sp., and sea fan-derived fungi Fusarium sp. PSU-F14 | 37–41 |
| 6 C16H16O6 | Nigrosporin B | Antibacterial, antimycobacterial, cytotoxic, and phytotoxic activities | Sea anemone-derived fungus Nigrospora sp., sea fan-derived fungi Fusarium sp. PSU-F14 | 38, 39 and 43 |
| 7 C16H20O7 | 1-Deoxytetrahydrobostrycin | Antibacterial and cytotoxic activities | Sea anemone-derived fungus Nigrospora sp., sea fan-derived fungi Fusarium sp. PSU-F14, and marine-derived fungus Aspergillus sp. | 38, 39, 42 and 46 |
| 8 C16H20O8 | Tetrahydrobostrycin | Antibacterial, antimalarial, antimycobacterial, and cytotoxic activities | Sea anemone-derived fungus Nigrospora sp., sea fan-derived fungi Fusarium sp. PSU-F14, and marine-derived fungus Aspergillus sp. | 38, 39 and 46 |
| 9 C16H16O7 | 4-Deoxybostrycin | Antibacterial, antimycobacterial, and cytotoxic activities | Sea anemone-derived fungus Nigrospora sp. | 38, 39 and 43 |
| 10 C16H16O8 | Bostrycin | Antibacterial, antimalarial, and cytotoxic activities | Sea anemone-derived fungus Nigrospora sp., sea fan-derived fungi Fusarium sp. PSU-F14, and marine-derived fungus Aspergillus sp. | 38, 39 and 45 |
| 11 C25H16O9 | Aspergiolide A | Cytotoxic activity | Marine-derived fungus A. glauca | 47 and 48 |
| 12 C26H18O9 | Aspergiolide B | Cytotoxic activity | Marine-derived fungus A. glauca | 47 |
| Compound MF | Name | Bioactivity | Source | Ref. |
|-------------|------|-------------|--------|------|
| 13 C16H16O5 | Physcion | Antifungal, antioxidant, and cytotoxic activities | Marine-derived fungi Microsporum sp., A. niger, and halotolerant A. variecolor, and marine algae-derived fungus A. wentii EN-48 | 47, 49–52 |
| 14 C15H10O5 | Emodin | Antibacterial, antifungal, anti-HCV protease, antimycobacterial, and cytotoxic activities | Sea fan-derived fungus P. citrinum PSU-F51, marine-derived fungus T. aureoviride PSU-F95, Trichoderma sp., A. glaucus, and halotolerant A. variecolor, marine lichen-derived fungus Gloiocladium sp. T31, sea urchin-derived fungus Monodictys sp., marine mangrove fungus Paecilomyces sp., and marine-derived endophytic fungus Eu. rubrum | 40, 47, 50, 53–61, 63 and 67, 68, 72 |
| 15 C16H16O5 | Asperflavin | Antioxidant activity | Marine-derived fungus A. glaucus and marine algae-derived endophytic fungus 47 and 101 | RSC Cristatum EN-220 |
| 16 C16H16O5 | Isoasperflavin | Displayed no cytotoxic activity | Marine-derived fungus A. glaucus | 47 |
| 17 C16H16O5 | Questin | Antioxidant activity | Marine-derived fungi A. glaucus and halotolerant A. variecolor, and mangrove-derived fungus P. citrinum HL-5126 | 47, 50, 62 and 84 |
| 18 C15H10O5 | Catenarin | Antibacterial activity | Marine-derived fungi A. glaucus, Eu. Rubrum, and halotolerant A. variecolor | 47, 50, 63 and 103 |
| 19 C16H16O5 | Rubrocrustin | Displayed no antibacterial activity | Marine-derived fungi A. glaucus, Eu. Rubrum, and halotolerant A. variecolor | 47, 50, 63 and 103 |
| 20 C20H20O7 (+)-variecolorquinone A | Cytotoxic activity | Marine-derived fungi A. glaucus and halotolerant A. variecolor, and marine algae-derived endophytic fungus Eu. cristatum EN-220 | 47, 50 and 101 |
| 21 C32H36O8 | Physcion-10,10'-biantrophe | Was not evaluated for any relevant bioactivity | Marine-derived fungus A. glaucus | 47 |
| 22 C31H28O8 | (trans)-emodin-physcion biantrophe | Cytotoxic activity | Marine-derived fungus A. glaucus | 47 |
| 23 C31H28O8 | (cis)-emodin-physcion biantrophe | Cytotoxic activity | Marine-derived fungus A. glaucus | 47 |
| 24 C42H42O13 | 6,6'-oxybis(1,3,8-trihydroxy-2-((S)-1-methoxyhexyl)anthracene-9,10-dione) | Antibacterial and cytotoxic activities | Marine-derived fungus A. versicolor | 64 |
| 25 C40H36O12 | 6,6'-oxybis(1,3,8-trihydroxy-2-((S)-1-hydroxyhexyl) anthracene-9,10-dione) | Antibacterial activity | Marine-derived fungus A. versicolor | 64 |
| 26 C20H20O7 | Averatin | Antibacterial, antioxidant, and cytotoxic activities | Marine-derived fungi A. versicolor and P. purpurogenum G59 | 64, 65 and 66, 68 and 118 |
| 27 C21H24O7 | 1'-O-methyl-averatin | Antibacterial, antioxidant, and cytotoxic activities | Marine-derived fungi A. versicolor and P. purpurogenum G59, and the mangrove endophytic fungus (ZSUH-36) | 64, 65 and 66, 68 and 116 |
| 28 C20H14O6 | Averythrin | Antioxidant and cytotoxic activities | Marine-derived fungi A. versicolor and Aspergillus sp. SC50, FOS F063 | 64, 66 and 67 |
| 29 C22H24O7 | 6,8-O,8'-dimethyl-averatin | Antibacterial activity | Marine-derived fungus A. versicolor EN-7 | 69 |
| 30 C20H16O7 | Averufin | Antibacterial, antioxidant, antiviral, and cytotoxic activities | Marine-derived fungi A. versicolor and A. niger (MF-16), mangrove endophytic fungi ZSUH-36 and (isolate 1850), and mangrove-derived endophytic fungus A. nidulans MA-143 | 67, 70, 71, 116 and 119 |
| 31 C21H18O7 | 6-O-methyl-averufin | Displayed no antimicrobial activity | Marine-derived fungus A. versicolor EN-7 | 69 |
| 32 C22H26O7 | 6,8-O,8'-dimethyl-averufin | Displayed no anti-neuroinflammatory activity | Marine-derived fungi Aspergillus sp. SF-6796 and A. versicolor EN-7, and the mangrove endophytic fungus (ZSUH-36) | 69, 72 and 116 |
| 33 C18H12O7 | Versicolorin B | Antioxidant activity | Marine-derived fungus A. versicolor and mangrove endophytic fungus ZSUH-36 | 67 |
| Compound MF | Name | Bioactivity | Source | Ref. |
|-------------|------|-------------|--------|------|
| C_{19}H_{16}O_{7} | Noraverufanin | Anti-HIV activity | Sponge-associated fungi | 73 and 112 |
| C_{15}H_{12}O_{6} | Eurotinone | Antioxidant activity and kinase insertion domain receptor inhibitory activity | Microsphaeropsis sp. and A. versicolor | 67 and 121 |
| C_{16}H_{12}O_{5} | 1,5-Dihydroxy-3-methoxy-7-methylanthraquinone | | Marine-derived fungus | 59 and 122 |
| C_{17}H_{14}O_{5} | 5-Hydroxy-1,3-dimethoxy-7-methylanthraquinone | | Marine-derived endophytic fungus A. wentii pt-1 | 81 |
| C_{16}H_{12}O_{5} | 1,5-Dihydroxy-3-methoxy-7-methylanthraquinone | | Marine-derived endophytic fungus A. wentii pt-1 | 81 |
| C_{15}H_{14}O_{6} | Aversin | | Marine-derived fungus | 65, 67, 68, 70 and 119 |
| C_{20}H_{14}O_{7} | Aversin | | Mangrove endophytic fungus | 40 and 41 |
| C_{16}H_{14}O_{5} | Damnacanthal | | | 59 and 77 |
| C_{16}H_{14}O_{5} | 6,8-O,O‘-dimethyl-nidurufin A | Antibacterial activity | Marine-derived fungus A. versicolor | 69 |
| C_{16}H_{14}O_{5} | Versiconol | Cytotoxic activity | Marine-derived fungus A. versicolor | 68 |
| C_{20}H_{16}O_{7} | Averufanin | Antioxidant activity | Marine-derived fungus A. versicolor and mangrove-derived endophytic fungus A. nidulans MA-143 | 67 and 75 |
| C_{18}H_{16}O_{6} | Isorhodoptilometrin-1-methyl- | | Marine-derived fungus | 65, 67, 68, 70 and 119 |
| C_{16}H_{12}O_{7} | Wentiquinone | | | 69 and 120 |
| C_{15}H_{10}O_{5} | Alatinone | | | 69 and 120 |
| C_{16}H_{12}O_{6} | Evariquinone | | | 69 and 120 |
| C_{17}H_{14}O_{5} | 2-(Dimethoxy methyl)-1-hydroxy- | | | 69 and 120 |
| C_{20}H_{18}O_{7} | Niduruquinone | | | 69 and 120 |

