aJava

Asian Journal of Animal and Veterinary Advances

Academic
Journals Inc.

www.academicjournals.com

Asian Journal of Animal and Veterinary Advances 10 (9): 443-460, 2015
ISSN 1683-9919 / DOI: 10.3923/ajava.2015.443.460

Plants as Future Source of Anti-Mycobacterial Molecules and Armour for Fighting Drug Resistance

[1]Brajesh Singh, [1]Mukta Jain, [2]S.V. Singh, [3]Kuldeep Dhama, [1]G.K. Aseri, [4]Neelam Jain, [4]Manali Datta, [1]Neeraj Kumar, [5]Parul Yadav, [1]Sujata Jayaraman, [2]Saurabh Gupta, [2]Kundan Kumar Chaubey and [1]Jagdip Singh Sohal

[1]Amity Institute of Microbial Technology, Amity University Rajasthan, Kant Kalwar, NH-11C Delhi, Jaipur Highway, Jaipur, 303002, India

[2]Animal Health Division, Central Institute for Research on Goats, Makhdoom, PO-Farah, Mathura, 281122, Uttar Pradesh, India

[3]Division of Pathology, Indian Veterinary Research Institute, Izatnagar, Bareilly, 243122, Uttar Pradesh, India

[4]Amity Institute of Biotechnology, Amity University Rajasthan, Kant Kalwar, NH-11C Delhi, Jaipur Highway, Jaipur, 303002, India

[5]Amity University Science and Instrumentation Centre, Amity University Rajasthan, Kant Kalwar, NH-11C Delhi Jaipur Highway, Jaipur, 303002, India

Corresponding Author: Jagdip Singh Sohal, Amity Institute of Microbial Technology, Amity University Rajasthan, Kant Kalwar, NH-11C Delhi, Jaipur Highway, Jaipur, 303002, India

ABSTRACT

Mycobacteria are dreadful human and animal pathogens causing range of mycobacterioses in different tissues. Due to their cell wall composition and their adaptability mycobacteria can survive in different habitats for years. Emergence of Multi-drug Resistant (MDR) and extensively drug resistant (XDR) strains has complicated the problem of mycobacterial disease control. Therefore new drugs should evolve to fight drug resistance. Medicinal plants may offer a new hope as source of bioactive molecules for developing alternative medicines for the mycobacterial diseases. Presently used anti-mycobacterial medicines produce serious side-effects and cannot be used in animals because of risk of entry into food chain. Plant derived medicines may help solving this problem and fighting the drug resistance. The present study reviews the literature available on anti- mycobacterial plants and their bioactive molecules with hope that this effort will expedite the research on development of a novel plant derived drugs against mycobacterial diseases.

Key words: Tuberculosis, leprosy, paratuberculosis, bovine tuberculosis, Johne's disease, herbal drugs, bioactive plant metabolites

INTRODUCTION

World Health Organization (WHO) has stated that 80% of the world's population depends on traditional medicine for primary health care (Hiremath and Taranath, 2013). Rising cases of resistant pathogenic strains has caused a focus to develop plant derived antibiotics. Plant derived medicines are supposed to absorb easily in the body and cause less or no side effects (Sibanda and Okoh, 2007). Though Minimum Inhibitory Concentrations (MICs) of plant based antimicrobials is generally higher than antimicrobials obtained from microorganisms, but they have resistance modifying properties (Sibanda and Okoh, 2007). Venkitanarayana (2014) has stated that the plant derived antimicrobials contain different functional groups, hence, their antimicrobial activity is attributed to multiple mechanisms, thereby limiting the development of bacterial resistance against these compounds. Therefore, plants provide a great hope for fighting against antimicrobial resistance.

Plant secondary metabolites can affect the microbial cell in several ways; the disruption of membrane function and structure, interference with DNA replication, interference with RNA transcription and protein synthesis, coagulation of cytoplasmic contents, interruption of quorum sensing, interference with metabolic processes, interference in gene regulation and inhibition of cell wall synthesis enzymes etc (Radulovic *et al*., 2013). However, literature on the antimicrobial action of plant metabolites shows that cell membrane is their primary target (Ahmad *et al*., 2011; Deva, 2010). They may affect its structural integrity, permeability or functionality. It has been shown that the action of plant metabolites as antibacterial agents increases with their increasing lipophilicity, which may be attributed to fact of their increased ability to interact with the cell membrane (Sikkema *et al*., 1995).

Antimicrobial potential of plant metabolites is influenced and dependent on factors like; type of target cell (bacterial/fungal cell, gram-positive/gram-negative bacteria) and also the environment conditions-hydrophilicity (i.e., solubility in water), concentration, temperature and pH (Denyer and Stewart, 1998). Therefore, it may be predicted that action of plant metabolites is expected to be similar for gram-positive bacteria and fungal organisms, where the main target is the cell envelope, whose disintegration or changes in permeability are followed by an efflux of the intracellular compounds and coagulation of cytoplasm (Kalemba and Kunicka, 2003). Plant metabolites can also reduce the production of bacterial and fungal toxins (Rammanee and Hongpattarakere, 2011; Filgueiras and Vanetti, 2006; Daifas *et al*., 2004). One of the very important features of the plant metabolites in fighting microbial diseases is inhibition of quorum sensing. It has been shown that many plant metabolites are inhibitors of quorum sensing (Koh and Tham, 2011; Pan and Ren, 2009). Quorum sensing is the important tool employed by microbial pathogens during virulence like production of toxins, biofilm formation etc.

Interesting observation is that many plant extracts are reported to enhance the activity of several available antibiotics (Adwan and Mhanna, 2008; Braga *et al*., 2005). Therefore, many plant-derived compounds have been evaluated not only for their antimicrobial activity, but also for their action as potentiators of antibiotics and as reversal antibiotic resistance. Hence, plant extracts or metabolites can also be used as antibiotic coadjuvants to enhance their activity as well as reverse the antibiotic resistance. Plant extracts are supposed to enhance the antibiotic activity due to multi-target effect (Ulrich-Merzenich *et al*., 2009). Majority of thoroughly studied medicinal plants contain broad spectrum of bioactive compounds (Efferth and Koch, 2011) with each phytochemicals have different antimicrobial mode (Simoes *et al*., 2009). Multitarget effects of phytochemicals include alteration in structure and function of proteins, interference with synthesis of DNA or RNA or proteins, disruption of the cell membrane and change in its function, inhibition of cytochrome P450 or enhanced absorption and thus bioavailability of active metabolites (Efferth and Koch, 2011; Wink, 2008).

It has been shown that extracts of different plants contain inhibitors of efflux pumps in bacteria (Garvey *et al*., 2011; Hsieh *et al*., 1998), therefore can help fighting multidrug resistance by inhibiting the action of efflux pumps. Another strategy to overcome resistance is to improve the delivery or enhance the accessibility of antibiotics to their sites of action. Many plant metabolites have been reported to affect membrane permeability of a diverse range of microorganisms

(Helander *et al*., 1998), mainly due to the disturbances in lipids of the cell membrane. Also, because of their lipophilic nature, they can increase membrane permeability (Trombetta *et al*., 2005). Therefore, plant metabolites can enhance the permeability of bacterial cells to exogenous products, including antimicrobial agents and hence potentiate the antibacterial activity of antibiotics (Simoes *et al*., 2009). Potentiation of antibiotic action by plant metabolites may also be done by inhibition of biofilm formation. It is well known that bacteria in biofilms are more resistant compared to individual cells. Biofilms constitute a major threat in the clinical environment by acting as reservoirs of multidrug resistant bacteria. As mentioned in previous paras, quorum sensing regulates the formation of biofilms, as plant metabolites can inhibit the quorum sensing therefore will inhibit the formation of biofilm and thereby help in fighting drug resistance.

