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Finding Antitubercular Leads from Marine-Derived and Entomopathogenic Fungi

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Abstract— The occurrence of *Mycobacterium tuberculosis* resistance encourages the discovery of new antitubercular candidates. Microbes including fungi and bacteria are well known reservoir for isolating antibiotic compounds, among natural product resources. In this review, we report promising antitubercular compounds from marine-derived and entomopathogenic fungi, reported from 2000 to 2022. A comprehensive literature search was conducted through scientific websites, including Google Scholar, Springer, and Pubmed. This review includes only research publications reporting antitubercular action of well-defined secondary metabolites with MIC values less than 100 M. Eighty-three antitubercular compounds were reported, where 57 of them derived from fungi associated with marine ecosystem. Those fungi belong to 10 fungal genera. The remaining active compounds were isolated from 7 genera of entomopathogenic fungi. Gliotoxin, 12,13-dihydroxy-fumitremorgin, and helvolic acid as well as hirsutellones A-D are among bioactive compounds reported for their remarkable antitubercular activity, which promising to be investigated further in the search of antitubercular leads. Deeper investigation on these compounds might be promising for the the discovery of antitubercular candidates in the future.

Keywords—Antitubercular; entomopathogenic fungi; marine-derived fungi; *Mycobaterium tuberculosis*; secondary metabolites

1. INTRODUCTION

Tuberculosis is one of the deadly diseases caused by Mycobacterium, that require long-term antibiotic treatment (Swain et al., 2022). However, the increasing threat of bacterial resistance to current antibiotics has urged researchers to find new and more potent antibiotics, including those against Mycobacterium. The search for new antitubercular compounds from natural products is one of the strategic steps that can be taken. Therefore, research on antitubercular from natural resources is currently being carried out intensively. Based on the report of Bull and Stach (2007), compounds derived from natural products are a potential source for isolating bioactive secondary metabolites promising as lead compounds for various biological activities. Drug candidates from natural products can be isolated from various sources such as plants, animals and microorganisms (Ye et al., 2020). In this review we explore the search for antitubercular candidates from natural materials produced by microorganisms. Among microbes, fungi are one of well-known sources of antibiotics, as exemplified by the finding on penicillin and cephalosporin antibiotics. Fungi can be found in various biotic and abiotic environments (Ameen et al., 2021), indicating their huge distribution in nature which could lead to their high chemical and biological diversities. Exploration of fungi as sources of bioactive natural products has been widely reported. For example, research by Zang et al. (2022) has been reported antimicrobial compounds produced by *Aspergillus flavus* QQYZ isolated from the mangrove *Kandelia candel* namely aflaxanthone A. This compound can inhibit Methicillin-Resistant *Staphylococcus aureus* with MIC value of 12.5 μM. Apart from the marine environment, fungi can also be isolated from animals, such as insects. These fungi are better known as entomopathogenic fungi, a parasitic microorganisms with an ability to infect and kill arthopods (Litwin et al., 2020). A report by Isaka et al. (2012) isolated a potential antimicrobial compound namely torrubiellin B, which capable of inhibiting *Candida albicans* and *Bacillus cereus* with IC_{50} <10 μg mL-1. The compound was isolated from the entomopathogenic fungus, *Torrubiella* sp. BCC 28517. These studies indicate that marine-derived and entomopathogenic fungi could be a potential source for finding lead compounds promising for the development of antituber-

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cular agents. Therefore, in this review, we focus on reporting the presence of antitubercular compounds from marine-derived and entomopathogenic fungi.

2. METHODS

As for inclusion criteria, we restricted our literature search to original research paper on antitubercular compounds produced by marine-derived and entomophatogenic fungi, published on 2000 to 2022. Moreover, only research papers describing antitubercular activity of well-defined secondary metabolites with MIC values under 100 μM were included in this review. Research papers that do not fulfill the inclusion criteria and reported the antitubercular activity of the crude extract were excluded. The literature search was conducted using online scientific search through Google Scholar, Springer, Pubmed, Science Direct, Elsevier, and MDPI. The following keywords were used for literature search: antitubercular, *Mycobacterium tuberculosis*, algae-, coral-, mangrove-, deep sea sediment-, sponge-derived fungi, and entomopathogenic fungi

3. RESULTS AND DISCUSSION

Based on our literature search, 70 original research articles were obtained. Thirty of those journals fulfill the inclusion criteria. All papers that met the inclusion criteria were used in this literature review. Minimum inhibitory concentration (MIC) values in the original papers will be converted to μM, as the antibiotic-mediated bacterial interactions evoke a biological response in the recipient bacteria in a dose-dependent manner (Bernier and Surette, 2013) and are not dependent on the weight of the compound.

Antitubercular from marine-derived fungi

Marine-derived fungi are well known as promising producer of various bioactive natural products, some of which show remarkable pharmacological activity for future drug development (Zhen Liu et al., 2020). The following sections describe antitubercular compounds from marine sources including algae-, coral-, deep sea sediment-, mangrove-, and sponge derived fungi.