**Table 1 (Contd.)**
### Table 1 (Contd.)

| Compound MF | Name | Bioactivity | Source | Ref. |
|-------------|------|-------------|--------|------|
| C₁₆H₁₂O₆  | 2-O-methyl-eurotinone | Antioxidant activity | Marine mangrove-derived endophytic fungus *Eu. rubrum* and marine-derived halotolerant fungus *A. variecolor* | 50 and 62 |
| C₁₉H₁₆O₉  | (2S)-2,3-dihydroxypropyl 1,6,8-trihydroxy-3-methyl-9,10-dioxo-9,10-dihydro-2-anthracencarboxylate | Was not evaluated for any relevant bioactivity | Marine-derived halotolerant fungus *A. variecolor* | 50 |
| C₁₆H₁₀O₆  | Questinol | Anti-inflammatory and anti-obesity activities | Marine-derived halotolerant fungus *A. variecolor* and marine-derived fungi *Eu. amstelodami* and *Talaromyces stipitatus* KUFA 0207 | 50, 82 and 83 |
| C₁₆H₁₂O₈  | Erythroglaucin | Displayed no antibacterial activity | Marine-derived halotolerant fungus *A. variecolor* | 50 and 63 |
| C₁₉H₁₂O₇ | Versicolorin C | Antibacterial activity | Marine-derived mango endophytic fungus (isolate 1850) and mango-derived endophytic fungus *A. nidulans* MA-143 | 71 and 119 |
| C₁₈H₁₂O₇ | Isoversicolorin C | Antibacterial activity | Mangrove-derived endophytic fungus *A. nidulans* MA-143 | 71 |
| C₂₀H₁₄O₆ | Norsolorinic acid | Was not evaluated for any relevant bioactivity | Mangrove-derived endophytic fungus *A. nidulans* MA-143 | 71 |
| C₂₁H₂₂O₇ | (1’S) 6-O-methyl-averantin | Displayed no cytotoxic activity | Marine-derived fungus *Aspergillus* sp. SCSIO F063 | 66 |
| C₂₂H₂₄O₇ | (1’S) 6,1’-O,O’-dimethyl-averantin | Displayed no cytotoxic activity | Marine-derived fungus *Aspergillus* sp. SCSIO F063 | 66 |
| C₂₄H₂₆O₇ | Averantin-1’-butyl ether | Cytotoxic activity | Marine-derived fungus *Aspergillus* sp. SCSIO F063 | 66 |
| C₂₀H₁₆ClO₅ | (1’S)-7-chloroaverantin | Cytotoxic activity | Marine-derived fungus *Aspergillus* sp. SCSIO F063 | 66 |
| C₂₁H₂₄ClO₅ | (1’S) 6-O-methyl-7-chloroaverantin | Cytotoxic activity | Marine-derived fungus *Aspergillus* sp. SCSIO F063 | 66 |
| C₂₁H₂₄ClO₅ | (1’S) 1’-O-methyl-7-chloroaverantin | Cytotoxic activity | Marine-derived fungus *Aspergillus* sp. SCSIO F063 | 66 |
| C₂₂H₂₄ClO₅ | (1’S) 6,1’-O,O’-dimethyl-7-chloroaverantin | Displayed no cytotoxic activity | Marine-derived fungus *Aspergillus* sp. SCSIO F063 | 66 |
| C₂₄H₂₄ClO₅ | (1’S) 7-chloroaverantin-1’-butyl ether | Cytotoxic activity | Marine-derived fungus *Aspergillus* sp. SCSIO F063 | 66 |
| C₂₀H₁₈O₆ | 7-Chloroaverthrin | Displayed no cytotoxic activity | Marine-derived fungus *Aspergillus* sp. SCSIO F063 | 66 |
| C₂₁H₂₁O₆ | 6-O-methyl-7-chloroaverthrin | Cytotoxic activity | Marine-derived fungus *Aspergillus* sp. SCSIO F063 | 66 |
| C₂₁H₂₂ClO₆ | (1’S) 6-O-methyl-7-bromoaverantin | Cytotoxic activity | Marine-derived fungus *Aspergillus* sp. SCSIO F063 | 66 |
| C₂₂H₂₃BrO₆ | (1’S) 6,1’-O,O’-dimethyl-7-bromoaverantin | Displayed no cytotoxic activity | Marine-derived fungus *Aspergillus* sp. SCSIO F063 | 66 |
| C₂₃H₂₅O₇ | 6,8,1’-O,O’,O”-trimethyl-averantin | Anti-inflammatory activity | Marine-derived fungus *Aspergillus* sp. SF-72 and 6796 and mangrove endophytic fungus ZSUH-36 | 50 and 53 |
| C₂₈H₂₄O₁₀ | Penicillanthranin A | Antibacterial and cytotoxic activities | Sea fan-derived fungus *P. citrinum* PSU-F51 | 53 |
| C₂₈H₂₅O₁₁ | Penicillanthranin B | Displayed no cytotoxic activity | Sea fan-derived fungus *P. citrinum* PSU-F51 | 53 |
| C₁₅H₁₀O₄ | Chrysophanol | Anti-acetylcholinesterase, antibacterial, and cytotoxic activities | Sea fan-derived fungus *P. citrinum* PSU-F51, marine-derived fungi *T. aureoviride* PSU-F95 and *Trichoderma* sp., mangrove endophytic fungi *Halorosellinia* sp. (no. 1403) and *Guignardia* sp. (no. 4382), sea urchin-derived fungus *Monodictys* sp., and marine mangrove fungus *Paecilomyces* sp. | 40, 53–55, 57 and 100 |
| Compound | MF      | Name                        | Bioactivity                                                                                        | Source                                                                 | Ref. |
|----------|---------|-----------------------------|----------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------|------|
| 84       | C15H10O6 | ω-hydroxyemodin             | Antibacterial, anti-mycobacterial, anti-obesity, and cytotoxic activities                            | Sea fan-derived fungus *P. citrinum* PSU-F51, mangrove-derived fungus *P. citrinum* HL-5126, marine-derived fungi *T. aureoviride* PSU-F95, and *Talaromyces stipitatus* KUFA 0207, and marine lichen-derived fungus *Gliocladium* sp. T31 | 53, 54, 56, 61, 82, 84 |
| 85       | C18H13ClO7 | 2′-Acetoxy-7-chlorocitreorosein | Antibacterial activity                                                                            | Mangrove-derived fungus *P. citrinum* HL-5126                        | 84   |
| 86       | C15H10O6S | Citreorosein-3-O-sulphate   | Was not evaluated for any relevant bioactivity                                                   | Marine-derived fungus *P. oxalicum* 2HL-M-6                           | 85   |
| 87       | C15H10O6S | Emodin-3-O-sulphate         | Was not evaluated for any relevant bioactivity                                                   | Marine-derived fungus *P. oxalicum* 2HL-M-6                           | 85   |
| 88       | C15H10O5  | Aloe-emodin                 | Antibacterial and antimalarial activities                                                        | Marine-derived fungus *P. oxalicum* 2HL-M-6                           | 85–87|
| 89       | C21H19NO8 | Emodacidamide A             | Immunomodulatory activity                                                                        | Marine-derived fungus *Penicillium* sp. SCSIO sof101                  | 88   |
| 90       | C20H18NO8 | Emodacidamide B             | Immunomodulatory activity                                                                        | Marine-derived fungus *Penicillium* sp. SCSIO sof101                  | 88   |
| 91       | C20H18ClNO8 | Emodacidamide C            | Immunomodulatory activity                                                                        | Marine-derived fungus *Penicillium* sp. SCSIO sof101                  | 88   |
| 92       | C22H18NO8 | Emodacidamide D             | Immunomodulatory activity                                                                        | Marine-derived fungus *Penicillium* sp. SCSIO sof101                  | 88   |
| 93       | C24H18NO8 | Emodacidamide E             | Immunomodulatory activity                                                                        | Marine-derived fungus *Penicillium* sp. SCSIO sof101                  | 88   |
| 94       | C24H18NO8 | Emodacidamide F             | Immunomodulatory activity                                                                        | Marine-derived fungus *Penicillium* sp. SCSIO sof101                  | 88   |
| 95       | C24H18NO8 | Emodacidamide G             | Immunomodulatory activity                                                                        | Marine-derived fungus *Penicillium* sp. SCSIO sof101                  | 88   |
