Antimycobacterials from Fungi

Sunil Kumar Deshmukh,¹,* Shilpa Amit Verekar² and B.N. Ganguli³

ABSTRACT

Tuberculosis is an endemic disease of the poverty ridden, undernourished and over populated countries of the world. It is also a systemic disease that is extremely dependent on the physiology of the system it invades and thus varies significantly from person to person. New developments in the treatment of this disease have rarely percolated down to the larger sections of the under privileged in our societies. The need for highly active, long acting, yet less expensive drugs against Multi-Drug Resistant (MDR) Mycobacterium tuberculosis still exists. Research initiative on endophytic fungi as a source of such biotherapeutics is an important step that could help to tackle the need. Complete eradication of tuberculosis is certainly possible by integration of research results and public health programs. However, such initiatives have been hindered by the lack of effective communication lines in many countries of the world. Language is just one of the several hurdles! Nationalistic jingoism is another!!

A major initiative could be to investigate the effects of the mixtures of compounds already known to have activities against different strains of M. tuberculosis. Such as, those reported in the local knowledge forums of Ayurvedics in villages of India and in allopathic medical publications. We must have a “United Front to Combat Tuberculosis” (UFCT)—A Worldwide Effort.

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Introduction

In the many countries of the world, the hunt for new anti-mycobacterial compounds is going on. In most of them, a marker MIC level is set so that both synthetic and natural (plants, fungal) compounds can be selected that have better therapeutic potential especially against clinically relevant Multi Drug Resistant strains of Mycobacteria. The marker compounds used are Isoniazid with a Minimum Inhibitory Concentration (MIC) of 0.04–0.09 µg/mL and Kanamycin sulphate with an MIC of 2.0–5.0 µg/mL usually. In the opinion of the authors, the use of selective mixtures of anti-tubercular compounds could be better, so that development of resistance is slowed down if not totally prevented. Choice of several different mixtures of compounds could be of advantage after extensive evaluation. Serum binding may not be a disadvantage if a slow but continuous release is observed and measured over time. What needs also to be borne in mind is that this chronic disease usually affects the poorer populations of the world where public health efforts are negligible, if not totally absent, and communications extremely difficult.

Scrutiny of the available literature of the years from 2002 to 2013 clearly indicated that research initiatives against M. tuberculosis are discouraging with the publication of 1–2 papers on anti-mycobacterial per year. Moreso, to our utter surprise, during the year 2006–2007 there was no report in the journals we reviewed. But in the year 2010 the largest number of publications appeared. This poses a million dollar question. What made the researches to jump on it too heavily and suddenly? But this momentum is a welcome move.

The World Health Organization (WHO) estimated that currently ca. 50 million people were infected and 1500 people die per hour from Tuberculosis worldwide. After the detection of strains of Mycobacterium tuberculosis resistant to multiple drugs (MDRTB), the search for new antimycobacterials has been intensified (WHO, 2008). The world recognizes medicinal plants as repositories of fungal endophytes that produce metabolites with novel molecular structures that are active against various human diseases. For example, extracts of endophytic fungi isolated from Thailand’s Garcinia plant species inhibit M. tuberculosis (Wiyakrutta et al., 2004). Several compounds reported from fungi with anti-mycobacterial activities are shown in Table 1.

Antimycobacterials from Fungi

From Ascomycetes

3-Nitropropionic acid (3-NPA) (1) (Fig. 1) is found in the extracts of several strains of endophytic genus Phomopsis sp. It is highly active against M. tuberculosis H37Ra with an MIC of 3.3 µM, but no in vitro cytotoxicity was seen in a number of cell lines. Endophytes produce high levels of 3-NPA which accumulates in certain plants and could, therefore be a marker.
### Table 1. Antimycobacterial from fungi.

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Fungus</th>
<th>Source</th>
<th>Compounds Isolated</th>
<th>Biological Activity*</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td><em>Phomopsis</em> sp.</td>
<td><em>Urobothrya siamensis</em>, <em>Grewia</em> sp., <em>Mesua ferrea</em>, <em>Rhododendron</em></td>
<td>3-Nitropropionic acid (3-NPA) (1)</td>
<td>Compound (1) inhibits <em>Mycobacterium tuberculosis</em> H37Ra strain (MIC of 3.3 µM). Inhibits the isocitrate lyase (ICL), the enzyme involved in fatty acid catabolism and virulence in <em>M. tuberculosis</em></td>
<td>Chomcheon et al., 2005 Munoz-Elias et al., 2005</td>
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<tr>
<td>2.</td>
<td><em>Nodulisporium</em> sp.</td>
<td>Marine derived fungus</td>
<td>Vermelhotin (3), Aspergillusidone</td>
<td>Vermelhotin (3) inhibits five reference strains of <em>M. tuberculosis</em> with MICs of 3.1–6.2 µg/mL. Aspergillusidone D (4) has an MIC value of 50.0 µg/mL</td>
<td>Kasettrathat et al., 2008; Ganihigama et al., 2015</td>
</tr>
<tr>
<td>3.</td>
<td><em>Phomopsis</em> sp. BCC 1323</td>
<td>Leave of <em>Tectona grandis</em> L.</td>
<td>Phomoxanthones A (5) and B (6)</td>
<td>Compounds (5) and (6), <em>M. tuberculosis</em> H37Ra strain (MIC of 0.5 and 6.25 µg/mL respectively)</td>
<td>Isaka et al., 2001</td>
</tr>
<tr>
<td>4.</td>
<td><em>Phomopsis</em> sp. PSU-D15</td>
<td><em>Garcinia dulcis</em></td>
<td>Phomoenamide (7)</td>
<td>Compound (7) <em>M. tuberculosis</em> (MIC of 6.25 mg/mL)</td>
<td>Rukachaisirikul et al., 2008</td>
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<tr>
<td>5.</td>
<td><em>Diaporthe</em> sp. BCC 6140</td>
<td></td>
<td>Diaportheins A (8) and B (9)</td>
<td>Compound (8) <em>M. tuberculosis</em> (MIC 200 µg/mL) and Compound (9) at (MIC 3.1 µg/mL)</td>
<td>Dettrakul et al., 2003</td>
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<tr>
<td>6.</td>
<td><em>Phoma</em> sp. NRRL 46751</td>
<td><em>Saurauia scaberrinae</em></td>
<td>Phomapyrrolidones B-C (10-11)</td>
<td>Compound (10) and (11) inhibits <em>M. tuberculosis</em> H37Pv (weak in vitro anti-tubercular activity when tested using the microplate Alamar Blue assay (MABA) for replicating cultures with MIC of 9.9 and 5.2 µg/ml respectively) In the low oxygen recovery assay (LORA) with MIC 15.4 and 13.4 µg/ml respectively for non-replicating</td>
<td>Wijeratne et al., 2013</td>
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</table>
### Table 1. contd....

