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Natural Remedies against Multi-Drug Resistant *Mycobacterium tuberculosis*

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Abstract

Tuberculosis (TB), caused by *Mycobacterium tuberculosis* is an infectious deadly disease and the treatment of which is one of the most severe challenges at the global level. Currently more than 20 chemical medications are described for the treatment of TB. Regardless of availability of several drugs to treat TB, the causative agent, *M. tuberculosis* is nowadays getting resistant toward the conventional drugs and leading to conditions known as Multidrug-resistant tuberculosis (MDR-TB) and extensively drug resistant tuberculosis (XDR-TB). This situation has terrified the global health community and raised a demand for new anti-tuberculosis drugs. Medicinal plants have been used to cure different common as well as lethal diseases by ancient civilizations due to its virtue of variety of chemical compounds which may have some important remedial properties. The aim of the present review is to focus the anti-tubercular medicinal plants native to India as well as the plants effective against MDR or XDR-TB across the globe. In the present review, we have addressed 25 medicinal plants for TB and 16 plants effective against MDR-TB testified from India and 23 herbal plants described for MDR-TB across the world during 2011-2015. These herbal plants can serve as promising candidates for developing novel medications to combat multi-drug resistant *M. tuberculosis*.

Keywords

Drug Resistant, *Mycobacterium tuberculosis*, Medicinal Plants, MDR or XDR-TB

1. Introduction

Tuberculosis (TB), an infectious deadly disease caused by the various species of *Mycobacterium*, especially *Mycobacterium tuberculosis*, was emerged from East Africa more than three million years ago [1].

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According to World Health Organization (WHO), TB is the second most fatal disease after HIV, accountable for human death across the globe and about one third of human population is estimated to be infected with *M. tuberculosis*. However, it is not necessary that all infected person may get the tuberculosis. The carrier stage is called latent tuberculosis, in which *M. tuberculosis* infected person does not show any symptoms of disease. Still, about 5% to 10% of the infected people have a chance to develop TB, depending upon the immunity of the individual. Around 6.1 million TB patients have been reported in year 2013, of these, about 5.7 million (93%) cases were new. About 9 million people were reported ill due to TB in 2013, of which approximately 1.5 million died due to the disease (**Figure 1**) [2]. The disease is highly progressive in Asia and Africa and more than 80% of all TB cases were reported from these two continents [3]. When we talk about Indian scenario, one report said that TB was reported about 3300 years ago [4] while according to ancient literature [5] TB have been reported since 1500BC. Treatment of TB is one of the most severe challenges at the global level. Presently, there are more than 20 drugs which are described for the treatment of TB [6] among them. Isoniazid, rifampin, ethambutol, pyrazinamide and streptomycin are most commonly used.

However, recent few years have revealed that the causative agent of Tuberculosis, *M. tuberculosis* is getting resistant towards conventional drugs used for treatment. The development of drug-resistant in *M. tuberculosis* has frightened the global health community [8] [9]. Multidrug-resistant tuberculosis (MDR-TB) is a condition where the *M. tuberculosis* strain is resistant to two most frequently used drugs *i.e.* first-line oral (**Table 1**) specifically isoniazid, rifampicin and it was first developed in USA during 1990s [10] [11]. The improper use of antimicrobial drugs, early treatment cessation, genetic mutation in *M. tuberculosis*, an inadequate administered treatment, etc. may cause drug resistance [12] [13] which can then be transmitted to other people in the community. Among all, genetic mutation is the most important cause for the MDR-TB and 7 hotspots loci have been identified across the chromosome which includes RNA polymerase beta subunit gene, rpoB (rifampicin), nicotinamidase, pncA (pyrazinamide), catalase-peroxidase gene, katG (isoniazid); inhibin alpha, mabA(fabG1)-inhA (isoniazid), DNA gyrase subunit A&B (quinolone), and 16S rRNA gene, rrs (streptomycin) [14] [15]. According to WHO, around 480,000 cases of MDR-TB were reported in 2013-14 and between 20% to 30% of the new cases were from Soviet Union countries. MDR-TB treatment requires the use of second-line drugs (SLDs), which are less effective [6] and highly expensive compared to first-line drugs [16]. Other drugs which are recommended for TB treatment includes sulfamethoxazole and mefloquine, however, both the drugs require further validation [17]. Recently two new anti-TB drugs, bedaquiline which affects the proton pump for ATP synthase and delamanid which blocks the synthesis of mycolic acids have been approved by the US Food and Drug Administration and European Medicines Agency [18] [19]. Together with MDR-TB, XDR-TB (extensively drug resistant tuberculosis) has also been described where *M. tuberculosis* is resistant to at least four of the core anti-

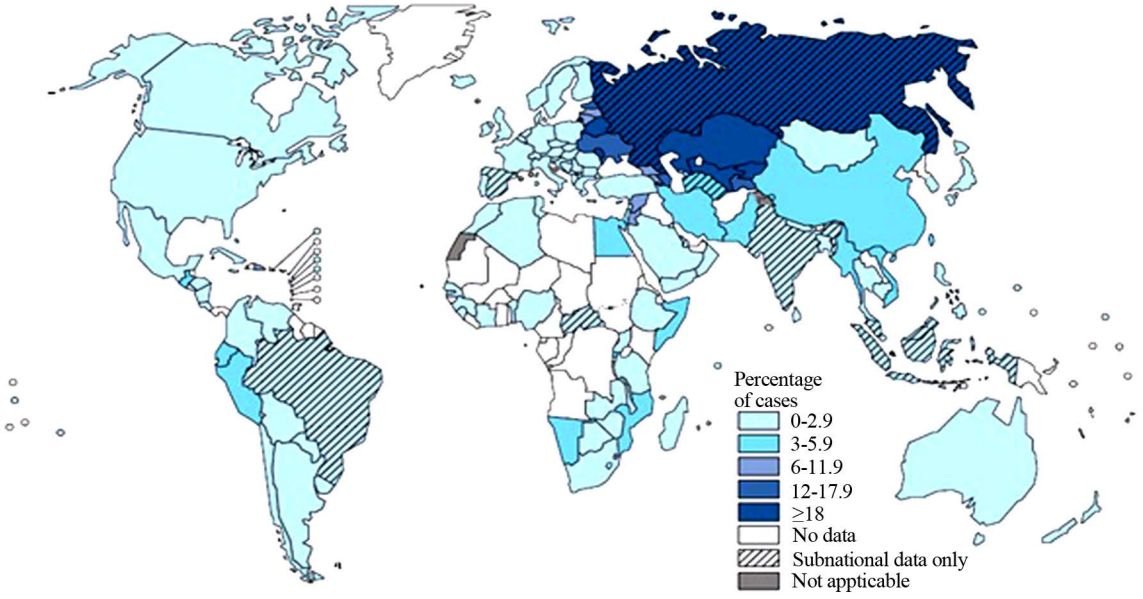

Figure 1. Percentage of new TB cases with MDT-TB in 2013-2014 [7].

Table 1. First and second line recommended by WHO [7].

Group	Drug
First-line oral	Isoniazid, Rifampicin, Ethambutol, Pyrazinamide, Rifabutin and Rifapentine
Injectables	Streptomycin, Kanamycin, Amikacin and Capreomycin
Fluoroquinolones	Levofloxacin, Moxifloxacin, Gatifloxacin and Ofloxacin
Oral bacteriostatic second-line anti-TB drugs	Ethionamide, Prothionamide, Cycloserine, Terizidone, p-Aminosalicylic acid and p-Aminosalicylate sodium
Anti-TB drugs with limited data on efficacy and/or long-term safety in the treatment of drug-resistant TB	Linezolid, Clofazimine, Amoxicillin/clavulanate, Imipenem/cilastatin, Meropenem, High-dose isoniazid, Thioacetazone, Clarithromycin, Bedaquiline and Delamanid
Other drugs (need clinical trials)	Sulfamethoxazole, Mefloquine, Pretomanid, Sutezolid, SQ109 and Benzothiazinones

TB drugs including, isoniazid, rifampicin and any of the fluoroquinolones and to one of the three injectable second line drugs (**Table 1**). Nowadays completely drug–resistant *Mycobacterium tuberculosis* strains have also been evolved which are resistant to all the first and second line drugs used for TB treatment [20]-[22]. Types of report have directed attention of researchers worldwide to find a novel potent drug molecule for the treatment of TB. Recently, [23] researchers have reviewed new drugs for tuberculosis including PA-824 (Nitroimidazole), Linezolid (Oxazolidinones), Sutezolid (Oxazolidinones), AZD5847 (Oxazolidinones) and SQ109 (1,2-diamine). Most of these drugs are under the clinical trial phase II. Therefore, there is an urgent demand to find out some potential anti-tuberculosis medicines which are effective against the resistant deadly strains. As usual, the "hope for the best" is the natural system and generally mankind is always looking into actinomycetes [24]-[26], fungi [27] [28], cyanobactria [29] and plants [30] [31] for the new drug molecules. Various drugs have already been identified and still being identified from the natural resources by the mankind.

