# Plants: A Source for New Antimycobacterial Drugs

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Key words

- alkaloids
- flavonoids
- chalcones
- coumarins
- lignans
- phenols
- terpeneschromones
- alkane
- alkene
- plants

Solution Mycobacterium tuberculosis

 received
 June 7, 2013

 revised
 August 12, 2013

 accepted
 Sept. 23, 2013

# Bibliography

DOI http://dx.doi.org/ 10.1055/s-0033-1350978 Published online November 11, 2013 Planta Med 2014; 80: 9–21 © Georg Thieme Verlag KG Stuttgart - New York -ISSN 0032-0943

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## Abstract

Tuberculosis, also called TB, is currently a major health hazard due to multidrug-resistant forms of bacilli. Global efforts are underway to eradicate TB using new drugs with new modes of action, higher activity, and fewer side effects in combination with vaccines. For this reason, unexplored new sources and previously explored sources were examined and around 353 antimycobacterial compounds (Nat Prod Rep 2007; 24: 278–297) [7] have been previously reported. To develop drugs from these new sources, additional work is required for preclinical and clinical results. Since ancient times, different plant part extracts have been used as traditional medicines against diseases including tuberculosis. This knowledge may be useful in developing future powerful drugs. Plant natural products are again becoming important in this regard. In this review, we report 127 antimycobacterial compounds and their antimycobacterial activities. Of these, 27 compounds had a minimum inhibitory concentration of < 10 µg/mL. In some cases, the mechanism of activity has been determined. We hope that some of these compounds may eventually develop into effective new drugs against tuberculosis.

# Introduction

Mycobacterium tuberculosis spreads through aerosols and causes pulmonary and extrapulmonary tuberculosis where it infects human lungs and other body parts, respectively. In infected body parts, bacilli remain dormant for a longer period and get reactivated in immunosuppressed conditions. According to World Health Organization (WHO), in 2011 alone, an estimated 1.4 million mortalities were reported due to TB. A potent antitubercular drug rifampicin (RMP), which was introduced fifty years ago, is being used for treatment in combination with isoniazid (INH), ethambutol (EMB), and pyrazinamide (PZA) as a multidrug regimen for a period of six months. Spontaneous mutations accumulated in the genome due to poor patient compliance to this long treatment schedule led to the development of multidrug-resistant (MDR) and extremely drugresistant (XDR) forms of bacilli in patients [1]. TB caused by MDR/XDR is very difficult to control as it takes a long time to cure and by this time it again spreads to other individuals. Recently, a new drug, bedaquiline (Sirturo<sup>®</sup>, FDA), and a second new vaccine, MVA85-A, were introduced

against MDR forms. According to the WHO, it is estimated that by 2050, drugs and vaccines in various phases of clinical trials would help to eradicate TB. From new sources, by characterising more antimycobacterial compounds in preclinical and clinical trials, the resistant form of bacilli emerging during the eradication programme can also be eliminated.

Various natural compounds like alkaloids, flavonoids, terpenoids, etc., present in balanced diets orchestrate like a multidrug regimen and can maintain a healthy population. Identification of natural products with an antimycobacterial effect and the further development of drugs [2] is difficult as it requires expensive, sophisticated facilities and animal models. Combinatorial chemistry is mainly followed to develop new drug molecules. But among the millions of compounds generating, only very few show biological activity and many do not have true drug qualities. Natural products from microbes and plants have various biological activities and properties of a drug. Aspirin and penicillin are famous natural products commercialised as drugs from willow bark and Penicillium notatum, respectively. Natural products are widely exploited in pharmaceutical in-



Fig. 1 Alkaloids.

dustries as a valuable source for lead drugs. Presently, in combinatorial chemistry, the compounds with a structural base similar to that of natural products are only considered [3] because natural products are sterically complex and interact with respective molecular targets three-dimensionally with more specificity. Even though many scaffolds from natural product databases are not found in trade drugs. The unexploited scaffolds of natural products would be a promising starting point in future drug discovery [4]. Among recently explored sources, compounds from marine sponge-associated microbes have been exploited for new drugs [5]. But still, plants having more biodiversity remains as a main source of natural products because of an abundant metabolite content and common pathways which can be easily manipulated. Plants are aesthetic and can be easily cultivated because of their cosmopolitan nature.

Plant extracts having terpenes, steroids, alkaloids, flavonoids, chalcones, coumarines, lignans, phenols, polyketides, alkanes, alkenes, alkynes, simple aromatics, and peptides have been used in

the treatment of different human diseases [6,7] around the globe, including tuberculosis. From plant extracts, antimycobacterial compounds with a mechanism of activity have been reported. This review reports various groups of compounds having antimy-cobacterial activity with their sources, structure, and *in vitro* activity with the available mechanism of action. In **• Table 1**, the activity values of compounds effective against both sensitive and resistant forms of *M. tuberculosis* are described.

### Alkaloids

Alkaloids (20–25%), which mainly protect plants from the aggression of animals, include a few members with antimycobacterial activity (**• Fig. 1**). *Adhatoda vasica* Ness., Acanthaceae, which is used in the treatment of colds, cough, and other respiratory disorders, contains antimicrobial compounds. Alkaloids present in the hexane extract like vasicine acetate (**1**) and 2-acetyl ben-

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| esistant forms of <i>M. tu</i> |                        |
| gainst sensitive and r         | nt forms, respectively |
| ctivity values tested a        | sensitive and resistar |
| of compounds with ac           | ld letters are against |
| Table 1 List o                 | regular and bo         |