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<thead>
<tr>
<th></th>
<th>Antimycobacterials from Fungi</th>
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<tr>
<td>7.</td>
<td>Fruit hull of <em>Garcinia mangostana</em> L.</td>
<td>α-Mangostin (12)</td>
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<td></td>
<td>Compound (12) Incubation with <em>C. gloeosporioides</em> (EYL131)</td>
<td>Mangostin 3-sulfate (13), Mangostanin 6-sulfate (14), 17,18-Dihydroxymangostanin 6-sulfate (15), Isomangostanin 3-sulfate (16)</td>
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<td></td>
<td>Compound (12) Incubation with <em>N. spathulata</em> (EYR042)</td>
<td>Mangostin 3-sulfate (13)</td>
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<td>8.</td>
<td><em>Chaetomium globosum</em> strain IFB-E036</td>
<td>Cynodon dactylon</td>
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<td></td>
<td>Cynodon dactylon</td>
<td>Chaetoglucins A-B (17-18)</td>
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<td></td>
<td>Compound (17-18) inhibits <em>B. subtilis</em>, <em>Streptococcus pyogenes</em>, <em>Mirococcus luteus</em> and <em>M. smegmatis</em> with MICs between 8 and 32 µg/mL</td>
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<td>9.</td>
<td><em>Chaetomium globosum</em> KMITL-N0802</td>
<td>Thai soil</td>
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<td></td>
<td>Echinuline (19) and Chaetomanone (20)</td>
<td>Compounds (19-20) inhibits <em>M. tuberculosis</em> with MIC of 169.92 and 216.62 µM respectively</td>
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<td>10.</td>
<td><em>Chaetomium brasiliense</em></td>
<td>Mollicellins K (21)</td>
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<td></td>
<td>Compound (21) inhibits <em>M. tuberculosis</em> MIC 12.5 µg/mL</td>
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<td>11.</td>
<td><em>Chaetomium cochliodes</em> VTh01 and <em>C. cochliodes</em> CTh05</td>
<td>Cochliodone C (22), Chaetovirdine E and F (23-24), Chaetoalasain A (25), 24(R)-5α,8α-Epidioxyergosta-6-22-diene-3β-ol (26)</td>
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<td></td>
<td>Compounds (22–26) inhibits <em>M. tuberculosis</em> (MICs 200, 50, 100, 100, and 200 µg/mL, respectively)</td>
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<td>12.</td>
<td><em>Trichoderma</em> sp. Marine sponge-derived fungus</td>
<td>Trichoderins A (27), A1 (28), and B (29)</td>
</tr>
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<td></td>
<td>Compounds (27–29) active against both dormant and multiplying <em>M. tuberculosis</em> strain H37Rv, <em>M. smegmatis</em>, <em>Mycobacterium bovis</em> BCG, and <em>M. tuberculosis</em> H37Rv with MIC values in the range of 0.02–2.0 µg/mL</td>
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### Table 1. contd....

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<tbody>
<tr>
<td>13.</td>
<td>Coniothyrium cereale</td>
<td>Marine green alga Enteromorpha sp.</td>
<td>(−)-Trypethelone (30)</td>
<td>Compounds (30) is active against <em>M. phlei</em>, <em>S. aureus</em>, and <em>E. coli</em>, at 20 µg/disk with inhibition zones of 18, 14, and 12 mm, respectively</td>
<td>Elsebai et al., 2011</td>
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<tr>
<td>14.</td>
<td>Biscogniauxia formosana BCRC 33718</td>
<td>Cinnamomum sp.</td>
<td>Biscogniauxaphilones A (31) and B (32), N-trans-feruloy-3-O-methyl dopamine (33), 5-Hydroxy-3,4-trimethoxy flavone (34), 4-Methoxy cinnamaldehyde (35), Methyl 3,4-methylenedioxy cinnamate (36), 4-Methoxy-trans-cinnamic acid (37)</td>
<td>Compounds (31) and (32) inhibits <em>M. tuberculosis</em> strain H37Rv with MIC of ≤ 5.12 and ≤ 2.52 µg/mL, respectively Compounds (33–37) inhibits <em>M. tuberculosis</em> strain H37Rv with MIC of 12.5, 25.0, 42.1, 58.2 and 50.0 µg/mL, respectively</td>
<td>Cheng et al., 2012</td>
</tr>
<tr>
<td>15.</td>
<td>Fusarium sp. BCC14842</td>
<td>Bamboo leaf</td>
<td>Javanicin (38), 3-O-Methyl fusarubin (39), a diastereomer of Dihydronaphthalene (40) and 5-Hydroxy-3-methoxy dihydro fusarubin A (41)</td>
<td>Compounds (38) and (40), anti-mycobacterial activity (MICs of 25 µg/mL) Compounds (39) and (41), anti-mycobacterial activity (MICs of 50 µg/mL)</td>
<td>Kornsakulkarn et al., 2011</td>
</tr>
<tr>
<td>16.</td>
<td>Fusarium sp.</td>
<td>Mangrove plant</td>
<td>Cadmium (42) and copper (43) metal complexes of Fusaric acid</td>
<td>Compounds (42–43) <em>M. bovis</em> BCG (MIC 4 µg/mL) and the <em>M. tuberculosis</em> H37Rv strain (MIC 10 µg/mL)</td>
<td>Pan et al., 2011</td>
</tr>
<tr>
<td>17.</td>
<td>Fusarium spp. PSU-F14</td>
<td>Sea fan-derived fungi</td>
<td>9α-hydroxyhalorosellinia A (44), Nigrosporin B (45) anhydro fusarubin (46)</td>
<td>Compounds (44–46) inhibits <em>M. tuberculosis</em> H37Ra (MIC of 39, 41 and 87 µM respectively)</td>
<td>Trisuwan et al., 2010</td>
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<td></td>
<td><strong>Microsphaeropsis sp. BCC 3050</strong></td>
<td><strong>Lichenicolous fungus isolated from <em>Dirinaria applanata</em></strong></td>
<td><strong>3'-O-Demethylpreussomerin I (47), Preussomerins E–I (48–52), Deoxypreussomerin A (53) and Bipendensin (Palmarumycin C11) (54)</strong></td>
<td><strong>Compounds (47–54) inhibits <em>M. tuberculosis</em> H37Ra (MIC 25, 3.12, 3.12–6.25, 6.25, 12.5, 25, 1.56–3.12, 50 µg/mL, respectively)</strong></td>
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<tr>
<td>18.</td>
<td><strong>Phaeosphaeria sp.</strong></td>
<td>(3S,4R)-4,8-Dihydroxy-3-methoxy-3,4-dihydronaphthalen-1(2H)-one (55), (4S)-3,4,8-Trihydroxy-6-methoxy-3,4-dihydronaphthalen-1(2H)-one (56), (5)-4,6,8-Trihydroxy-3,4-dihydronaphthalen-1(2H)-one (57), 1-(1-Hydroxy-3,6-dimethoxy-5,8-dioxo-5,8-dihydronaphthalen-2-yl) ethyl acetate (58), 2,5,7-Trihydroxy-3-(1-(1-hydroxy-3,6-dimethoxy-5,8-dioxo-5,8-dihydronaphthalen-2-yl)ethyl)naphthalene-1,4-dione (59), 6-Ethyl-5-hydroxy-2,7-dimethoxynaphthalene-1,4-dione (60)</td>
<td>Compounds (55-56) <em>M. tuberculosis</em> MICs 12.50 µg/mL, Compound (58) MIC of 12.50 µg/mL, compound (59), MIC 0.39 µg/mL, Compound (60) MIC of 6.25 µg/mL, compound (57) MIC of 25 µg/mL.</td>
<td><strong>Pittayakhajonwut et al., 2008</strong></td>
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<tr>
<td>19.</td>
<td><strong>Dothideomycete sp. LRUB20</strong></td>
<td>Leea rubra</td>
<td>2-hydroxymethyl-3-methylcyclopent-2-enone (61), Asterric acid (62), and hydrazine derivative of cis-2-hydroxymethyl-3-methylcyclopentanone (63)</td>
<td>Compounds (61–63), have mild anti-mycobacterial activities with MIC values of 200 µg/mL.</td>
<td><strong>Chomcheon et al., 2006</strong></td>
</tr>
<tr>
<td>20.</td>
<td><strong>Penicillium dipodomyicola - HN4-3A</strong></td>
<td>Stem of the mangrove plant <em>Acanthus ilicifolius</em></td>
<td>Peniphenone B (64), Peniphenone C (65)</td>
<td>Compounds (64), (65), inhibited Mptp B with IC₅₀ values of 0.16 ± 0.02 and 1.37 ± 0.05 µM, respectively</td>
<td><strong>Li et al., 2014</strong></td>
</tr>
</tbody>
</table>