| 96       | C14H9O7   | Emodic acid                 | Inhibitory activity on tyrosine kinase proteins                                                  | Marine-derived endophytic fungus *Eu. rubrum* and marine-derived fungus *Penicillium* sp. SCSIO sof101 | 58, 88, and 89 |
| 97       | C15H8O7   | 2-Chloro-1,3,8 trihydroxy-6 (hydroxymethyl)-anthracene-9,10 dione     | Immunomodulatory activity                                                                        | Marine-derived fungus *Penicillium* sp. SCSIO sof101                  | 88   |
| 98       | C15H9ClO6 | 2-Chloro-1,3,8 trihydroxy-6 (hydroxymethyl)-anthracene-9,10 dione     | Immunomodulatory activity                                                                        | Marine-derived fungus *Penicillium* sp. SCSIO sof101                  | 88   |
| 99       | C16H16O6  | Altersolanol A              | Antibacterial and cytotoxic activities, as well as protein kinase inhibitory activity              | Marine-derived fungus *Stemphylium* sp. 33 231 and coral-associated fungus *Stemphylium lycopersici* | 90, 92 |
| 100      | C16H16O7  | Dihydroaltersolanol A       | Displayed no antibacterial or cytotoxic activity                                                 | Marine-derived fungus *Stemphylium* sp. 33 231, deep-sea-derived fungus *Alternaria tenuissima* DFFSCS013, and soft coral-derived *Alternaria* sp. ZJ-2008003 | 90, 93, 99 |
| 101      | C16H16O6  | Altersolanol B              | Antibacterial, anticoagulant, anti-mycobacterial, and cytotoxic activities                        | Marine-derived fungus *Stemphylium* sp. 33 231, mangrove endophytic fungus *Alternaria* sp. ZJ9-6B, and soft coral-derived *Alternaria tenuissima* DFFSCS013 and marine-derived fungus *Sporendionema casei* HDN16-802 | 90, 92, 93, 98, 99, 107 |
| 102      | C16H20O6  | Tetrahydroaltersolanol B    | Antibacterial and antifungal activities                                                          | Marine-derived fungus *Phomopsis* sp.PSU-MA214, *Stemphylium* sp. 33 231, *Phoma* sp. L28, mangrove endophytic and 111 fungus *Alternaria* sp. ZJ9-6B, and soft coral-derived *Alternaria* sp. ZJ-2008003 | 90, 91, 93, 98, 107 |
| 103      | C18H18O7  | 2-O-acetylaltersolanol B    | Antibacterial activity                                                                            | Marine-derived fungus *Stemphylium* sp. 33 231                        | 90   |
| 104      | C16H16O7  | Altersolanol C              | Antibacterial activity                                                                            | Marine-derived fungus *Stemphylium* sp. 33 231 and soft coral-derived *Alternaria* sp. ZJ-2008003 | 90, 93 |
| Compound | MF Name | Bioactivity | Source | Ref. |
|----------|---------|-------------|--------|------|
| 105 | C_{16}H_{20}O_{7} | Altersolanol L | Antifungal and cytotoxic activities | Mangrove-derived fungi Stemphylium sp. 33 231 and Phoma sp. L28, and deep-sea derived fungi Alternaria tenuissima and DFFSCS013 and soft coral-derived Alternaria sp. ZJ-2008003 | 90, 91, 93, 99 and 123 |
| 106 | C_{18}H_{22}O_{8} | 2-O-acetylaltersolanol L | Displayed no antibacterial or cytotoxic activity | Mangrove-derived fungus Stemphylium sp. 33 231 | 90 |
| 107 | C_{16}H_{20}O_{8} | Ampelanol | Cytotoxic activity | Mangrove-derived fungi Phomopsis sp.PSU-MA214, Stemphylium sp. 33 231, and Phoma sp. L28, coral-associated fungus Stemphylium lycopersici and Alternaria sp. ZJ-2008003 | 90–94, 99 and 111 |
| 108 | C_{16}H_{12}O_{5} | Macrosporin | Antibacterial, antifungal, and cytotoxic activities as well as protein kinases' inhibitory activity | Mangrove-derived fungi Phomopsis sp.PSU-MA214, Stemphylium sp. 33 231, Alternaria sp. ZJ9-6B and Phoma sp. L28 and coral-associated fungus Stemphylium lycopersici and Alternaria sp. ZJ-2008003 | 90–94, 98, 111 and 123 |
| 109 | C_{16}H_{16}O_{9} | Auxarthrol C | Antibacterial activity | Mangrove-derived fungus Stemphylium sp. 33 231 and coral-associated fungus Stemphylium lycopersici | 90 and 92 |
| 110 | C_{24}H_{24}O_{11} | Alterporriol A | Displayed no antibacterial or cytotoxic activity | Mangrove-derived fungus Stemphylium sp. 33 231 | 90 and 93 |
| 111 | C_{16}H_{16}O_{13} | Alterporriol B | Antibacterial activity | Mangrove-derived fungus Stemphylium sp. 33 231 and so coral-derived Alternaria sp. ZJ-2008003 and, deep-sea derived fungus Alternaria tenuissima DFFSCS013 | 90 and 94 |
| 112 | C_{32}H_{26}O_{13} | Alterporriol C | Antibacterial and antiviral activities | Mangrove-derived fungus Stemphylium sp. 33 231 and soft coral-derived Alternaria sp. ZJ-2008003 | 90 and 93 |
| 113 | C_{32}H_{22}O_{10} | Alterporriol D | Antibacterial and cytotoxic activities | Mangrove-derived fungus Stemphylium sp. 33 231 | 90 and 94 |
| 114 | C_{32}H_{22}O_{10} | Alterporriol E | Antibacterial and cytotoxic activities | Mangrove-derived fungus Stemphylium sp. 33 231 | 90 and 94 |
| 115 | C_{32}H_{26}O_{13} | Alterporriol N | Antibacterial and anti-inflammatory activities | Marine-derived fungus Stemphylium sp. FJJ006 and mangrove-derived fungus Stemphylium sp. 33 231 | 90, 95 and 97 |
| 116 | C_{32}H_{30}O_{12} | Alterporriol Q | Antibacterial activity | Mangrove-derived fungus Stemphylium sp. 33 231 | 90 and 93 |
| 117 | C_{32}H_{26}O_{13} | Alterporriol R | Displayed no antiviral, antibacterial or cytotoxic activity | Mangrove-derived fungus Stemphylium sp. 33 231 | 90 and 93 |
| 118 | C_{32}H_{30}O_{12} | Alterporriol T | Displayed no antibacterial activity | Mangrove-derived fungus Stemphylium sp. 33 231 | 90 |
| 119 | C_{32}H_{30}O_{12} | Alterporriol U | Antibacterial activity | Mangrove-derived fungus Stemphylium sp. 33 231 | 90 |
| 120 | C_{32}H_{30}O_{13} | Alterporriol V | Antibacterial activity | Mangrove-derived fungus Stemphylium sp. 33 231 | 90 |
| 121 | C_{32}H_{30}O_{13} | Alterporriol W | Displayed no antibacterial or cytotoxic activity | Mangrove-derived fungus Stemphylium sp. 33 231 | 90 |
| 122 | C_{32}H_{30}O_{13} | Alterporriol F | Anti-inflammatory and cytotoxic activities | Marine-derived fungus Stemphylium sp. FJJ006 | 95 and 96 |
| 123 | C_{32}H_{30}O_{13} | Alterporriol G | Antibacterial, anti-inflammatory, and cytotoxic activities as well as protein kinase inhibitory activity | Marine-derived fungus Stemphylium sp. FJJ006 | 95, 97 and 123 |
| 124 | C_{32}H_{30}O_{13} | Alterporriol Z | Anti-inflammatory activity | Marine-derived fungus Stemphylium sp. FJJ006 | 95 |
| 125 | C_{32}H_{30}O_{13} | Alterporriol Z | Anti-inflammatory activity | Marine-derived fungus Stemphylium sp. FJJ006 | 95 |
| Compound | MF | Name | Bioactivity | Source | Ref. |
|----------|----|------|-------------|--------|-----|
| 128      | C_{32}H_{26}O_{11} | Alterporriol Z3 | Displayed no antibacterial or cytotoxic activity | Marine-derived fungus *Stemphylium* sp. | 95 |
| 129      | C_{22}H_{12}O_{10} | Macrosporin 2-O-α-D-glucopyranoside | Displayed no cytotoxic activity | Marine-derived fungus *Stemphylium* sp. | 92 |