Further, the interest in herbal medications is due to adverse effect of chemical based anti-TB drugs on the patients, who generally have to administer the drug for longer durations. The adverse effects of first-line oral and second line drugs are summarized in the **Table 2**. According to one survey in India, the adverse drug reactions during MDR-TB treatment ranges from 57.14% to 94.3% and the most common adversarial effect was found to be gastrointestinal problems (71.7%) [32]. In contrast to this, herbal medicines are naturally occurring chemical compounds which can be administrated in the form of whole plant or it particular part. The advantages of herbal medications are fewer side effects, affectivity in multiple diseases as they are crude mixture of many plant compounds and are low cost.

2. Medicinal Plants for Tuberculosis

The significance of plants has been recognized and documented since ancient time due to virtue of its variety of chemical compounds, which may have some important medicinal properties that can be used to cure diverse diseases. Medicinal plants have been widely used as preventives and curative solutions against different common as well as lethal diseases by ancient cultures. There are some prehistoric data available, in which recipes for medicine preparation from the plants have been discussed [35]-[38]. The World Health Organization (WHO) estimated that about 80 percent of world's population still relied on traditional medicinal plants for their primary health care. The uses of herbs and herbal products have been broadly being accepted in our modern way of life. Moreover [39], the majority of new drugs introduced in the United States are derived primarily from the plants. As discussed, most of the chemical drugs cause adverse effects and are costlier, therefore, nowadays there is an increasing inclinations towards the use of an alternative source of medicine, especially based on medicinal plants [40]. A number of medicinal plants have been reported for anti-mycobacterial activity across the globe [41]-[46].

Ayurveda, means the science of life (Ayur = Life, Veda = Science), is an ancient medical knowledge which was developed in India thousands of years ago and describes numerous plants to treat several diseases. When we particularly talk about TB, more than 250 medicinal plants from India have been reported [47] [48]. The comprehensive safety, toxicity and clinical studies are needed for these plants before using them effectively as curative and/or preventive medications against TB. **Table 3** summarizes the Indian plants reported for anti-mycobacterial activity during last 5 (2011-2015) years.

Table 2. Adversarial effects of commonly used anti-mycobacterial drugs [33] [34].

Group	Drug	Adverse effects
First-line oral	Isoniazid	Nausea, vomiting, epigastric pain, hepatotoxic, psychosis, convulsive seizures, mental confusion, and coma etc.
	Rifampin	Exanthema, hepatotoxicity, immunological reactions, nausea, anorexia, abdominal pain, fatigue, dizziness, headache, dyspnea, and ataxia etc.
	Pyrazinamide	Nausea, vomiting, anorexia, severe exanthema, pruritus, rhabdomyolysis with myoglobinuria, kidney failure, acute arthritis in gouty individuals and hepatotoxicity.
	Ethambutol	Retrobulbar neuritis, nausea, vomiting, abdominal pain, hepatotoxicity, hematological symptoms, hematological symptoms and hypersensitivity etc.
Second-line drugs	Aminoglycosides	Ototoxic, neurotoxic, nephrotoxic, neuromuscular blockage and hypersensitivity.
	Fluoroquinolones	Affects that gastrointestinal, central nervous system, musculoskeleta, cardiovascular system, urinary tract, endocrine system and also cause skin reactions and allergies.
	Oral bacteriostatic second-line anti-TB drugs	Neurological adverse effects (headache, vertigo, dysarthriasomnolence, convulsion, mental confusion, and memory deficit) and psychiatric adverse effects (psychotic states with catatonic, paranoid, and depressive reactions, with a risk of suicide.

Table 3. Indian medicinal plants possessing anti-mycobacterial activity (Reported during 2011-2015).

Plant name (Botanical)	Family	Part Used	Solvent used for extraction	Chemical constituents	Anti-TB activity/MIC values	Reference
Mallotus philippensis (*Linn.*) *Muell Arg*.	Euphorbiaceae	Leaves	First in 95% ethanol, than fractionation using t hexane, chloroform, ethyl acetate and metahnol	Ursolic acid and *β*-sitosterol	MIC for *M. tuberculosis* $H_{37}Rv$ and *M. tuberculosis* $H_{37}Ra$ is 0.25 and 0.125 mg/mL respectively in ethyl acetate fraction	[49] [50]
Vetiveria zizanioides L. Nash	Poaceae	Roots	Hexane, ethyl acetate and methanol fractions from ethanolic extract	Need to be identify	MIC of the ethanolic extract of intact as well as spent root is 500 µg/mL whereas for the hexane fraction it is 50 µg/mL against *M. tuberculosis* $H_{37}Rv$	[51]
Withania somnifera (*Linn.*)	Solanaceae	Fresh leaves and roots	Water	Need to be identify	1.0 mg/mL - 64.47% and 0.01 mg/mL - 17.88% inhibition of *M. tuberculosis* $H_{37}Rv$	[52]
Piper nigrum L.	Piperaceae	Seeds	Acetone, ethanol and distilled water	Piperine	MIC of acetone extract is 100 µg/mL and combination of acetone and ethanol extracts is 50 µg/mL against *M. tuberculosis* $H_{37}Rv$	[53]
Alstonia scholaris	Apocynaceae	Bark, flower, fruit and leaf	Ethyl acetate, butanol and water	Need to be identify	MIC of butanol extracts of flower and bark is of 500 and 100 µg/mL respectively against *M. tuberculosis* $H_{37}Rv$	[54]
Acacia catechu (L.) *Willd*	Mimosaceae	Roots	Sequentially extracted in water, ethanol, chloroform and hexane	Need to be identify	Most potent anti-mycobacterium activity shown by ethanol extracts of *A. paniculata* and *A. catechu* with MIC value 2.5 ± 1.45 mg/mL (5.0 mg/mL by [55] followed by chloroform extract of *A. paniculata* and ethanol extract of *D. metel* (05 ± 1.24 mg/mL) against *M. tuberculosis* $H_{37}Rv$	[55] [56]
Ailanthus excels Roxb.	Simaroubaceae	Roots				
Aegle marmelos Corr.	Rutaceae	Leaf				
Andrographis paniculata Nees.	Acanthaceae	Leaf				
Datura metel L.	Solanaceae	Leaf				
Vitex trifolia L. (*syn. Vitex rotundifolia*	Verbenaceae	Leaves	Cold methanol followed by fractionation in hexane, chloroform and *n*-butanol	*Compound*-1: **13-*hydroxy*-5(10), 14-*halimadien*-6-*one*** *Compound*-2: **6*α*,7*α*-*diacetoxy*-13-*hydroxy*-8(9),14-*labdadiene*** *Compound*-3: **9-*hydroxy*-13(14)-*labden*-15, 16-*olide*) *and*** *Compound*-4: ***Isoambreinolide***	MIC for compound 3 and 4 is 100 and 25 µg/mL respectively against *M. tuberculosis* HRv (ATCC27294)	[57]

