Review Paper

Fungal-derived compounds and mycogenic nanoparticles with antimycobacterial activity: a review

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Abstract
Tuberculosis (TB) is a persistent lung infection caused by *Mycobacterium tuberculosis*. The disease is characterized by high mortality rates of over 1 million per year. Unfortunately, the potency and effectiveness of currently used anti-TB drugs is gradually decreasing due to the constant development of persistence and resistance by *M. tuberculosis*. The adverse side effects associated with current anti-TB drugs, along with anti-TB drug resistance, present an opportunity to bioprospect novel potent anti-TB drugs from unique sources. Fundamentally, fungi are a rich source of bioactive secondary metabolites with valuable therapeutic potential. Enhancing the potency and effectiveness of fungal-based anti-TB drug leads by chemical synthesis and/or modification with nanomaterials, may result in the discovery of novel anti-TB drugs. In this review, the antimycobacterial activity of fungal-derived compounds and mycogenic nanoparticles are summarized. Numerous fungal-derived compounds as well as some mycogenic nanoparticles that exhibit strong antimycobacterial activity that is comparable to that of approved drugs, were found. If fully explored, fungi holds the promise to become key drivers in the generation of lead compounds in TB-drug discovery initiatives.

Keywords *Mycobacterium tuberculosis* · Fungi · Secondary metabolites · Bioprospecting · Drug discovery · Mycogenic nanoparticles

1 Tuberculosis

Mycobacterium tuberculosis is the causative agent of tuberculosis (TB). TB results in high yearly mortalities and negatively impacts economies of the most affected countries each year [1]. The World Health Organization (WHO) estimates that one-third of the global population is infected with the latent form of TB [2]. In 2020, an estimated 5.8 million new TB cases and 1.5 million TB-related deaths were reported worldwide [3].

The recommended treatment for drug susceptible TB involves the use of four first-line drugs which include isoniazid (**1**), rifampicin (**2**), pyrazinamide (**3**) and ethambutol (**4**), which are administered for six months (Table 1 and Fig. 1) [4, 5]. The principle of using multidrug therapy for TB treatment is founded upon the fact that these drugs have different mechanisms of action. When used together, they reduce selective pressure that may lead to mutant strains surviving because of using a single antibiotic. Isoniazid (**1**) is a prodrug activated by KatG (a catalase-peroxidase

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Table 1 Frist-, second- and third-line drugs commonly used for the treatment of TB

No	Compound name	Compound type	Year	Inhibited activity	Target protein/enzyme	Resistance mutations	MIC range	
							µg/mL	µM
1	Isoniazid	Synthetic	1952	Mycolic acid synthesis	InhA	*katG*, *kasA*, *inhA*	0.02–0.2	0.15–1.46
2	Rifampicin	Semi-synthetic	1963	Nucleic acid synthesis	DNA-dependent RNA polymerase	*rpoB*	0.05–1	0.06–1.22
3	Pyrazinamide	Synthetic	1954	Pantothenate, co-enzyme A synthesis	PanD	*rpsA*, *pncA*, *panD*	16–100	129.97–812.28
4	Ethambutol	Synthetic	1961	Arabinogalactan, lipoarabinomannan synthesis	EmbA, EmbB, EmbC	*embA, embB, embC*	1–5	4.89–24.47
5	Bedaquiline	Synthetic	2005	ATP synthesis	F_1F_0 ATP synthase	*atpE*, *rv0678*	0.06–1	0.11–1.80
6	Pretomanid	Synthetic	2000	ATP synthesis, mycolic acids synthesis	Cytochrome oxidase, fHMAD	*fbiA, fbiB, fbiC, fbiD, ddn*	0.15–0.25	0.42–0.70
7	Linezolid	Synthetic	1996	Protein synthesis	50 ribosomal subunit	*rplC*, *rrl*	0.25–0.5	0.74–1.48
8	Streptomycin	Natural	1944	Protein synthesis	30S ribosomal subunit	*rpsl*, *rrs*	2–8	3.44–13.76
9	Amikacin	Semi-synthetic	1976	Protein synthesis	30S ribosomal subunit	*rrs*, *tlyA*	2–4	2.56–5.12
10	Kanamycin	Natural	1957	Protein synthesis	30S ribosomal subunit	*rrs*, *tlyA*	2–4	4.13–8.26
11	Capreomycin	Natural	1963	Protein synthesis	30S and 50S ribosomal subunit	*rrs*, *tlyA*	2–4	1.51–3.03
12	Delamanid	Synthetic	2006	Mycolic acid synthesis	fHMAD	*fbiA, fbiB, fbiC, fbiD, ddn*	0.006–0.24	0.01–0.45
13	Clofazimine	Semi-synthetic	1954	Poorly understood	Poorly understood	*rv1979c*, *rv2535c*, *pepQ*	0.1–1.2	0.21–2.53
14	Moxifloxacin	Synthetic	1996	Nucleic acid synthesis	Inhibits DNA synthesis	*gyrA*, *gyrB*	0.5–2.5	1.14–5.41
15	Levofloxacin	Synthetic	1987	Nucleic acid synthesis	Inhibits DNA synthesis	*gyrA*, *gyrB*	0.5–2.5	1.38–6.92
16	Ofloxacin	Synthetic	1982	Nucleic acid synthesis	Inhibits DNA synthesis	*gyrA*, *gyrB*	0.5–2.5	1.38–6.92
17	Ciprofloxacin	Synthetic	1980	Nucleic acid synthesis	Inhibits DNA synthesis	*gyrA*, *gyrB*	0.5–2.5	1.51–7.55

Table 1 was adapted from Zhang and Yew [6] and modified using other sources [7–14]

enzyme in Mycobacteria), which blocks the synthesis cell wall mycolic acids by inhibiting the enoyl-acyl carrier protein reductase, InhA, which forms part of the class II fatty acid synthase multi-enzyme (FAS-II) system [6]. Resistance to isoniazid (**1**) by *M. tuberculosis* commonly results from mutations in the *katG*, *kasA* and *inhA* genes. Rifampicin (**2**) is known to bind to the RNA polymerase β subunit which results in the inhibition of DNA-dependent RNA synthesis, resistance is commonly caused by mutations in the *rpoB* gene [7].

Pyrazinamide's (**3**) mechanism of action is poorly understood, the current hypothesis is that the drug is activated by pyrazinamidase in *M. tuberculosis* to form pyrazinoic acid, which then binds to aspartate decarboxylase PanD and causes its degradation [8]. This action leads to a halt in the synthesis of pantothenate and co-enzyme A downstream. Mutations in *rpsA*, *pncA* and *panD* genes have been implicated in pyrazinamide (**3**) resistance [9]. Ethambutol (**4**) targets three arabinosyltransferases, namely EmbA, EmbB and EmbC [10]. Both EmbA and EmbB are involved arabinogalactan synthesis, while EmbC is involved in lipoarabinomannan synthesis, both metabolites being essential components of the cell wall. Mutations in the *embA, embB* and *embC* genes commonly result in resistance.