| 130      | C_{16}H_{20}O_{6} | Alterporriol Y | Displayed no cytotoxic activity | Coral associated fungus *Stemphylium* sp. | 92 |
| 131      | C_{16}H_{20}O_{6} | Alterporriol E | Displayed no antibacterial, antiviral, or cytotoxic activity | Marine-derived fungus *Alternaria* sp. | 98 |
| 132      | C_{16}H_{20}O_{6} | Alterporriol C | Antiviral activity | Marine-derived fungus *Alternaria* sp. | 98 |
| 133      | C_{16}H_{20}O_{6} | Alterporriol L | Cytotoxic activity | Marine-derived fungus *Alternaria* sp. | 98 |
| 134      | C_{16}H_{20}O_{6} | Alterporriol O | Displayed no antibacterial, antiviral, or cytotoxic activity | Marine-derived fungus *Alternaria* sp. | 98 |
| 135      | C_{32}H_{26}O_{11} | Alterporriol K | Displayed no antibacterial, antiviral, or cytotoxic activity | Marine-derived fungus *Alternaria* sp. | 98 |
| 136      | C_{16}H_{20}O_{6} | Tetrahydroaltersolanol C | Antiviral activity | Marine-derived fungus *Alternaria* tenuissima DFFSCS013 | 99 |
| 137      | C_{16}H_{20}O_{6} | Tetrahydroaltersolanol D | Displayed no antibacterial, antiviral, or cytotoxic activity | Marine-derived fungus *Alternaria* tenuissima DFFSCS013 | 99 |
| 138      | C_{16}H_{20}O_{6} | Tetrahydroaltersolanol E | Displayed no antibacterial, antiviral, or cytotoxic activity | Marine-derived fungus *Alternaria* tenuissima DFFSCS013 | 99 |
| 139      | C_{16}H_{20}O_{6} | Tetrahydroaltersolanol F | Displayed no antibacterial, antiviral, or cytotoxic activity | Marine-derived fungus *Alternaria* tenuissima DFFSCS013 | 99 |
| 140      | C_{22}H_{22}O_{10} | Anthrininone A | Inhibitory activity on protein tyrosine phosphatases and stimulatory effect on intracellular calcium levels | Deep-sea derived fungus *Alternaria tenuissima* DFFSCS013 | 99 |
| 141      | C_{16}H_{14}O_{6} | 6-O-methyl-alaternin | Inhibitory activity on protein tyrosine phosphatases | Deep-sea derived fungus *Alternaria tenuissima* DFFSCS013 | 99 |
| 142      | C_{16}H_{14}O_{6} | (3R)-1-deoxyasturocortilutein | Displayed no stimulation of intracellular calcium levels | Deep-sea derived fungus *Alternaria tenuissima* DFFSCS013 | 99 |
| 143      | C_{15}H_{14}O_{6} | Harzianumnone A | Displayed no anti-acetylcholinesterase or DNA Topo I inhibitory activities | Marine-derived fungus *T. harzianum* XS-20090075 | 100 |
| 144      | C_{15}H_{14}O_{6} | Harzianumnone B | Displayed no anti-acetylcholinesterase or DNA Topo I inhibitory activities | Marine-derived fungus *T. harzianum* XS-20090075 | 100 |
| 145      | C_{15}H_{14}O_{6} | Phomarin | Anti-acetylcholinesterase activity | Marine-derived fungus *T. harzianum* XS-20090075 | 100 |
| 146      | C_{15}H_{14}O_{6} | ω-hydroxydigitoxin | Anti-acetylcholinesterase activity | Marine-derived fungus *T. harzianum* XS-20090075 | 100 |
| 147      | C_{15}H_{14}O_{6} | Pachybasin | Anti-acetylcholinesterase and cytotoxic activities | Marine-derived fungus *T. harzianum* XS-20090075 | 100 |
| 148      | C_{17}H_{14}O_{6} | (+)-2′S-isorhodoptilometrin | Anti-acetylcholinesterase, antibacterial, and cytotoxic activities, as well as DNA Topo I inhibitory activity | Marine-derived fungus *T. harzianum* XS-20090075, marine lichen-derived fungus *Gloioctadium* sp. T31, and marine-derived fungus *T. aureoviride* PSU-F95 | 100 |
| 149      | C_{15}H_{14}O_{6} | ω-hydroxypachybasin | Anti-acetylcholinesterase, antibacterial, and cytotoxic activities, as well as DNA Topo I inhibitory activity | Marine-derived fungus *T. aureoviride* PSU-F95 | 100 |
| 150      | C_{15}H_{14}O_{6} | Coniothranthraquinone 1 | Anti-bacterial activity | Marine-derived fungus *T. aureoviride* PSU-F95 | 100 |
| 151      | C_{15}H_{14}O_{6} | Trichodermaquinone | Antibacterial activity | Marine-derived fungus *T. aureoviride* PSU-F95 | 100 |
| 152      | C_{15}H_{14}O_{6} | 2-Methyl-quinizarin | Was not evaluated for any relevant bioactivity | Marine-derived fungus *T. aureoviride* PSU-F95 | 100 |
| Compound | MF | Name | Bioactivity | Source | Ref. |
|----------|----|------|-------------|--------|------|
| 153      | C_{15}H_{16}O_4 | 1-Hydroxy-3-methoxyanthraquinone | Was not evaluated for any relevant bioactivity | Marine-derived fungus T. aureoviride PSU-F95 | 54 |
| 154      | C_{15}H_{16}O_5 | Coniothyrinone A | Antibiocytotoxic and antiangiogenic activities | Marine-derived fungus Trichoderma sp. | 60 |
| 155      | C_{15}H_{14}O_6 | Lentisone | Antibiocytotoxic and antiangiogenic activities | Marine-derived fungus Trichoderma sp. | 60 |
| 156      | C_{15}H_{14}O_6 | 9-Dehydroxyeurotinone | Antibacterial and antitumor activities | Marine-derived endophytic fungus Eu. rubrum | 58 |
| 157      | C_{16}H_{14}O_6 | 2-O-Methyl-9-dehydroxyeurotinone | Antioxidant activity | Marine-derived endophytic fungus Eu. rubrum | 58 |
| 158      | C_{21}H_{22}O_9 | 2-O-Methyl-4-O-(x-o-ribofuranosyl)-9-dehydroxyeurotinone | Antioxidant activity | Marine mangrove-derived endophytic fungus Eu. rubrum | 62 |
| 159      | C_{33}H_{30}O_13 | Engyodontochone A | Antibacterial and antitumor activities | Marine mangrove-derived endophytic fungus Eu. rubrum and marine algae-derived endophytic fungus Eu. cristatum EN-220 | 62 |
| 160      | C_{33}H_{28}O_12 | Engyodontochone | Antibacterial and antitumor activities as well as brine shrimp lethality | Marine mangrove-derived endophytic fungus Eu. rubrum | 62 |
| 161      | C_{33}H_{28}O_12 | Engyodontochone B | Antibacterial and antitumor activities | Marine algae-derived endophytic fungus Eu. cristatum | 62 |
| 162      | C_{33}H_{28}O_12 | Engyodontochone C | Antibacterial and antitumor activities | Marine algae-derived endophytic fungus Eu. cristatum EN-220 and marine algae-derived endophytic fungus Eu. cristatum EN-220 | 62 |
| 163      | C_{21}H_{20}O_8 | Fusarinthraquinone | Displayed no antibacterial activity or brine shrimp lethality | Marine algae-derived endophytic fungus | 101 |
| 164      | C_{16}H_{18}O_6 | Fusarquinone A | Cytotoxic activity | Marine-derived fungus Fusarium sp. ZH-210 | 104 |
| 165      | C_{16}H_{20}O_9 | Fusarquinone B | Cytotoxic activity | Marine-derived fungus Fusarium sp. ZH-210 | 105 |
| 166      | C_{16}H_{18}O_8 | Fusarquinone C | Cytotoxic activity | Marine-derived fungus Fusarium sp. ZH-210 | 104 |
| 167      | C_{21}H_{20}O_9 | 6,8-Dimethoxy-1-methyl-2-[3-oxobutyl]anthracene-9,10-dione | Cytotoxic activity | Marine-derived fungus Fusarium sp. ZZF60 | 106 |
| 168      | C_{16}H_{16}O_6 | 5-Acetyl-2-methoxy-1,4,6-trihydroxy-anthraquinone | Was not evaluated for any relevant bioactivity | Marine endophytic fungus Fusarium sp. | 124 |
| 169      | C_{16}H_{20}O_9 | 4-Dehydroxylsolenol A | Antibacterial and anticoagulant activities | Marine-derived fungus Sporendonema casei HDN16-802 | 107 |
| 170      | C_{16}H_{18}O_6 | Auxarthrol D | Antibacterial, anticoagulant, and cytotoxic activities | Marine-derived fungus Sporendonema casei HDN16-802 | 107 |
| 171      | C_{16}H_{18}O_6 | Auxarthrol E | Antibacterial and anticoagulant activities | Marine-derived fungus Sporendonema casei HDN16-802 | 107 |
### Table 1 (Contd.)