Algae-derived fungi

Algae-derived fungi were reported to produced diverse bioactive metabolites, some of which were confirmed to demonstrate promising antitubercular activities. Three antimycobaterial compounds were isolated from algae-derived fungi, as shown in Figure 1. Halogenated bianthrones called neobulgarones D (1) and F (2) were isolated from *Penicillium roseopurpureum* (KP1-135C), derived from alga species, Petalonia fascia. This alga was collected at the shores of Green's Point, L'Etete, NB, Canada. Neobulgarones D and F showed moderate antitubercular activity with MIC values of 46.10 and 31.10 μM (Morehouse et al., 2020). Moreover, investigation on azaphilone derivative, sclerotiorin (3), produced by seaweed-associated fungus, *Penicillium* sp. strain ZJ27, collected in the South China Sea revealed its antitubercular effect through inhibition of protein kinase G (PknG) of *Mycobacterium tuberculosis* H37Ra with an IC_{50} value of 76.50 μM (Chen et al., 2017a).

Coral-derived fungi

Coral-derived fungi have proven to be a treasure trove of structurally unique and biologically active secondary metabolites. Eight antimycobaterial compounds were isolated from coral-derived fungi, as shown in Figure 2. Asperversiamides A (4), B (5), and C (6) were obtained from *Aspergillus versicolor* CHNSCLM-0063, isolated from *Rumphella aggregata* in the South China Sea. All isolated compounds showed mild to weak antitubercular activity towards *Mycobacterium marinum* with MIC values of 23.4, 81.2, and 87.5 μM, respectively (Hou et al., 2019). Furthermore, the fungus *Fusarium graminearum* SYSU-MS5127 was isolated from an anemone in Laishizhou Island, Shenzhen City, Guangdong Province, China. This fungus produced several bioactive compounds with inhibitory effects on M. tuberculosis protein-tyrosine-phosphatase B (MptpB). Among these active compounds, fusarielin G (7) gave mild activity with an IC_{50} value of 23.75 μM, while fusarielins M (8) and N (9) possessed potent to weak inhibition with IC_{50} values of 1.05 and >40.00 μM, respetively (Chen et al., 2021). Another Fusarium spp. PSU-F14 was isolated from *Annella* sp. in Gorgonian Sea which produced nigrosporin B (10) and anhydrofusarubin (11). These compounds showed moderate to weak inhibition against *M. tuberculosis* H37Ra with MIC values of 41.00 and 87.00 μM (Trisuwan et al., 2010).

Deep sea sediment-derived fungi

A large number of fungal species with the ability to produce bioactive compounds were found in deep sea sediments from different regions of the world and also have proven to be treasure secondary metabolite (Yan et al., 2022). The extreme environment creates the great potential to produce natural products with significant biological properties. Nine antimycobaterial compounds were isolated from deep sea sediment-derived fungi, as shown in Figure 3. In particular, *Aspergillus* sp. SCSIO Ind09F01 was isolated from deep-sea sediment, collected in the South China Sea. This fungus produced gliotoxin (12), 12,13-dihydroxy-fumitremorgin (13), and helvolic acid (14). These compounds revealed remarkable antitubercular activity against *M. tuberculosis* with IC_{50} value of 0.03, 0.89, and 2.41 μM, respectively (Luo et al., 2017). Furthemore, polypropionate derivatives, namely fiscpropionates A (15), B (16), C (17), D (18), E (19), and F (20), were obtained from *Aspergillus fischeri* FS452, isolated from deep-sea sludge of Indian Ocean sediments at 3000 m depth. All compounds exhibited strong to mild inhibition on the MptpB activity with IC_{50} values ranging from 4.00 until >50.00 μM (Zhaoming Liu et al., 2019).

Mangrove-derived fungi

Mangrove-derived fungi have been proven as a valuable source in the search of structurally and biologically diverse substances (Qiu et al., 2018). Twenty-seven antimycobaterial compounds were isolated from mangrove-derived fungi, as shown in Figure 4. Mangrove-associated fungi were revealed to produce a vast range of antitubercular metabolites. An endophytic fungus, identified as *Diaporthe* sp. SYSU-HQ3, was isolated from fresh branch of the mangrove *Excoecaria agallocha*. This fungus was found to produce isoprenylisoindole type of alkaloids, characterized as diaporisoindole A (21) and tenellone C (22), which showed prominent inhibition against MptpB with IC_{50} values