*Table 1. contd....*
22. *Geotrichum* sp.  
Source: *Crassocephalum crepidoides*

- 7-butyl-6,8-dihydroxy-3(R)-pent-11-enylisochroman-1-one (66)
- 7-but-15-enyl-6,8-dihydroxy-3(R)-pent-11-enylisochroman-1-one (67)
- 7-butyl-6,8-dihydroxy-3(R)-pentylisochroman-1-one (68)

*Compound (66–68) inhibits* *M. tuberculosis* *H27Ra*. MICs are respectively, 25 µg/mL, 50 µg/mL, and inactive

Kongsaeeree et al., 2003

23. *Verticillium hemipterigenum*  
Pathogenic fungus

- Enniatins H (69), I (70), B (71), and B4 (72)

*Compound (69–72) inhibits* *M. tuberculosis* *H37Ra* (MICs 3.12–6.25 µg/mL)

Nilanonta et al., 2003

24. Unidentified fungus

- Analogues H, I and MK1688 (73–75)

*Compound (73–75) (MICs 3.12–6.25 µg/mL)*

Vongvilai et al., 2004

25. *Nigrospora* sp.  
Mangrove endophyte

- 4-Deoxybostrycin (80) and Nigrosporin (45)

*Compound (80 and 45) In the Kirby-Bauer disk diffusion susceptibility test, both had inhibition zone sizes of over 25 mm against* *M. tuberculosis*

Wang et al., 2013

26. *Hirsutella kobayasii* BCC 1660  
Entomopathogenic fungus

- Hirsutellide A (81)

*Compound (81) M. tuberculosis H37Ra using the microplate Alamar Blue Assay (MABA) showed a MIC with 6–12 µg/mL*

Vongvanich et al., 2002

27. *Hirsutella nivea* BCC 2594  
Pathogenic fungus

- Hirsutellones A–D (82–85)

*The compounds (82–85), inhibits* *M. tuberculosis* *H37Ra (MIC 0.78, 3.125, 0.78, 0.78 µg/mL)*