| Compound | MF       | Name                     | Bioactivity                                      | Source                        | Ref. |
|----------|----------|--------------------------|--------------------------------------------------|-------------------------------|------|
| 180      | C₁₆H₂₀O₈ | Auxarthrol E             | Anticoagulant activity                            | Marine-derived fungus Sporendonema casei HDN16-802 | 107  |
| 181      | C₁₆H₂₀O₈ | Auxarthrol F             | Antibacterial, anticoagulant, and cytotoxic activities | Marine-derived fungus Sporendonema casei HDN16-802 | 107  |
| 182      | C₁₆H₁₅ClO₈| Auxarthrol G             | Antibacterial, anticoagulant, and antifungal activities | Marine-derived fungus Sporendonema casei HDN16-802 | 107  |
| 183      | C₁₆H₁₅O₈ | Auxarthrol H             | Anticoagulant activity                            | Marine-derived fungus Sporendonema casei HDN16-802 | 107  |
| 184      | C₁₇H₁₄O₄ | 1,3-Dimethoxy-6-methyl-anthracene-9,10-dione | Cytotoxic activity                               | Halorosellinia sp. No. 1403 and Guignardia sp. No. 4382 | 40   |
| 185      | C₁₅H₁₀O₄ | Demethoxyastrococtirubin | Cytotoxic activity                               | Halorosellinia sp. No. 1403 and Guignardia sp. No. 4382 | 40   |
| 186      | C₁₄H₈O₄ | Dantron                  | Cytotoxic activity                               | Halorosellinia sp. No. 1403 and Guignardia sp. No. 4382 | 40   |
| 187      | C₁₆H₁₂O₈ | Auxarthrol E             | Cytotoxic activity                               | Marine-derived fungus Sporendonema casei HDN16-802 | 107  |
| 188      | C₁₇H₁₄O₆ | 1,7-Dihydroxy-2,4-dimethoxy-6-methyl-anthracene-9,10-dione | Cytotoxic activity                               | Halorosellinia sp. No. 1403 and Guignardia sp. No. 4382 | 40   |
| 189      | C₁₆H₁₂O₄ | 8-Hydroxy-1-methoxy-3-methyl-9,10-anthraquinone | Cytotoxic activity                               | Halorosellinia sp. No. 1403 and Guignardia sp. No. 4382 | 40   |
| 190      | C₁₇H₁₄O₆ | 1,7-Dihydroxy-2,4-dimethoxy-6-methyl-anthracene-9,10-dione | Cytotoxic activity                               | Halorosellinia sp. No. 1403 and Guignardia sp. No. 4382 | 40   |
| 191      | C₁₄H₈O₃ | 1,3,8-Trihydroxanthraquinone | Cytotoxic activity                               | Halorosellinia sp. No. 1403 and Guignardia sp. No. 4382 | 40   |
| 192      | C₁₆H₁₂O₆ | 1,4,7-Trihydroxy-2-methoxy-6-methyl-9,10-anthraquinone | Displayed no cytotoxic activity                   | Halorosellinia sp. No. 1403 and Guignardia sp. No. 4382 | 40   |
| 193      | C₁₆H₁₀O₆ | SZ-685C                  | Cytotoxic activity                               | Marine-derived fungus Sporendonema casei HDN16-802 | 108–110 |
| 194      | C₁₉H₂₀O₈ | Phomopsanthraquinone     | Antibacterial and cytotoxic activities            | Marine-derived fungus Phomopsis sp. PSU-MA214 | 111  |
| 195      | C₁₆H₁₂O₄ | 1-Hydroxy-3-methoxy-6-methylanthraquinone | Displayed no antibacterial or cytotoxic activity | Marine-derived fungus Phomopsis sp. PSU-MA214 | 111  |
| 196      | C₁₆H₁₂O₇ | Tetrahydroxanthraquinone | Protein kinases' inhibitory activity             | Sponge-associated fungus Microsphaeropsis sp | 112  |
| 197      | C₁₇H₁₄O₇ | Methoxy-tetrahydroxanthraquinone | Protein kinases' inhibitory activity             | Sponge-associated fungus Microsphaeropsis sp | 112  |
| 198      | C₁₇H₁₄O₆ | 1,2,3,6,8-Pentahydroxy-7-[1R]-1-methoxyethyl]-9,10-anthraquinone | Protein kinases' inhibitory activity             | Sponge-associated fungus Microsphaeropsis sp | 112  |
| 199      | C₁₅H₁₀O₆ | Lunatin                  | Antibacterial activity                            | Marine-derived fungus Curvularia lunata | 113  |
| 200      | C₁₃H₁₀O₂₁₂ | Cytoskyrin A             | Antibacterial activity                            | Marine-derived fungus Curvularia lunata | 113  |
| 201      | C₁₄H₈O₄ | Rheeomodin               | Displayed no significant anti-obesity activity    | Marine sponge-associated fungus Talaromyces stipitatus KUFA 0207 | 82   |
| 202      | C₂₀H₁₄O₁₀ | 2, 2’-Bis-(7-methyl-1,4,5-trihydroxyanthracene-9,10-dione) | Not evaluated for any relevant activity         | Marine sponge-associated fungus Talaromyces stipitatus KUFA 0207 | 82   |
| 203      | C₁₇H₁₄O₄ | 7-Methoxymacroropin      | Antifungal activity                               | Marine-derived fungus Phoma sp. L28 91 | 91   |
| 204      | C₁₇H₂₀O₅ | 7-(γ,γ)-Dimethyl-allyloxy-macroropin | Antifungal activity                               | Marine-derived fungus Phoma sp. L28 91 | 91   |
| 205      | C₁₆H₁₅O₅ | Monodicyquinone A        | Antibacterial and antifungal activities           | Marine-derived fungus Monodictys sp | 55   |
| 206      | C₁₆H₁₂O₆ | 1,3,6-Trihydroxy-7-(1-hydroxyethyl)anthracene-9,10-dione | Inhibitory activity against α-glycosidase | Marine-derived fungus Cladosporium sp. HNWSW-1 | 114  |
5 tested drug-likeness rules (7, 48, 7, 4, 10, 16, 10, 9, 2, and 20 anthraquinones from Nigrospora, Aspergillus, Penicillium, Stemphylium, Alternaria, Trichoderma, Eurotium, Fusarium, Sporendonema casei, and the other genera, respectively). Noteworthy, all anthraquinones identified from Trichoderma species fulfilled the 5 rules. On the other hand, all Engyodontium album derived compounds violated the 5 tested rules (Fig. 15, 16, and S† Table 1).