Plant materials have been used to promote the animal/ human health by strengthening the host defenses. Therefore besides antimicrobial properties, plants are also fascinating to scientists for their immune-modulatory effects on host. A number of plants have immune modifying properties. These immune modifying properties can help clearing infections by boosting the host innate defenses and promoting immune reactions against pathogens. Plants have been shown to have various immune-modulatory effects including; enhancing phagocytosis, enhancing lysosomal activity, stimulating release of cytokines, enhanced antibody production, stimulation of immune cells (CD4, CD8, macrophages etc), enhance expression of MHC molecules, increases activity of NK cells, enhances NO and superoxide production in macrophages etc (Mahima *et al*., 2012; Dhama *et al*., 2014; Mukherjee *et al*., 2014). Therefore, plant materials not only exert antimicrobial effects but also boost the immune system for clearing the infection.

Mycobacterial infections are chronic (like leprosy, tuberculosis, bovine tuberculosis, paratuberculosis, etc) diseases and control of these diseases is a daunting task in several ways (Singh *et al*., 2014a). Firstly, there are no specific clinical symptoms in affected individuals. Secondly, lack of sensitive and specific diagnostic tests to identify mycobacterial infection in sub-clinical stage. Thirdly, lack of effective vaccines for preventing these diseases. At present, the chemo-therapeutic options for mycobacterial diseases are extremely few and cannot be used in animals due to concern of entry of these drugs in food chain through milk and meat (Ayele *et al*., 2001). Therefore, phytomedicine based approach if implemented in modern anti-mycobacterial therapies can be helpful in reducing the incidence of mycobacterial infections both in humans and animals, especially in current era of emerging antibiotic resistance (Tiwari *et al*., 2013). The present review is a compilation on the data available on testing of plants for the anti-mycobacterial activity as wells as ethno-medicinal data with an objective to raise awareness for treating human and animal mycobacterial diseases with plant derived drugs.

MYCOBACTERIAL DISEASES

Tuberculosis: Tuberculosis (TB) is a fearful disease in developing nations especially in the Asian and African continents, mainly due to insufficient means of disease management. Globally nine million people get tuberculosis and two million people die from it (Anonymous, 2014). These numbers are likely to increase because the Human Immunodeficiency Virus (HIV) is knotted with tuberculosis and also due to the evolution of multidrug-resistant strains. India alone account for 24% of total tuberculosis cases worldwide. It is scary to note there are estimated 2,10,000 deaths from MDR-TB annually. On average, an estimated 9% of people with MDR-TB have extensively drug-resistant TB (XDR-TB) (Anonymous, 2014). Though tuberculosis mortality decreased considerably from 1990-2013, but the number of MDR-TB cases tripled from 2009-2013 (Anonymous, 2014). Recent studies report approximately 50,000 XDR (extensively drug resistant) cases of tuberculosis occur annually and are on the rise (Llamas-Gonzalez and Flores-Valdez, 2013).

The XDR cases do not response to any treatment. These data alarm for the development of new drugs especially to fight MDR and XDR cases.

Paratuberculosis: Paratuberculosis or Johne's Disease (JD) is an economically devastating non-treatable chronic intestinal inflammatory condition of domestic ruminants caused by *Mycobacterium avium* subspecies *paratuberculosis* (MAP) and is characterized by un-thriftiness, reduced productivity, loss in body weight with or without diarrhea (Singh *et al*., 2014b). Economic losses due paratuberculosis in US dairy herds exceeds annually over $1.5 billion (Stabel, 1998). In US burden of disease increased from 21.6% infected dairy cattle herds in 1999-68.1% infected dairy herds in 2007 (Pillars *et al*., 2009). Therefore losses might have increased over the years. In India also burden of the disease has increased to a great extent in domestic ruminants over a period of last 28 years (Singh *et al*., 2014a). Besides paratuberculosis being economically important disease also has serious zoonotic concerns with humans Crohn's disease (Singh *et al*., 2010). Milk has been considered as the major source of infection transmission to humans. Therefore, it is critical to control this infection in animals to secure animal productivity and restrict human exposure to this pathogen. Unfortunately, vaccines are not completely efficacious in controlling this disease and chemotherapy is not practiced due to risk to entrance of antibiotics in food chain through meat and milk. Therefore, plant derived medicines may prove safer option for controlling of this disease in animals.

PLANTS OF ANTI-MYCOBACTERIAL NATURE

Traditionally plant based medicines/plant extracts have been extensively used in different parts of the world for treating mycobacterial diseases. In recent past, efforts have been done to rediscover the traditional knowledge of plant based therapeutics used to treat mycobacterial diseases with plant species in different parts of the world including India. Surveys have been undertaken to collect this traditional knowledge. A questionnaire based interview of Traditional Medicine Practitioners (TMPs) of Mpigi and Butambala regions of Uganda reported 90 plant species used to cure tuberculosis traditionally (Bunalema *et al*., 2014). In this survey, *Zanthoxylum leprieurii, Piptadeniastrum africanum, Albizia coriaria* and *Rubia cordifolia* were most common species used to treat tuberculosis by TMPs (Bunalema *et al*., 2014). This survey also highlighted that leaves were the most commonly used plant part to cure the diseases. Survey done by Semenya and Maroyi (2013) showed that Bapedi tribes of Limpopo province of South Africa are dependent on traditional medicines for treating tuberculosis and are using about 21 plant species. Ethnobotanical survey in Eastern Cape province, South Africa reported about 30 plants used to treat tuberculosis by TMPs (Lawal *et al*., 2014). This survey reported that *Clausena anisata, Haemanthus albiflos* and *Artemisia afra* were most commonly used plant to tuberculosis treatment (Lawal *et al*., 2014). Reports from India also exit on traditional use of plants in mycobacterial infections. A survey of tribal population of Bankura district (West Bengal, India) reported use of plants like *Andrographis paniculata, Azadirachta indica, Commelina benghalensis, Evolvulus alsinoides* and *Mussaenda frondosa* for treatment of leprosy (Sinhababu and Banerjee, 2013). Another survey from South India, reported traditional use of *Anacardium occidentale, Corallocarpus epigaeus, Indigofera aspalathoides* and *Trichosanthes lobata* plants in treatment of leprosy (Kingston *et al*., 2009). Table 1 and 2 highlight surveys conducted in India and other parts of the world to list plants used to cure mycobacterial diseases in traditional medicine. Recently, there has been increased interest in testing of plants for anti-mycobacterial activity and a number of plants have been reported to have this activity. Table 3 summarizes the studies conducted in different plants of the world to identify plants with anti-mycobacterial activity.