Continued

Allium sativum	Amaryllidaceae	Bulb	Petroleum ether, ethyl acetate and chloroform	Either fats and fixed oils or phenol and aryl amine derivative	MIC of *Acalyphaindica*, *Adhatodavasica* and*Allium sativum* is 5, 10 and 1.25 mg/mL respectively (80 mg/mL of garlic oil against *M. tuberculosis* HRv_{37} [58]	[58] [59]
Acalypha indica	Euphorbiaceae	Leaves				
Adhatoda vasica	Acanthaceae	Leaves				
Actiniopteris radiata Linn.	Actiniopteridaceae	Whole plant	n-Hexane, chloroform and ethanol	Need to be identify	MIC of n-Hexane, chloroform and ethanolic extracts was 12.5, 3.125, 25 µg/mL respectively against *M. tuberculosis* $H_{37}RV$	[60]
Syzygium aromaticum	Fabaceae	Buds	Hexane, acetone and methanol	Terpenoids, alkaloids, flavonoids and saponins	Lowest MIC was of metahnol extract of *Syzygium aromaticum*, 0.8 µg/mL against *M. tuberculosis* $H_{37}RV$	[61]
Piper nigrum	Piperaceae	Seeds		Alkaloids and carbohydrates		
Glycyrrhiza glabra	Fabaceae	Rhizome		Terpenoids, alkaloids, flavonoids, Saponins and carbohydrates		
Aegele marmelos	Rutaceae	Leaves		Terpenoids, alkaloids and flavonoids		
Lawsonia inermis	Lythraceae	Leaves		Terpenoids, alkaloids, flavonoids and saponins		
Strophanthus wallichii	Apocynaceae	Whole plant	Methanol	2-hydroxy-4-methoxy-benzaldehyde	Showed anti-tubercle activity against *M. tuberculosis*	[62]
Quercus infectoria	Fagaceae	Seed	Methanol crude extract	Need to be identify	The MIC of pet-ether, chloroform and methanol extracts were 12.5 µg/mL, 50 µg/mL and 100 µg/mL Potential anti-tuberculosis activity against *M. tuberculosis* $H_{37}RV$	[63]
Leucas marrubioides	Lamiaceae	Roots	Petroleum ether, chloroform and methanol	Need to be identify	The MIC of pet-ether, chloroform and methanol extracts were 12.5 µg/mL, 50 µg/mL and 100 µg/mL against *M. tuberculosis*	[64]
Cassia fistula Linn	Fabaceae	Roots	Petroleum ether, chloroform and ethanol (95%)	Alkaloids and tannins could be responsible	A alcoholic extract showed good activity at 12.5 µg/mL against *M. tuberculosis* $H_{37}Rv$	[65]
Glycyrrhiza glabra L.	Fabaceae	Rhizomes	Acetone and then fractionated with n-hexane and ethyl acetate	Isoliquiritigenin and liquiritigenin	MIC 12.5 - 100 µg/mL	[66]

The above data shows that some plants and/or their fractions have very low MIC value (>25 µg/mL) (**Table 2**) and are effective. These plants are promising candidates to find novel medication for the treatment of TB. However, the emergence of MDR and XDR-TB has further inspired the scientific community to find novel and more potent anti-mycobacterial drug molecules. Various plants across the globe possess anti-mycobacterial activity against MDR-TB [67]-[70]. **Table 4** summarizes the medicinal plants having anti-mycobacterial activity against MDR-TB reported during 2011-2015 in countries other than India.

India is also one of the leading countries in herbal medicines and researchers are continuously engaged in searching novel drug molecules to combat MDR/XDR-TB. Since last few years several plants have been reported for their anti-mycobacterial activity from India (**Table 5**).

The review suggests that many plants either confined to India or elsewhere have the unique capability to counter the deadly tuberculosis pathogen. Some plants showed very low MIC values against the clinical isolates of MDR-*M. tuberculosis* and few of them were also found effective against XDR-TB. These plants surely must be chosen for further researches and attempts should be made to translate this knowledge into some potential anti-TB therapies, either curative or preventive. In some cases the active molecule(s) need to be identified and where the molecule has been identified one should go for generation of safety, efficacy, pharmacokinetics, stability, etc. data through approved clinical experiments, which are essential for drug development, regulatory approval and commercialization. In few studies, it was also observed that most of the data required by the regulatory authorities are available and if some more efforts are made to find out evidences of safety, stability, etc. then these herbal leads may be converted into an alternative and novel solutions to combat MDR and XDR-TB in future.

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Table 4. Medicinal plants having anti-mycobacterial activity against MDR-TB reported during 2011-2015 in countries other than India.

Plant name (Botanical)	Part Used	Solvent used for extraction	Chemical constituents	Strain and method used	MIC value/Anti-TB activity	Reference
Prunella vulgaris L.	Whole plant	20% ethanol	Identification needed	MDR *M. tuberculosis*, ELISA and RT-PCR	The extract of *Prunella vulgaris* L. can enhance the cellar immunological Function in rats.	[71]
Celastrus vulcanicola	Dried leaves	Ethanol	Dihydro-*β*-agarofuransesquiterpenes	$H_{37}Rv$ ATCC 27,294 and clinical isolate, strain 02TBDM039EP097. MTT assay.	*α*-Acetoxy-6*β*,9*β*-dibenzoyloxy-dihydro-*β*-agarofuran exhibited anti-tuberculosis activity against the MDR TB strain with a MIC value of 6.2 µg/mL	[72]
Flourensia cernua	Whole plant	n-hexane, ethanol, ethyl acetate, n-butanol, and methanol	Identification needed	*M. tuberculosis* $H_{37}Rv$ (ATCC 27,294 and *M. tuberculosis* CIBIN/UMF 15:99 MDR strain, Microplate Alamar Blue Assay (MABA)	Decoction of *F. cernua* leaves combined with *n*-Hex fractionation is more efficient	[73]
Allium sativum	Cloves	70% ethanol	Identification needed	15 MDR and 5 non-MDR MTB isolates of *M. tuberculosis*	MIC of garlic extract was ranged from 1 to 3 mg/mL	[74] [75]
Aristolochia brevipes	Root	Dichloromethane	(1) 6*α*-7-dehydro-N-formylnornantenine; (2) E/Z-N-formylnornantenine; (3) 7,9-dimethoxytariacuripyrone; (4) 9-methoxytariacuripyrone; (5) aristololactam I; (6) *β*-sitosterol; (7) stigmasterol; and (8) 3-hydroxy-*α*-terpineol	*M. tuberculosis* $H_{37}Rv$ (27,294); isoniazid-resistant $H_{37}Rv$ (35,822); streptomycin-resistant $H_{37}Rv$ (35,820); rifampicin-resistant $H_{37}Rv$ (35,838), and etambutol-resistant $H_{37}Rv$ (35,837), Microplate Alamar Blue Assay (MABA)	The most active compound against all mycobacterial strains tested was the compound aristolactam I (5), with MIC values ranging between 12.5 and 25 µg/mL	[76]
Tiliacora triandra	Roots	[77]	Bisbenzylisoquinoline alkaloids, tiliacorinine 1), 2'-nortiliacorinine 2), and tiliacorine 3)	59 isolates of MDR *M. tuberculosis*	All the alkaloids showed MIC 3.1 µg/mL against most MDR-MTB isolates	[67]
Humulus lupulus	Whole plant (stems, leaves and roots)	Alcohol	Identification needed	Sensitivity and resistant strains of *M. tuberculosis*	MIC is 4 and 8 mg/mL for sensitive and resistant strains respectively	[78]
Citrus essential oils	---	---	Cold pressed terpeneless Valencia oil (CPT)	MTB (ATCC $H_{37}Rv$), *M. bovis* BCG (BCG, ATCC Pasteur 35,734), *M. avium* (ATCC 700,898) and various clarithromycin resistant clinical isolates, *M. avium*subspecies *paratuberculo*sis (ATCC 19,698) and various drug resistant clinical isolates of *M. abscessus* and *M. chelonae*	CPT demonstrated potent activity against drug-resistant strains of the *M. avium* complex and *M. abscessus*	[79]
Struthanthus marginatus *Struthanthu sconcinnus*	Aerial parts Leaves	Water hexane, dichloromethane, ethyl acetate and n-butanol	Obtusifoliol, 3-O-n-acil-lup-20(29)-en-3*β*,7*β*,15*α*-triol	*M. tuberculosis* strains $H_{37}Rv$ (sensitive) and ATCC 35,338 (resistant to rifampicin) by the microdilution method using resazurin as an indicator of cell viability	Obtusifoliol: MIC $H_{37}Rv$ 50 µg/mL, MIC ATCC 35338 12.5 µg/mL; 3-O-n-acil-lup-20(29)-en-3*β*,7*β*,15*α*-triol: MIC $H_{37}Rv$ 200 µg/mL, MIC ATCC 35338 100 µg/mL	[68]