Isaka et al., 2005
<table>
<thead>
<tr>
<th>No.</th>
<th>Species/Strain</th>
<th>Compound(s) Description</th>
<th>MIC or Activity Value</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>28</td>
<td>Trichoderma sp. BCC 7579</td>
<td>Hirsutellone F (86), Hirsutellones A, B, and C</td>
<td>Compound (86) inhibits <em>M. tuberculosis</em> H37Ra (MIC 3.12 µg/mL)</td>
<td>Isaka et al., 2006</td>
</tr>
<tr>
<td>29</td>
<td>Periconia sp.</td>
<td>Piper longum</td>
<td>Compound (87) inhibits <em>M. tuberculosis</em> and <em>M. smegmatis</em> with MIC of 1.74 and 2.62 µg/ml respectively</td>
<td>Verma et al., 2011</td>
</tr>
<tr>
<td>30</td>
<td>Aschersonia tubulata BCC 1785</td>
<td>Insect pathogenic fungus</td>
<td>Dustanin (88), 3 beta-acetoxy-15 alpha, 22-dihydroxyhopane (89)</td>
<td>Boonphong et al., 2001</td>
</tr>
<tr>
<td>31</td>
<td>Aspergillus sp.</td>
<td>Physcion (90)</td>
<td>Compound (90) exhibited mycobacterial detoxification enzyme mycothiol-S-conjugate amidase (MAC), with IC₅₀ value of 50 µM against <em>M. smegmatis</em></td>
<td>Nicholas et al., 2003</td>
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<tr>
<td>32</td>
<td>Lichen</td>
<td>Usnic acid (91)</td>
<td>Compound (91) <em>M. tuberculosis</em> (MIC 2.5–5 µg/mL)</td>
<td>Ingólfsdóttir, 2002</td>
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<td>33</td>
<td>Menisporopsis theobromae</td>
<td>Seed fungus</td>
<td>Menisporopsin A (92)</td>
<td>Chinworrunsee et al., 2004</td>
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<td>34</td>
<td>fungal strain WZ-4-11 of Aspergillus carbonarius</td>
<td>8'-O-Demethyl nibgerone (93) and 8'-O-demethyl isonigerone (94)</td>
<td>Compounds (93) and (94) inhibits <em>M. tuberculosis</em> H37Rv with MIC values of 43.0 and 21.5 µM, respectively</td>
<td>Zhang et al., 2008</td>
</tr>
<tr>
<td>35</td>
<td>Cordyceps sp. BCC 1861</td>
<td>Insect pathogenic fungus from <em>Homoptera cicada</em> nymph</td>
<td>Cordyol A (95)</td>
<td>Bunyapaiboonsri et al., 2007</td>
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<tr>
<td>36</td>
<td>Ophiocordyceps communis BCC 16475</td>
<td>Insect pathogenic Fungus</td>
<td>Cordycommunin (96)</td>
<td>Haritakun et al., 2010</td>
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</tbody>
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<td></td>
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<td>Ophiobolin K (97) was also effective against the biofilm formation of <em>M. bovis</em> BCG and was able to restore the antimicrobial activity of isoniazid against <em>M. smegmatis</em> by inhibiting biofilm formation</td>
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<tr>
<td>38</td>
<td><em>Emericella rugulosa</em></td>
<td></td>
<td>Bicyclo[3.3.1]nonya-2,6-diene derivative, rugulosone (100)</td>
<td>Compound (100), anti-mycobacterial active</td>
<td>Moosophon et al., 2009</td>
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<tr>
<td>39</td>
<td><em>Conioideocrella tenuis</em> BCC 18627</td>
<td>Insect pathogenic fungus</td>
<td>Hopan-27-al-6β,22-triol (101), Hopane-6β,11r,22,27-tetraol (102), Hopane-6β,7β,22-triol (103), (atropisomer of ES-242-2) (104), Compound (105)</td>
<td>Compounds (101–105) active against <em>M. tuberculosis</em> H37Ra with MIC of &gt; 105, &gt; 52, &gt; 107, &gt; 75, &gt; 75 µM/ml, respectively</td>
<td>Isaka et al., 2011</td>
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<td>40</td>
<td><em>Scleroderma citrinum</em></td>
<td>Thai mushroom</td>
<td>4,4'-dimethoxyvulpinic acid (106), dibromo derivative of (106), 3,3'-dibromo-4,4'-dimethoxyvulpinic acid (107), acetyl 4,4'-dimethoxyvulpinate (108)</td>
<td>Compounds (106–108) inhibits <em>M. tuberculosis</em> H37Ra with MIC of 25, 100 and 100 µg/ml</td>
<td>Kanokmedhakul et al., 2003</td>
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<td>41</td>
<td><em>Astraeus pteridis</em></td>
<td>Truffle-mimicking mushroom</td>
<td>3-epi-astralhygrol (109), astralhygrone (110) and 3-epi-astralhygrone (111)</td>
<td>Compounds (109–111) inhibits <em>M. tuberculosis</em> with MIC values of 58.0, 64.0 and 34.0 µg/mL, respectively</td>
<td>Stanikunaite et al., 2008</td>
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<tr>
<td>No.</td>
<td>Fungus/Strain</td>
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<td>Compound(s)</td>
<td>Activity</td>
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<td>42.</td>
<td><em>Astraeus odoratus</em></td>
<td>Edible mushroom</td>
<td>Astraodoric acids A (112) and B (113)</td>
<td>Compounds (112-113) inhibits <em>M. tuberculosis</em> H37Ra with MICs of 50 and 25 µg/mL</td>
<td>Arpha et al., 2012</td>
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<td>43.</td>
<td><em>Kionochaeta ramifera</em> BCC 7585</td>
<td>The coral mushroom</td>
<td>Ramiferin (114)</td>
<td>Compound (114) anti-tubercular MIC 12.7 µM</td>
<td>Bunyapaiboonsri et al., 2008</td>
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<td>44.</td>
<td><em>Ramaria cystidiophora</em></td>
<td>The coral mushroom</td>
<td>Ramariolide (115)</td>
<td>Compound (115) <em>M. smegmatis</em> and <em>M. tuberculosis</em> active</td>
<td>Centko et al., 2012</td>
</tr>
<tr>
<td>45.</td>
<td><em>Mycena</em> sp. (F205435)</td>
<td>Basidiomycetes</td>
<td>Gliotoxin (116), and S,S dimethyl gliotoxin (117)</td>
<td>Compounds (116-117) exhibit mycobacterial detoxication enzyme mycothiol-S-conjugate amidase (MAC), with IC₅₀ values of 50 and 70 µM against <em>M. tuberculosis</em>. Gliotoxin inhibits MAC. Its IC₅₀ value is 50 µM against <em>M. smegmatis</em></td>
<td>Nicholas et al., 2003</td>
</tr>
<tr>
<td>46.</td>
<td><em>Ganoderma orbiforme</em> BCC 22324</td>
<td>Reishi mushroom</td>
<td>Ganoderic acid T (118), and the C-3 epimer of Ganoderic acid T (119)</td>
<td>Compounds (118-119), <em>M. tuberculosis</em> H37Ra with MIC of 10.0 and 1.3 µM respectively</td>
<td>Isaka et al., 2013</td>
</tr>
<tr>
<td>47.</td>
<td>Endophytic fungi PSU-N24</td>
<td></td>
<td>9α-Hydroxyhalorosellinia A (120)</td>
<td>Compound (120) inhibits <em>M. tuberculosis</em> with the MIC value of 12.50 µg/ml</td>
<td>Sommart et al., 2008</td>
</tr>
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<td>48.</td>
<td>Nonsporulating filamentous fungus, F7524</td>
<td></td>
<td>Agonodepside A (121) and B (122)</td>
<td>Inhibit the 2-trans-enoyl-acyl-reductase involved in mycolic acid biosynthesis. Agonodepside A (121) has IC₅₀ value of 75 µM, B (122) is not active at 100 µM</td>
<td>Cao et al., 2002</td>
</tr>
<tr>
<td>49.</td>
<td><em>Mortierella alpina</em> FKI-4905</td>
<td></td>
<td>Calpinactam (123)</td>
<td>Calpinactam (123) inhibits <em>M. smegmatis</em> and <em>M. tuberculosis</em> with MICs of 0.78 and 12.5 µg/ml, respectively</td>
<td>Koyama et al., 2010</td>
</tr>
</tbody>
</table>
for endophytic fungi (Chomcheon et al., 2005). 3-NPA inhibits Isocitrate Lyase (ICL), the enzyme involved in fatty acid catabolism and virulence in M. tuberculosis (Munoz-Elias et al., 2005). 3-NPA has MIC values of 12.5 and 50.0 µg/mL against the MTB H37Rv and H37Ra strains, respectively. Out of three derivatives of 3-Nitropropionic acid, Methyl 4-Nitrobutyrate (2) is active.
with MIC values of 12.5 and 25.0 μg/mL against H37Ra and H37Rv strains, respectively (Ganihigama et al., 2015).