Table 1: Ethno-medicine surveys for identification of plants used to treat mycobacterial diseases in India

States	Plants	Plant parts	References
Amravati District, Maharashtra	*Sida acuta*	Leaf powder	Jagtap *et al*. (2006)
Terai Arc Landscape	*Acacia concinna*	Leaves powder	Poonam and Singh (2009)
	Andrographis paniculata	Whole plant	
	Clerodendron infortunatum	Flowers infusion	
	Datura metel	Root paste	
	Drypetes roxburhgii	Leaves, fruits decoction	
	Feronia limonia	Fruits	
	Jatropha curcas	Stem, bark decoction	
	Mallotus philippinensis	Seeds	
Eastern Sikkim Himalayan region	*Abies wabbiana*	Leaves	Das *et al*. (2012)
	Stephania glabra	Root bulb	
Chhatarpur District, Madhaya Pradesh	*Adhatoda visica*	Leaf	Chaturvedi and Saxena (2014)
	Sanseviera roxburghiana	Root	
	Withania sominifera	Seed	
	Boerhaavia diffusa	Root	
	Allium sativum	Bulb	
	Zingiber officinale	Rhizome	
	Enicostemma littorale	Whole plant	
	Tinospora cordifolia	Stem	
	Asparagus racemosus	Root	
	Cissampelos pareira	Root	
	Argyreia speciosa	Root	
Adilabad District, Andhra Pradesh	*Adhatoda vasica*	Leaf decoction	Murthy (2012)
Gadchiroli District, Maharashtra	*Dendrocalamus strictus*	Culms	Chavhan and Margonwar (2015)
Khammam District, Andhra Pradesh	*Acacia leucocephalia*	Bark	Krishna *et al*. (2011)
	Ficus hispida	Latex	
Western Ghats in Hassan district, Karnataka	*Kingiodendron pinnatum*	ND	Kumar *et al*. (2015)
	Humboldtia brunonis	ND	
	Ceasalpinia mimosiodes	ND	
	Derris scandens	ND	
	Indigoferra cassiodes	ND	
Banda District, Uttar Pradesh	*Centella asiatica*	Whole plant	Maheshwari and Singh (1987)
ND	*Cissampelos pareira*	Leaf stem	Jain *et al*. (1973)
Punjab	*Acacia nilotica*	Seeds	Kaur (2015)
	Ziziphus jujube	Fruit	
	Azadirachta indica	Bark, leaf, root, flowers and fruits	
ND	*Achillea millefolium*	Flower, leaf	Gautam *et al*. (2007)
	Beta vulgaris	Leaf	
	Allium sativum	Leaf	
	Apium graveolens	Leaf	
	Asparagus officinalis	Leaf	

*Not Described

Table 2: Ethno-medicine surveys for identification of plants used to treat mycobacterial diseases in other parts of the world

Country name (Place)	Plants	Plant parts	References
Uganda (Mpigi and Butambala Districts)	*Zanthoxylum leprieurii*	Leaves	Bunalema *et al*. (2014)
	Piptadeniastrum africanum	Stem bark	
	Albizia coriaria	Root bark	
	Rubia cordifolia	Root bark	
South Africa (Eastern Cape Province)	*Acacia karroo*	Bark and leaf	Lawal *et al*. (2014)
	Ptaeroxylon		
	Obliquum	Leaf	
	Prunus africana	Bark and leaf	
	Clausena africana	Bark and leaf	
	Haemanthus albiflos	Leaf and root	
	Hypoxis argentea	Leaf	
	Ficus sur	Leaf	
	Hippobromus pauciflorus	Leaf	
	Araujia sericifera	Rhizome and leaf	
	Rosmarinus officinalis	Leaf	
	Cannabis sativa	Leaf	

Table 2: Continue

Country name (Place)	Plants	Plant parts	References
	Daucus carota	Leaf and fruit	
	Bidens pilosa	Leaf and bark	
	Corymbia citriodora	Leaf	
	Ziziphus mucronata	Leaf	
	Capsicum frutescens	Fruit and leaf	
	Withania somnifera	Leaf	
	Silene undulate	Leaf	
	Scabiosa albanensis	Leaf and root	
	Rubia petiolaris	Leaf	
	Tulbaghia acutiloba	Rhizome	
	Asparagus africanus	Leaf	
	Centella coriacea	Leaf	
	Carpobrotus edulis	Leaf	
	Eucalyptus camadulensis	Leaf and bark	
Limpopo Province, South Africa	*Agapanthus inapertus*	Tuber	Semenya and Maroyi (2013)
	Artemisia afra	Shrub	
	Cannabis sativa	Leaves	
	Carica papaya	Leaves	
	Combretum hereroense	Bark and seeds	
	Chironia baccifera	Roots	
	Eucomis pallidiflora	Bulb	
	Merwilla plumbea	Bulb	
	Hypoxis hemerocallidea	Tuber	
	Ficus carica	Bark	
	Ficus platypoda	Roots	
	Myrothamnus flabellifolius	Whole plant	
	Eucalyptus camaldulensis	Leaves and root	
	Pellaea calomelanos	Root	
	Eriobotrya japonica	Root	
	Citrus lemon	Leaves	
	Zanthoxylum capense	Root	
	Salix mucronata	Seeds	
	Lippia javanica	Leaves	
	Aframomum melegueta	Roots	
Lesotho	*Ajuga ophrydis*	-	Kose *et al*. (2015)
	Buddleja salviifolia	-	
	Clematis brachiata	-	
	Dianthus basuticus	-	
	Dicoma anomala subsp. *anomala*	-	
	Drimia depressa	-	
	Elephantorrhiza elephantina	-	
	Eragrostis plana	-	
	Gazania krebsiana subsp *krebsiana*	-	
	Helichrysum caespititium	-	
	Helichrysum odoratissimum	-	
	Helichrysum pallidum	-	
	Hypoxis hemerocallidea	-	
	Leobordea lanceolata	-	
	Malva parviflora var. *parviflora*	-	
	Metalasia muricata	-	
	Morella serrata	-	
	Othonna natalensis	-	
	Pennisetum glaucum	-	
	Pentanisia prunelloides	-	
	Senecio asperulus	-	
	Trifolium burchellianum subsp. *burchellianum*	-	
	Withania somnifera	-	
	Xysmalobium undulatum	-	
	Zantedeschia albomaculata subsp. *albomaculata*	-	