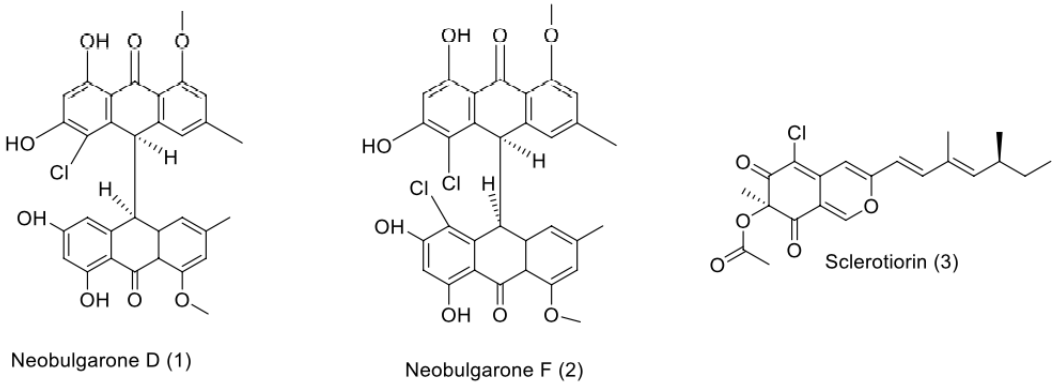

Figure. 1: Structures of compounds (1-3) from algae-derived fungi

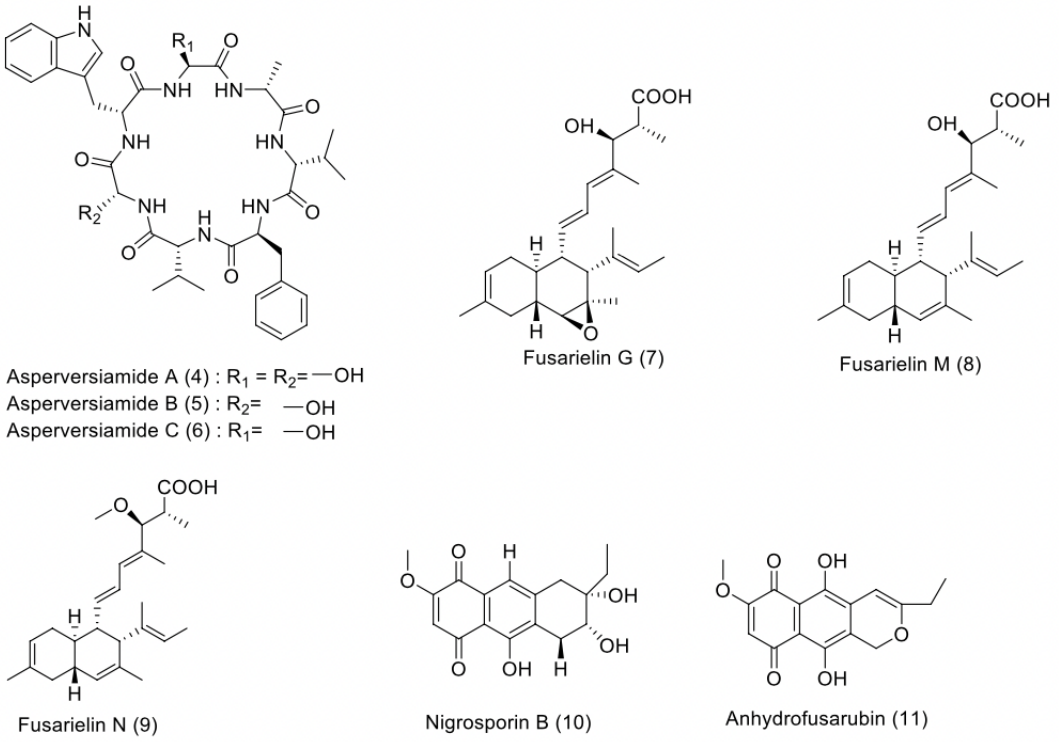

Figure. 2: Structures of compounds (4-11) from coral-derived fungi

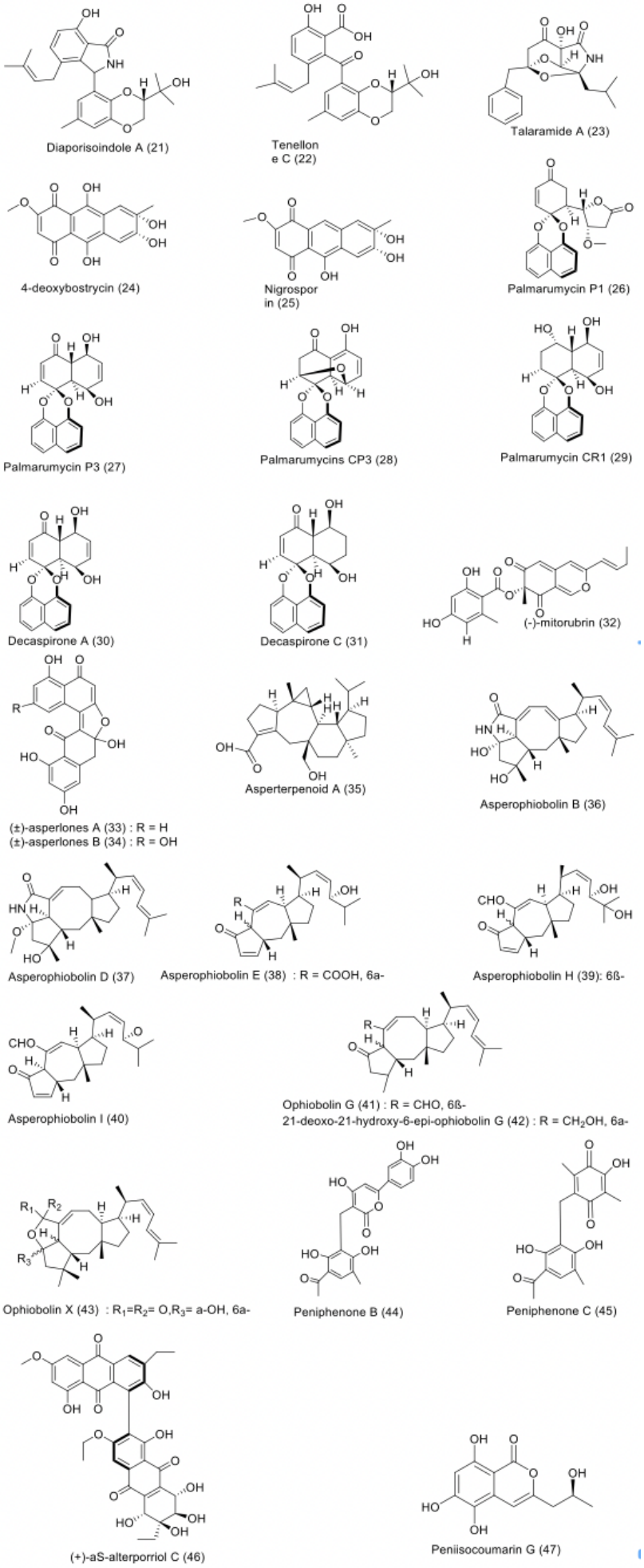

Figure. 3: Structures of compounds (**12-20**) from deep sea sediment-derived fungi

of 4.20 and 5.20 μM (Cui et al., 2017). Moreover, fermentation of another mangrove-associated fungus, *Talaromyces* sp. (HZ-YX1), isolated from the leaves of *Kandelia obovata* collected in South China Sea, led to the production of alkaloid talaramide A (23), capable of inhibiting mycobacterial PknG activity with an IC_{50} value of 55.00 μM (Chen et al., 2017b). Furthermore, two anthraquinones, namely 4-deoxybostrycin (24) and nigrosporin (25) were obtained from unidentified mangrove-derived fungus in the South China Sea. These compounds showed inhibition against *M. tuberculosis* H37Rv with MIC values of 46.83 and 65.72 μM, respectively (Chen et al., 2016). Various naphtalene derivatives were discovered from mangrove-derived fungi as well. Palmarumycins P1 (26), P3 (27), CP3 (28), and CR1 (29), together with decaspirones A (30) and C (31) were obtained from mangrove-associated fungus strain BCC 25093, belonging to a member of the Pleosporales. It was isolated from unidentified mangrove wood in Hat Khanom, Mu Ko Thale Tai National Park, Surat Thani province, Thailand. All isolated compounds showed strong to moderate antitubercular activity with MIC values starting from 1.56 to 12.50 μM (Bunyapaiboonsri et al., 2015). Likewise, three dinaphthalenones, namely ()-mitorubrin (32) and (±)-asperlones A (33), and B (34) isolated from *Aspergillus* sp. 16-5C associated with the leaves of *Sonneratia apetala* collected in Hainan Island, China, strongly inhibited MptpB enzyme with IC_{50} values of 3.99, 4.24, and 4.32 μM, respectively (Xiao et al., 2015). Moreover, several sesterterpenoid metabolites from *Aspergillus* species residing in mangrove were also proved to possess antitubercular property. For instance, investigation on *Aspergillus* sp. 16-5c derived from unidentified mangrove species in South China Sea resulted in the isolation asperterpenoid A (35), which displayed strong inhibitory activity against MptpB with an IC_{50} value of 2.20 μM (Huang et al., 2013). In addition, eight ophiobolin-type sesterterpenoids, namely asperophiobolins B (36), D (37), E (38), H (39), and I (40), ophiobolin G (41), 21-deoxo-21-hydroxy-6-epi-ophiobolin G (42) and ophiobolin X (43) were afforded from *Aspergillus* sp. ZJ-68 isolated from leaves of *Kandelia candel* at Zhanjiang Mangrove Nature Reserve in Guangdong Province, China. Compounds 36-43 showed moderate inhibition against MptpB activity with IC_{50} values of 19.00 to 42.00 μM, respectively (Cai et al., 2019). A miscellaneous compound from mangrove-derived fungi also exerted antitubercular potency. For example, peniphenones B (44) and C (45) from *Penicillium dipodomyicola* HN4-3A, a fungal endophyte residing in the stem of mangrove species *Acanthus ilicifolius*, collected in the South China Sea, in Hainan Province, China, showed strong inhibition against MptpB with IC_{50} values of 0.16 and 1.37 μM, respectively (Li et al., 2014). Additionally, alterporriol-type anthranoid dimer, namely (+)-aS-alterporriol C (46) obtained from *Alternaria* sp. (SK11) cultures inhibiting root of *Excoecaria agallocha*, collected in Shankou, Guangxi Province, China, exhibited Antitubercular potency, when evaluated against MptpB, with an IC_{50} value of 8.70 μM (Xia et al., 2014). Moreover, an isocoumarin, peniisocoumarin G (47), was obtained from *Penicillium commune* QQF- 3 derived from fruits of *Kandelia candel*. The mangrove was collected Zhuhai Mangrove Nature Reserve in Guangdong Province, China. Compound 47 moderately inhibited the activity of MptpB enzymes with an IC_{50} value of 20.70 μM (Cai et al., 2018).