| Alkaloids   | Flavonoids   | Chalcones and quinones   | Coumarins, lignans, and phenols  | Chromones, fatty acids,<br>and terpenoids  | Alkanes, alkenes, alkynes,<br>aromatics, and miscellaneous  |
|---|--|--|--|--|---|
| 2-acetyl benzylamine and<br>vasicine acetate (50 μg/mL)<br><b>(200 μg/mL)</b> [8]   | cryptocaryone<br>(25µg/mL) [18]  | (E)-2',4'-dihydroxychalcone<br>(195.3 µM) [21]   | dihydroguaiaretic acid<br>(50 µg/mL)<br><b>(12.5-50 µg/mL) [</b> 28]   | pisonin B<br>(25 µg/mL) [32]   | falcarindiol<br>(26.7 µg/mL) [65]   |
| 2'- nortiliacorinine and tiliacorine<br>(3.1 µg/mL)<br><b>(3.1 µg/mL) [</b> 12]   | pinocembrin<br>(3.5 µg/mL) [18]  | (£)-3,2',4'-trihydroxy-3'-methoxy-<br>chalcone<br>(174.8,µM) [21]  | 4 <i>-ep</i> i-larreatricin<br>(50 μg/mL)<br><b>(25 μg/mL)</b> [28]  | 1,3-benzenediol<br>(200 µg/mL)<br><b>(100–200 µg/mL)</b> [46]  | 9Z,17-octadiene-12,14-diyne-<br>1,11,16-triol,1-acetate<br>(25.3 µg/mL) [65]  |
| Tiliacorinine<br>(3.1–6.2 µg/mL)<br><b>(1.5–6.2 µg/mL)</b> [12]   | isobachalcone<br>(2.44–19.53 µg/mt) [19]   | 2',4',6'-trihydroxy-3'-prenylchalcone<br>and 4',6',5''-trihydroxy-6'',6''-<br>dimethyldihydropyrano[2'',3''-2',3']<br>chalcone<br>(50 µq/ml)[33] | licarin A<br>(25 µg/ml)<br><b>(3.12–12.5 µg/ml)</b> [42]   | linoleic acid and oleic acid<br>(100 µg/mL) [46]<br><b>(100 µg/mL)</b> [46]  | 1,3 dimethoxy-2-methyl-5-pentyl ben-<br>zene<br>(≤ 2.5 μg/ml) [66]  |
| 13'-bromo-tiliacorinine<br>(3.1–6.2 µg/mL)<br><b>(1.5–3.1 µg/mL)</b> [12]<br>Mauritine M<br>(IC <sub>50</sub> – 72.8 µM) [13] | kanzanol C, 4-hydroxylonchocar-<br>pin, stipulin, and amentoflavone<br>(9.76 – 39.06 µg/mL) [19]<br>genistein<br>(35 µg/ml) [20] | aminoacetate derivative of diospyrin<br>(> 10 - ≤ 50µg/mL)<br>(> 10 - ≤ 50µg/mL) [34]<br>diospyrin<br>(100µg/mL)                                 | licarin B<br>(50 µg/mL)<br>(12.5–50 µg/mL) [42]<br>eupomatenoid-7<br>(25 µg/mL)  | undecanal<br>(100 µg/mL)<br>(50-200 µg/mL) [46]<br>2,4-undecadienal<br>(25 µg/mL)  | 3-methoxy-2-methyl-5-pentyl phenol<br>(≤ 2.58 µg/mL) [66]<br>mono-O-methylcurcumin isoxazole<br>(0.09 µg/mL)                |
| Nummularine H<br>(IC <sub>50</sub> – 4.5 µM) [13]   | (25)- naringenin<br>(< 2.8 μg/mL) [20]<br>prunetin<br>(30 μg/mL) [20]  | <b>( 'uu µg/mu,</b>   34 <br>shinanolone<br>(100 µg/ml) [36]<br>7-methyljuglone<br>(0.5 µg/ml) [37]  | (2.5 µg/mL) [42]<br>beilschmin A<br>(2.5 µg/mL) [43]<br>beilschmin B<br>(7.5 µg/mL) [43]   | <ul> <li>(ab) [day] [day]</li> <li>(ab) [day] [day]</li> <li>(ab) [day]</li> <li>(ab) [day]</li> <li>(ab) [day]</li> <li>(b) [day]</li> <li>(b) [day]</li> <li>(b) [day]</li> <li>(b) [day]</li> <li>(b) [day]</li> <li>(b) [day]</li> </ul> | (v ol <b>Luz) -s с. радпи</b> )<br>5,6-dehydro-7,8-dihydromethysticin<br>(4 µg/ml) [68]<br>piperolactam A<br>(8 µg/ml) [68] |
|   | (25)-5,7,2'-trihydroxy flavonone<br>(367.6 µМ) [21]  | isodiospyrol A<br>(50 µg/mL) [39]  | <ul> <li>(E)-1-[2,4-dihydroxy-3-(3-methyl-<br/>but-2-enyl)phenyl]-3-(2,2-dimethyl-<br/>8-hydroxy-2H-benzopyran-6-yl)<br/>prop-2-en-1-one</li> <li>(30 µg/ml) [45]</li> </ul> | cordiachrome C<br>(1.5 µg/ml) [52]   | aromatic alkene, and pyrrolidine amide<br>(25µg/mL) [69]  |
|   | 5,4'-dihydroxy-3,7,8,3'-tetrame-<br>thoxy flavones<br>(> 50 µg/mL) [28]  | раІтагитусіп JC2<br>(6.25 µg/mt) [39]  | lsobavachalcone<br>(18µg/ml) [45]  | globiferin<br>(6.2 µg/mL) [52]   | tetrahydroxy squalene<br>(10 µg/mL)<br>[70]   |
|   | 5,4'-dihydroxy-3,7,8-trimethoxy-<br>flavone<br>(> 50 µg/mL)<br><b>(25-50 µg/mL)</b> [28]   | a-tocopheryl quinone<br>(25 µg/mL) [40]  | scopoletin<br>(42 µg/ml) [45]  | diol derivative of labdane<br>(250 µg/mt) [53]   | <i>trans,trans</i> -1,7,diphenylhepta-4,6-di-<br>en-3-one<br>(> 128 µg/mL) [71]   |
|   | nevadensin and isothymusin<br>(200 µg/mL) [29]   |  | 2',5''-dimethoxysesamin<br>(63 µg/ml) [47]   | dioxime derivative of lab-<br>dane and labdane<br>(500 µg/mL) [53]   | xanthones<br>(10 µg/mt) [72]  |
|   | pisonivanone<br>(12.5 µg/mL) [32]  |  | ethoxycubebin<br>(62.4 µM) [49]  | caniojane<br>(25 µg/mL) [54]   | continued   |

|                  | Alkanes, alkenes, alkynes,      | aromatics, and miscellaneous |                        |             |                    |             |              |                   |                                     |                     |                 |                              |                     |                      |                 |                |                 |               |                        |                |                |                |                      |                    |                      |        |                  |  |
|------------------|---------------------------------|------------------------------|------------------------|-------------|--------------------|-------------|--------------|-------------------|-------------------------------------|---------------------|-----------------|------------------------------|---------------------|----------------------|-----------------|----------------|-----------------|---------------|------------------------|----------------|----------------|----------------|----------------------|--------------------|----------------------|--------|------------------|--|
|                  | Chromones, fatty acids,         | and terpenoids               | trachybalone diterpine | derivatives | (24–61 µg/mL) [55] | leubethanol | (12.5 µg/mL) | (6.25 µg/mL) [56] | 24,24-dimethyl-5 $\beta$ -tirucall- | 9(11),25-dien-3-one | (64 µg/mL) [57] | abietane and its derivatives | (3.12 – > 25 μg/mL) | (0.39–25 µg/mL) [58] | bonianic acid A | (34.8 µM) [59] | bonianic acid B | (9.9 μM) [59] | 3-O-acetyluncaric acid | (75.5 µM) [59] | oleanolic acid | (50–100 µg/mL) | (100–200 µg/mL) [62] | phytol derivatives | (15.6–50 µg/mL) [64] | phytol | (100 µg/mL) [64] |  |
|                  | Coumarins, lignans, and phenols |                              |                        |             |                    |             |              |                   |                                     |                     |                 |                              |                     |                      |                 |                |                 |               |                        |                |                |                |                      |                    |                      |        |                  |  |
|                  | Chalcones and quinones          |                              |                        |             |                    |             |              |                   |                                     |                     |                 |                              |                     |                      |                 |                |                 |               |                        |                |                |                |                      |                    |                      |        |                  |  |
|                  | Flavonoids                      |                              |                        |             |                    |             |              |                   |                                     |                     |                 |                              |                     |                      |                 |                |                 |               |                        |                |                |                |                      |                    |                      |        |                  |  |
| able 1 Continued | Alkaloids                       |                              |                        |             |                    |             |              |                   |                                     |                     |                 |                              |                     |                      |                 |                |                 |               |                        |                |                |                |                      |                    |                      |        |                  |  |

