

Plants: A Source for New Antimycobacterial Drugs

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Key words

- alkaloids
- flavonoids
- chalcones
- coumarins
- lignans
- phenols
- terpenes
- chromones
- alkane
- alkene
- plants
- *Mycobacterium tuberculosis*

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

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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 drug-resistant (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[®], 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-

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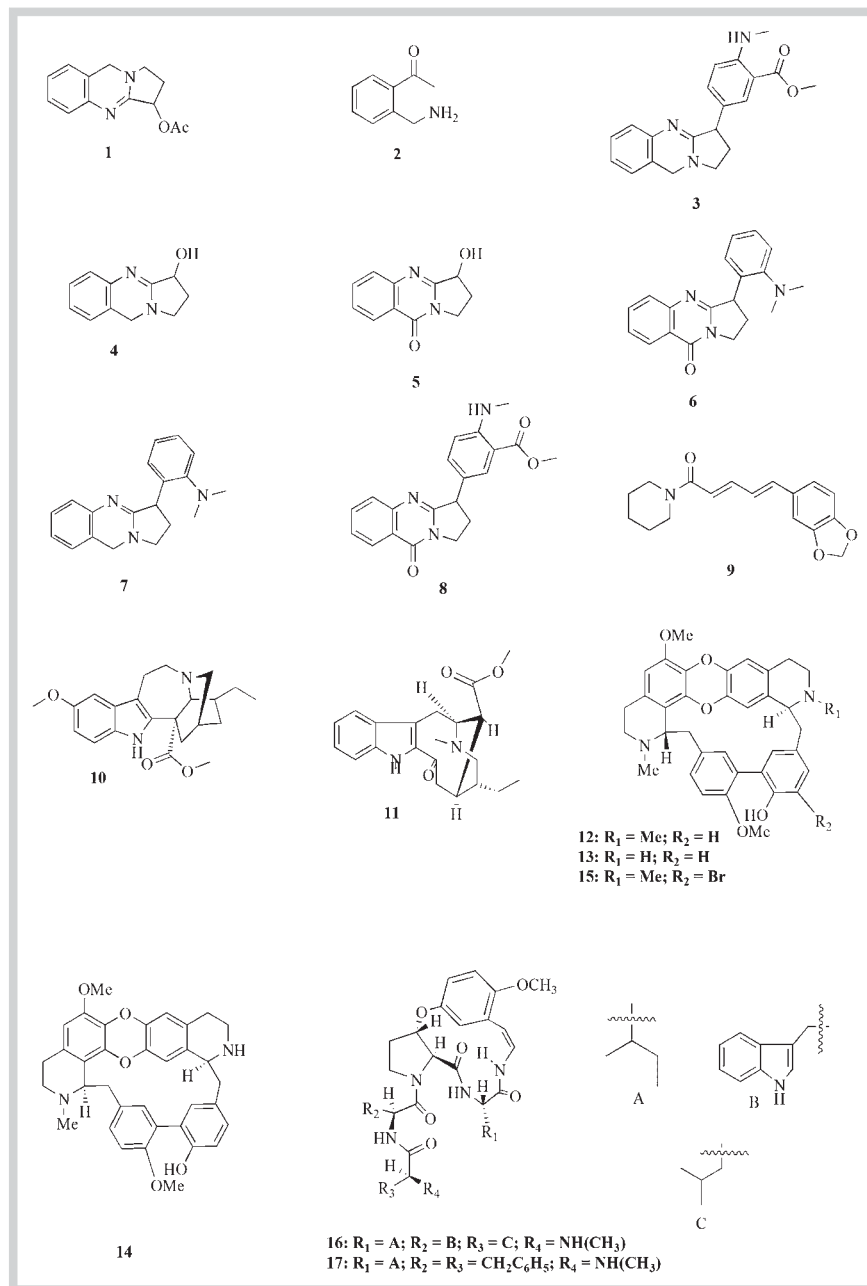


Fig. 1 Alkaloids.

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 antimycobacterial 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-

Table 1 List of compounds with activity values tested against sensitive and resistant forms of *M. tuberculosis*. Compound name with its activity value in () and reference in [] are included under each class of compounds. The values in regular and bold letters are against sensitive and resistant forms, respectively.

Alkaloids	Flavonoids	Chalcones and quinones	Coumarins, lignans, and phenols	Chromones, fatty acids, and terpenoids	Alkanes, alkenes, alkynes, aromatics, and miscellaneous
2-acetyl benzylamine and vasicine acetate (50 µg/mL) (200 µg/mL) [8]	cryptocaryone (25 µg/mL) [18]	(E)-2',4'-dihydroxychalcone (195.3 µM) [21]	dihydroguaiaretic acid (50 µg/mL) (12.5–50 µg/mL) [28]	pisonin B (25 µg/mL) [32]	falcarindiol (26.7 µg/mL) [65]
2'-nortiliacorinine and tiliacorinine (3.1 µg/mL) [12]	pinocembrin (3.5 µg/mL) [18]	(E)-3,2',4'-trihydroxy-3'-methoxy-chalcone (174.8 µM) [21]	4- <i>epi</i> -larreatricin (50 µg/mL) (25 µg/mL) [28]	1,3-benzenediol (100 µg/mL) (100–200 µg/mL) [46]	9Z,17-octadiene-12,14-diyne-1,11,16-triol,1-acetate (25.3 µg/mL) [65]
Tiliacorinine (3.1–6.2 µg/mL) (1.5–6.2 µg/mL) [12]	isobachalcone (2.44–19.53 µg/mL) [19]	2',4',6'-trihydroxy-3'-prenylchalcone and 4',6',5''-trihydroxy-6'',6''-dimethyldihydropyrano[2'',3''-2',3']chalcone (50 µg/mL) [33]	licarin A (25 µg/mL) (3.12–12.5 µg/mL) [42]	linoleic acid and oleic acid (100 µg/mL) (100 µg/mL) [46]	1,3-dimethoxy-2-methyl-5-pentylbenzene (≤ 2.5 µg/mL) [66]
13'-bromo-tiliacorinine (3.1–6.2 µg/mL) (1.5–3.1 µg/mL) [12]	kanzanol C, 4-hydroxyonchocar-pin, stipulin, and amentoflavone (9.76 – > 39.06 µg/mL) [19]	aminooacetate derivative of diospyrin (> 10 – ≤ 50 µg/mL) (> 10 – ≤ 50 µg/mL) [34]	licarin B (50 µg/mL) (12.5–50 µg/mL) [42]	undecanal (100 µg/mL) (50–200 µg/mL) [46]	3-methoxy-2-methyl-5-pentyl phenol (≤ 2.58 µg/mL) [66]
Mauritine M (IC ₅₀ – 72.8 µM) [13]	genistein (35 µg/mL) [20]	diospyrin (100 µg/mL) (100 µg/mL) [34]	eupomatenoïd-7 (25 µg/mL) (6.25–50 µg/mL) [42]	2,4-undecadienal (25 µg/mL) (25–50 µg/mL) [46]	mono-O-methylcurcumin isoxazole (0.09 µg/mL) (0.195–3.125 µg/mL) [67]
Nummularine H (IC ₅₀ – 4.5 µM) [13]	(2S)-naringenin (< 2.8 µg/mL) [20]	shinanolone (100 µg/mL) [36]	beilschimin A (2.5 µg/mL) [43]	kaurenoic acid (50 µg/mL) [48]	5,6-dehydro-7,8-dihydromethysticin (4 µg/mL) [68]
	prunetin (30 µg/mL) [20]	7-methyljuglone (0.5 µg/mL) [37]	beilschimin B (7.5 µg/mL) [43]	1 α -acetoxy-6 β ,9 β -dibenzoyloxy-dihydro- β -agarofuran (> 25 µg/mL) (6.2 µg/mL) [50]	piperolactam A (8 µg/mL) [68]
	(2S)-5,7,2'-trihydroxy flavonone (367.6 µM) [21]	isodiospyrol A (50 µg/mL) [39]	(E)-1-[2,4-dihydroxy-3-(3-methyl-but-2-enyl)phenyl]-3-(2,2-dimethyl-8-hydroxy-2H-benzopyran-6-yl)prop-2-en-1-one (30 µg/mL) [45]	cordiachrome C (1.5 µg/mL) [52]	aromatic alkene, and pyrrolidine amide (25 µg/mL) [69]
	5,4'-dihydroxy-3,7,8,3'-tetramethoxy flavones (> 50 µg/mL) (25 µg/mL) [28]	palmanumycin C2 (6.25 µg/mL) [39]	Isobavachalcone (18 µg/mL) [45]	globiferin (6.2 µg/mL) [52]	tetrahydroxy squalene (10 µg/mL) [70]
	5,4'-dihydroxy-3,7,8-trimethoxy flavone (> 50 µg/mL) (25–50 µg/mL) [28]	α -tocopheryl quinone (25 µg/mL) [40]	scopoletin (42 µg/mL) [45]	diol derivative of labdane (250 µg/mL) [53]	<i>trans,trans</i> -1,7-diphenylhepta-4,6-dien-3-one (> 128 µg/mL) [71]
	nevaednsin and isothymusin (200 µg/mL) [29]		2',5''-dimethoxysesamin (63 µg/mL) [47]	dioxime derivative of labdane and labdane (500 µg/mL) [53]	xanthones (10 µg/mL) [72]
	pisonivanone (12.5 µg/mL) [32]		ethoxycubebin (62.4 µM) [49]	cariojane (25 µg/mL) [54]	<i>continued</i>

Table 1 Continued

Alkaloids	Flavonoids	Chalcones and quinones	Coumarins, lignans, and phenols	Chromones, fatty acids, and terpenoids	Alkanes, alkenes, alkynes, aromatics, and miscellaneous
				trachybalone diterpine derivatives (24–61 µg/mL) [55]	
				leubethanol (12.5 µg/mL) (6.25 µg/mL) [56]	
				24,24-dimethyl-5β-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]	

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 quinazoline alkaloids (3–8) from the above plant having significant antimycobacterial activity, and *in silico* analysis confirmed that these alkaloids inhibit β-ketoacyl-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* mc² 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 tiliacrine (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; moderately active), and a cyclopeptide alkaloid, nummularine H (17; active) [13].

Flavonoids

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'-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-α-L-rhamnopyranoside (18), kaempferol-3-O-α-L-rhamnopyranosyl-(1→6)-β-D-glucopyranoside (19), quercetin-3-O-α-L-rhamnopyranosyl-(1→6)-β-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 moderately active [18]. *Dorstenia barberi* 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-hydroxylochocarpin (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 ≤2.8 µg/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 moderately 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 quercetin (36) equivalent/kg of dry mass] and PE is particularly active against *M. tuberculosis* (IC₅₀ 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

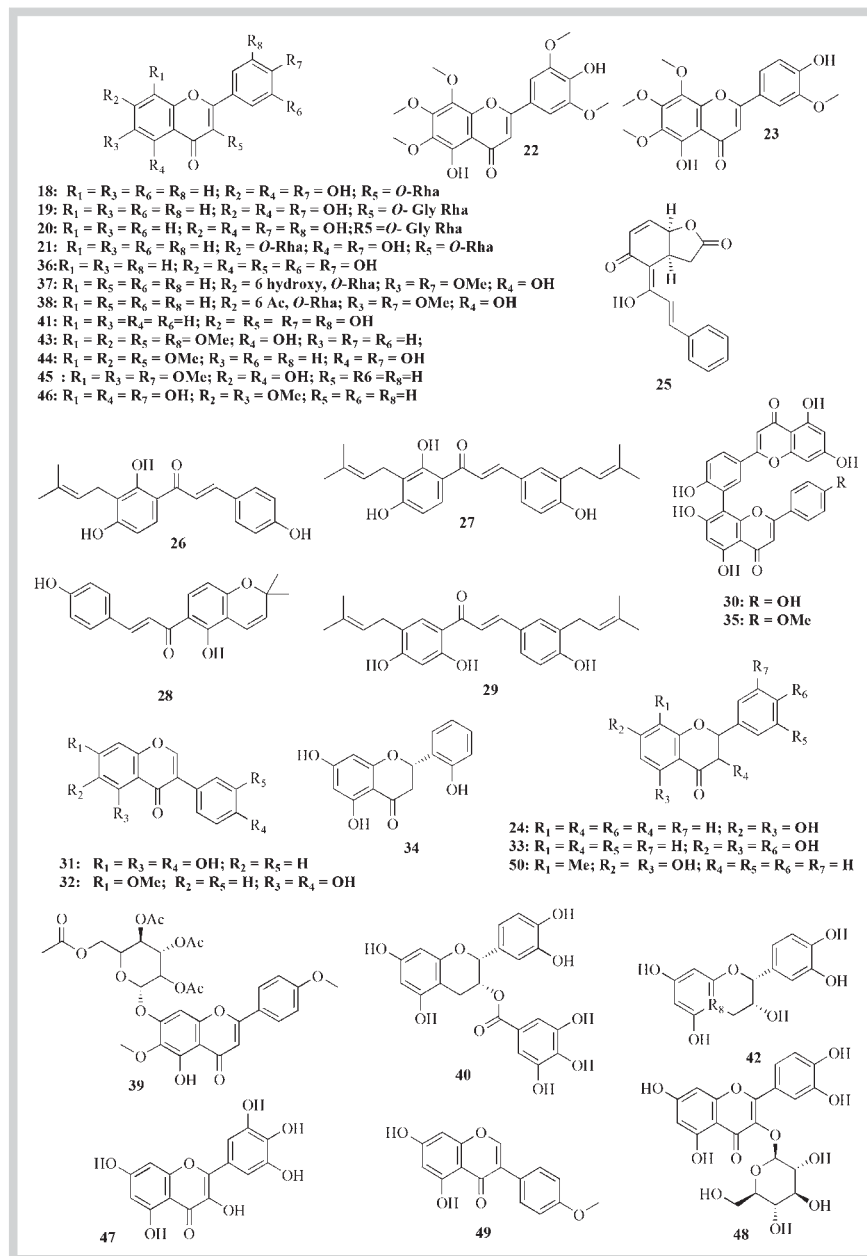


Fig. 2 Flavonoids.

fatty acyl chain. In 2008, Sharma et al. reported that epigallocatechin gallate/epigallocatechin-3-gallate (**40**) directly inhibits the above-mentioned enzyme (IC₅₀ 17.4 μM) by interacting with the residues near the NADH binding site. Compound **40** also acts synergistic with triclosan, a common additive of household products known to target InhA of bacterium and plasmodium [25]. Fisetin (**41**), from *Cotinus coggygia* 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 phagosome-lysosome 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'-dihydroxy-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 lactagogue. 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 quercetin-3-*O*-β-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

antipyretic, expectorant, and a lactagogue. 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 quercetin-3-*O*-β-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

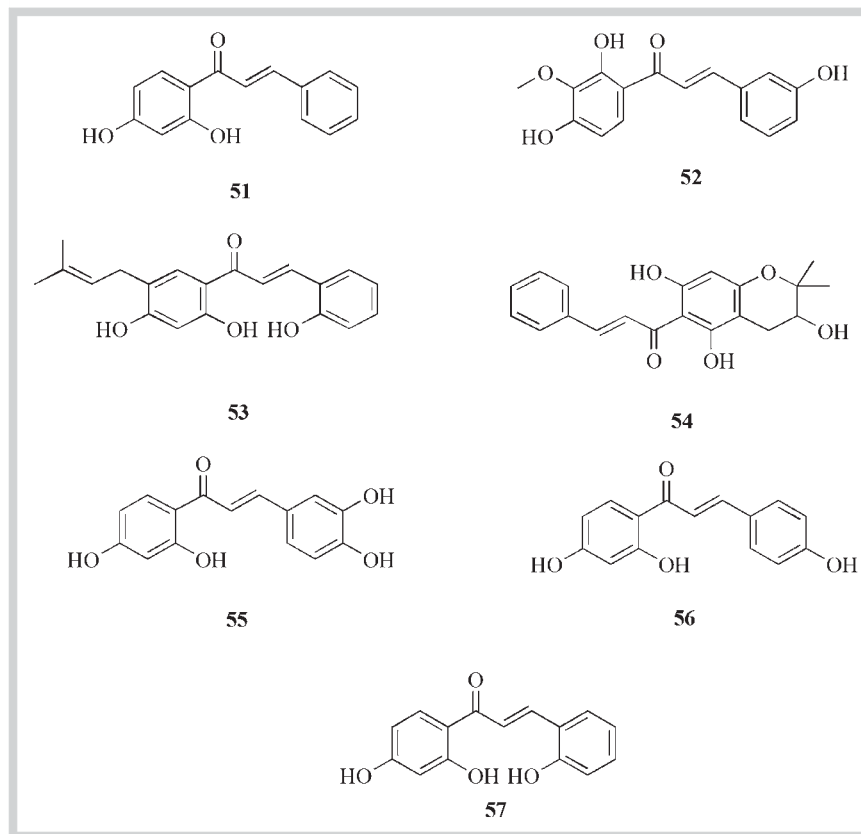


Fig. 3 Chalcones.

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

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''-dimethyl-dihydroprano[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 ethnic 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 naphthoquinone 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 α -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 *Symplocos*, 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 eupomatenoide-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

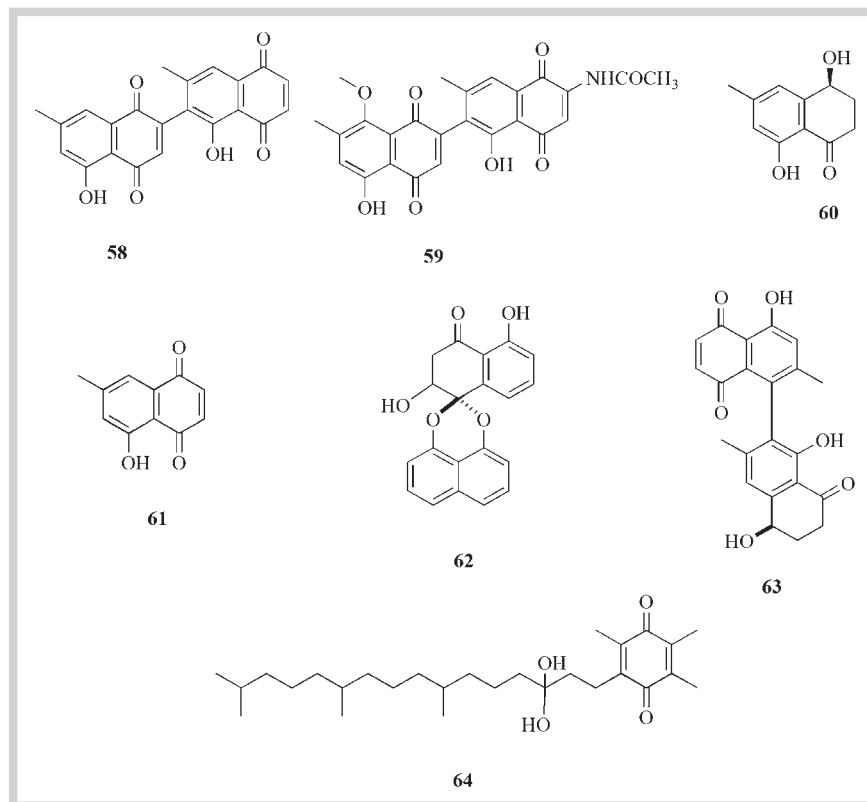


Fig. 4 Quinones.

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 bergapton (**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 furofuran, 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 *Pleurothyrium 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., Myristicaceae, 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 (● Fig. 6). The sesquiterpene polyesters with a dihydro-β-agarofuran skeleton are predominant secondary metabolites in plants belonging to the family Celastraceae. In 2011, Torres-Romero et al. isolated twenty different dihydro-β agarofuran sesquiterpene derivatives from *Celastrus vulcanicola* Donn. Sm., Celastraceae, and among them, 1α-acetoxy-6β,9β-dibenzoyloxy-dihydro-β-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* mc²155 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 trachyalone 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-

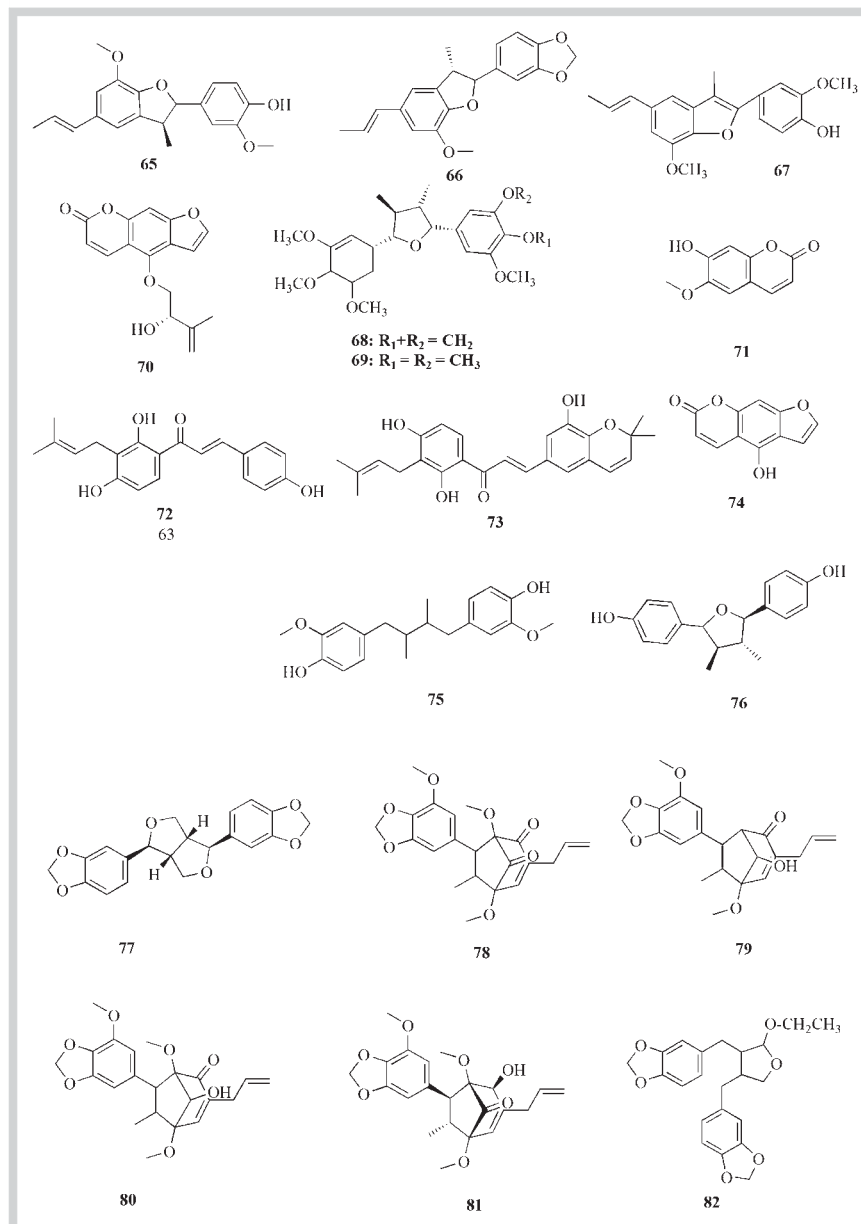


Fig. 5 Coumarins, lignans and phenols.

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-5 β -tirucall-9(11),25-dien-3-one (**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, kaurenic 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-O-acetylundaric 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 β , 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 2,4-undecadienal (**112**) from the isolates of *Foeniculum vulgare* Mill., Apiaceae, had activity against MDR forms [46]. Chromones, a benzopyran derivative, can be developed as antimycobacterial

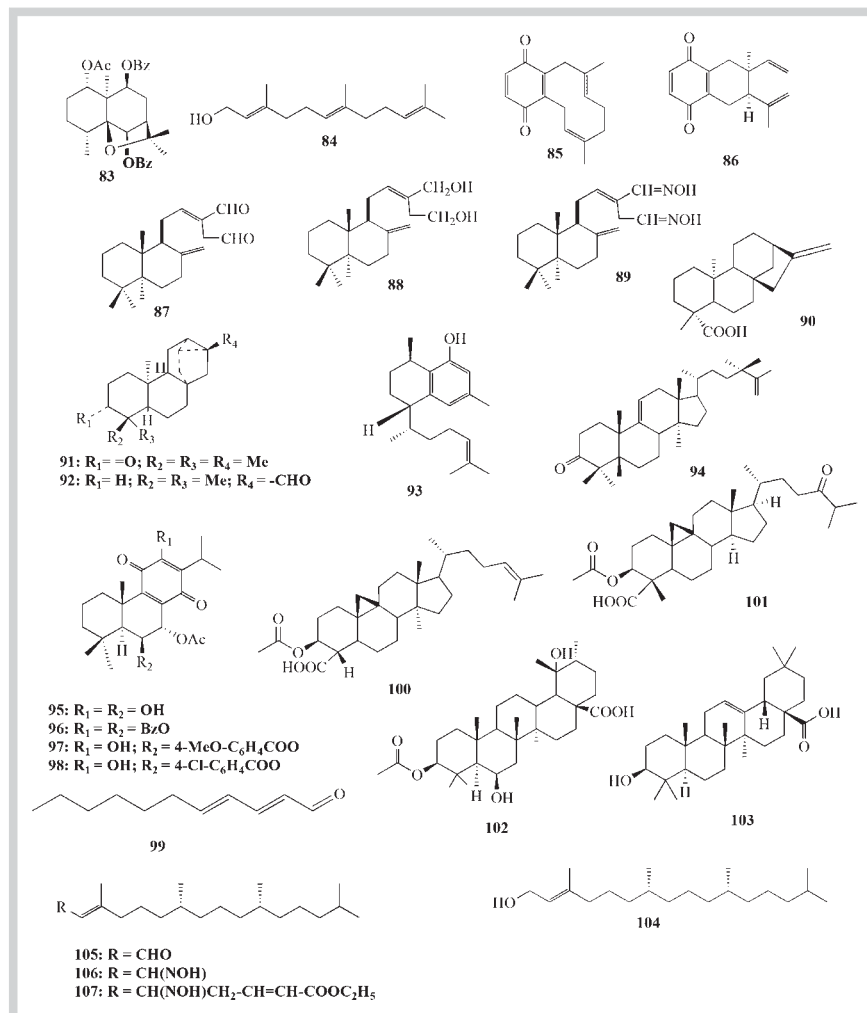


Fig. 6 Terpenoids.

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 falcariindiol (**114**) and 9Z,17-octadecadiene-12,14-diyne-1,11,16-triol,1-acetate (**115**) were found to have antimycobacterial activity [65]. *Ardisia cornudentata* Mez., Myrsinaceae, 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 1,3-dimethoxy-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 tai-tensis* Guill., Anacardiaceae, had activity [70] with modest cytotoxicity. The structure of this class of compounds having antimycobacterial activity is shown in ● Fig. 7.

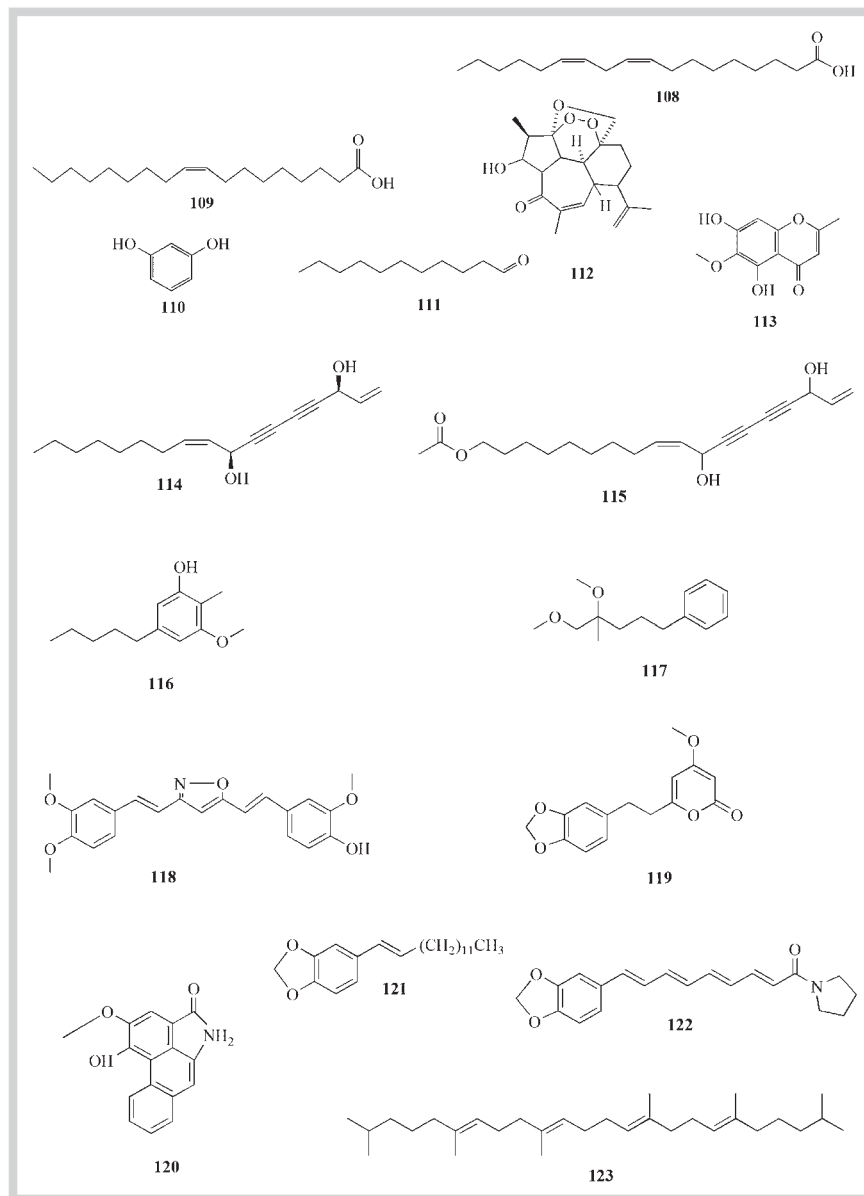


Fig. 7 Fatty acids, chromones, alkanes, alkenes, alkynes and aromatics.

Miscellaneous

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. Xanthenes (**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 experiment [72] (● Fig. 8).

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 paving 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-

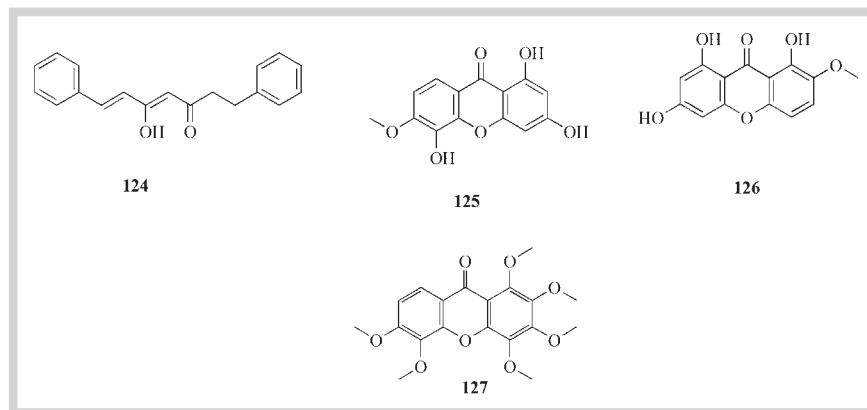


Fig. 8 Miscellaneous compounds.

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.

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Conflict of Interest

No conflict of interest.

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