Vermelhotin (3) and Aspergillusidone D (4) (Fig. 1), were isolated from the marine derived fungus, a Nodulisporium sp. (Kasettrathat et al., 2008). Vermelhotin (3) is active against five reference strains of M. tuberculosis with MICs of 3.1–6.2 μg/mL. Aspergillusidone D (4) has an MIC value of 50.0 μg/mL in comparative assays (Ganihigama et al., 2015).

Phomoxanthone A (5) and B (6) (Fig. 1) were obtained from Phomopsis sp. BCC 1323, collected from the leaves of Tectonagrandis from the Mee Rim district of Chiangmai Province, Northern Thailand. These compounds show moderate in vitro activities with MICs of 0.5 and 6.25 μg/mL, respectively against M. tuberculosis H37Ra strain, as compared to Isoniazid and Kanamycin sulphate (MICs of 0.050 and 2.5 μg/mL, respectively) (Isaka et al., 2001). Phomoenamide (7) isolated from the endophyte Phomopsis sp. PSU-D15 of Garcinia dulcis has an MIC of 6.25 μg/mL against M. tuberculosis (Rukachaisirikul et al., 2008).

The pimarane diterpenes Diaporthein A (8) and B (9) (Fig. 1), were isolated from Diaporthe sp. BCC 6140. Diaporthein B strongly inhibits M. tuberculosis with a MIC 3.1 μg/mL, while A is less active (MIC 200 μg/mL). As compared to Isoniazid, MIC 0.04–0.09 μg/mL and Kanamycin sulfate, MIC of 2.0–5.0 μg/mL (Dettrakul et al., 2003). The results suggest that the carbonyl function C-7 of Diaporthein B is essential for its anti-TB activity (Asres et al., 2001).

Phomapyrrolidone B-C (10-11) (Fig. 1), were isolated from the endophyte Phoma sp. NRRL 46751, of the plant Saurauiasca berrinae. Phomapyrrolidone B (10) and C (11) have weak in vitro anti-tubercular activities when tested in the microplate Alamar Blue assay (MABA) for replicating cultures with MICs of 5.9 and 5.2 μg/mL, respectively and the low oxygen recovery assay (LORA) with MICs of 15.4 and 13.4 μg/mL, respectively for non-replicating M. tuberculosis H37Rv (Wijeratne et al., 2013).

α-Mangostin (12) (Fig. 1), a prenylated xanthone from the fruit hull of Garcinia mangostana, was individually metabolized by two fungi, Colletotrichum gloeosporioides (EYL131) and Neosartorya spathulata (EYR042), respectively. Incubation of compound (12) with C. gloeosporioides (EYL131) gave four metabolites identified as Mangostin 3-sulfate (13), Mangostanin 6-sulfate (14), 17,18-Dihydroxymangostanin 6-sulfate (15) and Isomangostanin 3-sulfate (16) (Fig. 1). Compound (13) was also formed by incubation with N. spathulata (EYR042). Compounds (12) and (13) are active against M. tuberculosis (MICs 15.24 and 6.75 μM for 12 and 13, respectively). In contrast, 14–16 showed very weak activity (MIC > 50 μg/mL) (Arunrattiyakorn et al., 2011).

Chaetoglocin A (17) (Fig. 1) Chaetoglocin B (18) (Fig. 2) isolated from Chaetomium globosum strain IFB-E036, an endophyte of Cynodon dactylon are active against B. subtilis, Streptococcus pyogenes, Mirococcus luteus and M. smegmatis with MICs between 8 and 32 μg/mL (Ge et al., 2011). Echinuline (19) and Chaetomanone (20) (Fig. 2) were isolated from Chaetomium globosum KMITL-N0802 isolated from a Thai soil. Chaetomanone and Echinuline have week activities against M. tuberculosis with MICs of 169.92 and 216.62
µM, respectively (Kanokmedhakul et al., 2002). Mollicellin K (21) (Fig. 2) was isolated from the fungus Chaetomium brasiliense showed activity against *M. tuberculosis* (MIC 12.5 µg/ml) (Khumkomkhet et al., 2009).

Cochliodone C (22), Chaetoviridine E and F (23-24), Chaetochalasin A (25), 24(R)-5a,8a-epidioxyergosta-6,22-diene-3β-ol (26) (Fig. 2) were isolated from
the fungi Chaetomium cochliodes VTh01 and C. cochliodes CTh05. Compounds (22–26) are active against M. tuberculosis with MIC values of 200, 50, 100, 100, and 200 µg/mL, respectively (Phonkerd et al., 2008).

Trichoderins A (27), A1 (28), and B (29) (Fig. 2), aminolipopeptides from a Trichoderma sp., a marine sponge-derived fungus, are reported to be active against both dormant and multiplying M. tuberculosis strain H37Rv. Trichoderins are highly active against M. smegmatis, M. bovis BCG, and M. tuberculosis H37Rv with MIC values in the range of 0.02–2.0 µg/mL (Pruksakorn et al., 2010).

(--)-Trypethylone (30) (Fig. 2), isolated from the endophyte Coniothyrium cereale of the marine green alga Enteromorpha sp. is active against M. phlei, S. aureus, and E. coli, at 20 µg/disk/6 mm with inhibition zones of 18, 14, and 12 mm, respectively (Elsebai et al., 2011).