Table 3: Summary of the plants with potential anti-mycobacterial activity

Plant names	Plant parts	Place/Country name	References
Zanthoxylum capense	Roots	Mozambique	Luo *et al*. (2013)
Sterculia setigera	Leaves	Nigeria	Babalola *et al*. (2012)
Galenia Africana	Leaves	South Africa	Mativandlela (2009)
Dodonaea angustifolia	Leaves	South Africa and Ethiopia	Mativandlela (2009) and Balcha *et al*. (2014)
Ruta graveolens	Leaves	Tamil Nadu (India)	Muthuswamy *et al*. (2013)
Acalypha indica	Leaves	India	Gupta *et al*. (2010) and Chidambaram and Swaminathan (2013)
Adhatoda vasica	Leaves	India	Gupta *et al*. (2010) and Chidambaram and Swaminathan (2013)
Allium cepa	Bulb	India	Gupta *et al*. (2010), Chidambaram and Swaminathan (2013) and Shivkumar and Jayaraman (2011)
Allium sativum	Bulb	India	Gupta *et al*. (2010), Chidambaram and Swaminathan (2013) and Shivkumar and Jayaraman (2011)
Aloe vera	Leaves	Punjab (India)	Gupta *et al*. (2010) and Pandey *et al*. (2012)
Calpurnia aurea	Roots	Ethiopia	Gemechu *et al*. (2013)
Ocimum basilicum	Seeds	Ethiopia	
Artemisia abyssinica	Leaves	Ethiopia	
Croton macrostachyus	Leaves	Ethiopia	
Eucalyptus camaldulensis	Leaves	Ethiopia	
Ruta graveolens	Leaves	Tamil Nadu (India)	Muthuswamy *et al*. (2013)
Excoecaria agallocha	-	Tamil Nadu (India)	Prabu *et al*. (2014)
Aegiceras corniculatum	-	Tamil Nadu (India)	
Avicennia officinalis	-	Tamil Nadu (India)	
Achyrocline alata	Leaves and stem	Colombia	Bueno-Sanchez *et al*. (2009)
Swinglea glutinosa	Fruit	Colombia	
Piper nigram	Seeds	Maharashtra (India)	Birdi *et al*. (2012)
Andrographis paniculata	Leaves	Madhya Pradesh (India)	Shrivastava and Garg (2014)
Uvaria rufa	Leaves	Philippines	Macabeo *et al*. (2012)
Globularia alypum	Leaves	Tunisia	Khlifi *et al*. (2011)
Calotropis gigantean		India	Kumar *et al*. (2013)
Vetiveria zizanioides	Roots	India	Saikia *et al*. (2012)
Alstonia scholaris	Bark	Tamil Nadu (India)	Antony *et al*. (2012)
Pavetta corymbosa	Leaves	Nigeria	Nvau *et al*. (2011)
Euphorbia scarlatica	Stem	Kenya	Mariita *et al*. (2010)
Mallotus philippensis	Leaves	Uttaranchal (India)	Gupta *et al*. (2010)
Alpinia galanga	Rhizomes	Uttaranchal (India)	
Syzygium aromaticum	Flower	Tamil Nadu (India)	Shivkumar and Jayaraman (2011)
Cinnamomum verum	Bark	Tamil Nadu (India)	
Allium ursinum	-	Colombia	Balcha *et al*. (2014)
Calophyllum brasilience	Bark and leaf	Mexico	Gomez-Cansino *et al*. (2015)
Vismia baccifera	Bark and leaves	Mexico	
Vismia maxicana	Bark and leaves	Mexico	
Dodonaea angustifolia	-	Ethiopia	Balcha *et al*. (2014)
Petrolobium stellatum	-	Ethiopia	
Crinum jagus	Bulb	Nigeria	Akintola *et al*. (2013)
Scadoxus multiflorus	-	Kenya	Mariita *et al*. (2010)
Acacia nilotica	-	Kenya	
Vitex negundo	Leaves, seeds	Punjab (India)	Arya (2011)
Trichosanthes dioica	Roots, fruits	Punjab (India)	
Tinospora cordifolia	Stem, leaves	Punjab (India)	
Caesalpinia pulcherrima	Leaves, flowers	Punjab (India)	
Prunus Armeniaca	-	Punjab (India)	
Myrtus communis	Fruits	Punjab (India)	
Canscora decussate	Roots	Punjab (India)	
Piper species	Fruits	Punjab (India)	
Vitex trifolia	Leaves, roots and fruits	Punjab (India)	
Colebrookea oppositifolia	Leaves, fruits and roots	Punjab (India)	
Rumex hastatus	Root and bark	Punjab (India)	

Table 3: Continue

Plant names	Plant parts	Place/Country name	References
Kalanchoe Integra	Leaves	Punjab (India)	
Flacourtia ramontchii	Leaves, roots, bark and fruits	Punjab (India)	
Strophanthus wallichii	-	North East India	Suhitha *et al*. (2015)
Stephania hemandifolia	-	North East India	
Acacia senegal	Stem, bark	Punjab (India)	Gautam *et al*. (2012)
Lantana camara	Leaves	Punjab (India)	
Acorus calamus	Root	Maharashtra (India)	Birdi *et al*. (2012)
Andrographis paniculata		Maharashtra (India)	
Heliotropium Indicum	Leaves	Tamil Nadu (India)	Rajiniraja and Jayaraman (2014)
Aloaceae	-	Tamil Nadu (India)	
Albizia gummifera	Leaves	South Africa	Mmushi *et al*. (2010)
Xanthocercis zambesiaca	Leaves	South Africa	
Barringtonia racemosa	Leaves	South Africa	
Milletia stuhlmannii	Leaves	South Africa	
Kirkia acuminata	Leaves	South Africa	
Borrichia frutescens	-	United States	Cantrell *et al*. (1996)
Ferula communis	-	Italy	Appendino *et al*. (2004)
Heracleum maxicum	Root	-	Webster *et al*. (2010)
Leucas vokensii	-	Kenya	Rajab *et al*. (1998)
Moneses uniflora	-	Canada	McCutcheon *et al*. (1997)
Oplopanax horridus	Bark	Canada	
Salvia sp.	-	China	Fu *et al*. (2013)
Strobilanthus cusia	-	China	Ebadi (2007)
Humulus lupulus	Stem, leaves and flower	-	Serkani *et al*. (2012)
Stachys tmolea	-	Turkey	Askun *et al*. (2013)
Stachys thirkei	-	Turkey	
Thymus sibthorpii	-	Turkey	
Micromeria juliana	-	Turkey	
Ballota acetabulosa	-	Turkey	
Peschiera affinis	Leaves	Brazil	Ramos *et al*. (2008)
Punica granatum	Fruit	Iran	Ghaemi *et al*. (2011)
Allium ascalonicum	Root	Iran	Amin *et al*. (2009)
Peganum harmala	Fruit	Iran	Ghaemi *et al*. (2011)
Khaya senegalensis	Bark and leaves	Sudan	Abuzeid *et al*. (2014)
Rosmarinus officinalis	Leaves	Sudan	
Alpinia galanga	Rhizome	Thailand	Phongpaichit *et al*. (2006)
Piper chaba	-	Thailand	
Heracleum maximum	Root	-	Webster *et al*. (2010)
Apodytes dimidiata	Leaves	South Africa	Masoko and Nxumalo (2013)
Apodytes afra	Leaves	South Africa	
Combretum hereroense	Leaves	South Africa	
Lippia javanica	Leaves	South Africa	
Scadoxus multiflorus	-	Kenya	Mariita *et al*. (2010)
Eurphobia scarlatina	Stem	Kenya	
Cassia sophera	-	Uttar Pradesh (India)	Singh *et al*. (2013)
Utrica dioica	Leaves	Uttar Pradesh (India)	

Arbitrary use of antibiotics has led to the evolution of Multi Drug Resistant (MDR) and extensively drug resistant (XDR) strains of mycobacteria, thereby making the control of these diseases even more difficult. Emergence of MDR and XDR strains has necessitated the urgent development of anti-mycobacterial drugs. Recent reports described that approximately 30% of MDR cases present treatment failures (Brigden *et al*., 2014). The MDR cases require two years of treatment with second-line drugs, which are more toxic and more expensive than first-line drugs (Zazueta-Beltran *et al*., 2011). Therefore, newer effective and safer drugs are urgently needed in order to shorten the therapy of MDR and XDR cases. Plants can served as excellent source of molecules active against MDR and XDR strains. Reports suggest that extracts from plants are active against MDR strains (Table 4).