Continued

Aristolochia taliscana	Roots	Hexane	(−) Licarin A	*M. tuberculosis* $H_{37}Rv$ or MDR. TB murine model	Low toxicity together with the discrete bacteriostatic activity	[80]
Hypericum species	Aerial parts	Ethanol	Identification needed	*M. tuberculosis* $H_{37}Rv$ (ATCC 27,294), $H_{37}Rv$ isoniazid-resistant (ATCC 35,822), $H_{37}Rv$ rifampin-resistant (ATCC 35,838), $H_{37}Rv$ ethambutol-resistant (ATCC 35,837), *M. fortuitum*, *M. smegmatis* (ATCC 35,798), *M. avium* (ATCC 35,717), *M. chelonae*and four drug-resistant strains. Microplate Alamar Blue Assay (MABA)	Potent activity was observed from *H. foliosum*, *H. hircinum subsp. majus*, *H. grandifolium*, *H. humifusum* and *H. elodes*with MICs ranging from 25 to 50 µg/mL. *H. elodes* and *H. hircinum* subsp. majus were also active against drug resistant clinical isolates with MICs ranging from 12.5 to 50 µg/mL	[81]
Chamaedorea tepejilote *Robinia hispida*	Aerial parts	Hexane	Ursolic and oleanolic acids	*M. tuberculosis* $H_{37}Rv$ (ATCC 27294), four mono-resistant strains of *M. tuberculosis* $H_{37}Rv$. Modified Microplate Alamar Blue Assay (MABA)	Both the compounds showed MIC range from 12.5 µg/mL to 50 µg/mL	[82]
Diospyros anisandra	Stem bark	*n*-hexane	Maritinone and 3,3'-biplumbagin	Two strains of MTB ($H_{37}Rv$) susceptible and one MDR clinical isolates. Modified Microplate Alamar Blue Assay (MABA)	Plumbagin and its dimers maritinone and 3,3'-biplumbagin showed the strongest activity against both MTB strains (MIC = 1.56 - 3.33 µg/mL	[83]
Ranunculi Ternati Radix	Whole plant	*Water*, 70% *ethanol and* water eluted part of ethanol extract	Identification needed	$H_{37}Rv$ (ATCC 95054), MDR-TB (2314-2) and XDR-TB strains, Vivo experiments were performed on C57BL/6 mice	70% ethanol eluted part of EE from D101 macroporous resin showed stronger inhibitory effect on MDR2314-2 and XDR1220. MIC 1.0 mg/mL	[84]
Chiness Herble Remidies (*CHM*)	CHM as an adjuvant to anti-TB chemotherapy may have beneficial effect for MDR-TB					[70]
Andrographis paniculata *Annona muricata* *Centella asiatica* *Pluchea indica* *Rhoeospathacea*	Herbs Dried leaves Whole plant Dried leaves Dried leaves	Water, methylene chlolride, ethanol, nhexane and ethyl acetate	Identification needed	*M. tuberculosis* standard strain and MDR strain. Proportion methods using Lowenstein Jensen (L-J) medium	The proportion of inhibition of aqueous extract (2.5 mg/ml) of *Rhoeo spathacea* was 100% against *M. tuberculosis* $H_{37}Rv$ and MDR strain.	[85]
Croton tonkinensis	Whole plants or leaves	---	Diterpenoids including ent-kaurane, kaurane and grayanane	*M. tuberculosis* $H_{37}Ra$ (ATCC 27,294, $H_{37}rv$ (ATCC 35,835), MDR TB (KMRC 00116-00250), XDR TB (KMRC 00203-00197), (KMRC 00130-00064), (KMRC 00120-00137), (KMRC 00121-00341) and (KMRC 00122-00123, Resazurin Microtitre Assay (REMA)	All the di-terpenoids showed activity against susceptible and resistant strains. ent-1b,7a,14b-triacetoxykaur-16-en-15-one showed highest activity, MIC-3.125 - 6.25 µg/ml for MDR and XDR strains.	[86]

Table 5. Indian medicinal plants effective against MDR-TB.

Plant name (Botanical)	Family	Part Used	Solvent used for extraction	Chemical constituents	Strain and method used	MIC value/Anti-TB activity	Reference
Acalypha indica L.	Euphorbiaceae	Leaves	Water extract and pure gel of *Aloe vera*	Identification needed	Drug susceptible strain *M. tuberculosis* $H_{37}Rv$ as control, multi-drug resistant isolates DKU-156, JAL-1236 and fast growing mycobacterial pathogen *M. fortuitum* (TMC-1529). Lowenstein Jensen (L-J) medium and colorimetric BacT/ALERT 3D system	All these plants exhibited activity against MDR isolates of *M. tuberculosis*.	[87]
Adhatoda vasicaNees	Acanthaceae	Leaves					
Allium cepa	Alliaceae	Bulbs					
Allium sativum L.	Alliaceae	Cloves					
Aloe vera L.	Aloaceae	Pure gel					
Kaempferia galanga	*Zingiberaceae*	Rhizome	Ethanol	Ethyl p-methoxycinnamate	*M. tuberculosis* $H_{37}Ra$, $H_{37}Rv$, drug susceptible and multidrug resistant (MDR) clinical isolates. Resazurin Microtitre Assay (REMA)	MIC 0.242 - 0.485 mM	[88]
Piper nigrum L.	Piperaceae	Seeds	Acetone, ethanol and distilled water	Piperine	Reference strain $H_{37}Rv$; three susceptible (S1, S2 and S3) and three MDR (MDR1, MDR2 and MDR3. Microplate Alamar Blue Assay (MABA).	MIC of Acetone extract is 100 µg/mL	[53]
Vetiveria zizanioides	*Poaceae*	Fresh roots	Chloroform and methanol	5,10-pentadecadiyn-1 -ol, a-curcumene, hydroxyjunipene, (?) cycloisosativene, valencine and selino 3,7 (11)-diene	MDR *M. smegmatis*. Dilution and disc diffusion method	All these compounds showed good MIC.	[89]
Urtica dioica	*Urticaceae*	Leaves	Hexane, methanol, ethyl acetate and chloroform	*Anti-tubercle activity of C. sophera* may be due to presence of alkaloids or flavonoids and that of HEUD due to terpenoids.	*M. tuberculosis* standard strain $H_{37}Rv$ (ATCC- 35838), MDR strains, and clinical isolates CL-1 (+3) and CL-2 (+2). A disk diffusion and broth dilution method.	MIC for hexane extract of *U. dioica* and methanol extract of *C. sophera*, is 250 and 125 µg/mL respectively. Semipurified fraction F2 from MECS produced 86% inhibition against clinical isolate and 60% inhibition against MDR strain of *M. tuberculosis*. F18 from HEUD produced 81% inhibition against clinical isolate and 60% inhibition against MDR strain of *M. tuberculosis*.	[90]
Cassia sophera	*Urticaceae*	Dried seeds					
Plumeria bicolor	Apocynaceae	Bark	Methanol than chloroform	Plumericin and iso-Plumericin	*M. tuberculosis* ($H_{37}Rv$) and four multi-drug resistant (MDR) clinical isolates, Tetrazolium Microplate Assay (TEMA)	Plumericin showed better activity against all the four sensitive as well as MDR strains of *M. tuberculosis* with MIC values of 2.1 ± 0.12, 1.3 ± 0.15, 2.0 ± 0.07, 1.5 ± 0.13 & 2.0 ± 0.14 µg/mL and MBC values of 3.6 ± 0.22, 2.5 ± 0.18, 3.8 ± 0.27, 2.9 ± 0.20 & 3.7 ± 0.32 µg/mL than isoplumericin, respectively	[91]
Ventilago madraspatana	Rhamnaceae	Stem bark	[92]	Emodin	Drug resistant clinical isolates, Tetrazolium Microplate Assay (TEMA)	Among all the compounds, Plumbagin was found to be the most potent MIC 0.25 - 16 µg/mL	[93]
Plumbago indicalinn	Plumbaginaceae	Root	[94]	Plumbagin			
Diospyros montanaroxb	Ebenaceae	Stem bark		Diosyprin			
Andrographis paniculata	Acanthaceae	Whole plant	hexane and methanol (1:5)	Andrographolide	Drug resistant susceptible clinical isolate and *M. tuberculosis* $H_{37}Rv$, *Resazurin assay*	The methanolic extract of *A. paniculata* showed maximum anti-mycobacterial activity at 250 µg/mL against all the tested strains of *M. tuberculosis* (H37Rv, MDR, and drug sensitive	[95]