Biscogniazaphilone A (31) (Fig. 2) and B (32), N-trans-feruloy-3-O-methylidopamine (33), 5-Hydroxy-3,7,4-trimethoxyflavone (34), 4-Methoxycinnamaldehyde (35), Methyl 3,4-methylenedioxyxycinnamate (36), 4-Methoxy-trans-cinnamic acid (37) (Fig. 3), were all isolated from the endophyte Biscogniauxia formosana BCRC 33718, of a Cinnamomum sp. Compounds (31) and (32) are active against M. tuberculosis strain H37Rv in vitro with MIC values of ≤ 5.12 and ≤ 2.52 µg/mL, respectively, as compared to the clinical drug Ethambutol (MIC 6.25 µg/mL). Compounds (33–37) have either moderate or weak anti-mycobacterial activities, MICs of 12.5, 25.0, 42.1, 58.2 and 50.0 µg/mL, respectively (Cheng et al., 2012).

Javanicin (38), 3-O-methylfusarubin (39), a diastereomer of Dihydronaphthalone (40) and 5-Hydroxy-3-methoxydihydrafusarubin A (41) (Fig. 3) were isolated from the endophyte, a Fusarium sp. BCC 14842 of the Bamboo leaf, collected from a forest of Nam Nao National Park, Phetchabun Province, Thailand. Compounds (38) and (40), have moderate activities (MICs of 25 µg/mL), while 3-O-methylfusarubin (39), and 5-hydroxy-3-methoxydihydrafusarubin A (41), have weak antimycobacterial activities (MICs of 50 µg/mL) (Kornsakulkarn et al., 2011).

Fusaric acid was isolated from a Fusarium sp., an endophyte of a mangrove plant. Cadmium and Copper complexes were prepared. The Cadmium (42) and Copper (43) (Fig. 3), complexes showed potent activities against M. bovis BCG (MIC 4 µg/mL) and M. tuberculosis H37Rv (MIC 10 µg/mL) (Pan et al., 2011).

9α-Hydroxyhalorosellinia A (44), Nigrosporin (45) Anhydrofusarubin (46) (Fig. 3), were isolated from the sea fan-derived fungi Fusarium spp. PSU-F14. Compounds (44–46) were found active against M. tuberculosis H37Ra, with MICs of 39, 41 and 87 µM, respectively (Trisuwan et al., 2010).

3’-O-Demethylpreussomerin I (47), Preussomerin E (48), Preussomerins F–I (49–52) (Fig. 4), Deoxypreussomerin A (53) (Fig. 4) and Bipendensin (Palmarumycin C11) (54) (Fig. 4), were isolated from Microsphaeropsis sp. BCC 3050, a lichenicolous fungus of Dirinaria applanata collected from Phu Tee-Suan-Sai forest in Loei province, Northeastern
Thai. These compounds (47–54) are active against M. tuberculosis H37Ra (MICs 25, 3.12, 3.12–6.25, 6.25, 12.5, 25, 1.56–3.12, 50 µg/mL, respectively) (Seephonkai et al., 2002).

(3S,4R)-4,8-Dihydroxy-3-methoxy-3,4-dihydro-1(2 H)-naphthalenone (55), (S)-4,6,8-Trihydroxy-3,4-dihydro-1(2H)-naphthalenone (56), (3S,4S)-3,4,8-Trihydroxy-6-methoxy-3,4-dihydro-1(2 H)-naphthalenone (57), 6-Ethyl-5-hydroxy-2,7-dimethoxyphthoquinone (58), 6-(1-Acetoxyethyl)-5-hydroxy-2,7-dimethoxynaphthoquinone (59), Deacetylkirschsteinin (60) (Fig. 4) were isolated from a Phaeosphaeria sp. Compounds (55) and (56) have good anti-mycobacterial activity with MICs of 12.50 µg/mL. Compound (58)
Figure 4. Structures of antimycobacterials metabolites isolated from Ascomycetes (49-60).
exhibited anti-TB activity with MIC of 12.50 µg/mL, while its acetyl derivative, compound (59), has excellent anti-TB activity, MIC 0.39 µg/mL. Compound (60) has an MIC value of 6.25 µg/mL, while compound (57) has an MIC of 25 µg/mL as compared to MIC values of isoniazid and kanamycin sulphate that were 0.05 and 2.5 µg/mL, respectively (Pittayakhajonwut et al., 2008).

2-hydroxymethyl-3-methylcyclopent-2-enone (61), Asterric acid (62) and hydrazone derivative of cis-2-hydroxymethyl-3-methylcyclopentanone (63) (Fig. 4), were all isolated from a Dothideomycete sp. LRUB20, an endophyte of the stem of a medicinal plant Leearubra in Thai. Compounds (61-63) have low anti-mycobacterial activities with MIC values of 200 µg/mL (Chomcheon et al., 2006).

Peniphenone B (64) and C (65) (Fig. 5), were isolated from Penicillium dipodomyicola - HN4-3A of the stem of the mangrove plant Acanthusilicifolius collected from the South China Sea in Hainan Province, China. Both B and C exhibited strong inhibitory activity against protein tyrosine phosphatase B (MptpB) with IC50 values of 0.16 ± 0.02 and 1.37 ± 0.05 µM, respectively (Li et al., 2014).

7-butyl-6,8-dihydroxy-3(R)-pent-11-enylisochroman-1-one (66), 7-but-15-enyl-6,8-dihydroxy-3(R)-pent-11-enylisochroman-1-one (67) and 7-butyl-6,8-dihydroxy-3(R)-pentylisochroman-1-one (68) (Fig. 5) novel Dihydroisocoumarins were isolated from a Geotrichum sp., an endophyte of Crassocephalum crepidoides. The MICs of compounds (66–68) were, 25 µg/mL, 50 µg/mL, and inactive against M. tuberculosis H37Ra respectively. This suggests that the double bond C11-C12 and the aliphatic group at C14-C17 are important for the biological activities (Kongsaeree et al., 2003).

Four cyclic peptides, namely, Enniatins B (69), B4 (70), G (71), C (72) (Fig. 5) were isolated from a pathogenic fungus Verticillium hemipterigenum. Analogues H (73), I (74) and MK1688 (75) (Fig. 5), were prepared by feeding the substrate analogs L-leucine and L-isoleucine to the fermentation. Compounds (69–75), inhibited M. tuberculosis H37Ra (MIC 3.12, 3.12, 6.25, 6.25, 6.25, 6.25 and 1.56 µg/mL, respectively) (Nilanonta et al., 2003). Fermentation of an unidentified Thai fungus led to the isolation of new hydroxyl analogs Enniatins L (76), M1 (77), M2 (78) and N (79) (Fig. 5) with MICs of 6.25–12.5 µg/mL (Vongvilai et al., 2004).