PLANT METABOLITES WITH ANTI-MYCOBACTERIAL ACTIVITY

Natural products are of great interest since can provide novel structures for the drug discovery particularly effective as antimicrobial agents. As plants have high biodiversity therefore can serve as main source of natural compounds because of their rich metabolite content. Plant secondary metabolites have anti-mycobacterial properties. Alkaloids, flavonoids, phytosterols, saponins, tannins etc have been extracted from different plants with anti-mycobacterial activity. Table 5 lists important metabolites from plants with anti-mycobacterial activity.

Table 4: Plants having activity against MDR mycobacterial strains

Plants	Country of study	References
Aloe vera	India	Gupta *et al.* (2010)
Adhatoda vasica		
Allium sativum		
Pluchea indica	Indonesia	Radji *et al.* (2015)
Rhoeo spathacea		
Cassia sophera	India	Singh *et al.* (2013)
Urtica dioica		
Aristolochia taliscana	Mexico	Jimenez-Arellanes *et al.* (2014)
Excoecaria agollacha	India	Prabu *et al.* (2014)
Taxus baccata	India	Bernaitis *et al.* (2013)
Acalypha indica		
Crocus sativus	India	Hussain *et al.* (2014)
Aristolochia taliscana	Mexico	Leon-Diaz *et al.* (2010)
Peganum harmala	Iran	Davoodi *et al.* (2015)
Dracocephalum kotschyi	Iran	Asghari *et al.* (2015)
Aristolochia brevipes	Mexico	Navarro-Garcia *et al.* (2011)
Diospyros anisandra	Mexico	Uc-Cachon *et al.* (2014)

MDR: Multi drug resistant

Table 5: Active anti-tuberculosis molecules of plant origin

Plants name	Plant parts	Plant metabolite(s)	References
Galenia africana	Leaves	(2S)- 5, 7, 2'-trihydroxy flavanone, (E)- 3, 2', 4'- trihydroychalcone, (E)- 2', 4'- dihydroychalcone and (E)- 3, 2', 4'- trihydroy-3-methoxychalcone	Mativandlela (2009)
Withania somnifera	Leaves and roots	Ashwagandholine, withaferin A, Pterocarpan- hydroxy-tuberosin, hydroxyisoflavone, tuberostan, puerarone	Adaikkappan *et al.* (2012)
Zanthoxylum capense	Roots	Benzophenanthridine, decarine, 6- acetonyldyhydronitidine, N-isobutyl-(2E,4E)-2,4-tetradecadienamide	Luo *et al.* (2013)
Bocconia arborea	-	6-methoxydihydrochelerytrin, Pinostrobin, 1-hydroxy-benzoisochromanquinone, 23-hydroxy-5a-lanosta-7,9 and 24-triene-3-one	Camacho-Corona *et al.* (2009)
Achyrocline alata	Leaves and stem	Carvacrol	Bueno-Sanchez *et al.* (2009)
Swinglea glutinosa	Fruit peel	Thymol, p-cymene, p-cymene, 1,8-cineole, limonene and β-pinene	
Aloe vera	Leaves	Barbaloin	Pandey *et al.* (2012)
Andrographis paniculata	Leaves	Andrographolide	Shrivastava and Garg (2014)
Cirtullus colosnthis	Aerial parts and deseeded fruits	Ursolic acid, cucurbitacine E and cucurbitacin I	Mehta *et al.* (2013)
Adhatoda vasica	Leaves	Vasicine acetate, 2-acetyl benzylamine	Gupta *et al.* (2010)
Trichosanthes dioica	Stem, leaves	Berberine, columbin, chasmanthin, palmarin, tinosporon, tinosporic acid and tinosporol	Arya (2011)
Caesalpinia pulcherrima	Leaves, flowers	Myricitroside	
Ocimum sanctum	Leaves, flowers and seeds	Ursolic acid, apigenin, orientin, luteolin, apigenin-7-Oglucuronide and luteolin-7-Oglucuronide	Birdi *et al.* (2012)

Table 5: Continue

Plants name	Plant parts	Plant metabolite(s)	References
Morinda citrifolia,	Leaves, roots and fruits	Anthraquinonesalizarin, nordamnacanthol, Ursolic acid; β-Sitosterol, asperuloside and caproic acid	
Myrtus communis	Fruits	Myricetin, kaempferol, α-pinene, cineole, myrtenol, nerol, geraniol and dipentene	
Vitex trifolia	Leaves, roots and fruits	Artemeti, luteolin, orientin, casticin, iridoid, aucubin, agnuside and vitricin	
Mimosa pudica	Leaves, roots	Mimosine and turgorin	
Piper nigrum	Fruits	Piperine	
Helichrysum melanacme	Shoots	2,4,6-trihydroxy-3-prenylchalcone, 4,6,5-trihydroxy-6 and -dimethydihydroxyoyrano[2,3-2,3]chalcone	Lall *et al*. (2006)
Garcinia nobilis	Stem bark	Smeathxanthone, 8-hydroxycudraxanthone, morisignin, 4-prenyl-2-(3,7-dimethyl-2,-octadienyl) -1,3,5,8-tetrahydroxyvanthone	Fouotsa *et al*. (2013)
Garcinia polyantha	Stem bark	1,5-dihydroxyxanthone, bangangxanthone, 1,3,5-trihydroxyxanthone and tetrahydroxyxanthone	Kuete *et al*. (2007)
Garcinia livingstonei		Amentoflavone and 4'-methoxyamentoflavone	Kaikabo and Eloff (2011)
Terminalia avicennioides	Root bark	Arjunolic acid, friedelin and friedelin-3β-ol	Mann *et al*. (2011)
Combretum imberbe	Leaves	hydroxyimberbic acid, glycosides of hydroxyimberbic acid	Katerere *et al*. (2003)
Diospyros crassiflora	Stem bark	Crassiflorone, diospyrone, plumbagin	Tangmouo *et al*. (2006)
Euclea natalensis	Roots	diospyrin, isodiospyrin, neodiosspyrin, 7-methyljuglone, mamegakinone and Shinanolone	Van der Kooy *et al*. (2006)
Thecacoris annobonae	Stem bark	Aristolochic acid I	Kuete *et al*. (2010)
Ficus chlamydocarpa	Stem bark	Alpinumisoflavone, genistein, laburnetin and luteolin	
Ficus cordata	Stem bark	β-sistosterol-3-β-glucopyranoside, catechin and Epiafzepelin	
Balsamocritus camerunensis	Stem bark	Kokusaginine	Fouotsa *et al*. (2013)
Oricia suaveolens	Stem bark	Evoxanthine and 1-hydroxy-2,3-dimethoxy-10-methylacridone	
Ajuga remota	Whole plant	Ergosterol-5-8-endoperoxide	Cantrell *et al*. (1999)

CONCLUDING REMARKS AND FUTURE DIRECTIONS

Review of both traditional knowledge and testing of plants for anti-mycobacterial activity suggests that plants can serve as excellent source for anti-mycobacterial drugs. Plants are sole treatment of leprosy and tuberculosis in some African countries. Though anti-mycobacterial MIC of plant materials is higher but they have resistance modifying properties. Therefore, plant derived drugs can help in fighting the drug resistance.