Continued

Punica granatum	*Lythraceae*	Fruit	Water, boiling water and Methanol	Identification needed	MDR and XDR-TB strains, Tetrazolium Microplate Assay (TEMA)	Methanol (M) and water (W) extracts of pomegranate fruit pericarp exhibited greater antitubercular activity (MIC 64 - 512, and 64 - 1024 mg/mL, respectively) than J, the lyophilised juice (MIC 256 - >1024 mg/mL)	[96]

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References

[1] Gutierrez, M.C., Brisse, S., Brosch, R., Fabre, M., Omaïs, B., *et al*. (2005) Ancient Origin and Gene Mosaicism of the Progenitor of *Mycobacterium tuberculosis*. *PLoS Pathogens*, **1**, e5. http://dx.doi.org/10.1371/journal.ppat.0010005

[2] (2014) Organization WH Global Tuberculosis Report 2014. World Health Organization, Geneva.

[3] Zager, E.M. and McNerney, R. (2008) Multidrug-Resistant Tuberculosis. *BMC Infectious Diseases*, **8**, 10. http://dx.doi.org/10.1186/1471-2334-8-10

[4] Brothwell, D. and Sandison, A.T. (1967) Diseases in Antiquity. A Survey of the Diseases, Injuries and Surgery of Early Populations. Diseases in Antiquity a Survey of the Diseases, Injuries and Surgery of Early Populations.

[5] Herzog, B. (1998) History of Tuberculosis. *Respiration*, **65**, 5-15. http://dx.doi.org/10.1159/000029220

[6] D'Ambrosio, L., Centis, R., Sotgiu, G., Pontali, E., Spanevello, A., *et al*. (2015) New Anti-Tuberculosis Drugs and Regimens: 2015 Update. *ERJ Open Research*, **1**, 00010-02015. http://dx.doi.org/10.1183/23120541.00010-2015

[7] WHO (2014) Global Tuberculosis Report 2014. World Health Organization, Geneva.

[8] Zignol, M., Hosseini, M.S., Wright, A., Lambregts-van Weezenbeek, C., Nunn, P., *et al*. (2006) Global Incidence of Multidrug-Resistant Tuberculosis. *Journal of Infectious Diseases*, **194**, 479-485. http://dx.doi.org/10.1086/505877

[9] Control, CfD. and Prevention (2006) Emergence of *Mycobacterium tuberculosis* with Extensive Resistance to Second-Line Drugs—Worldwide, 2000-2004. *MMWR Morbidity and Mortality Weekly Report*, **55**, 301.

[10] Dooley, S.W., Jarvis, W.R., Marione, W.J. and Snider, D.E. (1992) Multidrug-Resistant Tuberculosis. *Annals of Internal Medicine*, **117**, 257-259. http://dx.doi.org/10.7326/0003-4819-117-3-257

[11] Edlin, B.R., Tokars, J.I., Grieco, M.H., Crawford, J.T., Williams, J., *et al*. (1992) An Outbreak of Multidrug-Resistant Tuberculosis among Hospitalized Patients with the Acquired Immunodeficiency Syndrome. *New England Journal of Medicine*, **326**, 1514-1521. http://dx.doi.org/10.1056/NEJM199206043262302

[12] Sharma, S. and Mohan, A. (2004) Multidrug-Resistant Tuberculosis. *Indian Journal of Medical Research*, **120**, 354-376.

[13] India Tuberculosis (2012) Revised National Tuberculosis Control Programme. Annual Status Report. http://www.tbcindia.nic.in/showfile.php?lid=3141

[14] Ohno, H., Koga, H. and Kohno, S. (1998) Multidrug-Resistant Tuberculosis. 2. Mechanisms of Drug-Resistance in *Mycobacterium tuberculosis*—Genetic Mechanisms of Drug-Resistance. *Kekkaku*: [*Tuberculosis*], **73**, 657-663.

[15] Flandrois, J.P., Lina, G. and Dumitrescu, O. (2014) MUBII-TB-DB: A Database of Mutations Associated with Antibiotic Resistance in *Mycobacterium tuberculosis*. *BMC Bioinformatics*, **15**, 107. http://dx.doi.org/10.1186/1471-2105-15-107

[16] Diel, R., Rutz, S., Castell, S. and Schaberg, T. (2012) Tuberculosis: Cost of Illness in Germany. *European Respiratory Journal*, **40**, 143-151. http://dx.doi.org/10.1183/09031936.00204611

[17] Alsaad, N., van Altena, R., Pranger, A.D., van Soolingen, D., de Lange, W.C., *et al*. (2013) Evaluation of Co-Trimoxazole in the Treatment of Multidrug-Resistant Tuberculosis. *European Respiratory Journal*, **42**, 504-512. http://dx.doi.org/10.1183/09031936.00114812

[18] Skripconoka, V., Danilovits, M., Pehme, L., Tomson, T., Skenders, G., *et al*. (2013) Delamanid Improves Outcomes and Reduces Mortality in Multidrug-Resistant Tuberculosis. *European Respiratory Journal*, **41**, 1393-1400. http://dx.doi.org/10.1183/09031936.00125812

[19] Diacon, A.H., Pym, A., Grobusch, M.P., de los Rios, J.M., Gotuzzo, E., *et al*. (2014) Multidrug-Resistant Tuberculosis and Culture Conversion with Bedaquiline. *New England Journal of Medicine*, **371**, 723-732. http://dx.doi.org/10.1056/NEJMoa1313865

[20] Migliori, G., De Iaco, G., Besozzi, G., Centis, R. and Cirillo, D. (2007) First Tuberculosis Cases in Italy Resistant to All Tested Drugs. *Euro Surveillance*, **12**, Article ID: E070517.

[21] Udwadia, Z.F., Amale, R.A., Ajbani, K.K. and Rodrigues, C. (2012) Totally Drug-Resistant Tuberculosis in India. *Clinical Infectious Diseases*, **54**, 579-581. http://dx.doi.org/10.1093/cid/cir889

[22] Klopper, M., Warren, R.M., Hayes, C., van Pittius, N.C.G., Streicher, E.M., *et al*. (2013) Emergence and Spread of Extensively and Totally Drug-Resistant Tuberculosis, South Africa. *Emerging Infectious Diseases*, **19**, 449-455. http://dx.doi.org/10.3201/eid1903.120246

[23] Parida, S., Axelsson-Robertson, R., Rao, M., Singh, N., Master, I., *et al*. (2015) Totally Drug-Resistant Tuberculosis and Adjunct Therapies. *Journal of Internal Medicine*, **277**, 388-405. http://dx.doi.org/10.1111/joim.12264

[24] Mahajan, G.B. and Balachandran, L. (2011) Antibacterial Agents from Actinomycetes—A Review. *Frontiers in Bioscience* (*Elite Edition*), **4**, 240-253.