zylamine (2) inhibited both the sensitive and MDR strains of *M. tuberculosis* at minimum inhibitory concentrations (MIC) of 50 and 200 µg/mL, respectively [8]. Justicia adhatoda L., Acanthaceae, is known as vasaka in the Indian system of medicine. Its leaves, flowers, fruits, and roots are used against colds, cough, whooping cough, asthma, and bronchitis because of their sedative, expectorant, antispasmodic, and antihelminthic activity. In 2012, Jha et al. reported six guinazoline alkaloids (3-8) from the above plant having significant antimycobacterial activity, and in silico analysis confirmed that these alkaloids inhibit β-ketoacylacyl-carrier protein synthase III (FabH), an enzyme involved in the initial step of fatty acid biosynthesis, leading to poor cell wall development and survival of bacilli [9]. To develop drug resistance, the efflux pump (EP) in the bacteria release compounds preventing them from reaching their respective targets inside the cell. Piperine (9; Cat. no. P49007, SIGMA), a trans-trans isomer of 1-piperonyl-piperidine, is an antimycobacterial agent which at 128 µg/mL completely inhibits the efflux pump of *M. smegmatis*  $mc^2$  155. The compound (9) is commonly found in plants belonging to the family Piperaceae (Piper nigrum L., Piperaceae). Piperine has synergistic activity; hence, it reduces the MIC of ethidium bromide (EtBr) by 2- to 4-fold at subinhibitory concentrations of 32 and 64 µg/mL, respectively. Compound 9 also inhibits Rv1258c, a putative multidrug EP of M. tuberculosis [10]. The root extract of Tabernaemontana elegans Stapf., Apocynaceae, has an MIC of around 128-256 µg/mL against Mycobacterium sp. due to the presence of indole alkaloids [voacangine (10) and dregamine (11) [11]. Tiliacora triandra (Colebr.) Diels., Menispermaceae, an ingredient in Thai cuisine, has bisbenzylisoquinoline alkaloids such as tiliacorinine (12), 2'-nortiliacorinine (13), and tiliacorine (14) with activity comparable to INH, RMP, and EMB against sensitive (MIC 3.1-6.2 µg/mL) and resistant forms (MIC 3.1 µg/mL) of M. tuberculosis. The brominated derivative 13'-bromo-tiliacorinine (15) showed better antimycobacterial activity than 12 (MIC of 1.5-3.1 µg/mL) with less cytotoxicity while testing against MRC-5 cell lines (human foetal lung fibroblast cell line), and the possible mechanism of action in mycobacterium was proposed as the cause of inhibition of RNA and protein synthesis [12]. Ziziphus mauritiana Lam., Rhamnaceae, a medium-sized tree in Thailand and Asian countries, which has been used traditionally in the treatment of diarrhoea and ulcers, was reported to be rich in antimycobacterial cyclopeptide alkaloids. Upon further analysis of the plant root from the methanolic extract using nuclear magnetic resonance spectroscopy (NMR), two cyclic alkaloids and three cyclopeptide alkaloids were identified. The sensitive strain of *M. tuberculosis* was inhibited by a cyclic alkaloid, mauritine M (16; moderatively active), and a cyclopeptide alkaloid, nummularine H (17; active) [13].

### Flavonoids

V

Phenolic compounds conferring colour to plant parts having a flavane nucleus exhibit antimicrobial activity. Few plant extracts contain a high amount of antimycobacterial flavonoids and most of them belong to the classes of flavones and flavonones (**•** Fig. 2). Lin et al. tested a series of flavonoids for antimycobacterial activity [14]. *Argyreia speciosa* (Burm.f) Boj., Convolvulaceae, found in the Indian subcontinent and referred to as *vrudhadaruka* in Sanskrit, has been used in the Ayurvedic system of medicine against pulmonary tuberculosis. In 2009, Habbu et al. reported the antimicrobial activity of the ethyl acetate extract of

this plant (MIC 50 µg/mL) due to flavonoids. Flavonoid sulphates, quercetin 3'7 di-O methyl 3-sulphate and kaempferol 7-O methyl 3-sulphate, were reported with an MIC of 25 µg/mL, which is also synergistic with the usual antimycobacterial agents. Crude as well as purified compounds are less cytotoxic while comparing the hemolysis of RBC using chloramphenicol as a positive control [15]. The extract of Bromelia balansae Mez., Bromeliaceae, from the central region of Brazil has been used as a syrup against coughs and other bronchial infections. The methanolic extract showed moderate activity with an MIC of 128 µg/mL, and in chromatographic and spectrophotometric analyses, various flavonoid glycosides were identified such as kaempferol-3-O- $\alpha$ -Lrhamnopyranoside (18), kaempferol-3-O- $\alpha$ -L-rhamnopyranosyl- $(1 \rightarrow 6)$ - $\beta$ -D-glucopyranoside (**19**), quercetin-3-O- $\alpha$ -L-rhamnopyranosyl- $(1 \rightarrow 6)$ - $\beta$ -D-glucopyranoside (**20**), and kaempferol 3,7-di-O-α-L-rhamnopyranoside (21) [16]. 5,4'-Dihydroxy-6,7,8,3',5'-pentamethoxyflavone (22) and 5,4'-dihydroxy-6,7,8,3'-tetramethoxyflavone (23), isolated from Cleome droserifolia (Forssk.) Del., Capparaceae, suppress nitric oxide production and reduce oxidative stress in activated macrophages [17]. Two new flavonones, pinocembrin (24) and cryptocaryone (25), from the leaves of Cryptocarya chinensis Hemsl., Lauraceae, were effective against M. tuberculosis H37Rv. Among the two compounds, 24 was more active than EMB (MIC 6.25 µg/mL) and the latter was found to be moderatively active [18]. Dorstenia barteri Bureau., Moraceae, a small herb from most regions of tropical South America, contains active phytochemicals against bacteria and fungi. The dichloromethane: methanol (1:1) extract of it contains isobachalcone (26), kanzanol C (27), 4-hydroxylonchocarpin (28), stipulin (29), and amentoflavone (30). When comparing compounds from 27 to 30, isobachalcone was more active against M. smegmatis and M. tuberculosis [19]. Similarly, while purifying secondary metabolites from Ficus nervosa Roth., Moraceae, genistein (31), prunetin (32), and (2S)-naringenin (33) were obtained having MICs of 35, 30, and  $\leq 2.8 \,\mu\text{g/mL}$ , respectively [20]. The extracts of Galenia africana L., Aizoaceae, have been used as a medicine against asthma, coughs, wounds, eye infections, TB, and skin diseases in many places in Africa among which the ethanolic extract was very effective against M. tuberculosis (MIC 780 µg/mL) and M. smegmatis (MIC 1200 µg/mL). The extract contains (2S)-5,7,2'-trihydroxyflavonone (34), which was moderatively active against M. tuberculosis and was also found to be synergistic bringing down the MIC of INH by 16-fold [21]. Two biflavonoids, amentoflavone (30; MIC 600 µg/mL) and 4' monomethoxy amentoflavone (35; MIC 1400 µg/mL), from Garcinia livingstonei T. Anderson., Clusiaceae, were active against M. smegmatis [22]. Globularia alypum L., Globulariaceae, used in North African folk medicine, is rich in phenols. A study by Khlifi et al. in 2011 shows that the methanolic and petroleum ether (PE) extracts of G. alypum leaves contains polyphenols, tannins, anthocyanins, and flavonoids [0.31–19.8 g quercitin (36) equivalent/kg of dry mass] and PE is particularly active against M. tuberculosis ( $IC_{50}$ ) 77 µg/mL) [23]. Lantana camara L., Verbenaceae, contains two new flavonoids, linaroside (37) and lantanoside (38), which cause 30–37% inhibition of mycobacterial growth at 6.25 µg/mL, which is the MIC of EMB, whereas its common acetylated derivative (39) causes 98% inhibition [24]. Among fatty acid synthase systems I and II (FAS I and II), the latter is a prospective antibacterial drug target. The fourth step of the fatty acid elongation cycle is carried out by an enoyl-acyl carrier protein reductase (InhA in *M. tuberculosis*) which catalyses an NADH-dependent reduction of the trans-2-enoyl fatty acyl chain to the saturated