Topological polar surface area (TPSA), another measure, is the sum of the surfaces of all the polar atoms present in a molecule. TPSA has a substantial effect on the potential of a compound to penetrate through the cell membranes and blood–brain barrier. Veber highlighted those compounds with TPSA ≤ 140 Å² tend to be well absorbed and able to reach their molecular target within the body cells. Egan stated that molecules with TPSA less than 132 Å² and log-P between −1 and 6 could be considered leads with high drug-likeness potential and good orally bioavailability. Muegge utilized a pharmacophore point filter based on very simple structural rules to differentiate between drug-like and nondrug-like molecules, among them TPSA not greater than 150 Å² as well as rotatable bonds (RB), not more than 15. All anthraquinones from Fusarium, Trichoderma, Nigrospora (except compound 1), Aspergillus (except compounds 11, 12, 20, 24, 25, 39, and 61), Penicillium (except compounds 81, 82, 86, and 89–96), Stemphylium (except compounds 110–130), Alternaria (except compounds 114, 131–135, and 140), Eurotium (except compounds 20, 160, and 161), Sporendonema casei (except compound 180), and the other genera (except compounds 200 and 202) had TPSA less than 150 Å². On the other hand, all Engyodontium album derived compounds had TPSA greater than 150 Å². All anthraquinones had RB less than 15 (Fig. 15 and ESI Table S1†).