Unfortunately, there is no plant derived molecule either in market or under trial for treatment of mycobacterial infections. Majority of studies focused on identification of crude plant extracts with anti-mycobacterial properties and has not been extended to identification of bioactive plant metabolites. Therefore, an integrated approach of identification of plants with anti-mycobacterial activity followed by identification of bioactive molecule will speed up the research and development of plant derived drug molecules for mycobacterial infections.

REFERENCES

Abuzeid, N., S. Kalsum, R.J. Koshy, M. Larsson and M. Glader *et al*., 2014. Antimycobacterial activity of selected medicinal plants traditionally used in Sudan to treat infectious diseases. J. Ethnopharmacol., 157: 134-139.

Adaikkappan, P., M. Kannapiran and A. Anthonisamy, 2012. Anti-mycobacterial activity of *Withania somnifera* and *Pueraria tuberosa* against *Mycobacterium tuberculosis* H37Rv. J. Acad. Ind. Res., 1: 153-156.

Adwan, G. and M. Mhanna, 2008. Synergistic effects of plant extracts and antibiotics on *Staphylococcus aureus* strains isolated from clinical specimens. Middle-East J. Scient. Res., 3: 134-139.

Ahmad, A., A. Khan, F. Akhtar, S. Yousuf, I. Xess, L.A. Khan and N. Manzoor, 2011. Fungicidal activity of thymol and carvacrol by disrupting ergosterol biosynthesis and membrane integrity against *Candida*. Eur. J. Clin. Microb. Infect. Dis., 30: 41-50.

Akintola, A.O., A.O. Kehinde, O.E. Adebiyi and O.G. Ademowo, 2013. Anti-tuberculosis activities of the crude methanolic extract and purified fractions of the bulb of *Crinum jagus*. Niger. J. Physiol. Sci., 28: 135-140.

Amin, M., S. Segatoleslami and M. Hashemzadeh, 2009. Antimycobacterial activity of partial purified extract of *Allium ascalonicum*. Jundishapur J. Microbiol., 2: 144-147.

Anonymous, 2014. Global tuberculosis report. World Health Organization (WHO), Geneva, Switzerland.

Antony, M., J. James, C.S. Misra, L.D.M. Sagadevan, A. Kumar, T. Veetil and V. Thankamani, 2012. Anti mycobacterial activity of the plant extracts of *Alstonia scholaris*. Int. J. Curr. Pharmaceut. Res., 4: 40-42.

Appendino, G., E. Mercalli, N. Fuzzati, L. Arnoldi and M. Stavri *et al*., 2004. Antimycobacterial coumarins from the Sardinian giant fennel (*Ferula communis*). J. Nat. Prod., 67: 2108-2110.

Arya, V., 2011. A review on anti-tubercular plants. Int. J. PharmTech Res., 3: 872-880.

Asghari, G., B.N. Esfahani and P. Paydar, 2015. Evaluating the effect of *Dracocephalum kotschyi* methanol extract on *Mycobacterium tuberculosis*. Res. J. Pharmacogn., 2: 31-36.

Askun, T., E.M. Tekwu, F. Satil, S. Modanlioglu and H. Aydeniz, 2013. Preliminary antimycobacterial study on selected Turkish plants (Lamiaceae) against *Mycobacterium tuberculosis* and search for some phenolic constituents. BMC Complement. Altern. Med., Vol. 13. 10.1186/1472-6882-13-365

Ayele, W.Y., M. Machackova and I. Pavlik, 2001. The transmission and impact of paratuberculosis infection in domestic and wild ruminants. Veterinarni Medicina-Czech, 46: 205-224.

Babalola, I.T., E.A. Adelakun, Y. Wang and F.O. Shode, 2012. Anti-TB activity of *Sterculia setigera* Del., leaves (Sterculiaceae). J. Pharmacogn. Phytochem., 1: 17-23.

Balcha, E., B. Mengiste, M. Gebrelibanos, A. Worku and G. Ameni, 2014. Evaluation of *in-vitro* anti-mycobacterial activity of selected medicinal plants in Mekelle, Ethiopia. World Applied Sci. J., 31: 1217-1220.

Bernaitis, L., V.P. Shenoy, M. Ashok, M. Nath and R.P. Shenoy, 2013. Effects of selective medicinal plants against multi drug resistance *Mycobacterium tuberculosis* strains. Res. J. Pharmaceut. Biol. Chem. Sci., 4: 812-817.

Birdi, T., D. D'Souza, M. Tolani, P. Daswani and V. Nair *et al*., 2012. Assessment of the activity of selected Indian medicinal plants against *Mycobacterium tuberculosis*: A preliminary screening using the microplate alamar blue assay. Eur. J. Med. Plants, 2: 308-323.

Braga, L.C., A.A.M. Leite, K.G.S. Xavier, J.A. Takahashi, M.P. Bemquerer, E. Chartone-Souza and A.M. Nascimento, 2005. Synergic interaction between pomegranate extract and antibiotics against *Staphylococcus aureus*. Can. J. Microbiol., 51: 541-547.

Brigden, G., B.T. Nyang'wa, P. du Cros, F. Varaine and J. Hughes *et al*., 2014. Principles for designing future regimens for multidrug-resistant tuberculosis. Bull. World Health Organiz., 92: 68-74.

Bueno-Sanchez, J.G., J.R. Martinez-Morales, E.E. Stashenko and W. Ribon, 2009. Anti-tubercular activity of eleven aromatic and medicinal plants occurring in Colombia. Biomedica, 29: 51-60.

Bunalema, L., S. Obakiro, J.R.S. Tabuti and P. Waako, 2014. Knowledge on plants used traditionally in the treatment of tuberculosis in Uganda. J. Ethnopharmacol., 151: 999-1004.

Camacho-Corona, M.R., J.M.J. Favela-Hernandez, O. Gonzalez-Santiago, E. Garza-Gonzalez and G.M. Molina-Salinas *et al*., 2009. Evaluation of some plant-derived secondary metabolites against sensitive and multidrug-resistant *Mycobacterium tuberculosis*. J. Mexican Chem. Soc., 53: 71-75.

Cantrell, C.L., T. Lu, F.R. Fronczek, N.H. Fischer, L.B. Adams and S.G. Franzblau, 1996. Antimycobacterial cycloartanes from *Borrichia frutescens*. J. Nat. Prod., 59: 1131-1136.

Cantrell, C.L., M.S. Rajab, S.G. Franzblau, F.R. Fronczek and N.H. Fischer, 1999. Antimycobacterial ergosterol-5,8-endoperoxide from *Ajuga remota*. Planta Medica, 65: 732-734.