[25] Adegboye, M. and Babalola, O. (2013) Actinomycetes: A Yet Inexhaustive Source of Bioactive Secondary Metabolites. In: Mendez-Vilas, A., Ed., *Microbial Pathogens and Strategies for Combating Them*: *Science*, *Technology and Education*, Formatex, Badajoz, 786-795.

[26] Patel, J.D., Parmar, M., Patel, P., Rohit, P., Taviyad, R., *et al*. (2014) Dynamism of Antimicrobial Activity of Actinomycetes—A Case Study from Undisturbed Microbial Niche. *Advances in Microbiology*, **4**, 324-334. http://dx.doi.org/10.4236/aim.2014.46039

[27] Smith, D. and Ryan, M. (2009) Fungal Sources for New Drug Discovery. Access Science, © McGraw-Hill Companies. http://www.accessscience.com

[28] Aly, A.H., Debbab, A. and Proksch, P. (2011) Fifty Years of Drug Discovery from Fungi. *Fungal Diversity*, **50**, 3-19. http://dx.doi.org/10.1007/s13225-011-0116-y

[29] Singh, R.K., Tiwari, S.P., Rai, A.K. and Mohapatra, T.M. (2011) Cyanobacteria: An Emerging Source for Drug Discovery. *The Journal of Antibiotics*, **64**, 401-412. http://dx.doi.org/10.1038/ja.2011.21

[30] Abdallah, E.M. (2011) Plants: An Alternative Source for Antimicrobials. *Journal of Applied Pharmaceutilcal Science*, **1**, 16-20.

[31] Katiyar, C., Gupta, A., Kanjilal, S. and Katiyar, S. (2012) Drug Discovery from Plant Sources: An Integrated Approach. *Ayu*, **33**, 10-19.

[32] Akshata, J., Chakrabarthy, A., Swapna, R., Buggi, S. and Somashekar, M. (2015) Adverse Drug Reactions in Management of Multi Drug Resistant Tuberculosis, in Tertiary Chest Institute. *Journal of Tuberculosis Research*, **3**, 27-33. http://dx.doi.org/10.4236/jtr.2015.32004

[33] Arbex, M.A., Varella Mde, C., Siqueira, H.R. and Mello, F.A. (2010) Antituberculosis Drugs: Drug Interactions, Adverse Effects, and Use in Special Situations-Part 1: First-Line Drugs. *Jornal Brasileiro de Pneumologia*, **36**, 626-640. http://dx.doi.org/10.1590/S1806-37132010000500016

[34] Arbex, M.A., Varella Mde, C., Siqueira, H.R. and Mello, F.A. (2010) Antituberculosis Drugs: Drug Interactions, Adverse Effects, and Use in Special Situations-Part 2: Second Line Drugs. *Jornal Brasileiro de Pneumologia*, **36**, 641-656. http://dx.doi.org/10.1590/S1806-37132010000500017

[35] Glesinger, L. (1954) Medicine through Centuries. Zora, Zagreb, 21-38.

[36] Bottcher, H. (1965) Miracle Drugs. Zora, Zagreb, 23-139.

[37] Castiglioni, A., Krumbhaar, E.B. and Alfred, A. (1947) A History of Medicine. Knopf, New York.

[38] Petrovska, B.B. (2012) Historical Review of Medicinal Plants' Usage. *Pharmacognosy Reviews*, **6**, 1-5. http://dx.doi.org/10.4103/0973-7847.95849

[39] Cragg, G.M. and Newman, D.J. (2013) Natural Products: A Continuing Source of Novel Drug Leads. *Biochimica et Biophysica Acta* (*BBA*)—*General Subjects*, **1830**, 3670-3695. http://dx.doi.org/10.1016/j.bbagen.2013.02.008

[40] Santhosh, R.S. and Suriyanarayanan, B. (2014) Plants: A Source for New Antimycobacterial Drugs. *Planta Medica*, **80**, 9-21.

[41] Newton, S.M., Lau, C. and Wright, C.W. (2000) A Review of Antimycobacterial Natural Products. *Phytotherapy Research*, **14**, 303-322. http://dx.doi.org/10.1002/1099-1573(200008)14:5<303::AID-PTR712>3.0.CO;2-N

[42] Mohamad, S., Zin, N.M., Wahab, H.A., Ibrahim, P., Sulaiman, S.F., *et al*. (2011) Antituberculosis Potential of Some Ethnobotanically Selected Malaysian Plants. *Journal of Ethnopharmacology*, **133**, 1021-1026. http://dx.doi.org/10.1016/j.jep.2010.11.037

[43] Babalola, I.T., Adelakun, E.A., Wang, Y. and Shode, F.O. (2012) Anti-TB Activity of *Sterculia setigera* Del., Leaves (Sterculiaceae). *Journal of Pharmacognosy and Phytochemistry*, **1**, 19-26.

[44] Robles-Zepeda, R.E., Coronado-Aceves, E.W., Velázquez-Contreras, C.A., Ruiz-Bustos, E., Navarro-Navarro, M., *et*

al. (2013) *In Vitro* Anti-Mycobacterial Activity of Nine Medicinal Plants Used by Ethnic Groups in Sonora, Mexico. *BMC Complementary and Alternative Medicine*, **13**, 329. http://dx.doi.org/10.1186/1472-6882-13-329

[45] Balcha, E., Mengiste, B., Gebrelibanos, M., Worku, A. and Ameni, G. (2014) Evaluation of *In-Vitro* Anti-Mycobacterial Activity of Selected Medicinal Plants in Mekelle, Ethiopia. *World Applied Sciences Journal*, **31**, 1217-1220.

[46] Njeru, S.N., Obonyo, M.A., Ngari, S.M., Nyambati, S., Onsarigo, J.M.N., *et al*. (2015) Antituberculous, Antimicrobial, Cytotoxicity and Phytochemical Activity Study of *Piliostigma thonningii* Extract Fractions. *Journal of Medicinal Plants Research*, **9**, 655-663.

[47] Gautam, R., Saklani, A. and Jachak, S.M. (2007) Indian Medicinal Plants as a Source of Antimycobacterial Agents. *Journal of Ethnopharmacology*, **110**, 200-234. http://dx.doi.org/10.1016/j.jep.2006.12.031

[48] Arya, V. (2011) A Review on Anti-Tubercular Plants. *International Journal of PharmaTech Research*, **3**, 872-880.

[49] Chattopadhyay, D., Arunachalam, G., Mandal, A.B., Sur, T.K., Mandal, S.C., *et al*. (2002) Antimicrobial and Anti-Inflammatory Activity of Folklore: *Mallotus peltatus* Leaf Extract. *Journal of Ethnopharmacology*, **82**, 229-237. http://dx.doi.org/10.1016/S0378-8741(02)00165-4

[50] Gupta, V., Shukla, C., Bisht, G., Saikia, D., Kumar, S., *et al*. (2011) Detection of Anti-Tuberculosis Activity in Some Folklore Plants by Radiometric BACTEC Assay. *Letters in Applied Microbiology*, **52**, 33-40. http://dx.doi.org/10.1111/j.1472-765X.2010.02963.x

[51] Saikia, D., Parveen, S., Gupta, V.K. and Luqman, S. (2012) Anti-Tuberculosis Activity of Indian Grass KHUS (*Vetiveria zizanioides* L. Nash). *Complementary Therapies in Medicine*, **20**, 434-436. http://dx.doi.org/10.1016/j.ctim.2012.07.010

[52] Adaikkappan, P., Kannapiran, M. and Anthonisamy, A. (2012) Anti-Mycobacterial Activity of *Withania somnifera* and *Pueraria tuberosa* against *Mycobacterium tuberculosis* H37Rv. *Journal of Academia and Industrial Research*, **1**, 153-156.

[53] Birdi, T., D'souza, D., Tolani, M., Daswani, P., Nair, V., *et al*. (2012) Assessment of the Activity of Selected Indian Medicinal Plants against *Mycobacterium tuberculosis*: A Preliminary Screening Using the Microplate Alamar Blue Assay. *European Journal of Medicinal Plants*, **2**, 308-323. http://dx.doi.org/10.9734/EJMP/2012/1638

[54] Antony, M., James, J., Misra, C.S., Sagadevan, L., Veettil, A.T., *et al*. (2012) Anti Mycobacterial Activity of the Plant Extracts of *Alstonia scholaris*. *International Journal of Current Pharmaceutical Research*, **4**, 40-42.