Oral bioavailability, bioavailability score (BS), is another descriptor that indicates the possibility of a compound to be bioavailable with more than 10% in the absorption assays. Molecules obeying the Lipinski rule with BS of 0.55 are considered orally bioavailable. Interestingly, 166 anthraquinones showed a BS of 0.55. In alignment with other parameters, all Fusarium and Trichoderma derived anthraquinones showed a BS of 0.55 and all Engyodontium album derived compounds had a BS of 0.11. Compounds 3, 6, and 9, are of special interest as they showed a good BS of 0.56. Some other compounds, among them 10, 87, 97, and 109, showed good BS (0.56); however, violated one or more drug-likeness rules (Fig. 15 and ESI Table S1†).

Table 1 (Contd.)

| Compound MF | C₁₇H₁₂O₇ | Phaeolorin I | Displayed no cytotoxic activity | Deep-sea sediment-derived fungus | 115 |
|-------------|-----------|--------------|---------------------------------|---------------------------------|-----|
| 207         | C₁₂H₁₅O₅ | 6,8-O,O’-Dimethyl-averufanin | Antifungal and phytotoxic activities, as well as brine shrimp lethality | Mangrove endophytic fungus ZSUH-36 | 116 and 117 |

Oral bioavailability relies as well on the degree of the molecular flexibility of the molecule. Candidates with an extreme degree of flexibility do not typically display acceptable bioavailability as they tend to be less planar and with very complex 3D shapes. The sp³ carbons fraction (Fraction Csp³) and the number of RB are two crucial measures for molecular flexibility. Csp³ is the ratio of the sp³ carbon atoms to the total carbons present in a given compound. It assigns the degree of carbon saturation, characterizes the space complexity, and correlates to the solubility of the compound. A Csp³ score between 0.25 and 1 is considered optimum for drug-likeness. One hundred anthraquinones, distributed in all marine fungi species, displayed a Csp³ score ranging between 0.28 and 0.6. The water solubility, expressed as log S, is another essential measure for drug bioavailability. Compounds with poor water solubility have poor absorption and oral bioavailability, as well as low formulation potential. Anthraquinones revealed different solubility orders as Sporendonema casei derived compounds were the most soluble (mean value of −1.46), followed by Nigrospora sp (mean value of −2.34), while Engyodontium album derived anthraquinones, as expected, were the most poorly soluble (mean value of −5.44) (Fig. 15 and ESI Table S1†).