fatty acyl chain. In 2008, Sharma et al. reported that epigallocatechin gallate/epigallocatechin-3-gallate (40) directly inhibits the above-mentioned enzyme (IC<sub>50</sub> 17.4  $\mu$ M) by interacting with the residues near the NADH binding site. Compound 40 also acts synergestic with triclosan, a common additive of household products known to target InhA of bacterium and plasmodium [25]. Fisetin (41), from Cotinus coggygria syn Rhus continus Scop., Anacardiaceae, is an inhibitor of an unknown mycobacterial dehydratase (Rv0636) at MIC 63 µg/mL and is involved in mycolic acid synthesis [26]. Tryptophan aspartate containing coat protein (TACO) in macrophages prevents phagosome-lysosome fusion. A major green tea polyphenol (40) downregulates TACO expression by inhibiting the Sp1 transcription factor, thereby favouring phagososome-lysosme fusion to remove bacilli. But epicatechin (42), another tea polyphenol, had no effect [27]. In Mexico, Larrea tridentata Coville., Zygophyllaceae, has been used as a traditional medicine against respiratory infections and tuberculosis, and its antimycobacterial activity was confirmed using the chloroform extract. In 2012, Favela-Hernández et al. reported 5,4'-dihy-

droxy-3,7,8,3'-tetramethoxyflavone (43) and 5,4'-dihydroxy-3,7,8-trimethoxyflavone (44) from this plant as having activity against both sensitive and MDR forms with MICs of 25 and 25-50 µg/mL, respectively [28]. Limnophila geoffrayi Bon., Scrophulariaceae, a common ingredient in northeastern Thailand curry, is an antipyretic, expectorant, and a lactogogue. The antimycobacterial compounds nevadensin (45) and isothymusin (46) were reported from the chloroform extract of the above plant through bioassay-guided fractionation and the compounds were safe to use as evidenced from a mutagenic assay [29]. Pelargonium reniforme Spreng., Geraniaceae, of Africa is being used in the treatment of various ear, nose, and throat infections, and the main constituent of the tuberculosis remedy in the extract is known as "Umckaloabo". Myricetin (47) and quercitin-3-O- $\beta$ -D-glucoside (48) are present in the extract kill M. tuberculosis and previously it was used to reduce the intracellular survival of Leishmania donovani in macrophages [30]. A natural plant isoflavone, biochanin A (49; Catno.D2016, Fluka, SIGMA-Aldrich), inhibits EP of M. smegmatis at 256 µg/mL [31]. Pisonivanone (50), having an



MIC close to EMB, was purified from the root of *Pisonia aculeata* L., Nyctaginaceae. It is distributed in parts of the Asian subcontinent and the leaves, which are rich in phytochemicals, are used in the antitubercular screening programme [32].

# Chalcones

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Few chalcones are reported to possess antimycobacterial activity (**• Fig. 3**). *G. africana* L., Aizoaceae, an ethanolic extract containing (*E*)-2',4'-dihydroxychalcone (**51**) with moderate antimycobacterial activity, and (*E*)-3,2',4'-trihydroxy-3'-methoxychalcone (**52**) with synergistic activity, reduced the MIC of INH by fourfolds [21]. *Helichrysum melanacme* DC., Asteraceae, acetone extract contains two antimycobacterial compounds, 2',4',6'-trihydroxy-3'-prenylchalcone (**53**) and 4',6',5''-trihydroxy-6'',6''-dimethyldihydropyrano[2'',3''-2',3'] chalcone (**54**) [33]. Butein (**55**) from *Rhus verniciflua* Stokes., Anacardiaceae, and isoliquirtigenin (**56**) and 2,2',4'-trihydroxychalcone (**57**) from *Dalbergia odorifera* T.C. Chen., Leguminosae, can inhibit mycolic acid biosynthesis with MICs of 43, 50, and 55 µg/mL, respectively [26].

#### Quinones

#### ▼

Diospyrin (**58**), a bisnaphthoquinonoid, is an antimycobacterial agent against both sensitive and MDR which is present in South African *Euclea natalensis* A. DC., Ebenaceae [34] and *Diospyros montana* Roxb., Ebenaceae of India, which was traditionally used for the treatment of Ehrlich ascites carcinoma [35]. Studies showed an aminoacetate derivative (**59**) had better activity than the parent compound (**58**) [34]. The root bark of *E. natalensis* used against bronchial infections by the Zulu (an ethinic group

of South Africa) was extracted with ethanol that contains shinanalone (60), having an MIC of 100 µg/mL [36]. 7-Methyljuglone (61), which is a napthoquinone isolated from the root extracts of E. natalensis and its derivatives, shows antimycobacterial activity by inhibiting mycothiol disulphide reductase [37]. Compound 61 and RMP act synergistically against intracellular M. tuberculosis and reduce the MIC of both by fourfold. The fractional inhibitory concentration (FIC) 0.5 suggests only a borderline synergistic effect. The combination of 61 with INH reduced the MIC by sixfold and the FIC value of 0.24 indicates a significant interaction [38]. Palmarumycin JC2 (62) and isodiospyrol A (63) were isolated from Diospyros ehretioides Wall. Ex G. Don., Ebenaceae [39]. In the leaves of a deciduous tree, Pourthiaea lucida Decne., Rosaceae, which is found at low altitudes in Taiwan, contains  $\alpha$ -tocopheryl quinone (64) which has activity against M. tuberculosis [40]. Antimycobacterial quinone compounds with its structure is shown in • Fig. 4.

# **Coumarins, Lignans, and Phenols**

Few members of the coumarins, lignans, and phenols have an antimycobacterial property (**Fig. 5**). The extract of *Symplocus*, having a high amount of lignans, phenols, terpenoids, flavonoids, and steroids, has been used in the treatment of leprosy [41]. *Aristolochia taliscana* Hook. & Arn., Aristolochiaceae, was used as a traditional drug in Mexico against coughs and respiratory infections. The hexane extract contains antimycobacterial licarin A (**65**) and B (**66**) and eupomatenoid-7 (**67**). Of these, **65** was the most active compound against MDR forms of *M. tuberculosis* and non-tuberculosis mycobacteria (*M. smegmatis, M. fortuitum, M. chelonae*, and *M. avium*) [42]. Epoxyfuranoid lignans beilschmin A (**68**) and B (**69**), from *Beilschmiedia tsangii* Merr., Lauraceae



of southern Taiwan, were better than EMB when comparing the activity values [43]. Pangelin (**70**), isolated from *Ducrosia anethifolia* (DC.) Boiss., Apiaceae, has activity against *M. fortuitum*, *M. aurum*, *M. phlei*, and *M. smegmatis* (MIC 64–128 µg/mL) [44]. Amongst several formosan plants screened for antimycobacterial activity, *Fatoua pilosa* Gaud., Moraceae, contains more bioactive molecules. The fraction analysed for a bioassay contains new coumarin analogues such as scopoletin (**71**), isobavachalcone (**72**), and (*E*)-1-[2,4-dihydroxy-3-(3-methylbut-2-enyl)phenyl]-3-(2, 2-dimethyl-8-hydroxy-2*H*-benzopyran-6-yl)prop-2-en-1-one

(73), and has moderate antimycobacterial activity with an MIC < 50 µg/mL and among that 72 had the highest activity value (17.6 µg/mL) [45]. 5-Hydroxyfuranocoumarin, known as bergaptol (74), has previously been reported as an antimycobacterial agent isolated from Foeniculum vulgare Mill., Apiaceae. The hexane extract of the plant showed antimycobacterial activity against both sensitive and MDR forms of M. tuberculosis at a concentration of 100–200 µg/mL [46]. The lignans dihydroguaiaretic acid (75) and 4-epi-larreatricin (76) were extracted from L. tridentata Coville., Zygophyllaceae, where **75** and **76** showed activity against both sensitive and MDR forms, with 75 being the most active against MDR forms [28]. A furolignan, 2',5"-dimethoxysesamin (77) obtained from the root bark of Leucophyllum frutescens I.M. Johnst., Scrophulariaceae, exhibited moderate activity against *M. tuberculosis* and was also less cytotoxic when testing with Vero cell lines [47]. Four new antimycobacterial macrophyllin-type octanoid neolignans, cinerin A–D (78–81), were isolated from the leaves of *Pleurothvrium cinereum* van der. Werff., Lauraceae [48]. Among them, cinerin C (80) showed a half inhibition of mycobacterium at a concentration of 50 µg/mL. The lignan which disrupts mycolic acid biosynthesis, ethoxycubebin (82), was isolated from Virola flexuosa L., Myrstiaceae, with moderate activity (MIC 62.4 µM) and no cytotoxicity [49].

# Terpenoids

Reports show terpenoids, which usually impart scent, flavour, and colour, have antimycobacterial activity (OFig. 6). The sesquiterpene polyesters with a dihydro- $\beta$ -agarofuran skeleton are predominant secondary metabolites in plants belonging to the family Celastraceae. In 2011, Torres-Romero et al. isolated twenty different dihydro- $\beta$  agarofuran sesquiterpene derivatives from Celastrus vulcanicola Donn. Sm., Celastraceae, and among them,  $1\alpha$ -acetoxy-6 $\beta$ ,9 $\beta$ -dibenzoyloxy-dihydro- $\beta$ -agarofuran (83) had an activity value against bacilli comparable to that of INH, RMP, and EMB [50]. Farnesol (84; Cat. no. F203 SIGMA-Aldrich), a C15 isoprenoid natural acyclic sesquiterpene alcohol present in many natural sources, inhibits EP of M. smegmatis mc<sup>2</sup>155 at tested subinhibitory concentrations such as 8, 16, and 32 µg/mL [51]. Plants of the genus Cordia, found in the continents of Africa, Asia, and America, contain potential bioactive molecules. The root extract of Cordia globifera W.W.Sm., Boraginaceae, contains a meroterpene named globiferin (85), but its synthetic derivative cordiachrome C (86) had more potent activity than globiferin [52]. Curcuma amada Roxb., Zingiberaceae, used in Ayurveda and Unani systems of medicine in the Indian subcontinent, is effective against various respiratory disorders. From its chloroform extract, a diterpene dialdehyde, labdane (87), exhibited much less antimycobacterial activity (500 µg/mL), but two semisynthetic analogues, diol (88) and dioxime (89), had MICs of 250 and 500 µg/mL, respectively [53]. From Jatropha integerrima Jacq., Euphorbiaceae, fourteen compounds were isolated. Among them, caniojane (90) showed good activity [54]. Among eleven new trachybalone diterpene derivatives, *ent*-trachylobane-3-one (**91**) and ent-trachylobane-17-al (92) from Jungermannia exsertifolia ssp. cordifolia Steph., Jungermanniaceae, showed moderate activity against M. tuberculosis [55]. Leucophyllum frutescens I.M. Johnst., Scrophulariaceae, contained a new diterpene, leubetha-





nol (93), in a methanolic extract [56]. Pandanus species distributed worldwide are used in folk medicine for the treatment of various diseases including leprosy. The extract of Pandanus tectorius Soland., var. laevis., Pandanaceae, contains compounds of which a triterpene, 24,24-dimethyl-5β-tirucall-9(11),25-dien-3one (94), had activity against a sensitive tubercular strain [57]. Plectranthus species such as Plectranthus barbatus Andrews., Lamiaceae, and Plectranthus bojeri (Benth.) Hedge., Lamiaceae, distributed in tropical and subtropical Africa, are traditionally used in respiratory disorder treatments. Abietane (95) and its derivatives (96-98) isolated from Plectranthus grandidentatus Gurke., Lamiaceae, were reported to have activity against MDR forms, which were better than the usual antimycobacterial agents [58]. A diterpene, kaurenoic acid (99), was isolated from P. cinereum [48]. Three new antimycobacterial triterpenoids from ethyl acetate extracts, bonianic acid A (100) and B (101) and 3-0acetyluncaric acid (102), were isolated from the leaves and twigs of Radermachera boniana Dop., Bigoniaceae [59]. Oleanolic acid (103; Cat. no. O5504, SIGMA) is a commonly found triterpenoid in the human diet and in a few medicinal herbs. The antimycobacterial activity of *Quinchamalium majus* Brongn., Santalaceae [60], *Buddleja saligna* Willd., Buddlejaceae [60], and *Leysera gnaphyloides* L., Asteraceae [61] extracts were mainly due to the presence of **103**. In 2010, Ge et al. reported the synergistic interactions of **103** with commonly used antimycobacterial drugs, while **103** alone showed moderate activity [62]. Deng et al., in 2000, reported that **103** and its derivatives inhibit DNA polymerase  $\beta$ , which is an entirely different mechanism than that of INH, RMP, and EMB, which explains the synergism [63]. A diterpene alcohol such as phytol (**104**) and its modified derivatives (**105–107**) showed very good antimycobacterial activity [64].

## **Fatty Acids and Chromones**

Linoleic acid (**108**), oleic acid (**109**), and other organic compounds such as 1,3-benzenediol (**110**), undecanal (**111**), and 2,4undecadienal (**112**) from the isolates of *Foeniculum vulgare* Mill., Apiaceae, had activity against MDR forms [46]. Chromones, a benzopyran derivative, can be developed as antimycobacterial



drugs. *P. aculeate* L., Nyctaginaceae, a commonly distributed herb in Southeast Asia, has hepatoprotective and antioxidant activity in its leaves. In phytochemical identification, a new chromone, pisonin B (**113**), showed antimycobacterial activity [32] (**• Fig. 7**).

# Alkanes, Alkenes, Alkynes, and Aromatics

Angelica sinensis (Oliv.) Diels., Apiaceae, is a perennial apiaceous herb indigenous to northwest China. The root extract of this plant has been used against many diseases. Polyynes, a triple unsaturated natural product commonly found in seven plant families such as Araliaceae, Asteraceae, Campanulaceae, Santalaceae, Apiaceae, Pittisporaceae, and Oleaceae, exhibits antifungal, antibacterial, and antimycobacterial activities. Compounds like falcarindiol (114) and 9Z,17-octadecadiene-12,14-diyne-1,11,16triol,1-acetate (115) were found to have antimycobacterial activity [65]. Ardisia cornudentata Mez., Myrsiniceae, a small shrub commonly found in Taiwan, is being used to treat various diseases. In an antitubercular screening programme covering a wide range of formosan plants, the methanolic extract of these species exhibited antimycobacterial activity. On further analysis, the extract was found to contain various aromatic compounds and the activities of 3-methoxy-2-methyl-5-pentylphenol (116) and 1,3dimethoxy-2-methyl-5-pentyl benzene (117) were found to be better than EMB [66]. Curcuminoids form the major constituents in the plant Curcuma longa L., Zingiberaceae. The curcuminoid constituents were structurally modified to 55 analogs and the antimycobacterial activity of each compound was evaluated. An isoxazole analog, mono-O-methylcurcumin isoxazole (118), showed potent activity against sensitive and MDR clinical isolates. The activity was 1131-fold more than the parent compound curcumin [67]. Piper sanctum Miq., Piperaceae, is distributed in the central region of Mexico, where it is commonly known as "acuyo", "hierba santa", or "hoja santa". The leaves of this plant were also used as a remedy for bronchitis, tuberculosis, asthma, colds, and also against various other diseases. On analysis of the leaf extract, a series of alkanes with antimycobacterial activity were reported, among which 5,6-dehydro-7,8-dihydromethysticin (119) and piperolactam A (120) demonstrated appreciable activity [68]. Piper sarmentosum Roxb., Piperaceae, locally referred to as "cha-plu" in Thailand, leaves and root extracts were used in the treatment of toothaches, dermatitis, and pleurisy. At the same time, an aromatic alkene (121) and a pyrroliodine amide (122) from the ethyl acetate extract of the plant root had activity against M. tuberculosis [69]. Rhus contains 250 species of flowering plants and, recently, compounds having anti-HIV properties were reported from this genus. Tetrahydroxysqualene (123), isolated from the methanolic extract of leaves and twigs of Rhus taitensis Guill., Anacardiaceae, had activity [70] with modest cytotoxicity. The structure of this class of compounds having antimycobacterial activity is shown in **© Fig. 7**.

**Fig. 7** Fatty acids, chromones, alkanes, alkenes, alkynes and aromatics.



# Miscellaneous

ment [72] (**© Fiq. 8**).

▼
The seeds of Alpinia katsumadai Hayata., Zingiberaceae, were very well recognised in the traditional medicinal practice of China for the treatment of various stomach diseases and emesis. The seed extract was found to contain many compounds which demonstrated moderate antimycobacterial activity (MIC > 64 µg/mL). But trans,trans-1,7,diphenylhepta-4,6-dien-3-one (124) had a significant effect on EtBr accumulation and efflux, as well as a synergistic effect in combination with rifampicin (FIC, 0.28) [71]. Canscora decussata (Roxb.) Schult. & Schult.f., Gentianaceae (shankpushpi), is a common plant found in the Indian subcontinent. Xanthones (125–127), isolated from the plant extract, showed activity against *M. tuberculosis* comparable to that of streptomycin, which was used as a positive control in the experi-

# Conclusion

The present review covers 127 compounds of different classes from 58 plant species with activity against Mycobacterium species. There is a scope for 39 compounds which can be developed as future antimycobacterial drugs. Compounds 12-15, 24, 26, 33, 61, 62, 65, 68, 69, 83, 85, 86, 95-98, 116-120, 123, and 125-127, with MICs <10 µg/mL, are comparable to antimycobacterial agents such as INH, RMP, and EMB, and may become future potential antimycobacterial drugs. Compounds 9, 49, 84, and 124, which act as efflux pump inhibitors, may be useful in reversing drug resistance to TB caused by MDR forms. Drugs acting synergistically could be developed from plant extracts. Compounds such as **34**, **61**, and **103** act synergistically in combination with commercially available antimycobacterial agents and are paying the way as a new option for multidrug treatment. Compounds 22, 23, 40, 47, and 48 were effective against intracellular dormant bacilli. This review also highlighted some new sites and compounds (40, 41, 42, 55, 56, 57, 61, 82, and 103) for drug action, which determine survival of the bacilli. Common scaffolds may be identified for synthesis of new antimycobacterial drugs. Com-



pounds such as amentoflavone and diospyrin (**30** and **58**) may be isolated from two different plant species growing in different continents.

There are also many potent antimycobacterial plant extracts from which the active compounds still have to be isolated. In the current world scenario of global warming, afforestation using medicinal plants solves these two problems.

#### Acknowledgements

RSS and BS acknowledge the Indian Council of Medical Research, Government of India, India for research funding (No. 5/8/3(3)/ 2010-ECD-I) to identify new drug compounds against mycobacterium. The authors thank the reviewers for comments and suggestions, and SASTRA University for infrastructural facilities.

#### **Conflict of Interest**

#### ▼

No conflict of interest.

#### References

- 1 Jain A, Dixit P. Multidrug resistant to extensively drug resistant tuberculosis: what is next? J Biosci 2008; 33: 605–616
- 2 McChesney JD, Venkataraman SK, Henri JT. Plant natural products: back to the future or into extinction? Phytochemistry 2007; 68: 2015–2022
- 3 Jayaseelan KV, Moreno P, Truszkowski A, Ertl P, Steinbeck C. Natural product-likeness score revisited: an open-source, open-data implementation. BMC Bioinformatics 2012; 13: 106
- 4 Ortholand JY, Ganesan A. Natural products and combinatorial chemistry: back to the future. Curr Opin Chem Biol 2004; 8: 271–280
- 5 Amarendra V, Santhosh RS, Dhevendaran K. Sponges: a reservoir for microorganism derived bioactive metabolites. In: Kim S-K, editor. Marine microbiology: bioactive compounds and biotechnological applications. Weinheim: Wiley-VCH; 2013: 417–452
- 6 García A, Bocanegra-García V, Palma-Nicolás JP, Rivera G. Recent advances in antitubercular natural products. Eur J Med Chem 2012; 49: 1–23
- 7 Copp BR, Pearce AN. Natural product growth inhibitors of Mycobacterium tuberculosis. Nat Prod Rep 2007; 24: 278–297
- 8 *Ignacimuthu S, Shanmugam N.* Antimycobacterial activity of two natural alkaloids, vasicine acetate and 2-acetyl benzylamine, isolated from Indian shrub *Adhatoda vasica* Ness. leaves. J Biosci 2010; 35: 565–570
- 9 Jha DK, Panda L, Lavanya P, Ramaiah S, Anbarasu A. Detection and confirmation of alkaloids in leaves of Justicia adhatoda and bioinformatics approach to elicit its anti-tuberculosis activity. Appl Biochem Biotechnol 2012; 168: 980–990
- 10 Jin J, Zhang J, Guo N, Feng H, Li L, Liang J, Sun K, Wu X, Wang X, Liu M, Deng X, Yu L. The plant alkaloid piperine as a potential inhibitor of ethidium bromide efflux in *Mycobacterium smegmatis*. J Med Microbiol 2011; 60: 223–229