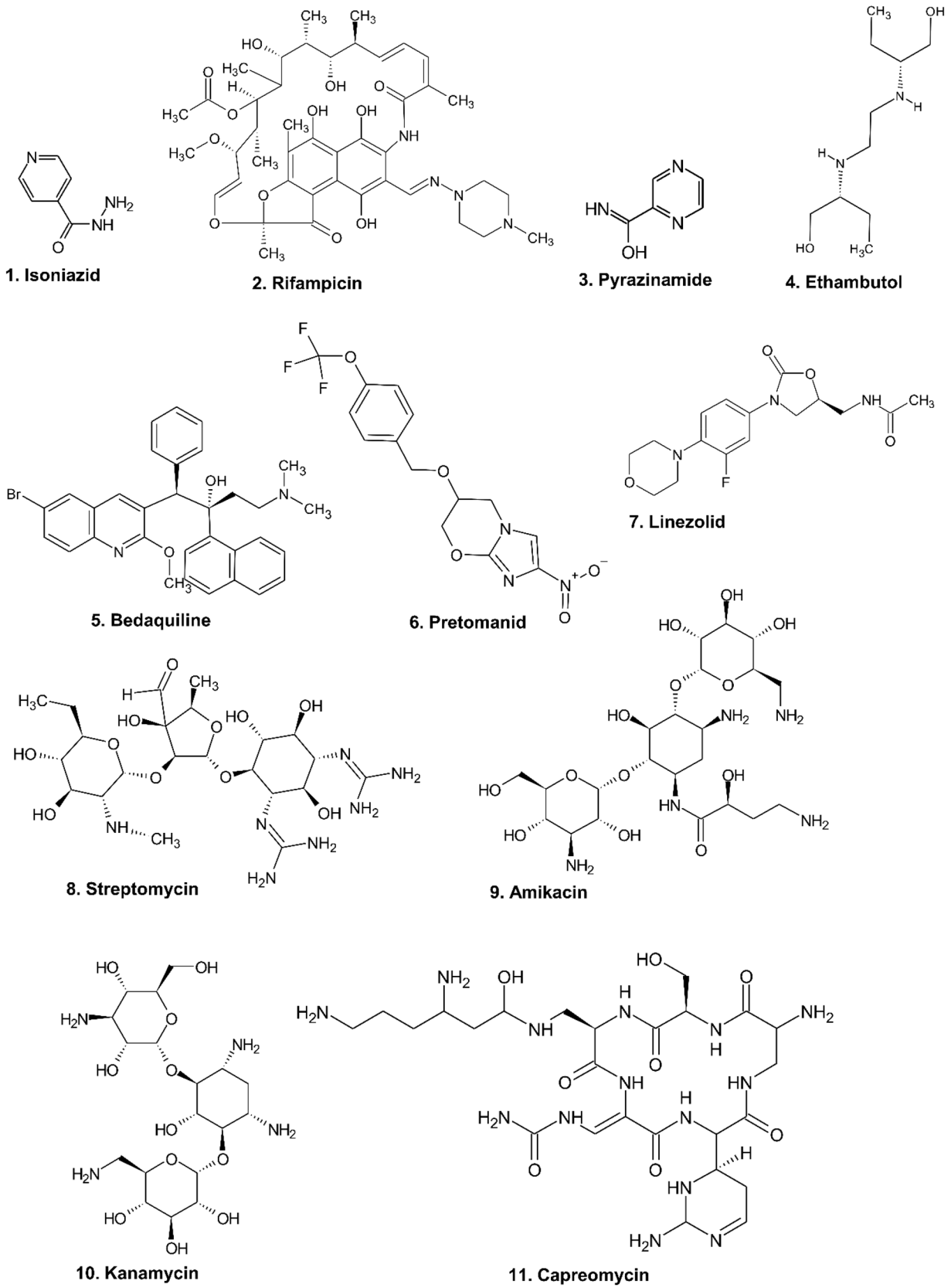


Fig. 1 Approved drugs (**1–11**) and (**12–17**) commonly used to treat TB

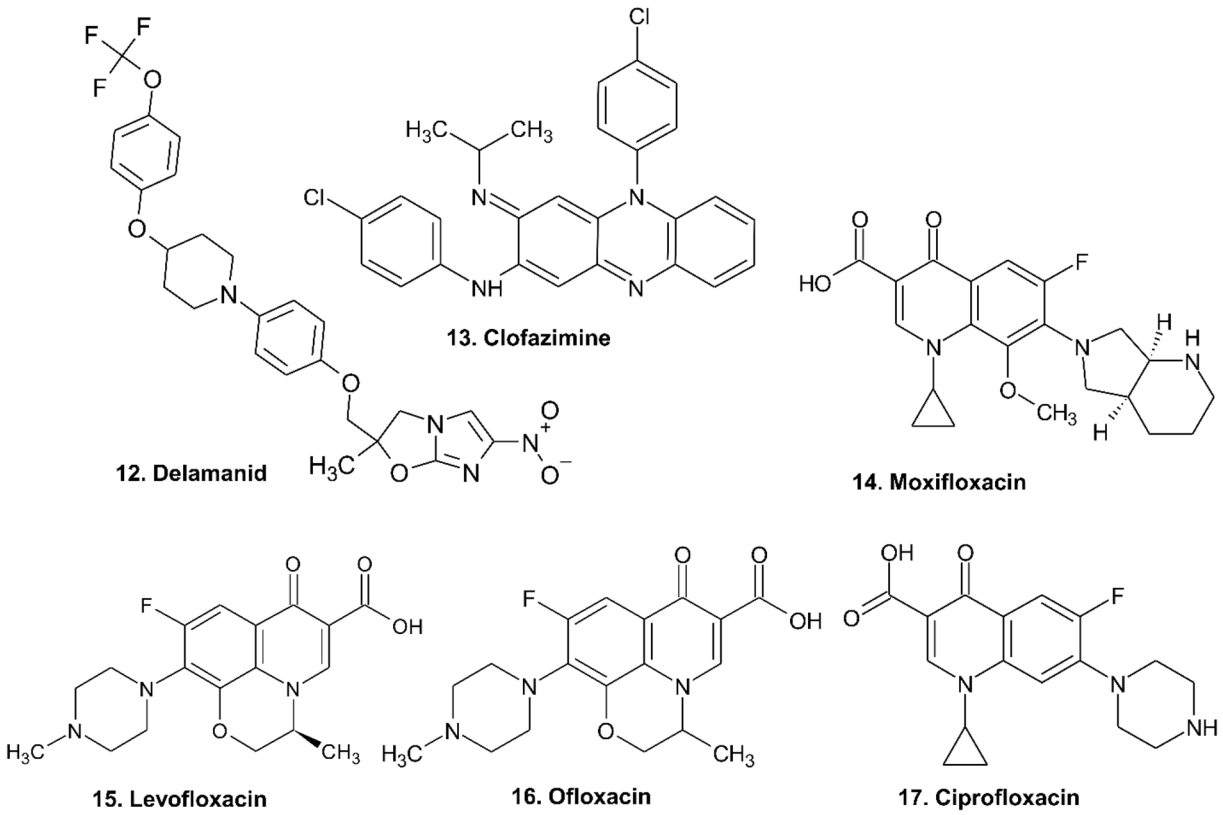


Fig. 1 (continued)

Multi-drug resistant (MDR) and extensively-drug resistant (XDR) *M. tuberculosis* simply refers to strains which no longer respond to first-line drugs. The occurrence of these strains is prevalent and necessitates the use of second-line anti-TB drugs which commonly include bedaquiline (**5**), pretomanid (**6**), linezolid (**7**), streptomycin (**8**) and amikacin (**9**), kanamycin **(10)**, capreomycin **(11)**, delamanid **(12)**, clofazimine **(13)**, moxifloxacin **(14)**, levofloxacin **(15)**, ofloxacin **(16)** and ciprofloxacin **(17)** [4, 5]. Second-line TB drugs have been reported to be more toxic and are administered for nine to 24 months with only about half the number of patients being cured [3]. Bedaquiline (**5**) inhibits the synthesis of ATP by inhibiting the F_1F_0 ATP synthase (proton pump), and mutations in *atpE* and *rv0678* genes are known to confer resistance [11, 12].

In hypoxic conditions where *M. tuberculosis* is non-replicating, lethality of the nitroimidazole, pretomanid (**6**), is due to its prior activation by a deazaflavin dependent nitroreductase (Ddn), which produces *des*-nitro metabolites that interfere with cytochrome oxidases and ATP homeostasis consequently [13]. In replicating *M. tuberculosis*, pretomanid (**6**) inhibits F_{420}-dependent hydroxy mycolic acid dehydrogenase (fHMAD) which produces ketomycolic acids and thus interferes with synthesis of mycolic acids [14]. Resistance to pretomanid (**6**) is conferred by mutations in *fbiA, fbiB, fbiC, fbiD* and *ddn* genes which are involved in the F_{420} system.

Linezolid (**7**) inhibits protein synthesis by binding to the 23S ribosomal RNA of the 50S subunit, thus preventing its complexation with the 30S subunit, mRNA and other components required for the assembly of a functional protein synthesis complex [15]. Mutations in the *rrl* gene encoding 23S rRNA, and the *rplC* gene encoding the L3 ribosomal protein, are both responsible for resistance to linezolid (**7**) [16]. The primary mechanism of action for aminoglycosides (streptomycin (**8**), amikacin (**9**), kanamycin (**10**) and capreomycin (**11**)) is very similar, they inhibit protein synthesis by irreversibly binding to RNA-binding S12 protein and 16S rRNA, which form part of the 30S ribosomal subunit and are encoded by the *rpsL* and *rrs* genes and [17, 18]. This alters the ribosome's shape which leads to failure in the formation of the protein synthesis complex. Mutations in the *rpsL*, *rrs* and *tlyA* genes have been observed to confer resistance to aminoglycosides.