Gastrointestinal (GI) absorption, blood–brain barrier (BBB) permeation, P-glycoprotein (P-gp) substrate and cytochrome P450 members inhibition potentials were also surveyed to draw insight about the pharmacokinetic behavior of the reviewed anthraquinones. Twenty anthraquinones (47, 48, 49, 51, 52, 57, 83, 147, 152, 153, 157, 169, 184, 185, 186, 188, 189, 195, 203, and 204) showed high GI absorption, passively crossed BBB and did not show any potential for P-gp substrate (ESI Table S2†). Surprisingly, compound 169 obeyed all the surveyed parameters (5 drug-likeness rules, log P, Csp³, RB, TPSA, log S, GI, BBB, Pgp) and the other 19 anthraquinones as well except for fraction Csp³. Noteworthy, all but one of the 20 anthraquinones have two benzenoid aromatic rings and two C=O groups. Also, several anthraquinones showed potential inhibition for some CYP 450 isofoms which necessitates awareness when co-administered with possible substrates of these enzymes (ESI Table S2†).

To sum up, marine fungi are a promising source of biologically active anthraquinones that obeyed all the criteria of several drug-likeness rules with promising pharmacokinetic behavior which promotes their utilization as well as further research to isolate their individual components and determine their pharmacological effects.
Conclusions and future prospective

The marine phoma is representing the most, the greatest and most diverse ecological structure on the planet. Over seven decades, marine natural products (MNPs) have owned credits and been privileged as a robust and sustainable supplier for pharmacologically active compounds that meet a huge interest in pharmaceutical and economical applications. Marine-derived fungi are valuable sources of structurally diverse MNPs due to their various habitats that range from the warm to the colder areas, and even at extreme temperatures and pressure like in hydrothermal outlets. One of the fascinating classes of fungal derived natural products is the anthraquinones. Herein, we presented a comprehensive literature review centered on marine-derived anthraquinones as a unique group of fungal polyketides over the period 2000–2020 from twenty marine fungal genera. A list of 208 anthraquinones have been reported from different marine fungi, featuring a myriad of structural and biological diversities. Investigating such extensive chemo-biological data has implied two remarkable points. First, it was clear that the marine fungi of the three genera *Aspergillus* sp., *Stemphylium* sp., and *Penicillium* sp., are the most creative fungal genera in terms of producing of anthraquinones. Secondly, the most common reported bioactivity was cytotoxicity, where a notable number of seventy-two compounds have been evaluated for their cytotoxic activity against planes of carcinoma cell lines, whilst the anthraquinones with antibacterial activity were the second on the list with sixty-nine compounds demonstrated bioactivity against a wide range of microorganisms. Meanwhile, an enormous spectrum of further biomedical potentialities exhibited by these compounds as antioxidant, antiviral, antifungal, immunomodulatory, anti-

Fig. 17  Distribution and total anthraquinones and their derivatives isolated from different species of marine-derived fungi.

Fig. 18  Total biological activities of various anthraquinones and their derivatives isolated from different species of marine-derived fungi.
inflammatory, ..., etc.) have been documented. Such a massive connection between chemical spaces and bioactivities highlights the huge capacity of marine-derived fungi as an attractive biological source that is worth further exploitations with distinguished anticipations for the global pharmaceuticals industries. Additionally, recent advances in the level of sampling techniques, fermentation, synthetic biology, genetic engineering, genome mining, and total chemical synthesis, all are crucial to the success of fungal MNPs as future drug leads. Furthermore, all reported anthraquinones were extensively investigated for their in silico Drug-likeness and pharmacokinetics properties using SWISSADME online platform, which intriguingly highlighted a list of 20 anthraquinone containing compounds (ESI†) that could be considered as potential drug leads scaffolds (Fig. 17 and 18).

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Conceptualization: Amr El-Demerdash. Validation: Amr El-Demerdash. Formal analysis: Mohamed Sebak, Fatma Molham, Claudio Greco Mohamed A. Tammam, Mansour Sobeh and Amr El-Demerdash. Investigation: Mohamed Sebak, Fatma Molham, Claudio Greco Mohamed A. Tammam, Mansour Sobeh and Amr El-Demerdash. Resources: Mohamed Sebak, Fatma Molham, Claudio Greco Mohamed A. Tammam, Mansour Sobeh and Amr El-Demerdash. Data curation: Mohamed Sebak, Fatma Molham, Claudio Greco Mohamed A. Tammam, Mansour Sobeh and Amr El-Demerdash. Writing original draft: Mohamed Sebak, Fatma Molham, Claudio Greco Mohamed A. Tammam, Mansour Sobeh and Amr El-Demerdash. Writing-review & editing: Mohamed Sebak, Fatma Molham, Claudio Greco Mohamed A. Tammam, Mansour Sobeh and Amr El-Demerdash.

Conflicts of interest
The authors declare that they have no known competing commercial interests or personal relationships that could have appeared to influence the work reported in this paper.

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List of abbreviations

**A.** Aspergillus  
ACP acyl carrier protein  
AT acyl transferase  
*B.* Bacillus  
BBB blood–brain barrier  
BS bioavailability score  
*C.* Candida  
Csp³ sp³ carbons  
DPPH 1,1-diphenyl-2-picrylhydrazyl  
*E.* Escherichia  
ED₅₀ median effective dose (the dose which produces a specified effect in 50% of the population in a study)  
*Eu.* Eurotium  
F. Fusarium  
FCsp³ fraction of sp³ carbons  
HCV Hepatitis C virus  
GI Gastrointestinal  
KS ketosynthase  
IC₅₀ inhibitory concentration that causes a 50% reduction in cell viability  
IL interleukin  
LD₅₀ lethal dose 50 (the dose which produces death in 50% of the population in a study)  
Log P lipophilicity  
Log S solubility  
*M.* Mycobacterium  
MdpF metallo-hydrolase protein  
MIC minimum inhibitory concentration  
MNP marine natural product  
MRSA methicillin-resistant *Staphylococcus aureus*  
Mwt molecular weight  
nrPKS non-reducing polyketide synthase  
P. Penicillium  
P-gp P-glycoprotein  
PT product template  
RB rotatable bond  
*S.* Staphylococcus  
SAT starter unit-ACP transacylase  
*Str.* Streptococcus  
*T.* Trichoderma  
Topo topoisomerase  
TPSA topological polar surface area  
*V.* Vibrio

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