Sponge-derived fungi

Various natural products have been discovered from sponge-derived fungi in recent years (Sandrawati et al., 2020). Ten antitubercular compounds were isolated from sponge-derived fungi, as shown in Figure 5. A fungus *Aspergillus fumigatus* MF029, isolated from a marine sponge, Hymeniacidon perleve, collected in Bohai Sea, China, was reported to produce emodin (48), and trypacidin (49). Both isolated compounds showed antitubercular activity against *Mycobacterium bovis* Bacillus Calmette–Guerin (BCG) with MIC values of 4.63 and 3.63 μM (Song et al., 2021). A number of peptides were also repeatedly isolated from fungi inhabiting sponges. For instance, three trichoderins, namely trichoderins A (50), A1 (51), and B (52) were obtained from fungus *Trichoderma* sp. strain 05FI48 isolated from unidentified marine sponge. These trichoderins showed pronounced Antitubercular activity against *Mycobacterium smegmatis* (M. sg) with MIC values ranging from 0.09 until 1.36 μM both under aerobic and hypoxic conditions. When tested against *M. bovis* BCG under aforementioned conditions, these trichoderins gave MIC values below 0.02 μM. Similar result was also shown in an assay against *M. tuberculosis* H37Rv (Pruksakorn et al., 2010), suggesting the promising antitubercular pharmacophore of trichoderin derivatives. Other peptides, belonging to the aspochracin-type cyclic tripeptides, namely sclerotiotides M (53) and N (54), isolated from *Aspergillus insulicola* HDN151418 associated with an unidentified sponge found at 410 m depth of Prydz Bay, Antarctica. These peptides showed antitubercular activity against *M. phlei* with MIC values of 3.13 and 12.50 μM, respectively (Sun et al., 2020). Additionally, several antitubercular polyketides were also discovered from sponge-derived fungi. A polyketide butyrolactone I (55), was afforded upon chemical investigation on *Aspergillus terreus* SCSIO 41008, isolated from sponge *Callyspongia* sp. collected from the seaside in Xuwen County, Guangdong Province, China. Butyrolactone I showed strong inhibitory activity against MptpB with an IC_{50} value of 12.03 μM (Thakur et al., 2015). Moreover, two aromatic polyketides, elucidated as isochaetochromin B2 (56), and ustilaginoidin D (57), were isolated from sponge-associated fungus, *Metarhizium anisopliae* mxh-99, collected in Naozhou island, Guangxi Province, China. These compounds showed weak inhibition to the growth of *M. phlei* with MIC value of 91.49 μM for both of them (Kong et al., 2013).

Antitubercular from entomopathogenic fungi

Insect pathogenic fungi refer to fungi which develop pathogenic relationship with their host insects, the so called entomopathogenic fungi. These fungi can directly infect and kill insects by transgressing their cuticle (Hu Bidochka, 2021). Twenty-six compounds with antitubercular activity were recovered from insect-derived fungi, as shown in Figure 6. Recent study reported insects-associated fungus, *Aschersonia confluens* BCC53152, isolated from Hala-Bala Wildlife Sanctuary in Narathiwat province, Thailand. An alkaloid, terpendole C (58), was afforded from this fungus and found to be moderately active against *M. tuberculosis* with MIC value of 48.10 µM (Sadorn et al., 2020). More alkaloids were recovered upon the fermentation of *Verticillium hemipterige-*

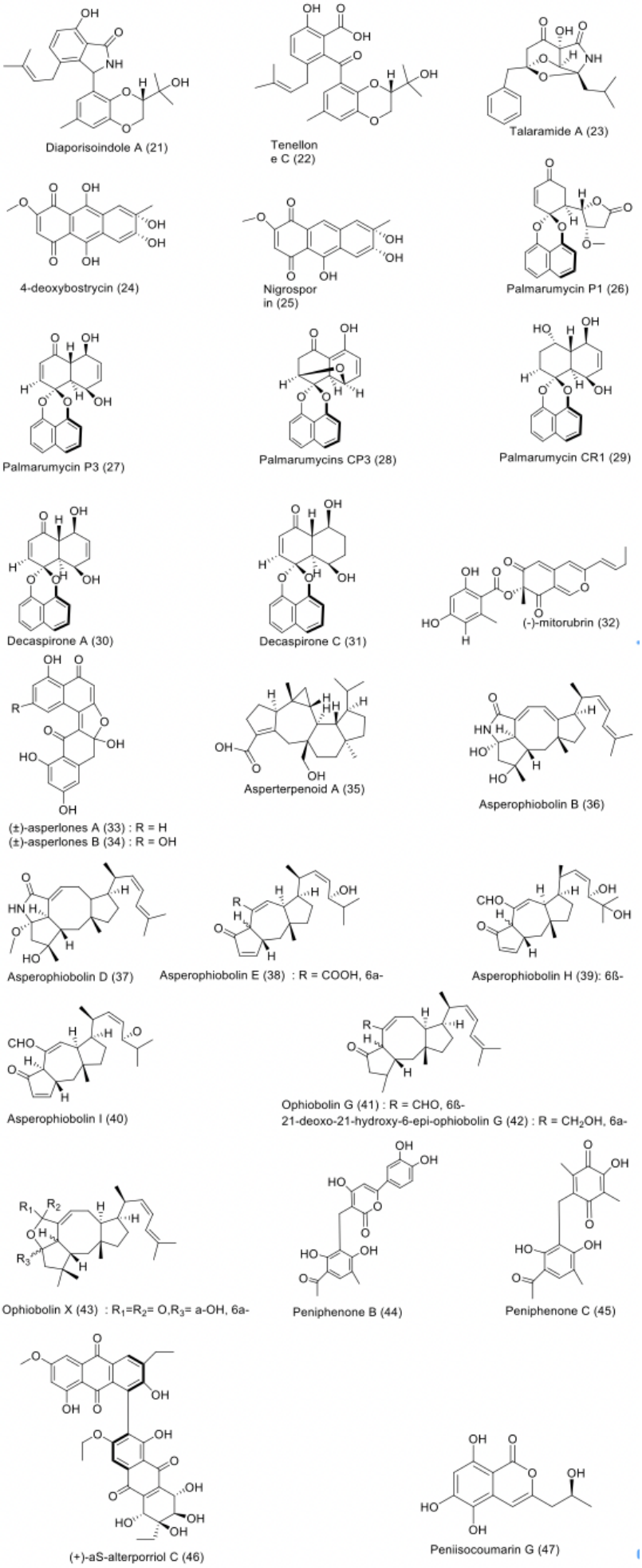

Figure. 4: Structures of compounds (**21-47**) from mangrove-derived fungi.

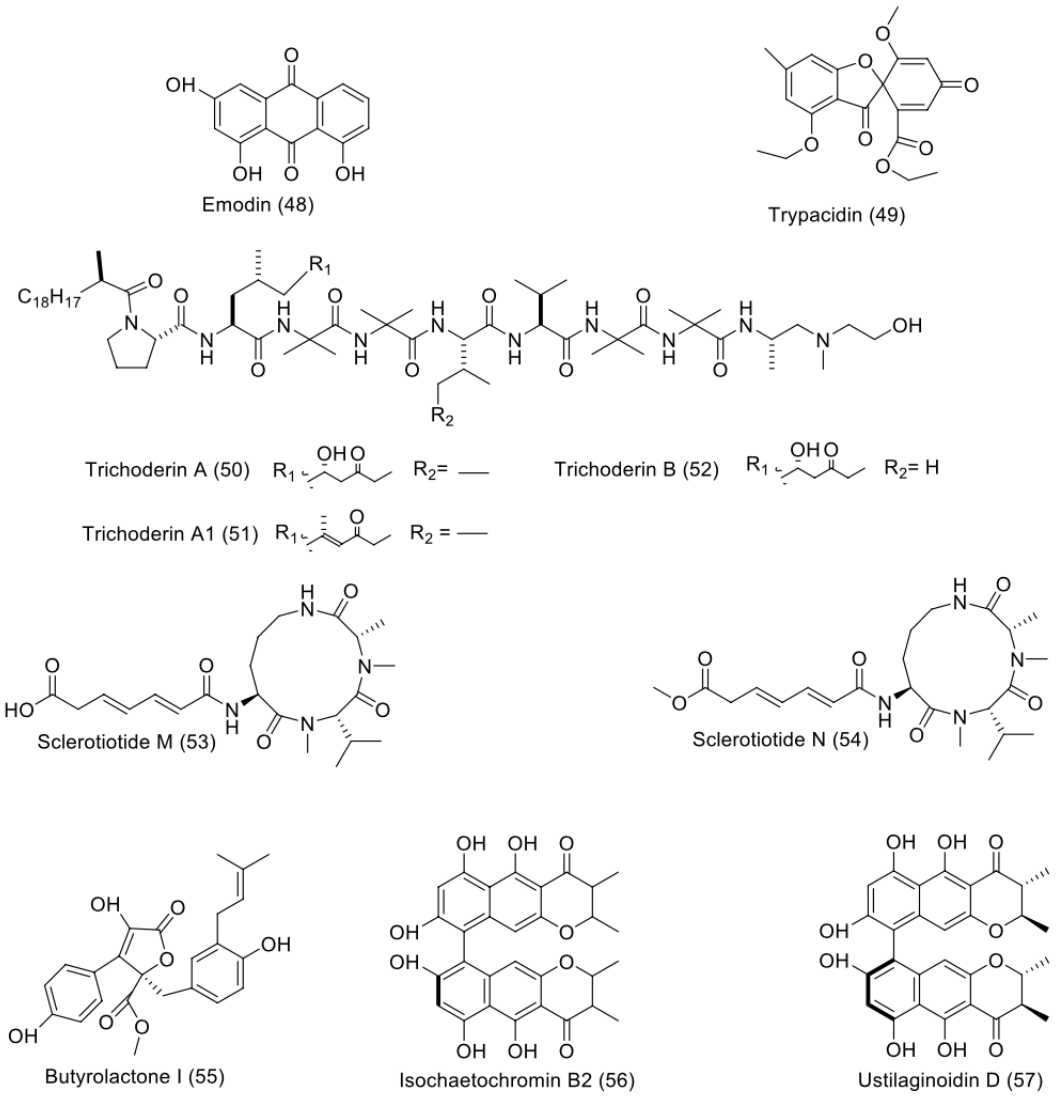

Figure. 5: Structures of compounds (48-57) from sponge-derived fungi.