Delamanid (**12**) is recognized as an inhibitor of mycolic acid synthesis [19] and is thought to undergo the same activation process and exhibit the same mechanism of action as pretomanid (**6**).

Clofazimine (**13**) has a poorly understood mechanism of action in *M. tuberculosis.* One hypothesis is that

it attaches to guanine residues in *M. tuberculosis* DNA and thus blocks DNA replication. Since clofazimine (**13**) appears to compete with menaquinone (type II NADH:quinone oxidoreductase substrate) for electrons, it is thought to undergo spontaneous oxidation which results in the generation of free oxygen species (ROS) which are antimicrobial. In addition, clofazimine (**13**) is a cationic amphiphile which is thought to inhibit ion transporting ATPases and thus interfering with ion uptake [20]. Mutations in the *rv1979c*, *rv2535c* and *pepQ* genes have been linked with clofazimine (**13**) resistance [21].

Moxifloxacin (**14**), levofloxacin (**15**), ofloxacin (**16**) and ciprofloxacin (**17**) are fluoroquinolones which also have a similar mechanism of action. These drugs inhibit the DNA ligase action of type II topoisomerases (DNA gyrase and topoisomerase IV) while allowing for the nuclease action to continue, this results in the release of DNA with single and double stranded breaks by the enzyme which consequently leads to cell death [22]. Mutations in the *gyrA* and *gyrB* genes confers resistance to fluoroquinolones.

It is evident that the discovery of new anti-TB drugs needs to be continued as resistance has been reported for drugs **1–17**. A very interesting natural source of chemically diverse and biologically active compounds is fungi. Over the years, numerous fungal compounds with excellent antimycobacterial activity have been reported, yet no reports on the exploration of these compounds in clinical trials are available. It is the view of the authors that fungal compounds have the potential of becoming key drivers in contributing lead compounds for TB-drug development studies. Enhancing these compounds using chemical synthesis (semi-synthesis) and nanotechnology can potentially impart novel properties that reduce cytotoxicity to normal cells and susceptibility to *M. tuberculosis* resistance, all without compromising bioactivity.

In this review, fungal-derived compounds with antimycobacterial activity and those that have been subjected to modification by chemical synthesis (semi-synthesis) are presented. Since mycogenic nanoparticles (nanoparticles synthesized using fungi) are stabilized by fungal compounds during synthesis, it may be viewed as a unique mechanism of modifying fungal compounds, thus mycogenic nanoparticles were included in this review. The list of compounds and nanoparticles was obtained by searching for articles in PubMed and by free-text searching using the following key words and their combinations: Fungi, TB, anti-TB, antimycobacterial, minimum inhibitory concentration (MIC), *M. tuberculosis*, nanoparticles, mycogenic nanoparticles, modification, synthesis, semi-synthesis. Only compounds which had an MIC of less than 100 µg/mL were considered for inclusion. Concentrations given in micromole (µM) in the original studies were converted to micrograms per milliliter (µg/mL) to maintain consistency.

2 Fungal secondary metabolites with antimycobacterial activity

Fungal secondary metabolites are produced in metabolic pathways encoded by genes often physically linked in fungal chromosomes and commonly known as biosynthetic gene clusters (BGCs) [23]. Numerous bioactive fungal secondary metabolites have been reported and include several antibiotics such as the penicillins, ergot alkaloids and cephalosporins, all commonly used in the treatment of microbial infections [24]. Even though there are no approved anti-TB drugs of fungal origin to date, there are numerous fungal-derived compounds which have been previously shown to possess strong natural antimycobacterial activity which is comparable to that of anti-TB drugs currently in use.

2.1 Compounds from endophytic fungi and plant-pathogenic fungi

Endophytes are a ubiquitous class of endosymbiotic microorganisms (most common are bacteria and fungi) that spend part/all of their life cycle in plant tissues without causing them harm or disease [25]. They can be isolated from any part of the plant, including roots, flowers, fruits, stems, leaves and buds. Endophytes often benefit the plants by producing phytohormones and metabolites that enhance plant growth and tolerance to abiotic and biotic stresses [25]. In the plant microbiome, fungal pathogens may also exist and have a rather negative effect to the plant's growth and health as compared to endophytes.

Fungal endophyte PSU-N24 was isolated from the branch of *Garcinia nigrolineata* collected in Thailand, and was fermented to produce 9α-hydroxyhalorosellinia A (**18**), which was found to have an MIC of 13.3 µg/mL after testing against *M. tuberculosis* H37Ra [26]. Desoxybostrycin (**19**) and 9β-hydroxydihydrodesoxybostrycin (**20**) produced by the same fungus were found to be less active against *M. tuberculosis* H37Ra, having an MIC of 50 and 25 µg/mL, respectively [26]. *Diaporthe* sp. P133 was isolated as an endophyte from *Pandanus amaryllifolius* leaves and was fermented in potto dextrose broth for three weeks to produce diaportheone B (**21**), a benzopyranone [27]. The MIC value of diaportheone B (**21**) against *M. tuberculosis* H37Rv was found to be 0.77 µg/mL. *Phomopsis* sp. BCC 1323, and endophyte isolated from a teak leaf (*Tectona grandis* L.), produced two novel xanthone dimers, phomoxanthones A and B (**22** and **23**), which had MIC values of 0.5 and 6.25 µg/mL respectively against *M. tuberculosis* H37Ra [28]. Three alkaloids designated phomapyrrolidones A–C (**24–26**) were purified from extracts of the endophytic fungus, *Phoma* sp. NRRL 46,751,

isolated from the lower crown of *Saurauia scaberrinae* collected in Papua New Guinea [29]. The phomapyrrolidones A–C (**24–26**) had MIC values of 20.1, 5.9 and 5.2 µg/mL, respectively against *M. tuberculosis* H37Rv. *Chaetomium globosum* IFB-E036 was isolated as a root endophyte of *Cynodon dactylon* in China and was fermented over a solid substrate to produce chaetoglocins A and B (**27** and **28**), which both had MIC values of 16 µg/mL against *M. smegmatis* CGMCC1.562 [30].

Fusarium avenaceum DAOM 196,490 was isolated as a pathogen from needles of the balsam fir tree (*Abies balsamea*) infested with spruce budworm (*Choristoneura funiferana* Clem.) [31]. *F. avenaceum* DAOM 196,490 was found to produce several enniatins, among them was enniatin A1 (**29**) which was tested in another study against *M. tuberculosis* H37Rv, *M. tuberculosis* H37Ra, *M. bovis, M. bovis* BCG and *M. smegmatis* mc^2155 [32]. Enniatin A1 (**29**) was found to be slightly more active against virulent *M. tuberculosis* H37Rv (MIC = 1 µg/mL), compared to the avirulent *M. tuberculosis* H37Ra (MIC = 2 µg/mL). Against *M. bovis* and *M. bovis* BCG, enniatin A1 (**29**) had an MIC of 2 µg/mL for both strains. *M. smegmatis* mc^2155 was the least susceptible with an MIC of 8 µg/mL.

2.2 Compounds from marine fungi

Marine fungi describes those fungi able to colonize and adapt to the conditions in marine environments [33]. They are ubiquitous in the ocean and can be found decomposing organic matter, sediments or as associated of other organisms. In one study, a water hyacinth pathogen, *Alternaria eichhorniae*, produced the anthraquinone, 4-deoxybostrycin (**30**), whose MIC values on *M. tuberculosis* H37Rv and clinical MDR *M. tuberculosis* K2903531 were 15 µg/mL and < 5 µg/mL respectively [34]. Transcriptomics of *M. tuberculosis* H37Rv exposed to 4-deoxybostrycin (**30**) showed that the compound significantly altered the expression of 119 genes, 46 of these genes (24 upregulated genes and 22 down-regulated) are known to be functional genes involved in DNA replication and translation, carbohydrate metabolism, signal transduction and lipid metabolism [34]. Sclerotiotides M and N (**31** and **32**) were isolated from the fungus *Aspergillus insulicola* HDN151418, a symbiont of a marine sponge collected 410 m deep from Prydz Bay, Antarctica [35]. Sclerotiotides M and N (**31** and **32**) were found to be active against *Mycobacterium phlei* with a MIC of 1.37 and 5.63 µg/mL [35].