Chaturvedi, Y. and M. Saxena, 2014. Ethnomedicinal study of plants with special reference to bacterial diseases in Kondar and Saur tribes of district Chhatarpur, Madhaya Pradesh, India. World J. Pharm. Pharmaceut. Sci., 3: 1899-1904.

Chavhan, P.R. and A.S. Margonwar, 2015. Ethnobotanical survey of Markanda forest range of Gadchiroli district, Maharashtra, India. Br. J. Res., 2: 55-62.

Chidambaram, S. and R. Swaminathan, 2013. Determination of anti-tubercular activity of four Indian medicinal plants against *Mycobacterium tuberculosis* by broth micro dilution method. Int. J. Pharm. Sci. Res., 4: 3932-3937.

Daifas, D.P., J.P. Smith, B. Blanchfield, G. Sanders, J.W. Austin and J. Koukoutisis, 2004. Effects of mastic resin and its essential oil on the growth of proteolytic *Clostridium botulinum*. Int. J. Food Microbiol., 94: 313-322.

Das, T., S.B. Mishra, D. Saha and S. Agarwal, 2012. Ethnobotanical survey of medicinal plants used by ethnic and rural people in Eastern Sikkim Himalayan region. Afr. J. Basic Applied Sci., 4: 16-20.

Davoodi, H., E. Ghaemi, M. Mazandarani, F. Shakeri, S.N. Javid and M. Klishadi, 2015. Anti-mycobacterial and anti-inflammatory activity of *Peganum harmala*. J. Chem. Pharm. Res., 7: 1611-1616.

Denyer, S.P. and G.S.A.B. Stewart, 1998. Mechanisms of action of disinfectants. Int. Biodeterior. Biodegrad., 41: 261-268.

Deva, R., 2010. Metabolism of arachidonic acid and formation of novel 3- hydroxyoxylipins by *Candida albicans* and interaction of HeLa cells *Candida albicans* as a model for vulvovaginal candidiasis: Redundancy of signaling pathways for activation of COX-2. Ph.D. Thesis, Faculty of Human Medicine, Freie Universitat, Berlin.

Dhama, K., R. Tiwari, S. Chakraborty, M. Saminathan and A. Kumar *et al*., 2014. Evidence based antibacterial potentials of medicinal plants and herbs countering bacterial pathogens especially in the era of emerging drug resistance: An integrated update. Int. J. Pharmacol., 10: 1-43.

Ebadi, M., 2007. Pharmacodynamics Basis of Herbal Medicine. 2nd Edn., Taylor and Francis Group, Boca Raton, FL., USA., pp: 383-384.

Efferth, T. and E. Koch, 2011. Complex interactions between phytochemicals. The multi-target therapeutic concept of phytotherapy. Curr. Drug Targets, 12: 122-132.

Filgueiras, C.T. and M.C.D. Vanetti, 2006. Effect of eugenol on growth and listeriolysin O production by *Listeria monocytogenes*. Braz. Arch. Biol. Technol., 49: 405-409.

Fouotsa, H., A.T. Mbaveng, C.D. Mbazoa, A.E. Nkengfack and S. Farzana *et al*., 2013. Antibacterial constituents of three Cameroonian medicinal plants: *Garcinia nobilis*, *Oricia suaveolens* and *Balsamocitrus camerunensis*. BMC Complement. Altern. Med., Vol. 13. 10.1186/1472-6882-13-81

Fu, Z., H. Wang, X. Hu, Z. Sun and C. Han, 2013. The pharmacological properties of *Salvia* essential oils. J. Applied Pharm. Sci., 3: 122-127.

Garvey, M.I., M.M. Rahman, S. Gibbons and L.J.V. Piddock, 2011. Medicinal plant extracts with efflux inhibitory activity against Gram-negative bacteria. Int. J. Antimicrob. Agents, 37: 145-151.

Gautam, A.H., R. Sharma and A.C. Rana, 2012. Review on herbal plants useful in tuberculosis. Int. Res. J. Pharm., 3: 64-67.

Gautam, R., A. Saklani and S.M. Jachak, 2007. Indian medicinal plants as a source of antimycobacterial agents. J. Ethnopharmacol., 110: 200-234.

Gemechu, A., M. Giday, A. Worku and G. Ameni, 2013. *In vitro* anti-mycobacterial activity of selected medicinal plants against *Mycobacterium tuberculosis* and *Mycobacterium bovis* Strains. BMC Complement. Altern. Med., Vol. 13. 10.1186/1472-6882-13-291

Ghaemi, E.A., M. Mazandarani, A.R. Mansourian and M.B. Kochaksaraeii, 2011. Antimycobacterial activity of some medicinal plants used in traditional medicine in North of Iran. Proceedings of the International Conference on Life Science and Technology, January 7-9, 2011, Mumbai, India, pp: 26-28.

Gomez-Cansino, R., C.I. Espitia-Pinzon, M.G. Campos-Lara, S.L. Guzman-Gutierrez and E. Segura-Salinas *et al*., 2015. Antimycobacterial and HIV-1 reverse transcriptase activity of julianaceae and clusiaceae plant species from Mexico. Evid. Based Complement. Altern. Med. 10.1155/2015/183036

Gupta, R., B. Thakur, P. Singh, H.B. Singh, V.D. Sharma, V.M. Katoch and S.V.S. Chauhan, 2010. Anti-tuberculosis activity of selected medicinal plants against multi-drug resistant *Mycobacterium tuberculosis* isolates. Indian J. Med. Res., 131: 809-813.

Helander, I.M., H.L. Alakomi, K. Latva-Kala, T. Mattila-Sandholm and I. Pol *et al*., 1998. Characterization of the action of selected essential oil components on gram-negative bacteria. J. Agric. Food Chem., 46: 3590-3595.

Hiremath, V.T. and T.C. Taranath, 2013. Indigenous traditional knowledge on tree species survey of Jogimatti forest, Chitradurga district, Karnataka, India. J. Ethnobiol. Tradit. Med., 118: 222-227.

Hsieh, P.C., S.A. Siegel, B. Rogers, D. Davis and K. Lewis, 1998. Bacteria lacking a multidrug pump: A sensitive tool for drug discovery. Proc. Natl. Acad. Sci. USA., 95: 6602-6606.

Hussain, S., A. Haq, M. Nisar, T. Ahmad and P. Bhardwaj, 2014. Evaluation of *in-vitro* anti-mycobacterial activity and isolation of active constituents from *Crocus sativus* L. (Iridaceae). Asian J. Med. Pharmaceut. Res., 4: 130-135.

Jagtap, S.D., S.S. Deokule and S.V. Bhosle, 2006. Some unique ethnomedicinal uses of plants used by the Korku tribe of Amravati district of Maharashtra, India. J. Ethnopharmacol., 107: 463-469.

Jain, S.K., D.K. Banerjee and D.C. Pal, 1973. Medicinal plants among certain Adibasis in India. Bull. Bot. Survey India, 15: 85-91.