[55] Mishra, P.K., Singh, R.K., Gupta, A., Chaturvedi, A., Pandey, R., *et al*. (2013) Antibacterial Activity of *Andrographis paniculata* (Burm. f.) Wall. ex Nees Leaves against Clinical Pathogens. *Journal of Pharmacy Research*, **7**, 459-462. http://dx.doi.org/10.1016/j.jopr.2013.05.009

[56] Tawde, K., Gacche, R. and Pund, M. (2012) Evaluation of Selected Indian Traditional Folk Medicinal Plants against *Mycobacterium tuberculosis* with Antioxidant and Cytotoxicity Study. *Asian Pacific Journal of Tropical Disease*, **2**, S685-S691. http://dx.doi.org/10.1016/s2222-1808(12)60244-8

[57] Tiwari, N., Thakur, J., Saikia, D. and Gupta, M.M. (2013) Antitubercular Diterpenoids from *Vitex trifolia*. *Phytomedicine*, **20**, 605-610. http://dx.doi.org/10.1016/j.phymed.2013.01.003

[58] Viswanathan, V., Phadatare, A. and Mukne, A. (2014) Antimycobacterial and Antibacterial Activity of *Allium sativum* Bulbs. *Indian Journal of Pharmaceutical Sciences*, **76**, 256-261.

[59] Rajiniraja, M. and Jayaraman, G. (2014) Bioautography Guided Screening of Selected Indian Medicinal Plants Reveals Potent Antimycobacterial Activity of *Allium sativum* Extracts-Implication of Non-Sulfur Compounds in Inhibition. *International Journal of Pharmacy and Pharmaceutical Sciences*, **6**, 671-676.

[60] Munna, S., Basha, S.C., Reddy, P.R., Pramod, N., Kumar, Y.P., *et al*. (2014) Antitubercular Activity of *Actiniopteris radiata Linn*. *Journal of Global Trends in Pharmaceutical Sciences*, **5**, 1443-1445.

[61] Kaur, R. and Kaur, H. (2015) Antitubercular Activity and Phytochemical Screening of Selected Medicinal Plants. *Oriental Journal of Chemistry*, **31**, 597-600.

[62] Suhitha, S., Devi, S.K., Gunasekaran, K., Carehome Pakyntein, H., Bhattacharjee, A., *et al*. (2015) Phytochemical Analyses and Activity of Herbal Medicinal Plants of North-East India for Anti-Diabetic, Anti-Cancer and Anti-Tuberculosis and Their Docking Studies. *Current Topics in Medicinal Chemistry*, **15**, 21-36. http://dx.doi.org/10.2174/1568026615666150112104344

[63] Sheeba, D.G., Gomathi, K.S. and Citarasu, D. (2015) Anti-Mycobacterial and Phytochemical Investigation of Methanol Extracts of Few Medicinal Plants. *Journal of Chemical and Pharmaceutical Sciences*, **8**, 480-486.

[64] Gowrish, A., Vagdevi, H. and Rajashekar, H. (2015) *In Vitro* Antioxidant and Antitubercular Activity of *Leucas marrubioides* Desf. Root Extracts. *Journal of Applied Pharmaceutical Science*, **5**, 137-142. http://dx.doi.org/10.7324/JAPS.2015.50220

[65] Channabasappa, H.S., Shrinivas, J.D. and Venkatrao, K.H. (2015) Evaluation of Antibacterial and Antitubercular Ac-

tivity of *Cassia fistula* Linn Root. *International Journal of Research in Pharmaceutical Sciences*, **6**, 82-84.

[66] Gaur, R., Thakur, J.P., Yadav, D.K., Kapkoti, D.S., Verma, R.K., *et al*. (2015) Synthesis, Antitubercular Activity, and Molecular Modeling Studies of Analogues of Isoliquiritigenin and Liquiritigenin, Bioactive Components from *Glycyrrhiza glabra*. *Medicinal Chemistry Research*, **24**, 3494-3503. http://dx.doi.org/10.1007/s00044-015-1401-1

[67] Sureram, S., Senadeera, S.P., Hongmanee, P., Mahidol, C., Ruchirawat, S., *et al*. (2012) Antimycobacterial Activity of Bisbenzylisoquinoline Alkaloids from *Tiliacora triandra* against Multidrug-Resistant Isolates of *Mycobacterium tuberculosis*. *Bioorganic & Medicinal Chemistry Letters*, **22**, 2902-2905. http://dx.doi.org/10.1016/j.bmcl.2012.02.053

[68] Leitão, F., Leitão, S.G., de Almeida, M.Z., Cantos, J., Coelho, T., *et al*. (2013) Medicinal Plants from Open-Air Markets in the State of Rio de Janeiro, Brazil as a Potential Source of New Antimycobacterial Agents. *Journal of Ethnopharmacology*, **149**, 513-521. http://dx.doi.org/10.1016/j.jep.2013.07.009

[69] Nguta, J.M., Appiah-Opong, R., Nyarko, A.K., Yeboah-Manu, D. and Addo, P.G. (2015) Medicinal Plants Used to Treat TB in Ghana. *International Journal of Mycobacteriology*, **4**, 116-123. http://dx.doi.org/10.1016/j.ijmyco.2015.02.003

[70] Wang, M., Guan, X., Chi, Y., Robinson, N. and Liu, J.P. (2015) Chinese Herbal Medicine as Adjuvant Treatment to Chemotherapy for Multidrug-Resistant Tuberculosis (MDR-TB): A Systematic Review of Randomized Clinical Trials. *Tuberculosis*, **95**, 364-372. http://dx.doi.org/10.1016/j.tube.2015.03.003

[71] Lu, J., Qin, R., Ye, S. and Yang, M. (2011) *Prunella vulgaris* L. Extract Improves Cellular Immunity in MDR-TB Challenged Rats. *Journal of Medical Colleges of PLA*, **26**, 230-237. http://dx.doi.org/10.1016/S1000-1948(11)60040-3

[72] Torres-Romero, D., Jimenez, I.A., Rojas, R., Gilman, R.H., Lopez, M., *et al*. (2011) Dihydro-Beta-Agarofuran Sesquiterpenes Isolated from *Celastrus vulcanicola* as Potential Anti-*Mycobacterium tuberculosis* Multidrug-Resistant Agents. *Bioorganic & Medicinal Chemistry*, **19**, 2182-2189. http://dx.doi.org/10.1016/j.bmc.2011.02.034

[73] Molina-Salinas, G.M., Pena-Rodriguez, L.M., Mata-Cardenas, B.D., Escalante-Erosa, F., Gonzalez-Hernandez, S., *et al*. (2011) *Flourensia cernua*: Hexane Extracts a Very Active Mycobactericidal Fraction from an Inactive Leaf Decoction against Pansensitive and Panresistant *Mycobacterium tuberculosis*. *Evidence-Based Complementary and Alternative Medicine*: *eCAM*, **2011**, Article ID: 782503.

[74] Hannan, A., Ikram Ullah, M., Usman, M., Hussain, S., Absar, M., *et al*. (2011) Anti-Mycobacterial Activity of Garlic (*Allium sativum*) against Multi-Drug Resistant and Non-Multi-Drug Resistant *Mycobacterium tuberculosis*. *Pakistan Journal of Pharmaceutical Sciences*, **24**, 81-85.

[75] Dini, C., Fabbri, A. and Geraci, A. (2011) The Potential Role of Garlic (*Allium sativum*) against the Multi-Drug Resistant Tuberculosis Pandemic: A Review. *Annali dell'Istituto Superiore di Sanita*, **47**, 465-473.