Trichoderins A, A1 and B (**33–35**) were isolated from the culture of *Trichoderma* sp., from an unidentified marine sponge, were tested for antimycobacterial activity against *M. tuberculosis* H37Rv, *M. bovis* BCG and *M. smegmatis* [36]. The MIC values of the trichoderins (**33–35**) were in the range of 0.02–2.0 µg/mL, the virulent *M. tuberculosis* H37Rv being more susceptible to trichoderin A (**33**) (MIC = 0.12 µg/mL). *Fusarium* spp. PSU-F14 was isolated from a sea fan (*Annella* sp.) and was found to produce nigrosporin B (**36**) and anhydrofusarubin (**37**), which had an MIC of 12.5 and 25.1 µg/mL respectively against *M. tuberculosis* H37Ra [37].

2.3 Compounds from entomopathogenic fungi

Entomopathogenic fungi can best be described as fungi that are capable of infecting and killing insects. They are popular in Agriculture where they are explored as natural biological control agents against insect pests that attack crops [38]. Fungi from the *Hirsutella* genus are among the most abundant and important entomopathogens and are popularly known for their antimicrobial proteins. The entomopathogenic fungus, *Hirsutella kobayasii* BCC 1660, was collected from the Kaeng Krachan National Park in Thailand and fermented in potato dextrose broth to produce hirsutellide A (**38**), a cyclohexadepsipeptide [39]. The MIC of hirsutellide A (**38**) against *M. tuberculosis* H37Ra ranged between 6–12 µg/mL, while showing no cytotoxicity on Vero cells at 50 µg/mL. Cyclohexadepsipeptides hirsutatins A and B (**39** and **40**) were isolated from *Hirsutella nivea* BCC 2594 and were found to possess antimycobacterial activity [40]. Hirsutatins A and B (**39** and **40**) both had an MIC of 50 µg/mL against *M. tuberculosis* H37Ra. The fungus, *Paecilomyces tenuipes* BCC 1614 was collected from Khlong Naka Wildlife Sanctuary in Thailand, and was shown to produce the two bioactive cyclodepsipeptides, beauvericin (**41**) and beauvericin A (**42**) [41]. The MIC of beauvericin (**41**) and beauvericin A (**42**) against *M. tuberculosis* H37Ra was found to be 12.5 and 25 µg/mL, respectively. *Torrubiella tenuis* BCC 12,732 is an entomopathogenic fungus which was isolated from a Homoptera scale insect, also collected in Thailand [42]. *T. tenuis* BCC 12,732 produced 6,8-dihydroxy-3-hydroxymethylisocoumarin (**43**) which had an MIC of 25 µg/mL against *M. tuberculosis* H37Ra.

Seven enniatins, namely, enniatins B, B4, C, G, H, I and MK1688 (**44–50**) were isolated from *Verticillium hemipterigenum* BCC 1449, a fungus isolated from an adult leaf hopper of the Homoptera suborder, collected in Thailand [43]. After testing against *M. tuberculosis* H37Ra, both enniatins B and B4 (**44** and **45**) were found to have an MIC of 2.12 µg/mL, while enniatins C, G, H and I (**46–48**) had an MIC 6.25 µg/mL. MK1688 (**50**) was the most active of the seven enniatins, exhibiting an MIC of 1.56 µg/mL. In another study also involving enniatins, a spore of an unidentified fungus BCC 2629, was collected from the synemma of *Hirsutella fornicarum*, attached to an unnamed ant [44]. Solvent extraction and purification of metabolites from the fermentation broth of the BCC 2629 yielded

enniatin L (**51**), a 1:1 mixture of enniatins M_1 and M_2 (**52**), and enniatin N (**53**). These enniatins were found to be active against *M. tuberculosis* H37Ra, whereby enniatin L (**51**) exhibited an MIC of 12.5 µg/mL, while the 1:1 mixture of enniatins M_1 and M_2 (**52**) and enniatin N (**53**) both exhibited an MIC of 6.25 µg/mL.

2.4 Compounds from lichenicolous fungi

Lichens are macroscopic structures which are a composite of heterotrophic filamentous fungi and autotrophic photosynthetic algae/cyanobacteria, which associate in a mutualistic relationship [45]. The type of fungi that are able to colonize lichens are called lichenicolous fungi and may sometimes be lichen specific. The crude extract of *Microsphaeropsis* sp. BCC 3050 was tested for antimycobacterial activity against *M. tuberculosis* H37Ra and was found to be active [46]. Following bioassay guided fractionation, preussomerins E-I (**54–58**), 3′-O-demethylpreussomerin I (**59**), deoxypreussomerin A (**60**) and bipendinsin (61) were isolated and their MICs were 25, 3.12, 3.12–6.25, 6.25, 12.5, 25, 1.56–3.12 and 50 µg/mL. The preussomerins E-I (**54–58)** and 3′-O-demethylpreussomerin I (**59**) was also found to be significantly cytotoxic to KB and BC-1 cancer cell lines, and Vero cells which are a model of normal mammalian cells. The lichenized fungus, *Trypethelium eluteriae* Spreng., was fermented for 240 days in malt-yeast extract to produce lactone (**62**), trypethelone (**63**) and 4′-hydroxy-8-methoxytrypethelone methyl ether (**64**), which had MIC values of 50, 12.5 and 50, respectively against *M. tuberculosis* H37Rv [47]. Lichenicolous fungi are still underexplored as sources of antimycobacterial agents, and thus studies in this area are very few.

2.5 Compounds from mushrooms (macrofungi), soil fungi and others

Mushrooms, also known as macrofungi, are distinct from their microfungi counterparts in that they produce visible sporocarps (fruiting bodies) which typically appear above the ground (epigeous), or below the ground (hypogeous). Several medicinal mushrooms and the pharmacological activities of their compounds have been widely reported [48, 49]. Mushrooms belong the phylum Basidiomycota and are predominantly found soils of grasslands and forests as decomposers of organic matter. In agricultural soils, fungi from the phylum Ascomycota have been found to be predominant [50].

Fresh fruiting bodies of the macro-fungus *Scleroderma citrinum* KMILT-SCL01, were extracted with methanol and later fractionated to obtain 4,4′-dimethoxyvulpinic acid (**65**) which had an MIC of 25 µg/mL against *M. tuberculosis* H37Ra [51]. Two lanostane triterpenes, astraodoric acids A and B (**66** and **67**), isolated from an edible mushroom, *Astraeus odoratus* collected in Thailand, were found to have MIC values of 50 and 25 µg/mL, respectively against *M. tuberculosis* H37Rv [52]. The fruiting body of the mushroom, *Ramaria cytidiophora*, was collected in Canada and was subjected to a series of extraction and purification step to yield ramariolide A (**68**) [53]. The MIC values of ramariolide A (**68**) were found to be 8 and 64–128 µg/mL against *M. smegmatis* and *M. tuberculosis*, respectively.

Mortierella alpina FKI-4905 was isolated from soil collected from the Bonin Islands in Japan, and was found to produce the peptide, calpinactam (**69**) [54]. The compound was tested against *M. smegmatis* and *M. tuberculosis* and the MIC values were found to be 0.78 and 12.5 µg/mL, respectively. A new meroterpenoid, 1-hydroxychevalone C (**70**), was isolated from a forest-soil fungus, *Neosartorya spinosa* KKU-1NK1 [55].

Neosartorya species are the telemorphic (sexual) state of the *Aspergillus* species and thus have been both found to have metabolites in common. 1-hydroxychevalone C (**70**) from *N. spinosa* KKU-1NK1 was found to have an MIC value of 12.5 µg/mL against *M. tuberculosis* H37Ra [55]. The fungus *Diaporthe* sp. BCC 6140 was isolated from an unidentified wood in Thailand and was found to produce a pimarane diterpene designated diaporthein B (**71**), which had an MIC value of 3.1 µg/mL against *M. tuberculosis* H37Ra [56].

2.6 Fungal compounds active against Mycobacterial enzymes

About half of the marketed drugs are profiled as enzyme inhibitors or inactivators [57]. This is clear evidence that mechanistic enzyme studies in drug discovery are increasingly being used for hit-identification and validation of enzyme-targeted drugs. [58]. Existence of substrate binding pockets and the inherent nature of enzymes to catalyze reactions, both make enzymes druggable targets. Furthermore, some enzymes are uniquely expressed by *M. tuberculosis* and thus allow for selectivity. The data generated from enzyme assays can be used to guide lead optimization [57].