Jimenez-Arellanes, M.A., G. Gutierrez-Rebolledo, S. Rojas-Tome and M. Meckes-Fischer, 2014. Medicinal plants, an important reserve of antimycobacterial and antitubercular drugs: An update. J. Infect. Dis. Ther., Vol. 2.

Kaikabo, A.A. and J.N. Eloff, 2011. Antibacterial activity of two biflavonoids from *Garcinia livingstonei* leaves against *Mycobacterium smegmatis*. J. Ethnopharmacol., 138: 253-255.

Kalemba, D. and A. Kunicka, 2003. Antibacterial and antifungal properties of essential oils. Curr. Med. Chem., 10: 813-829.

Katerere, D.R., A.I. Gray, R.J. Nash and R.D. Waigh, 2003. Antimicrobial activity of pentacyclic triterpenes isolated from African Combretaceae. Phytochemistry, 63: 81-89.

Kaur, R., 2015. Ethnobotanical studies of some of the traditionally important medicinal plants of Punjab (India). Int. J. Curr. Res. Acad. Rev., 3: 262-271.

Khlifi, D., M. Hamdi, A. El Hayouni, S. Cazaux, J.P. Souchard, F. Couderc and J. Bouajila, 2011. Global chemical composition and antioxidant and anti-tuberculosis activities of various extracts of *Globularia alypum* L. (Globulariaceae) leaves. Molecules, 16: 10592-10603.

Kingston, C., S. Jeeva, G.M. Jeeva, S. Kiruba, B.P. Mishra and D. Kannan, 2009. Indigenous knowledge of using medicinal plants in treating skin diseases in Kanyakumari district, Southern India. Indian J. Tradit. Knowledge, 8: 196-200.

Koh, K.H. and F.Y. Tham, 2011. Screening of traditional Chinese medicinal plants for quorum-sensing inhibitors activity. J. Microbiol. Immunol. Infect., 44: 144-148.

Kose, L.S., A. Moteetee and S. van Vuuren, 2015. Medicinal plants used for the treatment of tuberculosis in Lesotho: An ethnobotanical survey. South Afr. J. Bot., 98: 183-183.

Krishna, M.B., S. Mythili, K.S. Kumar, B. Ravinder, T. Murali and T. Mahender, 2011. Ethno botanical survey of medicinal plants in Khammam district, Andhra Pradesh, India. Int. J. Applied Biol. Pharmaceut. Technol., 2: 366-370.

Kuete, V., A.L. Meli, J. Komguem, G.N. Louh, J.G. Tangmouo, D. Lontsi, J.J.M. Meyer and N. Lall, 2007. Antimycobacterial, antibacterial and antifungal activities of the methanolic extract and compounds from *Garcinia polyantha*. Pharmacologyonline, 3: 87-95.

Kuete, V., H.M.P. Poumale, A.N. Guedem, Y. Shiono, R. Randrianasolo and B.T. Ngadjui, 2010. Antimycobacterial, antibacterial and antifungal activities of the methanol extract and compounds from *Thecacoris annobonae* (Euphorbiaceae). South Afr. J. Bot., 76: 536-542.

Kumar, J.K., A.G.D. Prasad and V. Chaturvedi, 2015. Phytochemical screening of five medicinal legumes and their evaluation for *in vitro* anti-tubercular activity. Ayu, 35: 98-101.

Kumar, P.S., E. Suresh and S. Kalavathy, 2013. Review on a potential herb *Calotropis gigantea* (L.) R. Br. Scholars Acad. J. Pharm., 2: 135-143.

Lall, N., A.A. Hussein and J.J.M. Meyer, 2006. Antiviral and antituberculous activity of *Helichrysum melanacme* constituents. Fitoterapia, 77: 230-232.

Lawal, I.O., D.S. Grierson and A.J. Afolayan, 2014. Phytotherapeutic information on plants used for the treatment of tuberculosis in Eastern Cape province, South Africa. Evid.-Based Complement. Altern. Med., Vol. 2014. 10.1155/2014/735423

Leon-Diaz, R., M. Meckes, S. Said-Fernandez, G.M. Molina-Salinas and J. Vargas-Villarreal *et al*., 2010. Antimycobacterial neolignans isolated from *Aristolochia taliscana*. Memorias Instituto Oswaldo Cruz, 105: 45-51.

Llamas-Gonzalez, Y.Y. and M.A. Flores-Valdez, 2013. [Extensively drug-resistant tuberculosis (XDR-TB): Successful therapies used in the clinic to the disease]. Revista Investigacion Clinica, 65: 255-262, (In Spanish).

Luo, X., D. Pires, J.A. Ainsa, B. Gracia and N. Duarte *et al*., 2013. *Zanthoxylum capense* constituents with antimycobacterial activity against *Mycobacterium tuberculosis in vitro* and *ex vivo* within human macrophages. J. Ethnopharmacol., 146: 417-422.

Macabeo, A.P.G., F.A. Tudla, K. Krohn and S.G. Franzblau, 2012. Antitubercular activity of the semi-polar extractives of *Uvaria rufa*. Asian Pac. J. Trop. Med., 5: 777-780.

Maheshwari, J.K. and J.P. Singh, 1987. Traditional phytotherapy amongst the Kol tribe of Banda district, Uttar Pradesh. J. Econ. Taxon. Bot., 9: 165-171.

Mahima, A. Rahal, R. Deb, S.K. Latheef and H.A. Samad *et al*., 2012. Immunomodulatory and therapeutic potentials of herbal, traditional/indigenous and ethnoveterinary medicines. Pak. J. Biol. Sci., 15: 754-774.

Mann, A., K. Ibrahim, A.O. Oyewale, J.O. Amupitan, M.O. Fatope and J.I. Okogun, 2011. Antimycobacterial friedelane-terpenoid from the root bark of *Terminalia avicennioides*. Am. J. Chem., 1: 52-55.

Mariita, R.M. C.K.P.O. Ogol, N.O. Oguge and P.O. Okemo, 2010. Antitubercular and phytochemical investigation of methanol extracts of medicinal plants used by the samburu community in Kenya. Trop. J. Pharmaceut. Res., 9: 379-385.

Masoko, P. and K.M. Nxumalo, 2013. Validation of antimycobacterial plants used by traditional healers in three districts of the Limpopo Province (South Africa). Evid.-Based Complement. Altern. Med., Vol. 2013. 10.1155/2013/586247

Mativandlela, S.P.N., 2009. Antituberculosis activity of flavonoids from *Galenia africana* L. var. Africana. Ph.D. Thesis, Faculty of Natural and Agricultural Sciences, University of Pretoria, Pretoria.

McCutcheon, A.R., R.W. Stokes, L.M. Thorson, S.M. Ellis, R.E.W. Hancock and G.H.N. Towers, 1997. Anti-mycobacterial screening of British Columbian medicinal plants. Int. J. Pharmacogn., 35: 77-83.

Mehta, A., G. Srivastva, S. Kachhwaha, M. Sharma and S.L. Kothari, 2013. Antimycobacterial activity of *Citrullus colocynthis* (L.) Schrad. against drug sensitive and drug resistant *Mycobacterium tuberculosis* and MOTT clinical isolates. J. Ethnopharmacol., 149: 195-200.

Mmushi, T.J., P. Masoko, L.K. