Plants: A Source for New Antimycobacterial Drugs

Authors **Ramachandran Sarojini Santhosh**[1,2], **Balasubramanian Suriyanarayanan**[1]

Affiliations
[1] School of Chemical and Biotechnology, SASTRA University, Thanjavur, India
[2] Genetic Engineering Lab, Anusandhan Kendra, SASTRA's Hub for Research & Innovation (SHRI), SASTRA University, Thanjavur, India

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

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-

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

ISSN 0032-0943

Correspondence
Dr. R. S. Santhosh, Senior Assistant Professor
School of Chemical and Biotechnology
SASTRA University
Tirumalaisamudram
Thanjavur 613401
India
Phone: + 91 43 62 30 40 00-23 21
Fax: + 91 43 62 26 41 20
santhosh@biotech.sastra.edu

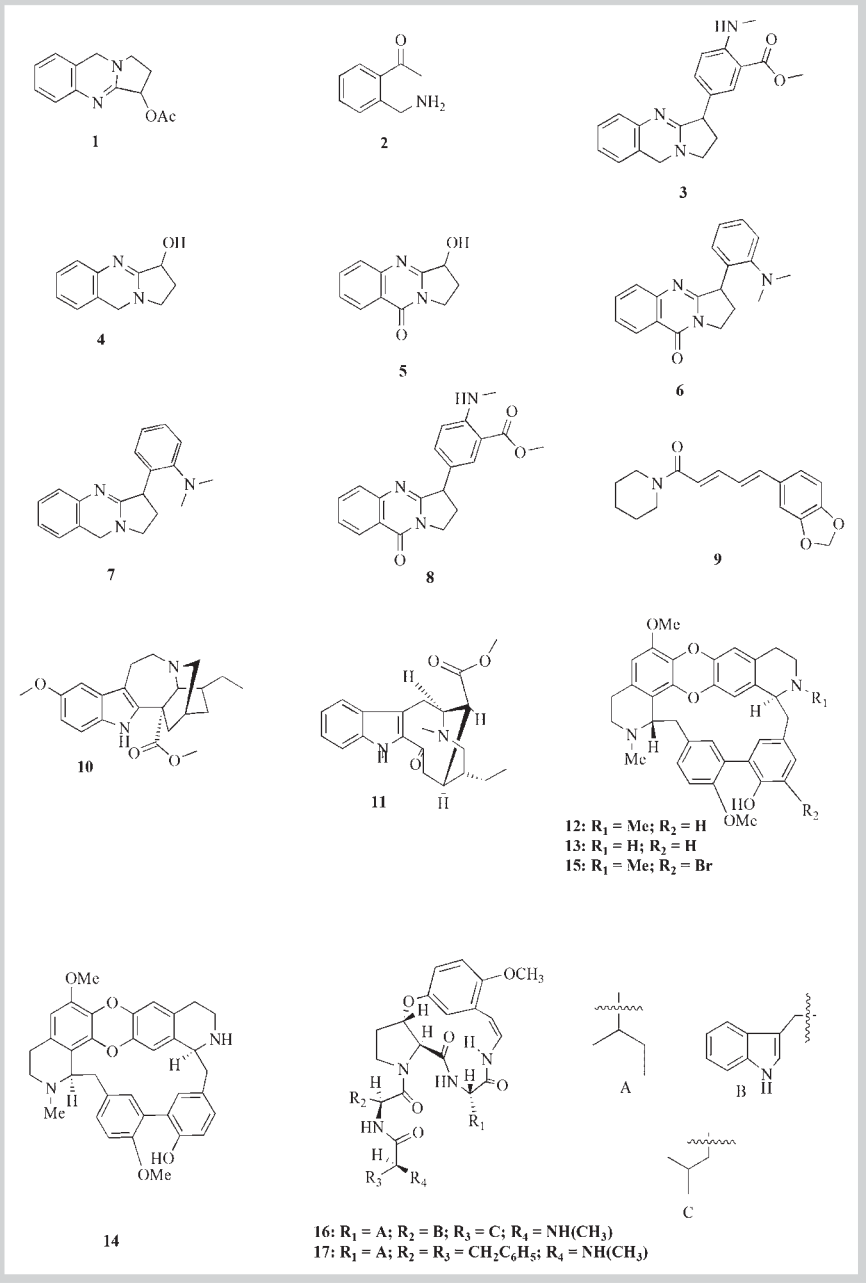

Fig. 1 Alkaloids.

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 tiliacorine (3.1 µg/mL) **(3.1 µg/mL)** [12]	pinocembrin (3.5 µg/mL) [18]	(*E*)-3,2′,4′-trihydroxy-3′-methoxy-chalcone (174.8 µM) [21]	4-*epi*-larreatricin (50 µg/mL) **(25 µg/mL)** [28]	1,3-benzenediol (200 µg/mL) **(100–200 µg/mL)** [46]	9*Z*,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-pentyl benzene (≤ 2.5 µg/mL) [66]
13′-bromo-tiliacorinine (3.1–6.2 µg/mL) **(1.5–3.1 µg/mL)** [12]	kanzanol C, 4-hydroxylonchocarpin, stipulin, and amentoflavone (9.76 – > 39.06 µg/mL) [19]	aminoacetate 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]	eupomatenoid-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]	(2*S*)- naringenin (< 2.8 µg/mL) [20]	shinanolone (100 µg/mL) [36]	beilschmin 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]	beilschmin 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]
	(2*S*)-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-2*H*-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]	palmarumycin JC2 (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]	*trans,trans*-1,7,diphenylhepta-4,6-dien-3-one (> 128 µg/mL) [71]
	nevadensin 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]	caniojane (25 µg/mL) [54]	

continued

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-acyl-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

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 flavononones (**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*-*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 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 ≤ 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 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

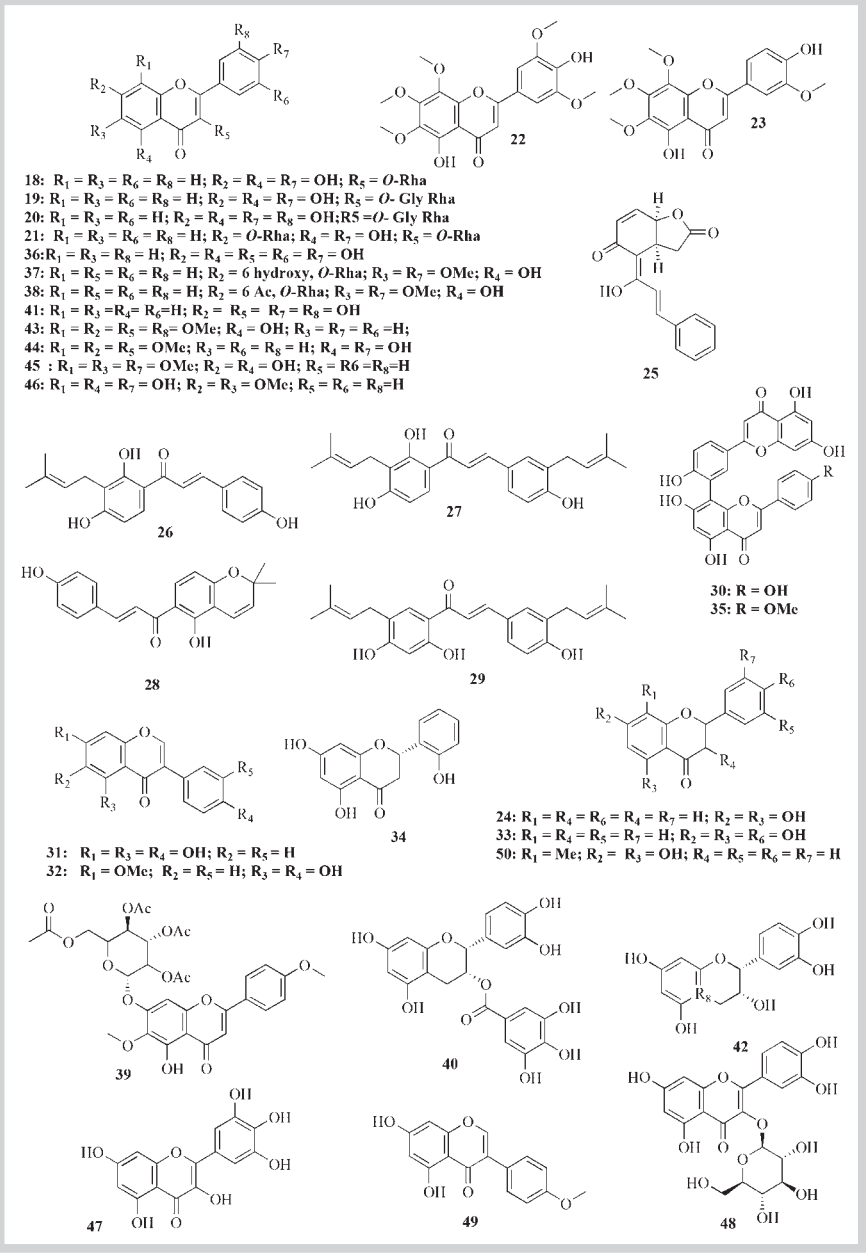

Fig. 2 Flavonoids.