num BCC 1449, an insect pathogenic fungus isolated from an adult leaf hopper of the Homoptera suborder, collected in Thailand. This fungus naturally synthesized diketopiperazine dimers, vertihemiptellides A (59) and B (60) which had moderate antitubercular activity with MIC values of 20.14 and 20.59 μM (Isaka et al., 2005a). Insect pathogenic fungi were also found to produce a number of antitubercular peptides, as reported by Nilanonta et al. (2000, 2002). This research group investigated a fungus *Paecilomyces tenuipes* BCC 1614 collected from Khlong Naka Wildlife Sanctuary, Ranong province, southern Thailand. From this fungus, they successfully isolated beauvericin (61), which was reported to have antitubercular activity against *M. tuberculosis* H37Ra with MIC value of 15.95 μM (Nilanonta et al., 2000). Further research on this fungus revealead that more beauvericins were afforded, including beauvericins A (62) and B (63) along with allobeauvericins A (64), B (65), and C (66). All compounds exhibited potent antitubercular activity with MIC values 2.00 μM (Nilanonta et al., 2002). Previously mentioned *V. hemipterigenum* BCC 1449 was also capable of producing enniatin derivatives, of which MK1688 (67) was the most active among the seven isolated enniatins in an assay against *M. tuberculosis*, with MIC value of 2.21 μM. Meanwhile, enniatins B (68), B4 (69), C (70) G (71), H (72), and I (73) were found to have lower activity with MIC values of 3.25-9.00 μM (Nilanonta et al., 2003). Moreover, other peptide was also found from *Ophiocordyceps communis* BCC 16475, an insect-associated fungus isolated from Isoptera collected in Khao Yai National Park, Nakhon Nayok Province, Thailand. Investigation of this fungus resulting in the isolation of cordycommunin (74), which capable of inhibiting the growth of *M. tuberculosis* H37Ra with MIC value of 15.00 μM (Haritakun et al., 2010). Another insect pathogenic fungi, namely *Hirsutella nivea* Hywel-Jones BCC 2594 was isolated from homoptera-leafhopper in Khao Yai National Park, Central Thailand. This fungus was reported to produce hirsutellones A (75), B (76), C (77), and D (78). Following antitubercular assay against *M. tuberculosis* H37Ra, all compounds were found to have strong activity with MIC values of 1.75, 1.74, 1.69, and 6.79 μM (Isaka et al., 2005b). Triterpenoids were isolated from insect pathogenic fungus *Aschersonia tubulata* BCC 1785. This fungus was collected from

Trang Province, Thailand and produced 3β-acetoxy-15α,22-dihydroxyhopane (79), and dustanin (80) with antitubercular activities against *M. tuberculosis* H37Ra with MIC values of 24.86 and 28.11 μM (Boonphong et al., 2001). Moreover, YM187781 (81), bislunatin (82), and morakotin C (83) were obtained from *Cordyceps morakotii* BCC 56811. The fungus was isolated from ant (Hymenoptera), collected in Evergreen Forest in Chiang Mai Province, Thailand. These compounds were found to have moderate activity against *M. tuberculosis* H37Ra with MIC values of 42.66, 43.82 and 82.99 μM (Wang et al., 2019).

4. CONCLUSIONS

This review highlights secondary metabolites from marine-derived and entomopathogenic fungi as promising source for the discovery and development of antitubercular candidates. Among the eighty-three metabolites described herein, several compounds showed remarkable antitubercular activity with MIC values less than 10 μM, including eniatin derivatives, fusarielin M, gliotoxin, 12,13-dihydroxyfumitremorgin, hirsutellones A–D, palmarumycins P1 and CP3, as well as trichoderins A and B. Investigation of these metabolites to understand their mode of actions as well as development of their structurally related compounds will be promising for future studies. Moreover, studies on the biosynthetic gene clusters involved in the production of these metabolites by fungal species belonging to Aspergillus, Fusarium, Hirsutella and Trichoderma will enhance our understanding to the capability of these fungi as producer of antitubercular compounds, which may lead to the discovery of more effective antitubercular candidates.