- 11 Pallant CA, Cromarty AD, Steenkamp V. Effect of an alkaloidal fraction of Tabernaemontana elegans (Stapf.) on selected micro-organisms. J Ethnopharmacol 2012; 140: 398–404
- 12 Sureram S, Senadeera SPD, Hongmanee P, Mahidol C, Ruchirawat S, Kittakoop P. Antimycobacterial activity of bisbenzylisoquinoline alkaloids from Tiliacora triandra against multidrug-resistant isolates of Mycobacterium tuberculosis. Bioorg Med Chem Lett 2012; 22: 2902–2905
- 13 Panseeta P, Lomchoey K, Prabpai S, Kongsaeree P, Suksamrarn A, Ruchirawat S, Suksamrarn S. Antiplasmodial and antimycobacterial cyclopeptide alkaloids from the root of Ziziphus mauritiana. Phytochemistry 2011; 72: 905–915
- 14 Lin YM, Zhou Y, Flavin MT, Zhou LM, Nie W, Chen FC. Chalcones and flavonoids as anti-tuberculosis agents. Bioorg Med Chem 2002; 10: 2795–2802
- 15 Habbu PV, Mahadevan KM, Shastry RA, Manjunatha H. Antimicrobial activity of flavanoid sulphates and other fractions of Argyreia speciosa (Burm.f) Boj. Indian J Exp Biol 2009; 47: 121–128
- 16 Coelho RG, Honda NK, Vieira MC, Brum RL, Pavan FR, Leite CQF, Cardoso CAL. Chemical composition and antioxidant and antimycobacterial activities of Bromelia balansae (Bromeliaceae). J Med Food 2010; 13: 1277–1280
- 17 Fushiya S, Kishi Y, Hattori K, Batkhuu J, Takano F, Singab AN, Okuyama T. Flavonoids from *Cleome droserifolia* suppress NO production in activated macrophages *in vitro*. Planta Med 1999; 65: 404–407
- 18 Chou TH, Chen JJ, Peng CF, Cheng MJ, Chen IS. New flavanones from the leaves of Cryptocarya chinensis and their antituberculosis activity. Chem Biodivers 2011; 8: 2015–2024
- 19 *Kuete V, Ngameni B, Mbaveng AT, Ngadjui B, Meyer JJ, Lall N.* Evaluation of flavonoids from *Dorstenia barteri* for their antimycobacterial, anti-gonorrheal and anti-reverse transcriptase activities. Acta Trop 2010; 116: 100–104
- 20 Chen LW, Cheng MJ, Peng CF, Chen IS. Secondary metabolites and antimycobacterial activities from the roots of Ficus nervosa. Chem Biodivers 2010; 7: 1814–1821
- 21 Mativandlela SPN, Muthivhi T, Kikuchi H, Oshima Y, Hamilton C, Hussein AA, van der Walt ML, Houghton PJ, Lall N. Antimycobacterial flavonoids from the leaf extract of Galenia africana. J Nat Prod 2009; 72: 2169–2171
- 22 Kaikabo AA, Eloff JN. Antibacterial activity of two biflavonoids from Garcinia livingstonei leaves against Mycobacterium smegmatis. J Ethnopharmacol 2011; 138: 253–255
- 23 Khlifi D, Hamdi M, El Hayouni A, Cazaux S, Souchard JP, Couderc F, Bouajila J. Global chemical composition and antioxidant and anti-tuberculosis activities of various extracts of *Globularia alypum* L. (Globulariaceae) leaves. Molecules 2011; 16: 10 592-10 603
- 24 Begum S, Wahab A, Siddiqui BS. Antimycobacterial activity of flavonoids from Lantana camara Linn. Nat Prod Res 2008; 22: 467–470
- 25 Sharma SK, Kumar G, Kapoor M, Surolia A. Combined effect of epigallocatechin gallate and triclosan on enoyl-ACP reductase of Mycobacterium tuberculosis. Biochem Biophys Res Commun 2008; 368: 12–17
- 26 Brown AK, Papaemmanouil A, Bhowruth V, Bhatt A, Dover LG, Besra GS. Flavonoid inhibitors as novel antimycobacterial agents targeting Rv0636, a putative dehydratase enzyme involved in *Mycobacterium tuberculosis* fatty acid synthase II. Microbiology 2007; 153: 3314–3322
- 27 Anand PK, Kaul D, Sharma M. Green tea polyphenol inhibits Mycobacterium tuberculosis survival within human macrophages. Int J Biochem Cell Biol 2006; 38: 600–609

- 28 Favela-Hernández JMJ, García A, Garza-González E, Rivas-Galindo VM, Camacho-Corona MR. Antibacterial and antimycobacterial lignans and flavonoids from Larrea tridentata. Phytother Res 2012; 26: 1957-1960
- 29 Suksamrarn A, Poomsing P, Aroonrerk N, Punjanon T, Suksamrarn S, Kongkun S. Antimycobacterial and antioxidant flavones from Limnophila geoffrayi. Arch Pharm Res 2003; 26: 816-820
- 30 Kim CE, Griffiths WJ, Taylor PW. Components derived from Pelargonium stimulate macrophage killing of Mycobacterium species. J Appl Microbiol 2009; 106: 1184-1193
- 31 Lechner D, Gibbons S, Bucar F. Plant phenolic compounds as ethidium bromide efflux inhibitors in Mycobacterium smegmatis. J Antimicrob Chemother 2008: 62: 345-348
- 32 Wu MC, Peng CF, Chen IS, Tsai IL. Antitubercular chromones and flavonoids from Pisonia aculeata. J Nat Prod 2011; 74: 976-982
- 33 Lall N, Hussein AA, Meyer JJ. Antiviral and antituberculous activity of Helichrysum melanacme constituents. Fitoterapia 2006; 77: 230-232
- 34 Lall N, Das Sarma M, Hazra B, Meyer JJM. Antimycobacterial activity of diospyrin derivatives and a structural analogue of diospyrin against Mycobacterium tuberculosis in vitro. J Antimicrob Chemother 2003; 51:435-438
- 35 Hazra B, Sur P, Roy DK, Sur B, Banerjee A. Biological activity of diospyrin towards Ehrlich ascites carcinoma in Swiss A mice. Planta Med 1984; 51:295-297
- 36 Weigenand O, Hussein AA, Lall N, Meyer IJM. Antibacterial activity of naphthoquinones and triterpenoids from Euclea natalensis root bark. | Nat Prod 2004; 67: 1936-1938
- 37 Mahapatra A, Mativandlela SPN, Binneman B, Fourie PB, Hamilton CJ, Meyer JJM, van der Kooy F, Houghton P, Lall N. Activity of 7-methyljuglone derivatives against Mycobacterium tuberculosis and as subversive substrates for mycothiol disulfide reductase. Bioorg Med Chem 2007; 15: 7638-7646
- 38 Bapela NB, Lall N, Fourie PB, Franzblau SG, Van Rensburg CEJ. Activity of 7-methyljuglone in combination with antituberculous drugs against Mycobacterium tuberculosis. Phytomedicine 2006; 13: 630-635
- 39 Prajoubklang A, Sirithunyalug B, Charoenchai P, Suvannakad R, Sriubolmas N, Piyamongkol S, Kongsaeree P, Kittakoop P. Bioactive deoxypreussomerins and dimeric naphthoquinones from Diospyros ehretioides fruits: deoxypreussomerins may not be plant metabolites but may be from fungal epiphytes or endophytes. Chem Biodivers 2005; 2: 1358-1367
- 40 Chen JJ, Lin WJ, Shieh PC, Chen JS, Peng CF, Sung PJ. A new long-chain alkene and antituberculosis constituents from the leaves of Pourthiaea lucida. Chem Biodivers 2010; 7: 717-721
- 41 Badoni R, Semwal DK, Kothiyal SK, Rawat U. Chemical constituents and biological applications of the genus Symplocos. J Asian Nat Prod Res 2010; 12: 1069-1080
- 42 León-Díaz R, Meckes M, Said-Fernández S, Molina-Salinas GM, Vargas-Villarreal J, Torres J, Luna-Herrera J, Jiménez-Arellanes A. Antimycobacterial neolignans isolated from Aristolochia taliscana. Mem Inst Oswaldo Cruz 2010; 105: 45-51
- 43 Chen JJ, Chou ET, Peng CF, Chen IS, Yang SZ, Huang HY. Novel epoxyfuranoid lignans and antitubercular constituents from the leaves of Beilschmiedia tsangii. Planta Med 2007; 73: 567-571
- 44 Stavri M, Mathew KT, Bucar F, Gibbons S. Pangelin, an antimycobacterial coumarin from Ducrosia anethifolia. Planta Med 2003; 69: 956-959
- 45 Chiang CC, Cheng MJ, Peng CF, Huang HY, Chen IS. A novel dimeric coumarin analog and antimycobacterial constituents from Fatoua pilosa. Chem Biodivers 2010; 7: 1728-1736
- 46 Esquivel-Ferriño PC, Favela-Hernández JMJ, Garza-González E, Waksman N, Rios MY, Camacho-Corona MR. Antimycobacterial activity of constituents from Foeniculum vulgare Var. Dulce grown in Mexico. Molecules 2012; 17: 8471-8482
- 47 Alanís-Garza B, Salazar-Aranda R, Ramírez-Durón R, Garza-González E, Waksman TN. A new antimycobacterial furanolignan from Leucophyllum frutescens. Nat Prod Commun 2012; 7: 597-598
- 48 Coy ED, Cuca LE, Sefkow M. Macrophyllin-type bicyclo[3.2.1]octanoid neolignans from the leaves of Pleurothyrium cinereum. J Nat Prod 2009; 72: 1245-1248
- 49 Baquero E, Quiñones W, Ribon W, Caldas ML, Sarmiento L, Echeverri F. Effect of an Oxadiazoline and a Lignan on Mycolic Acid Biosynthesis and Ultrastructural Changes of Mycobacterium tuberculosis. Tuberc Res Treat 2011; 2011: 986409
- 50 Torres-Romero D, Jiménez IA, Rojas R, Gilman RH, López M, Bazzocchi IL. Dihydro-β-agarofuran sesquiterpenes isolated from Celastrus vulcani-

cola as potential anti-Mycobacterium tuberculosis multidrug-resistant agents. Bioorg Med Chem 2011; 19: 2182-2189

- 51 Jin J, Zhang JY, Guo N, Sheng H, Li L, Liang JC, Wang XL, Li Y, Liu MY, Wu XP, Yu L. Farnesol, a potential efflux pump inhibitor in Mycobacterium smegmatis. Molecules 2010; 15: 7750-7762
- 52 Dettrakul S, Surerum S, Rajviroongit S, Kittakoop P. Biomimetic transformation and biological activities of globiferin, a terpenoid benzoquinone from Cordia globifera. J Nat Prod 2009; 72: 861-865
- Singh S, Kumar JK, Saikia D, Shanker K, Thakur JP, Negi AS, Banerjee S. A bioactive labdane diterpenoid from Curcuma amada and its semisynthetic analogues as antitubercular agents. Eur J Med Chem 2010; 45: 4379-4382
- 54 Sutthivaiyakit S, Mongkolvisut W, Prabpai S, Kongsaeree P. Diterpenes, sesquiterpenes, and a sesquiterpene-coumarin conjugate from Jatropha integerrima. | Nat Prod 2009; 72: 2024-2027
- 55 Scher JM, Schinkovitz A, Zapp J, Wang Y, Franzblau SG, Becker H, Lankin DC, Pauli GF. Structure and anti-TB activity of trachylobanes from the liverwort Jungermannia exsertifolia ssp. cordifolia. J Nat Prod 2010; 73:656-663
- 56 Molina-Salinas GM, Rivas-Galindo VM, Said-Fernández S, Lankin DC, Muñoz MA, Joseph-Nathan P, Pauli GF, Waksman N. Stereochemical analysis of leubethanol, an anti-TB-active serrulatane, from Leucophyllum frutescens. J Nat Prod 2011; 74: 1842-1850
- 57 Tan MA, Takayama H, Aimi N, Kitajima M, Franzblau SG, Nonato MG. Antitubercular triterpenes and phytosterols from Pandanus tectorius Soland. var. laevis. J Nat Med 2008; 62: 232-235
- 58 Rijo P, Simões MF, Francisco AP, Rojas R, Gilman RH, Vaisberg AJ, Rodríguez B, Moiteiro C. Antimycobacterial metabolites from Plectranthus: royleanone derivatives against Mycobacterium tuberculosis strains. Chem Biodivers 2010; 7: 922-932
- 59 Truong NB, Pham CV, Doan HTM, Nguyen HV, Nguyen CM, Nguyen HT, Zhang HJ, Fong HHS, Franzblau SG, Soejarto DD, Chau MV. Antituberculosis cycloartane triterpenoids from Radermachera boniana. J Nat Prod 2011; 74: 1318-1322
- 60 Gua JQ, Wang Y, Franzblau SG, Montenegro G, Timmermann BN. Constituents of Quinchamalium majus with potential antitubercular activity. Z Naturforsch C 2004; 59: 797-802
- 61 Bamuamba K, Gammon DW, Meyers P, Dijoux-Franca MG, Scott G. Antimycobacterial activity of five plant species used as traditional medicines in the Western Cape Province (South Africa). J Ethnopharmacol 2008; 117: 385-390
- 62 Ge F, Zeng F, Liu S, Guo N, Ye H, Song Y, Fan J, Wu X, Wang X, Deng X, Jin Q, Yu L. In vitro synergistic interactions of oleanolic acid in combination with isoniazid, rifampicin or ethambutol against Mycobacterium tuberculosis. | Med Microbiol 2010; 59: 567-572
- 63 Deng JZ, Starck SR, Hecht SM. Pentacyclic triterpenoids from Freziera sp. that inhibit DNA polymerase  $\beta$ . Bioorg Med Chem 2000; 8: 247–250
- 64 Saikia D, Parihar S, Chanda D, Ojha S, Kumar JK, Chanotiya CS, Shanker K, Negi AS. Antitubercular potential of some semisynthetic analogues of phytol. Bioorg Med Chem Lett 2010; 20: 508-512
- 65 Deng S, Wang Y, Inui T, Chen SN, Farnsworth NR, Cho S, Franzblau SG, Pauli GF. Anti-TB polyynes from the roots of Angelica sinensis. Phytother Res 2008: 22: 878-882
- 66 Chang CP, Chang HS, Peng CF, Lee SJ, Chen IS. Antitubercular resorcinol analogs and benzenoid C-glucoside from the roots of Ardisia cornudentata. Planta Med 2011; 77: 60-65
- 67 Changtam C, Hongmanee P, Suksamrarn A. Isoxazole analogs of curcuminoids with highly potent multidrug-resistant antimycobacterial activity. Eur J Med Chem 2010; 45: 4446-4457
- 68 Mata R, Morales I, Pérez O, Rivero-Cruz I, Acevedo L, Enriquez-Mendoza I, Bye R, Franzblau S, Timmermann B. Antimycobacterial compounds from Piper sanctum. J Nat Prod 2004; 67: 1961-1968
- 69 Tuntiwachwuttikul P, Phansa P, Pootaeng-On Y, Taylor WC. Chemical constituents of the roots of Piper sarmentosum. Chem Pharm Bull (Tokyo) 2006; 54: 149-151
- 70 Noro JC, Barrows LR, Gideon OG, Ireland CM, Koch M, Matainaho T, Piskaut P, Pond CD, Bugni TS. Tetrahdroxysqualene from Rhus taitensis shows antimycobacterial activity against Mycobacterium tuberculosis. [ Nat Prod 2008; 71: 1623-1624
- 71 Gröblacher B, Kunert O, Bucar F. Compounds of Alpinia katsumadai as potential efflux inhibitors in Mycobacterium smegmatis. Bioorg Med Chem 2012; 20: 2701-2706
- 72 Sethiya NK, Patel MB, Mishra SH. Phytopharmacologic aspects of Canscora decussata Roem and Schult. Pharmacogn Rev 2010; 4: 49-57