fatty acyl chain. In 2008, Sharma et al. reported that epigallocatechin gallate/epigallocatechin-3-gallate (**40**) directly inhibits the above-mentioned enzyme (IC_{50} 17.4 µM) 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′-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 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*-*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

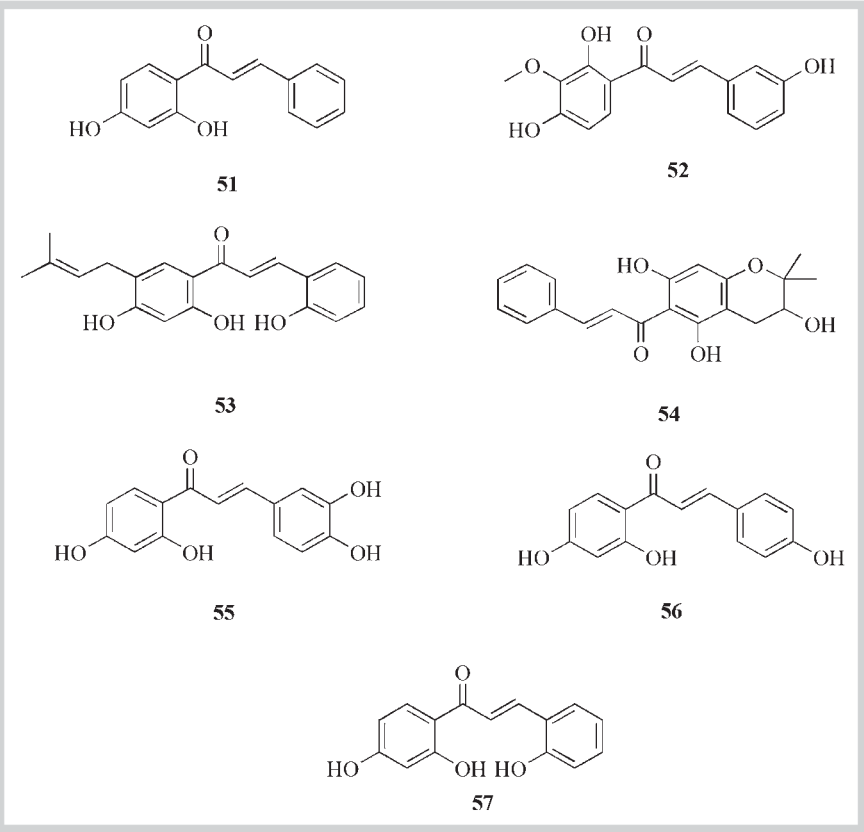

Fig. 3 Chalcones.

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″-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 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 *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

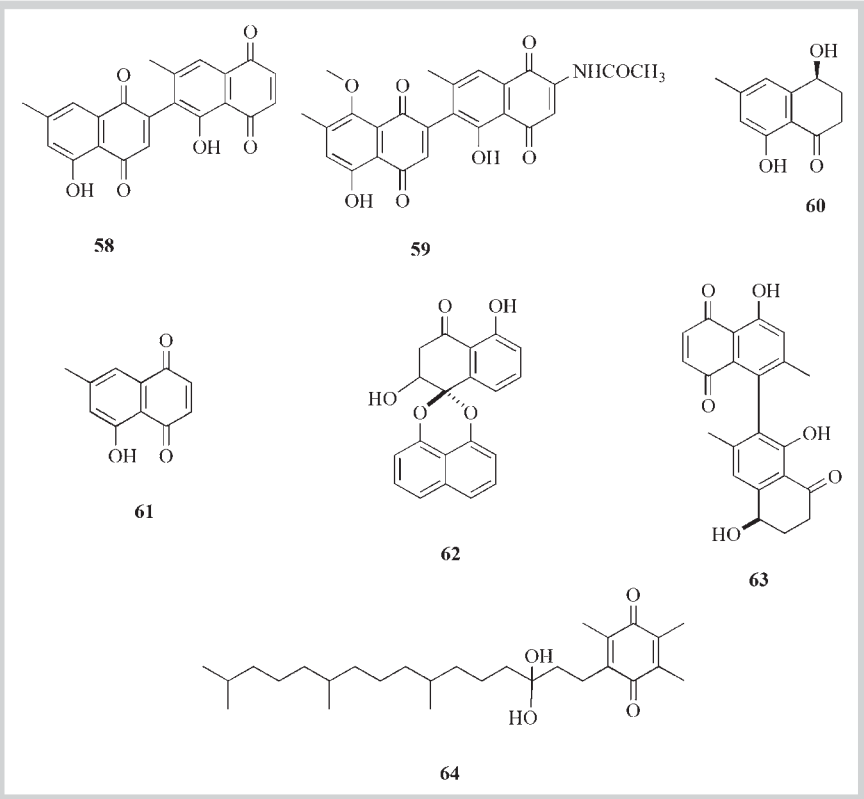

Fig. 4 Quinones.

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-*2H*-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 *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.*, 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 (**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, 1*α*-acetoxy-6*β*,9*β*-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 C_{15} isoprenoid natural acyclic sesquiterpene alcohol present in many natural sources, inhibits EP of *M. smegmatis* mc^2 155 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-

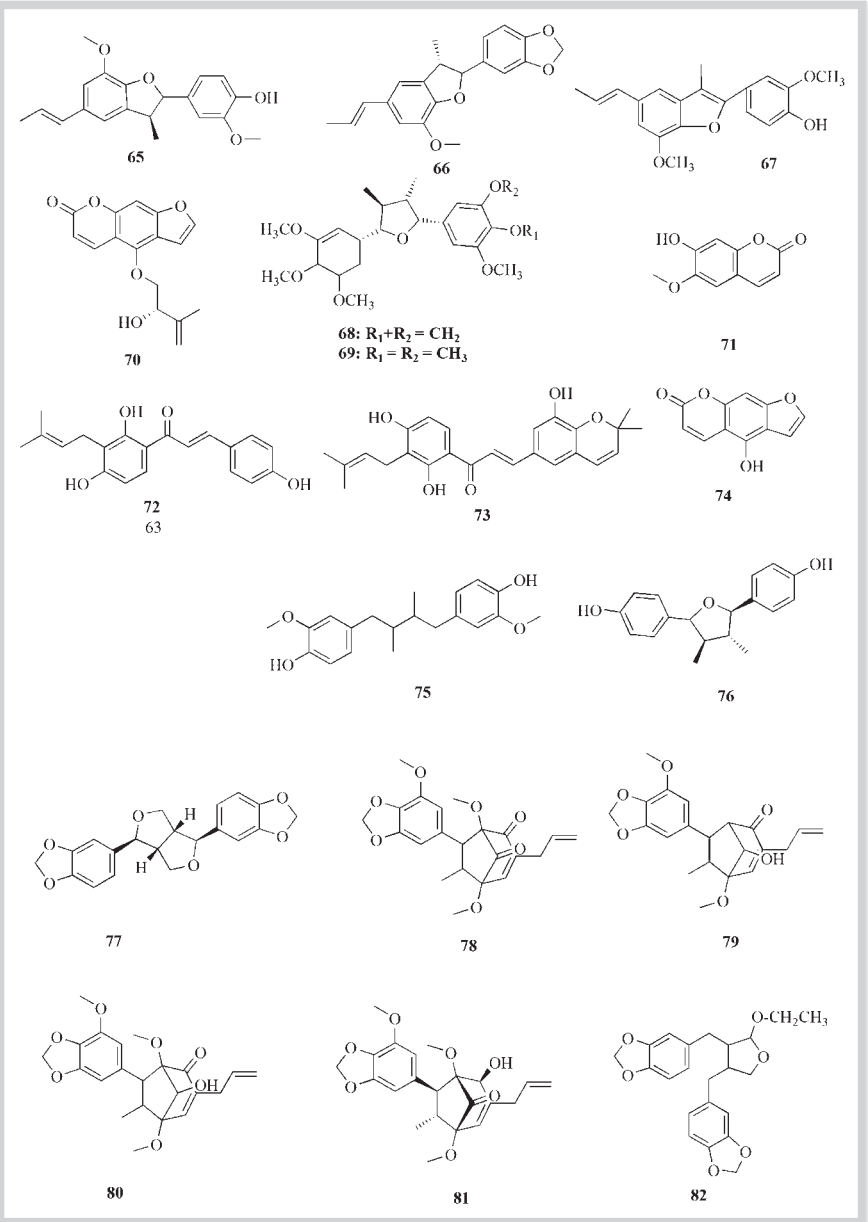

Fig. 5 Coumarins, lignans and phenols.

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, 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-*O*-acetyluncaric 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

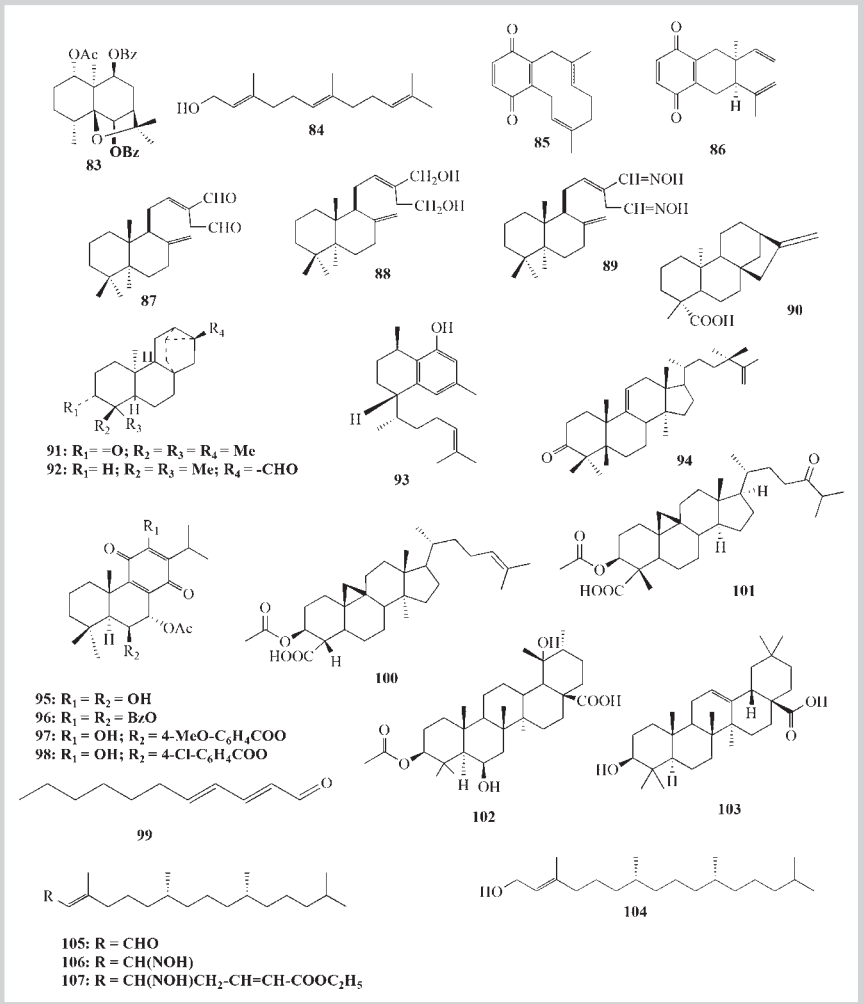

Fig. 6 Terpenoids.

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 falcarindiol (**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., 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 1,3-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-dihydromethystic-in (**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**.