Mycobacterial protein tyrosine phosphatase A and B (MptpA and MptpB) are two interesting enzymes which selectively dephosphorylate human host signalling proteins, and thus have been identified as attractive targets in TB-drug discovery [59]. They are secreted by *M. tuberculosis* in phagosomes and are translocated to the cytosol of macrophages, where MptpA binds to the H subunit of V-ATPase to selectively restrict to catalytic substrate (VPS33B) which is found on the phagosome-lysosome fusion region [59]. The dephosphorylation of VPS33B is accompanied by a failure of the macrophage in forming

the phagolysosome. At the same time, MptpB's activity in the cytosol leads to increased phosphorylation of Akt and decreased phosphorylation of p38, thus leading to reduced apoptosis and increased necrosis [59].

Several fungal compounds have been reported to exhibit activity against MptpA and MptpB. *Fusarium graminearum* SYSU-MS5127, a fungus isolated from an anemone and cultivated in rice medium produced fusarielin M (**72**) which was tested against MptpB [60]. Both the inhibition constant (K_i) and half-maximal inhibitory concentration (IC_{50}) were found to be 0.4 µg/mL (See Table 2). Fusarielin M (**72**) proved efficacious against intracellular *M. bovis* BCG in infected J774A.1 macrophage cells, where treatment with the compound resulted in a 62% decrease of bacterial load burden without significant macrophage cytotoxicity [60]. An MIC value of 12.3 µg/mL was reported after testing against *M. tuberculosis* H37Ra [60].

Asperlones A and B (**73** and **74**) and mitorubrin (**75**) were isolated from mangrove endophytic fungus *Aspergillus* sp. 16-5C and exhibited strong inhibitory activity against MptpB, with IC_{50} values between 1.5–1.6 µg/mL for the three metabolites [61]. Peniphenones B and C (**76** and **77**) were isolated from *Penicillium dipodomyicola*, an endophyte of mangrove *Acanthus ilicifolius*, collected from the South China Sea [62]. The two compounds (**76** and **77**) were found to have strong inhibitory activity against MptpB with IC_{50} values of 6.37 and 0.45 µg/mL respectively.

Chemical analysis of a marine-sponge derived fungus from the East China sea, *Aspergillus sydowii* MF357, resulted in the identification of sydowiols A and C (**78** and **79**) with weak bioactivity against *M. bovis* BCG and *M. tuberculosis* H37Rv, both compounds recording an MIC value of > 50 µg/mL on both cell lines [63]. However, sydowiols A and C (**78** and **79**) were more effective in inhibiting *M. tuberculosis* protein tyrosine phosphatase A (MptpA), with IC_{50} values of 14 and 24 µg/mL respectively for the two metabolites [63].

Mycobacterial proteasome is a protease which degrades intracellular proteins and has been validated as therapeutic target. Mycobacterial proteasome has been reported to offer protection from nitric oxide effects to the microbe [64, 65]. In one study, fellutamide B (**80**) (originally isolated from *Penicillium fellutanum*) was found to effectively inhibit the Mycobacterial proteasome by binding to the active site in a time dependent and single step mechanism, with the K_i found to be 0.004 µg/mL [66].

3 Chemically modified fungal compounds

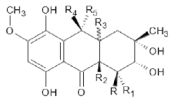
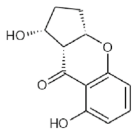
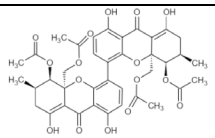
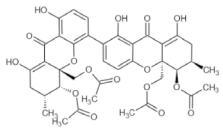
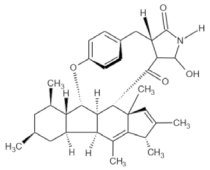
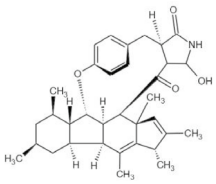
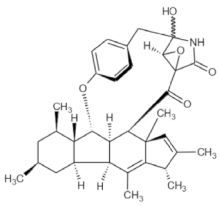
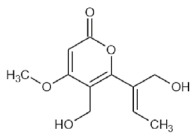
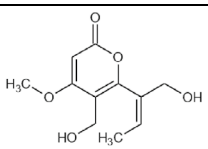
Synthetic chemical modification of natural products in drug discovery allows for tailor-made modifications of compound structures that could lead to successful medicinal drugs. Regrettably, isolation and bioactivity studies of secondary metabolites are seldom conducted together with synthetic modifications even though all three stages are mutually beneficial. Combining these three stages undoubtedly accelerates discovery of compounds with novel antimycobacterial activity [67].

Pleuromutilin (**81**) was first reported in 1951 from extracts of Basidiomycetes *Pleurotus mutilus* and *Pleurotus passeckerianus* (now *Clitopilus passeckerianus*) and was shown to possess a significant antibiotic effect against *M. smegmatis* with a MIC of 32 µg/mL [68]. In a more recent study, four pleuromutilin $_D$-leucine derivatives, UT-800, UT-810, UT-815 and UT-820 (**82–85**), which differed in the oxidation states of their C_3-carbonyl and C_{12}-vinyl groups exhibited MIC values ranging between 0.78–3.06 µg/mL against *M. tuberculosis* H37Rv, with UT-815 **(84)** showing the greatest MIC of 0.78 µg/mL [69]. Valnemulin (**86**), also a synthetic derivative of pleuromutilin (**81**) which is currently approved for treatment of a broad range of bacterial infections in animals exhibited antimycobacterial activity with a MIC value of 3.13 µg/mL in the same study [69]. Lefamulin (**87**) is another derivative of pleuromutilin (**81**) which is currently approved for treatment of community acquired pneumonia. In antimycobacterial studies involving clinical strains of rapid growing Mycobacteria, lefamulin (**87**) was found to have an MIC value of 16 µg/mL against 11 out of 30 *Mycobacterium abscessus* subsp. *abscessus* strains, an MIC value of 32 µg/mL against 15 out of 30 M. *abscessus* subsp. *massiliense* strains, and an MIC value of 16 µg/mL against all three *M. abscessus* subsp. *bolletii* strains used in the study (see Tables 3, 4) [70].

Methyl 4,4′-dimethoxyvulpinate (**88**) and 4,4′-dimethoxyvulpinic acid (**89**) were obtained from *S. citrinum* KMILT-SCL01 and subjected to synthetic modifications by bromination, methylation and acetylation to yield methyl 3,3′-dibromo-4,4′-dimethoxyvulpinate **(90)**, 3,3′-dibromo-4,4′-dimethoxyvulpinic acid **(91)** and acetyl 4,4′-dimethoxyvulpinate **(92)** [51]. 3,3′-dibromo-4,4′-dimethoxyvulpinate **(90)** (derivative of **88**) was found to be inactive against *M. tuberculosis* H37Ra at 200 µg/mL, while **91** and **92** (derivatives of **91**) exhibited weak activity with a MIC of 100 µg/mL [51].

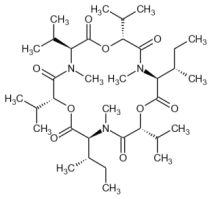
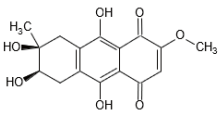
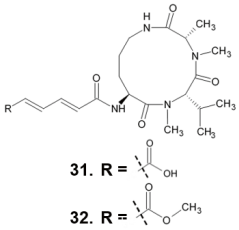
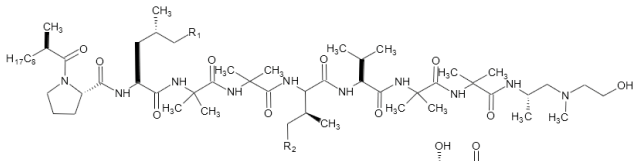
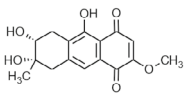
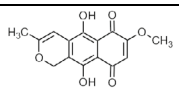
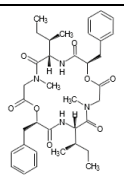
Ganoderma australe BCC 22,314 naturally produces a wide variety of lanostane triterpenoids, one of these being a (24*E*)-3β-acetoxy-15α-hydroxylanosta-7,9(11),24-trien-26-oic acid (also known as ganodermic acid T-O)