4-Deoxybostrycin (80) (Fig. 5) and Nigrosporin (45) (Fig. 3) were isolated from the mangrove endophyte, a Nigrospora sp. collected from the South China Sea. In the Kirby-Bauer disk diffusion susceptibility test, both showed zones of over 25 mm against M. tuberculosis. Compound (80) has activity against multidrug-resistant (MDR) M. tuberculosis strains with MICs of < 5–39.0 µg/mL. The gene expression profile of M. tuberculosis H37Rv after treatment with 4-Deoxybostrycin was compared with that of the untreated bacteria. One hundred and nineteen out of 3,875 genes were significantly different in M. tuberculosis exposed to 4-deoxybostrycin from that of the control. There are 46 functionally known genes involved in metabolism, information storage and processing, and cellular processes. The differential expressions of six...
Figure 5. Structures of antimycobacterial metabolites isolated from Ascomycetes (61-80).
genes were confirmed by quantitative real-time polymerase chain reaction (qRT-PCR) (Wang et al., 2013).

Hirsutellide A (81) (Fig. 6), was isolated from the entomopathogenic fungus *Hirsutella kobayasi* BCC 1660. It was active against *M. tuberculosis* H37Ra in Figure 6.

**Figure 6.** Structures of antimycobacterial metabolites isolated from Ascomycetes (81-92).
Microplate Alamar Blue Assay (MABA) with an MIC with 6–12 µg/mL and no cytotoxicity against Vero cells at 50 µg/mL (Vongvanich et al., 2002). Hirsutellones A–D (82–85) (Fig. 6), of the pathogenic fungus *Hirsutella nivea* BCC 2594 from Thailand, inhibited *M. tuberculosis* H37Ra (MIC 0.78, 3.125, 0.78, 0.78 µg/mL, respectively) (Isaka et al., 2005). Hirsutellone F (86) (Fig. 6), a new dimer alkaloid along with the known Hirsutellones A, B, and C, from the spores of the fungus *Trichoderma* sp. BCC 7579 showed a weaker activity against *M. tuberculosis* H37Ra (MIC 3.12 µg/mL) than the Hirsutellones A, B, and C (Isaka et al., 2006).

Piperine (87) (Fig. 5), is obtained from an endophytic *Periconia* sp. of *Piper longum*. Piperine has very good anti-mycobacterial activity against *M. tuberculosis* and *M. smegmatis* with MIC of 1.74 and 2.62 µg/mL, respectively (Verma et al., 2011).

Dustanin (88) and 3 beta-acetoxy-15 alpha, 22-dihydroxyhpane (89) (Fig. 6), were isolated from the insect pathogenic fungus *Aschersonia tubulata* BCC 1785. Compounds (88) and (89), have anti-mycobacterial activities with MICs of 12.5 µg/mL (Boonphong et al., 2001).

Physcion (90) (Fig. 6), isolated from an *Aspergillus* sp. inhibited the mycobacterial detoxification enzyme, mycothiol-S-conjugate amidase (MAC) with IC₅₀ of 50 µM against *M. smegmatis* (Nicholas et al., 2003). The dibenzofuran derivative, Usnic acid (91) (Fig. 6), a secondary metabolite of lichen, inhibits *M. tuberculosis*, MIC 2.5–5 µg/mL (König and Wright, 1999; Ingólfsdóttir, 2002).

A phenolic macrocyclic poly lactone, Menisporopsin A (92) (Fig. 6), reported from the seed fungus *Menisporopsis theobromae* has weak activity with MIC of 50 µg/mL against *M. tuberculosis* H37Ra (Chinworrungsee et al., 2004).

8'-O-Demethylnigerone (93) and 8'-O-Demethylisonigerone (94) (Fig. 7), dimericnaptho-gamma-pyrones, were isolated from strain WZ-4-11 of *Aspergillus carbonarius*. Compounds (93) and (94) have weak activities against *M. tuberculosis* H37Rv (MICs of 43.0 and 21.5 µM, respectively) (Zhang et al., 2008).

Cordyol A (95) (Fig. 7), was isolated from *Cordyceps* sp. BCC 1861 of *Homoptera cicada* nymph of the KhaoLaem National Park, Kanchanaburi Province, Thailand. Cordyol A has weak anti-mycobacterial activity with MIC 100 µg/mL (Bunyapaiboonsri et al., 2007).

A novel cyclodepsipeptide, Cordycommunin (96) (Fig. 7), isolated from the insect pathogenic fungus *Ophiocordyceps communis* BCC 16475 inhibits *M. tuberculosis* H37Ra, MIC 15 µM. This compound has weak cytotoxic effect on KB cell line with an IC₅₀ of 45 µM but inactive against BC, NCI-H187 and Vero cell lines at 88 µM (50 µg/mL) (Haritakun et al., 2010).

Ophiobolin K (97), 6-epi-ophiobolin K (98) and 6-epi-ophiobolin G (99) (Fig. 7), were isolated from the marine-derived fungus *Emerecilla variecolor*. Ophiobolins (97–99) inhibited biofilm formation of *M. smegmatis* at MICs of 4.1–65 mM, whereas these compounds do not show anti-microbial activity at the concentrations that show anti-biofilm formation. Ophiobolin K (97) is
Figure 7. Structures of antimycobacterial metabolites isolated from Ascomycetes (93-100).

also effective against the biofilm formation of M. bovis BCG and is thus able to restore the anti-microbial activity of isoniazid against M. smegmatis (Arai et al., 2013).

The Bicyclo[3.3.1]nona-2,6-diene derivative, Rugulosone (100) (Fig. 7), was isolated from Emericella rugulosa. It showed anti-malarial and antimycobacterial activities, as well as cytotoxicity against three cancer cell lines (Moosophon et al., 2009).
Hopan-27-al-6β,11α,22-triol (101), Hopane-6β,11r,22,27-tetraol (102), Hopane-6β,7β,22-triol (103), Compound (104) (atropisomer of ES-242-2) and Compound (105) (Fig. 8), were isolated from the scale insect pathogenic fungus Conoideocrella tenuis BCC 18627. Compounds (101–105) are active against M. tuberculosis H37Ra, MIC of > 105, 52, > 107, > 75, > 75 µM/ml, respectively. The MIC values of standard anti-TB drug Isoniazid were 0.17–0.34 µM (Isaka et al., 2011).

Figure 8. Structures of antitubercular metabolites isolated from Ascomycetes (101-105) and Basidiomycetes (106-111).
From Basidiomycetes

4,4’-dimethoxyvulpinic acid (106) (Fig. 8), was isolated from the Thai mushroom Scleroderma citrinum. In addition, the dibromo derivative of (106) 3,3’-dibromo-4,4’-dimethoxyvulpinic acid (107) and the acetate derivative acetyl 4,4’-dimethoxyvulpinate (108) were also prepared. All the compounds are active against M. tuberculosis H37Ra with MICs 25, 100 and 100 µg/ml, respectively (Kanokmedhakul et al., 2003).