[76] Navarro-Garcia, V.M., Luna-Herrera, J., Rojas-Bribiesca, M.G., Alvarez-Fitz, P. and Rios, M.Y. (2011) Antibacterial Activity of *Aristolochia brevipes* against Multidrug-Resistant *Mycobacterium tuberculosis*. *Molecules*, **16**, 7357-7364. http://dx.doi.org/10.3390/molecules16097357

[77] Patra, A., Ghosh, S. and Mukherjee, B. (2010) Structure Elucidation of Two New Bisbenzylisoquinoline Alkaloids and NMR Assignments of the Alkaloids from the Fruits of *Tiliacora racemosa*. *Magnetic Resonance in Chemistry*, **48**, 823-828. http://dx.doi.org/10.1002/mrc.2670

[78] Serkani, J.E., Isfahani, B.N., Safaei, H.G., Kermanshahi, R.K. and Asghari, G. (2012) Evaluation of the Effect of *Humulus lupulus* Alcoholic Extract on Rifampin-Sensitive and Resistant Isolates of *Mycobacterium tuberculosis*. *Research in Pharmaceutical Sciences*, **7**, 235-242.

[79] Crandall, P.G., Ricke, S.C., O'Bryan, C.A. and Parrish, N.M. (2012) *In Vitro* Effects of Citrus Oils against *Mycobacterium tuberculosis* and Non-Tuberculous Mycobacteria of Clinical Importance. *Journal of Environmental Science and Health Part B, Pesticides, Food Contaminants, and Agricultural Wastes*, **47**, 736-741. http://dx.doi.org/10.1080/03601234.2012.669331

[80] Leon-Diaz, R., Meckes-Fischer, M., Valdovinos-Martinez, L., Campos, M.G., Hernandez-Pando, R., *et al*. (2013) Antitubercular Activity and the Subacute Toxicity of (-)-Licarin A in BALB/c Mice: A Neolignan Isolated from *Aristolochia taliscana*. *Archives of Medical Research*, **44**, 99-104. http://dx.doi.org/10.1016/j.arcmed.2012.12.006

[81] Nogueira, T., Medeiros, M.A., Marcelo-Curto, M.J., García-Pérez, B., Luna-Herrera, J., *et al*. (2013) Profile of Antimicrobial Potential of Fifteen *Hypericum* Species from Portugal. *Industrial Crops and Products*, **47**, 126-131. http://dx.doi.org/10.1016/j.indcrop.2013.03.005

[82] Jimenez-Arellanes, A., Luna-Herrera, J., Cornejo-Garrido, J., Lopez-Garcia, S., Castro-Mussot, M.E., *et al*. (2013) Ursolic and Oleanolic Acids as Antimicrobial and Immunomodulatory Compounds for Tuberculosis Treatment. *BMC Complementory and Alternative Medicines*, **13**, 258. http://dx.doi.org/10.1186/1472-6882-13-258

[83] Uc-Cachon, A.H., Borges-Argaez, R., Said-Fernandez, S., Vargas-Villarreal, J., Gonzalez-Salazar, F., *et al*. (2014) Naphthoquinones Isolated from *Diospyros anisandra* Exhibit Potent Activity against Pan-Resistant First-Line Drugs *Mycobacterium tuberculosis* Strains. *Pulmonary Pharmacology and Therapeutics*, **27**, 114-120.

http://dx.doi.org/10.1016/j.pupt.2013.08.001

[84] Zhang, L., Li, R., Li, M., Qi, Z. and Tian, J. (2015) *In Vitro* and *in Vivo* Study of Anti-Tuberculosis Effect of Extracts Isolated from *Ranunculi Ternati* Radix. Sarcoidosis Vasculitis and Diffuse Lung Diseases. *Official Journal of WASOG/ World Association of Sarcoidosis and Other Granulomatous Disorders*, **31**, 336-342.

[85] Radji, M., Kurniati, M. and Kiranasari, A. (2015) Comparative Antimycobacterial Activity of Some Indonesian Medicinal Plants against Multi-Drug Resistant *Mycobacterium tuberculosis*. *Journal of Applied Pharmaceutical Science*, **5**, 19-22.

[86] Jang, W.S., Jyoti, M.A., Kim, S., Nam, K.W., Ha, T.K., *et al*. (2015) *In Vitro* Antituberculosis Activity of Diterpenoids from the Vietnamese Medicinal Plant *Croton tonkinensis*. *Journal of Natural Medicines*, **70**, 127-132.

[87] Gupta, R., Thakur, B., Singh, P., Singh, H., Sharma, V., *et al*. (2010) Anti-Tuberculosis Activity of Selected Medicinal Plants against Multi-Drug Resistant *Mycobacterium tuberculosis* Isolates. *Indian Journal of Medical Research*, **131**, 809-813.

[88] Lakshmanan, D., Werngren, J., Jose, L., Suja, K., Nair, M.S., *et al*. (2011) Ethyl *p*-Methoxycinnamate Isolated from a Traditional Anti-Tuberculosis Medicinal Herb Inhibits Drug Resistant Strains of *Mycobacterium tuberculosis in Vitro*. *Fitoterapia*, **82**, 757-761. http://dx.doi.org/10.1016/j.fitote.2011.03.006

[89] Gupta, S., Dwivedi, G.R., Darokar, M.P. and Srivastava, S.K. (2012) Antimycobacterial Activity of Fractions and Isolated Compounds from *Vetiveria zizanioides*. *Medicinal Chemistry Research*, **21**, 1283-1289. http://dx.doi.org/10.1007/s00044-011-9639-8

[90] Singh, R., Hussain, S., Verma, R. and Sharma, P. (2013) Anti-Mycobacterial Screening of Five Indian Medicinal Plants and Partial Purification of Active Extracts of *Cassia sophera* and *Urtica dioica*. *Asian Pacific Journal of Tropical Medicine*, **6**, 366-371. http://dx.doi.org/10.1016/S1995-7645(13)60040-1

[91] Kumar, P., Singh, A., Sharma, U., Singh, D., Dobhal, M., *et al*. (2013) Anti-Mycobacterial Activity of Plumericin and Isoplumericin against MDR *Mycobacterium tuberculosis*. *Pulmonary Pharmacology & Therapeutics*, **26**, 332-335. http://dx.doi.org/10.1016/j.pupt.2013.01.003

[92] Basu, S., Ghosh, A. and Hazra, B. (2005) Evaluation of the Antibacterial Activity of *Ventilago madraspatana* Gaertn., *Rubia cordifolia* Linn. and *Lantana camara* Linn.: Isolation of Emodin and Physcion as Active Antibacterial Agents. *Phytotherapy Research*, **19**, 888-894. http://dx.doi.org/10.1002/ptr.1752

[93] Dey, D., Ray, R. and Hazra, B. (2014) Antitubercular and Antibacterial Activity of Quinonoid Natural Products against Multi-Drug Resistant Clinical Isolates. *Phytotherapy Research*, **28**, 1014-1021. http://dx.doi.org/10.1002/ptr.5090

[94] Hazra, B., Sarkar, R., Bhattacharyya, S., Ghosh, P.K., Chel, G., *et al*. (2002) Synthesis of Plumbagin Derivatives and Their Inhibitory Activities against *Ehrlich ascites* Carcinoma *in Vivo* and *Leishmania donovani* Promastigotes *in Vitro*. *Phytotherapy Research*, **16**, 133-137. http://dx.doi.org/10.1002/ptr.867

[95] Prabu, A., Hassan, S., Prabuseenivasan Shainaba, A.S., Hanna, L.E., *et al*. (2015) Andrographolide: A Potent Antituberculosis Compound That Targets Aminoglycoside 2'-*N*-Acetyltransferase in *Mycobacterium tuberculosis*. *Journal of Molecular Graphics & Modelling*, **61**, 133-140. http://dx.doi.org/10.1016/j.jmgm.2015.07.001

[96] Dey, D., Ray, R. and Hazra, B. (2015) Antimicrobial Activity of Pomegranate Fruit Constituents against Drug-Resistant *Mycobacterium tuberculosis* and *β*-Lactamase Producing *Klebsiella pneumoniae*. *Pharmaceutical Biology*, **53**, 1474-1418. http://dx.doi.org/10.3109/13880209.2014.986687