Table 2 Fungal compounds with antimycobacterial activity

Type of fungi	Fungal species	No.	Compound name	Compound structure	Inhibited pathogen	MIC		Year	Ref.
						µg/mL	µM		
Endophytic and plant-pathogenic fungi	Endophytic fungus PSU-N24	**18**	9α-Hydroxyhalorosellinia A	 18. R = OH, R_1 = R_2 = R_4 = H, R_3 = α -H, R_5 = OH 19. R = R_1 = R_2 = R_4 = H, R_3 = β -H, R_5 = OH 20. R = R_1 = H, R_2 = R_3 = double bonde, R_4 + R_5 = O	*M. tuberculosis* H37Ra	12.5	36.7	2008	[26]
		19	Desoxybostrycin		*M. tuberculosis* H37Ra	50	154.2		
		20	9β-Hydroxy-dihydrodesoxybostrycin		*M. tuberculosis* H37Ra	50	146.9		
	Diaporthe sp. P133	**21**	Diaportheone B		*M. tuberculosis* H37Rv	0.77	3.5	2011	[27]
	Phomopsis sp. BCC 1323	**22**	Phomoxanthone A		*M. tuberculosis* H37Ra	0.5	0.67	2001	[28]
	Phomopsis sp. BCC 1323	**23**	Phomoxanthone B		*M. tuberculosis* H37Ra	6.25	8.33	2001	[28]
	Phoma sp. NRRL 46751	**24**	Phomapyrrolidone A		*M. tuberculosis* H37Rv	20.1	38.1	2013	[29]
Endophytic and plant-pathogenic fungi	*Phoma* sp. NRRL 46751	**25**	Phomapyrrolidone B		*M. tuberculosis* H37Rv	5.9	11.2	2013	[29]
	Phoma sp. NRRL 46751	**26**	Phomapyrrolidone C		*M. tuberculosis* H37Rv	5.2	9.56	2013	[29]
	C. globosum IFB-E036	**27**	Chaetoglocin A		*M. smegmatis* CGMCC1.562	16	70.7	2011	[30]
	C. globosum IFB-E036	**28**	Chaetoglocin B		*M. smegmatis* CGMCC1.562	16	70.7	2011	[30]

(**93**) which was modified by an acylation reaction with propionyl chloride to produce (24*E*)-3β-acetoxy-15α-propionyloxylanosta-7,9(11),24-trien-26-oic acid (also referred to as GA003) (**94**) [71]. GA003 (**94**) was tested against *M. tuberculosis* H37Ra and the MIC value was found to be 0.098 µg/mL [71]. An oversight in this study

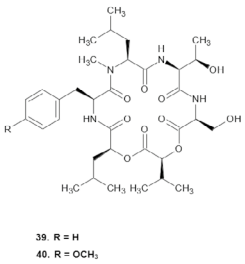
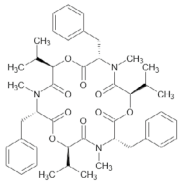
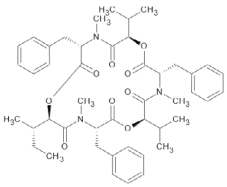
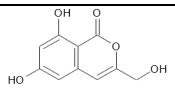
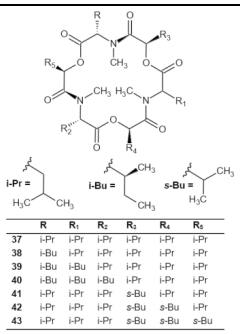
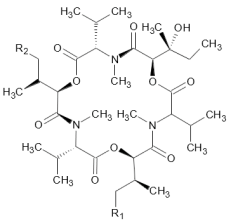
Table 2 (continued)

Endophytic and plant-pathogenic fungi	*F. avenaceum* DAOM 196490	**29**	Enniatin A1		*M. tuberculosis* H37Rv *M. tuberculosis* H37Ra *M. bovis* *M. bovis* BCG *M. smegmatis* mc^{2}155	1 2 2 2 8	1.50 2.99 2.99 2.99 12.0	2002, 2020	[31, 32]
Marine fungi	*A. eichhorniae*	**30**	4-Deoxybostrycin		*M. tuberculosis* H37Rv MDR *M. tuberculosis* K2903531	15 < 5	46.8 < 15.6	2013	[34]
Marine fungi	*A. insulicola* HDN151418	**31** **32**	Sclerotiotide M Sclerotiotide N		*M. phlei* *M. phlei*	1.37 5.63	3.13 12.5	2020	[35]
Marine fungi	*Trichoderma* sp. 05FI48	**33** **34** **35**	Trichoderin A Trichoderin A1 Trichoderin B		*M. bovis* BCG *M. tuberculosis* H37Rv *M. smegmatis* *M. bovis* BCG *M. tuberculosis* H37Rv *M. smegmatis* *M. bovis* BCG	0.02 2.0 1.56 0.16 0.13 0.63 0.02	0.02 1.72 1.36 0.14 0.11 0.55 0.02	2010	[36]
	Fusarium spp. PSU-F14	**36**	Nigrosporin B		*M. tuberculosis* H37Ra	12.5	41	2010	[37]
	Fusarium spp. PSU-F14	**37**	Anhydrofusarubin		*M. tuberculosis* H37Ra	25.1	87	2010	[37]
Entomopathogenic fungi	*H. kobayasii* BCC 1660	**38**	Hirsutellide A		*M. tuberculosis* H37Ra	6-12	9-18	2002	[39]

is that naturally occurring ganodermic acid T-O (**93**) was not tested for antimycobacterial activity.

Aspergillus versicolor CHNSCLM-0063 was isolated from the coral *Rumphella aggregata* and fermented on rice solid medium to produce asperversiamide A (**95**) which exhibited an MIC of 10.5 µg/mL against *M. marinum* [72, 73]. Synthetic modifications involving the reacting asperversiamide A (**95**) with cinnamic acid derivatives in the presence of 4-(dimethylamino)pyridine (DAMP) and ethylene diamine hydrochloride (EDA-HCL) in dichloromethane were performed [73]. Eighteen new derivatives were synthesized and tested for antimycobacterial activity against *M. tuberculosis* H37Ra, four unnamed derivatives (**96–99**) displayed activity with MIC values of 13.9 and 56.2 µg/mL for derivatives **96** and **97**, and 13.3 µg/mL for derivatives **98** and **99** [73].

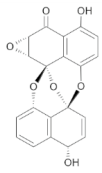
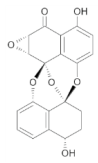
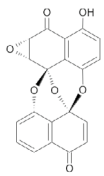
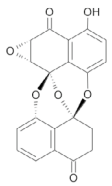
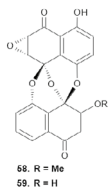
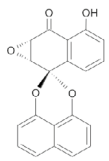
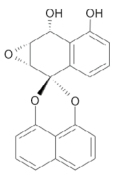
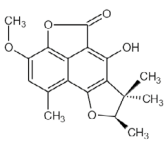
Table 2 (continued)

Entomopathogenic fungi	*H. nivea* BCC 2594	**39**	Hirsutatin A		*M. tuberculosis* H37Ra	50	73.9	2005	[40]
		40	Hirsutatin B		*M. tuberculosis* H37Ra	50	70.7		
				39. R = H 40. R = OCH_3					
	P. tenuipes BCC 1614	**41**	Beauvericin		*M. tuberculosis* H37Ra	12.5	16.0	2000	[41]
	P. tenuipes BCC 1614	**42**	Beauvericin A		*M. tuberculosis* H37Ra	25	31.3	2000	[41]
Entomopathogenic fungi	*T. tenuis* BCC 12732	**43**	6,8-Dihydroxy-3-hydroxymethylisocoumarin		*M. tuberculosis* H37Ra	25	120.1	2009	[42]
	V. hemipterigenum BCC 1449	**44**	Enniatin B		*M. tuberculosis* H37Ra	3.12	4.88	2003	[43]
		45	Enniatin B4		*M. tuberculosis* H37Ra	3.12	4.77		
		46	Enniatin C		*M. tuberculosis* H37Ra	6.25	9.17		
		47	Enniatin G		*M. tuberculosis* H37Ra	6.25	9.36		
		48	Enniatin H		*M. tuberculosis* H37Ra	6.25	9.56		
		49	Enniatin I		*M. tuberculosis* H37Ra	6.25	9.36		
		50	MK1688		*M. tuberculosis* H37Ra	1.56	2.29		
	Unidentified fungus BCC 2629	**51**	Enniatin L		*M. tuberculosis* H37Ra	12.5	18.7	2004	[44]
		52 (a/b)	Enniatin M_1/Enniatin M_2 (1:1 mixture)		*M. tuberculosis* H37Ra	6.25	9.14		
		53	Enniatin N		*M. tuberculosis* H37Ra	6.25	8.96		
				51. $R_1 = R_2 = H$ 52a. $R_1 = CH_3$, $R_2 = H$ 52b. $R_1 = H$, $R_2 = CH_3$ 53. $R_1 = R_2 = CH_3$					