3-Epi-astrahygrol (109), Astrahygrone (110) and 3-epi-astrapteridiol (111) (Fig. 8), were isolated from, the truffle-mimicking mushroom, Astraeus pteridis. Compounds (111) (109) and (110) showed moderate activity against M. tuberculosis with MIC values of 34.0, 58.0, and 64.0 µg/mL, respectively (Stanikunaite et al., 2008).

Lanostanetriterpenes, Astraodoric acids A (112) and B (113) (Fig. 9), were isolated from, an edible mushroom, Astraeus odoratus. Compounds (112) and (113) exhibited moderate activities against M. tuberculosis H₃₇Ra (MICs of 50 and 25 µg/mL) and cytotoxic activities (IC₅₀) values of 34.69 and 18.57 µg/mL against KB cancer cells lines and 19.99 and 48.35 µg/mL against NCI-H187 cancer cells lines, respectively (Arpha et al., 2012).

A new bisphenol-sesquiterpene, Ramiferin (114) (Fig. 9), isolated from the fungus Kionochaeta ramifera BCC 7585 has anti-tubercular activity, MIC 12.7 µM. It is toxic against three cancer cell lines (BC, KB and NCI-H187) and nonmalignant Vero cells with IC₅₀ values of 9.1, 12.6, 13.0, and 9.7 µM, respectively (Bunyapaiboonsri et al., 2008).

Ramariolides A (115) (Fig. 9), a Butenolides was isolated from the fruiting bodies of a coral mushroom Ramaria cystidiophora. Ramariolide A has an unusual spirooxiranebutenolide moiety and shows in vitro activity against M. smegmatis and M. tuberculosis (Centko et al., 2012).

Gliotoxin (116), and S,S dimethyl gliotoxin (117) (Fig. 9), isolated from Mycena sp. (F205435) inhibited the mycobacterial detoxification enzyme mycothiol-S-conjugate amidase (MAC) of M. tuberculosis with IC₅₀ of 50 and 70 µM. Both compounds inhibited MAC of M. smegmatis with IC₅₀ value of 50 µM each (Nicholas et al., 2003).

Ganoderic acid T (118), and the C-3 epimer of Ganoderic acid T (119) (Fig. 9), were isolated from Ganoderma orbiforme BCC 22324. Compounds (118-119), are active against M. tuberculosis H37Ra with MICs of 10.0 and 1.3 µM, respectively (Isaka et al., 2013).

From Unidentified Fungus

9α-hydroxyhalorosellinia A (120) (Fig. 9), was isolated from an endophytic fungus PSU-N24 from Garcinia nigrolineata, collected from the Ton Nga Chang wildlife sanctuary, Songkhla province, Southern Thailand. It is active against M. tuberculosis, MIC 12.50 µg/ml (Sommart et al., 2008).
Figure 9. Structures of antimycobacterial metabolites isolated from Basidiomycetes (107-119), Unidentified fungus (120-122) and Zygomycetes (123).

Agonodepside A (121) and B (122) (Fig. 9), were isolated from a non-sporulating filamentous fungus, F7524. They inhibited the mycobacterial InhA enzyme, a 2-trans-enoyl-acyl-reductase involved in Mycolic acid biosynthesis, which is a major lipid of the mycobacterial envelope.
Agonodepside A had moderate activity, with an IC₅₀ of 75 µM, while Agonodepside B is not active at 100 µM (Cao et al., 2002).

**From Zygomycetes**

Calpinactam (123) (Fig. 9) was isolated from Mortierella alpina FKI-4905. Calpinactam inhibits *M. smegmatis* and *M. tuberculosis* with MIC values of 0.78 and 12.5 µg/ml, respectively (Koyama et al., 2010).

**Volatile Organic Compounds (VOCs) as Antimycobacterials**

A stain of *Muscodor* namely, *Muscodor crispans* of *Ananas ananassoides* (wild pineapple) growing in the Bolivian Amazon Basin produces VOCs namely, Propanoic acid, 2-methyl-, 1-butanol, 3-methyl-1-butanol, 3-methyl-, acetate propanoic acid, 2-methyl-, 2-methylbutyl ester, and ethanol. The VOCs of this fungus are effective against *Xanthomonas axonopodis* pv. *citri*, a citrus pathogen and also on several human pathogens, including *Yersinia pestis*, *M. tuberculosis* and *Staphylococcus aureus*. *Muscodor crispans* is only effective against the vegetative cells of *Bacillus anthracis* and not against its spores. Artificial mixtures of the fungal VOCs were both inhibitory and lethal to a number of human and plant pathogens, including three drug-resistant strains of *M. tuberculosis* (Mitchell et al., 2010). The mechanism of action of the VOCs of *Muscodor* spp. on target bacteria is unknown. A microarray study of the transcriptional response analysis of *B. subtilis* cells exposed to *M. albus* VOCs show that the expression of genes involved in DNA repair and replication increased, suggesting that VOCs induce some type of DNA damage in cells, possibly through the effect of one of their naphthalene derivatives (Mitchell et al., 2010).

**Outlook /Conclusion/Suggestions**

In the poorer countries of the world and particularly those of the Asian Subcontinent, *M. tuberculosis* remains a persistent problem with very few solutions in sight. This is of course due to the extreme poverty of the populations in such third world countries. Typically Nepal, Tibet, North Eastern India (such as Assam), where communications are very weak both due to the inaccessibility of many of the remote area and language problem. The extreme poverty leads to very poor nutrition. Inadequate medical facilities, some time totally missing in many parts of North India, Nepal and Tibet exits even today. Distribution of effective of effective medicine is a huge and difficult task. Affordable medicine? Follow up? There is no light of the end of this tunnel of disease!! Unless there is a ‘United Front To Combat Tuberculosis’ worldwide This front must be supported by a world with consortium of countries such as UN WHO plus the other advanced countries of the world!!
Will it happen? The mindset of the nations of the world should change from “what can we suggest” to a “what can we do” to solve such great a problem!

Do!

Consider the use of complex mixture of Ayurvedic and allopathic compounds, already been used. Variations in regimens of treatment may also be the part such new initiatives.

References


Fungi: Applications and Management Strategies


Antimycobacterials from Fungi