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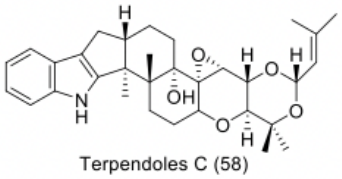
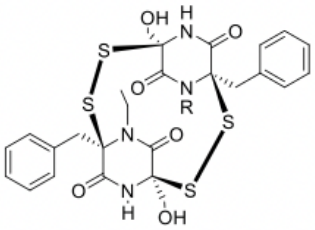
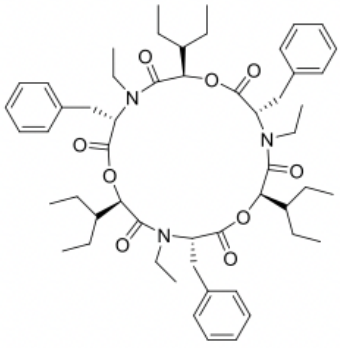


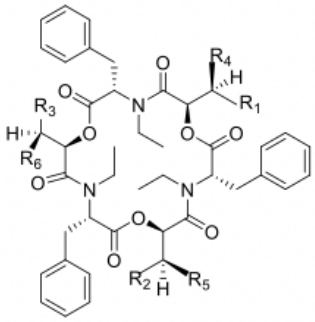
Terpendoles C (58)



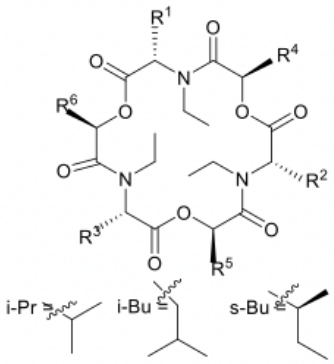
Vertihemiptellide A (59) : R = Me
Vertihemiptellide B (60) : R = H



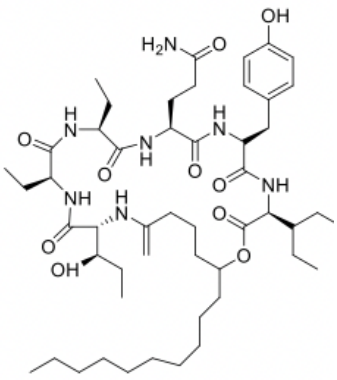
Beauvericin (61)



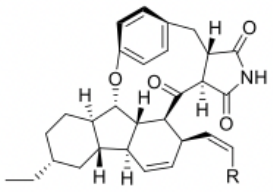
Beauvericin A (62) : R_1= CH_2—— , R_2= R_3= R_4= R_5=R_6= ——
Beauvericin B (63) : R_1= R_2= CH_2 ——,R_3= R_4= R_5=R_6= ——
Allobeauvericin A (64) : R_1= R_2= R_3= ——, R_4= Et, R_5=R_6= ——
Allobeauvericin B (65) : R_1= R_2= R_3= —— , R_4= R_5= Et, R_6= —
Allobeauvericin C (66) : R_1= R_2= R_3= ——, R_4= R_5=R_6= CH_2 —



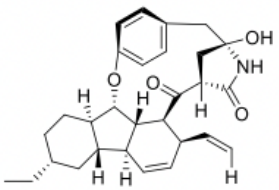
MK1688 (67): R_1= R_2= R_3= i-Pr, R_4= R_5=R_6= s-Bu
Enniatin B (68) : R_1= R_2= R_3= R_4= R_5=R_6= i-Pr
Enniatin B4 (69) : R_1= i-Bu, R2= R3= R_4= R_5=R_6= i-Pr
Enniatin C (70) : R_1= R_2= R_3= i-Bu, R_4= R_5=R_6= i-Pr
Enniatin G (71) : R_1= R_2= i-Bu, R_3= R_4= R_5=R_6= i-Pr
Enniatin H (72) : R_1= R_2= R_3= i-Pr, R_4= s-Bu, R_5=R_6= i-Pr
Enniatin I (73) : R_1= R_2= R_3= i-Pr, R_4= R_5= s-Bu, R_6= i-Pr



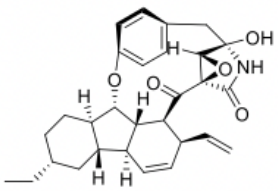
Cordycommunin (74)



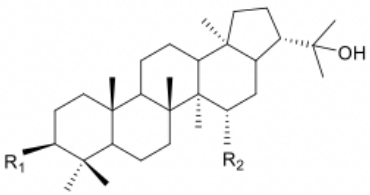
Hirsutellone A (75) : R =H
Hirsutellone D (78) : R = ——



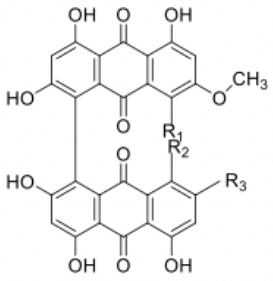
Hirsutellone B (76)



Hirsutellone C (77)



3ß- acetoxy-1 5a,22-dihydroxyhopane (79) : R_1= OAc, R_2= OH
Dustanin (80) : R_1= H, R_2 = OH



YM187781 (81) : R_1= OH, R_2=H, R_3 = OCH_1
Bislunatin (82) : R_1 = R_2 =H, R_3= OCH_1
Morakotin C (83) : R_1= R_2=OH, R_3= O——

Figure. 6: Structures of compounds (58-83) from insect-derived fungi