4 Mycogenic nanoparticles

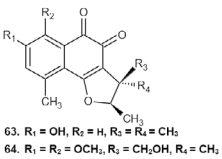
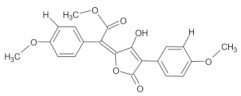
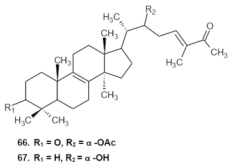
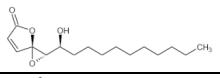
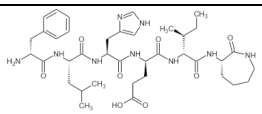
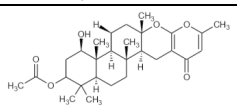
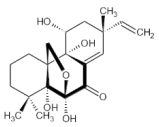
Nanoparticles are particles with two or more dimensions with a size range of 1 nm to 100 nm [74]. Research and application of nanomaterials has gained prominence due to their tunable chemical, physical and biological properties which enhances their performance with respect to their bulk analogues [75–77]. As such, nanomaterials have found several biomedical applications which include drug delivery and targeting, in vivo and in vitro diagnostics, gene manipulations and immunomodulation [78].

Table 2 (continued)

Lichenicolous fungi	*Microsphaeropsis* sp. BCC 3050	**54**	Preussomerin E		*M. tuberculosis* H37Ra	25	68.6	2002	[46]
	Microsphaeropsis sp. BCC 3050	**55**	Preussomerin F		*M. tuberculosis* H37Ra	3.12	8.52	2002	[46]
	Microsphaeropsis sp. BCC 3050	**56**	Preussomerin G		*M. tuberculosis* H37Ra	3.12-6.25	8.61-17.25	2002	[46]
	Microsphaeropsis sp. BCC 3050	**57**	Preussomerin H		*M. tuberculosis* H37Ra	6.25	17.2	2002	[46]
	Microsphaeropsis sp. BCC 3050	**58** **59**	Preussomerin I 3'-*O*-demethylpreussomerin I		*M. tuberculosis* H37Ra *M. tuberculosis* H37Ra	12.5 25	31.7 63.4	2002	[46]
	Microsphaeropsis sp. BCC 3050	**60**	Deoxypreussomerin A		*M. tuberculosis* H37Ra	1.56-3.12	4.69-9.39	2002	[46]
	Microsphaeropsis sp. BCC 3050	**61**	Bipendinsin (palmarumycin C_{11})		*M. tuberculosis* H37Ra	50	149.6	2002	[46]
	T. eluteriae Spreng.	**62**	Lactone		*M. tuberculosis* H37Rv	50	219.1	2020	[47]

Metallic nanoparticles, as their name suggests, contain an inorganic metal at their core. They are commonly explored for their antimicrobial properties which include the ability to trigger the production of ROS, interact and destabilize the membrane potential and interact with biomolecules such as DNA, ribosomes, proton efflux pumps, enzymes which regulate processes such as ATP synthesis and proteins involved in the electron transport chain [79]. Popular metallic nanoparticles used as antimicrobial agents include gold (Au), silver (Ag), copper (Cu), zinc oxide (ZnO) and iron oxide (Fe_2O_3 and Fe_3O_4) and bimetallic magnesium aluminum oxide ($MgAl_2O_4$) [80].

Table 2 (continued)

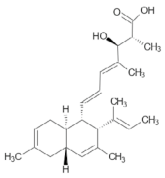
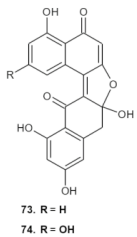
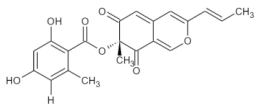
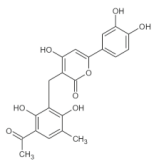
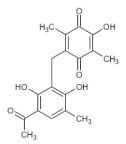
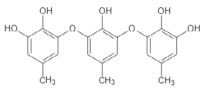
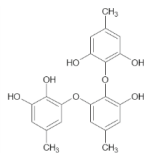
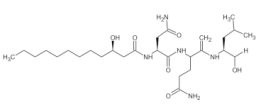
Lichenicolous fung	*T. eluteriae* Spreng.	**63**	Trypethelone	 63. R_1 = OH, R_2 = H, R_3 = R_4 = CH_3 64. R_1 = R_2 = OCH_3, R_3 = CH_2OH, R_4 = CH_3	*M. tuberculosis* H37Rv	12.5	45.9	2020	[47]
		64	4'-Hydroxy-8-methoxytrypethelone methyl ether		*M. tuberculosis* H37Rv	50	150.4		
Mushrooms and soil fungi	*S. citrinum* KMILT-SCL01	**65**	4,4'-dimethoxyvulpinic acid		*M. tuberculosis* H37Ra	25	65.4	2003	[51]
	A. odoratus	**66**	Astraodoric acid A	 66. R_1 = O, R_2 = α -OAc 67. R_1 = H, R_2 = α -OH	*M. tuberculosis* H37Ra	50	97.5	2012	[52]
		67	Astraodoric acid B		*M. tuberculosis* H37Ra	25	53.1	2012	[52]
	R. cystidiophora	**68**	Ramariolide A		*M. smegmatis*	8	28.3	2012	[53]
					M. tuberculosis	64-128	226-453	2012	[53]
	M. alpina FKI-4905	**69**	Calpinactam		*M. tuberculosis*	12.5	16.3	2010	[54]
					M. smegmatis	0.78	1.02	2010	[54]
	N. spinosa KKU-1NK1	**70**	1-Hydroxychevalone C		*M. tuberculosis* H37Ra	12.5	26.5	2016	[55]
Mushrooms and soil fungi	*Diaporthe* sp. BCC6140	**71**	Diaporthein B		*M. tuberculosis* H37Ra	3.1	8.51	2003	[56]

The use of fungi to synthesize nanoparticles is a "green synthesis" approach which is gaining momentum and is being used to overcome the limitations of chemical synthesis which requires the use of highly toxic reducing and stabilizing agents, sometimes generating nanoparticles which are also highly toxic and prone to aggregation [81]. Mycogenic synthesis of metal nanoparticles is usually performed by exposing the fungal to a metal salt under specified conditions. Intracellular or extracellular synthesis of nanoparticles can be achieved, the latter is preferred as harvesting the nanoparticles is easier. The use culture filtrate which is mixed with a metal salt is also common, this reduces complications in harvesting intracellular nanoparticles. The exact mechanism is often unclear, however reducing enzymes such as NADH- and NADPH-dependent reductases, nitrate and nitrite reductases, and non-enzyme proteins and peptides with metallo-interaction activities are thought to participate in the reduction of M^{n+} to M^0, thus resulting in nanoparticles [82]. Stabilization of the newly formed nanoparticles is then achieved by fungal secondary metabolites and proteins.

A few specific examples of mycosynthesis of metallic nanoparticles for antimycobacterial applications exist in literature. In one study, silver nitrate ($AgNO_3$) was reduced using the crude enzymes in the broth filtrate from cultures of the *Rhizopus stolonifera* to produce stable and predominantly spherical Ag nanoparticles (**100**) with a size range between 3–20 nm [83]. These Ag nanoparticles (**100**) were tested against *M. tuberculosis* (clinical strain) an MIC value of 12.5 µg/mL was reported. Sivaraj, et al. [84], used extracts from commercial yeast (*Saccharomyces cerevisiae*) and synthesized spherical silver chloride (AgCl) nanoparticles (**101**) which were found to be approximately 17 nm in size. The AgCl nanoparticles (**101**) had an MIC value of 37 µg/mL against *M. smegmatis* mc^2155 and *M. tuberculosis* H37Rv.

Instead of using fungi to synthesize and stabilize nanoparticles, there has been times when fungal derived compounds and their derivatives have been used in modifying, capping or stabilizing chemically synthesized nanoparticles. An interesting case is that of the antibiotic ampicillin, a β-lactam derivative of a *Penicillium* sp. metabolite (benzylpenicillin) which has been modified by the addition of an amino group, was conjugated on gold nanoparticles (AuNPs) nucleated on self-assembled

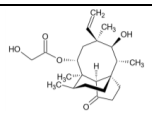
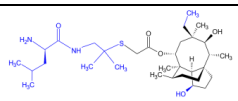
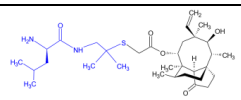
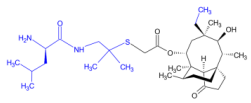
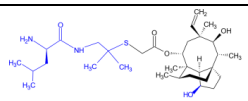
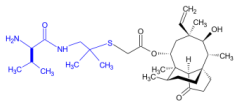
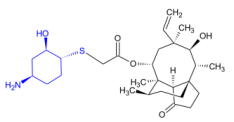
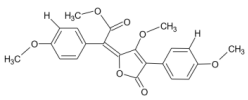
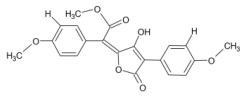
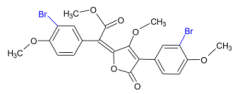
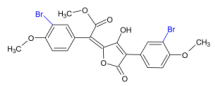
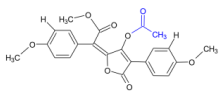
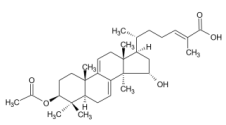
Table 3 Fungal compounds tested against Mycobacteria enzymes

Fungal species	No.	Compound name	Compound structure	Enzyme	IC_{50}		K_i		Year	Ref.
					µg/mL	µM	µg/mL	µM		
F. graminearum SYSU-MS5127	**72**	Fusarielin M		MptpB	0.40	1.05	0.40	1.03	2021	[60]
Aspergillus sp. 16-5C	**73**	Asperlone A	 73. R = H 74. R = OH	MptpB	1.54	4.24	No data		2015	[61]
	74	Asperlone B		MptpB	1.64	4.32	No data		2015	[61]
	75	Mitorubrin		MptpB	1.53	3.99	No data		2015	[61]
P. dipodomyicola	**76**	Peniphenone B		MptpB	6.37	16	No data			[62]
	77	Peniphenone C		MptpB	0.45	1.37	No data			[62]
A. sydowii MF357	**78**	Sydowiol A		MptpA	14	36.4	No data			[63]
	79	Sydowiol C		MptpA	24	62.4	No data			[63]
P. fellutanum	**80**	Fellutamide B		Proteasome	No data		0.004	0.0068		[66]

PEGylated rosette nanotubes (Amp-AuNPs-RNT) and utilized in antimicrobial studies [85].

Significant work has been done in synthesis of nanoparticles using fungi for medical and industrial applications[86], however their application as antimicrobial agents against *M. tuberculosis* has been limited. Mycogenic metallic nanoparticles present opportunities that may potentially lead to the development of anti-TB nanodrugs.

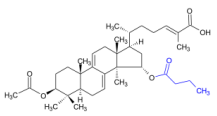
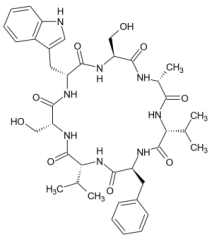
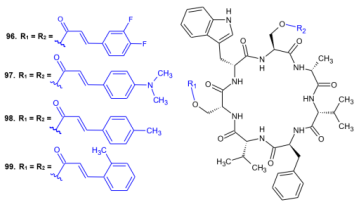
Table 4 Fungal compounds modified using chemical (semi-) synthesis and their antimycobacterial activity

Fungal species	No.	Compound name	Compound type	Compound structure	Inhibited pathogen	MIC		Year	Ref.
						µg/mL	µM		
P. mutilus; C. passeckerianus	**81**	Pleuromutilin	Natural		*M. smegmatis*	32	84.5	1951	[68]
	82	UT-800	Derivative of **81**		*M. tuberculosis* H37Rv	0.83	1.55	2018	[69]
	83	UT-810	Derivative of **81**		*M. tuberculosis* H37Rv	1.56	2.94	2018	[69]
	84	UT-815	Derivative of **81**		*M. tuberculosis* H37Rv	0.78	1.46	2018	[69]
	85	UT-820	Derivative of **81**		*M. tuberculosis* H37Rv	3.06	5.74	2018	[69]
	86	Valnemulin	Derivative of **81**		*M. tuberculosis* H37Rv	3.13	5.54	2018	[69]
	87	Lefamulin	Derivative of **81**		*M. abscessus subsp. abscessus* *M. abscessus* subsp. *massiliense* *M. abscessus subsp. bolletii*	≈ 16 ≈ 32 16	≈ 31.5 ≈ 63.0 31.5	2021	[70]
S. citrinum KMILT-SCL01	**88**	Methyl 4,4'-dimethoxyvulpinate	Natural		*M. tuberculosis* H37Ra	> 200	> 504	2003	[51]
	89	4,4'-dimethoxyvulpinic acid	Natural		*M. tuberculosis* H37Ra	25	65.4	2003	[51]
	90	Methyl 3,3'-dibromo-4,4'-dimethoxyvulpinate	Derivative of **88**		*M. tuberculosis* H37Ra	> 200	> 361	2003	[51]
	91	3,3'-dibromo-4,4'-dimethoxyvulpinic acid	Derivative of **89**		*M. tuberculosis* H37Ra	100	185	2003	[51]
	92	Acetyl 4,4'-dimethoxyvulpinate	Derivative of **89**		*M. tuberculosis* H37Ra	100	235	2003	[51]
G. australe BCC 22314	**93**	Ganodermic acid T-O	Natural		*No data provided*			2021	[71]

5 Concluding remarks

Robust anti-TB drug discovery studies are crucial for the discovery of new compounds with antimycobacterial activity. Previous studies have shown that fungi are a reservoir of structurally diverse and biologically active secondary metabolites which may be explored to discover novel anti-TB drugs. A total of 82 fungal derived compounds and

Table 4 (continued)

G. australe BCC 22314	**94**	GA003	Derivative of **93**		*M. tuberculosis* H37Ra	0.39	0.69	2021 [71]
A. versicolor CHNSCLM-0063	**95**	Asperversiamide A	Natural		*M. tuberculosis* H37Ra	> 77.7	> 100	2021 [73]
					M. marinum	18.6	24	2019 [72]
	96	Derivative 9			*M. tuberculosis* H37Ra	13.9	12.5	2021 [73]
	97	Derivative 12			*M. tuberculosis* H37Ra	56.2	50	2021 [73]
	98	Derivative 23			*M. tuberculosis* H37Ra	13.3	12.5	2021 [73]
	99	Derivative 24			*M. tuberculosis* H37Ra	13.3	12.5	2021 [73]

their semi-synthetic derivatives were presented in this review. A total of six fungal compounds were reported to have MIC values of ≤ 2 µg/mL against *M. tuberculosis*, namely diaportheone B (**21**), phomoxanthone A (**22**), enniatin A1 (**29**), trichoderin A (**33**), trichoderin B (**35**) and MK1688 (**50**). Derivatives UT-800 (**82**), UT-815 (**83**), UT-815 (**84**) and GA003 (**94**) were also found to exhibit excellent antimycobacterial activity with MIC values of ≤ 2 µg/mL. Even though mycogenic synthesis of metallic nanoparticles has been applied for both industrial and medical purposes, there is still a gap in research on mycogenic synthesis for antimycobacterial studies. After carefully going through the studies presented in this review, authors concluded that fungal kingdom is truly a reservoir of bioactive compounds which have the potential to become drivers of TB-drug discovery. Furthermore, mycogenic synthesis presents opportunities for the development of truly novel TB-drugs of the future.

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Author contributions KIT collected the data and wrote the manuscript. KN, LB, MK, LM, LS, NA, AL, RME and VM edited the manuscript and gave critical comments. All authors contributed to the article and approved the submitted version.

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Data availability All data are contained in this article.

Declarations

Conflict of interest The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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