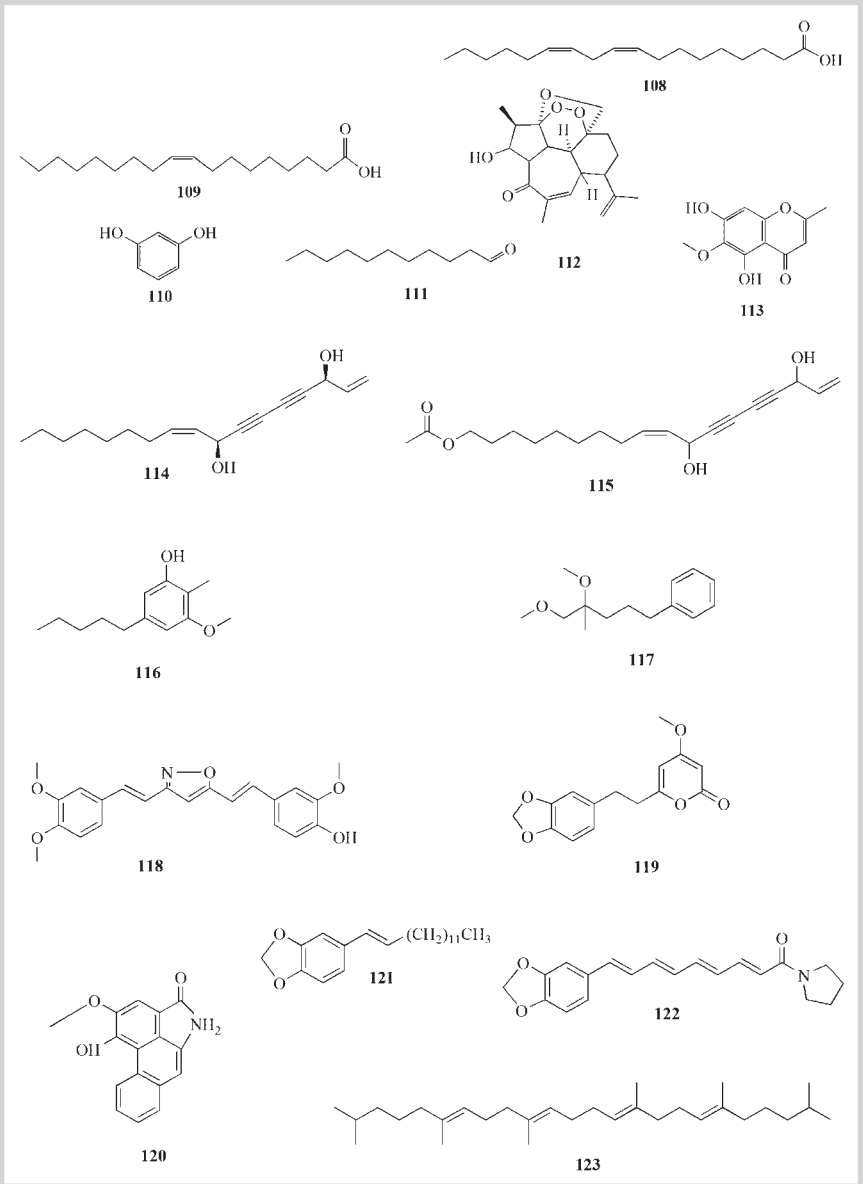

Fig. 7 Fatty acids, chromones, alkanes, alkenes, alkynes and aromatics.

Miscellaneous

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 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-

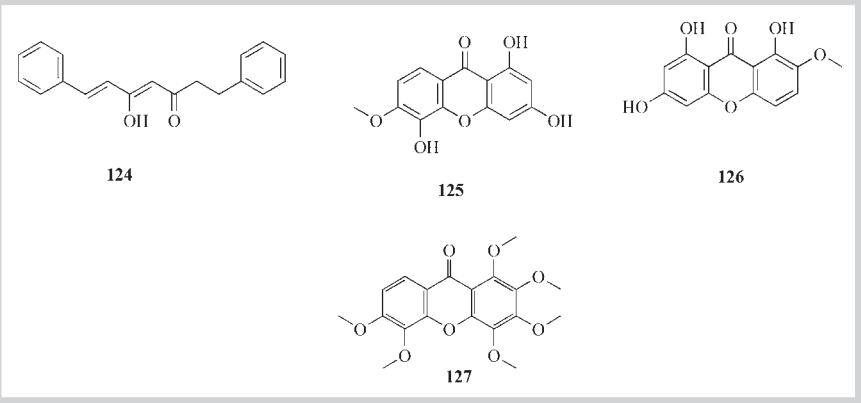

Fig. 8 Miscellaneous compounds.

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.

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, antigonorrheal 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 JJM.* Antibacterial activity of naphthoquinones and triterpenoids from *Euclea natalensis* root bark. J 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 IS, 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 vulcanicola* 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
53 *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*. J 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*. J Med Microbiol 2010; 59: 567–572
63 *Deng JZ, Starck SR, Hecht SM.* Pentacyclic triterpenoids from *Freziera sp.* that inhibit DNA polymerase *β*. 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*. J 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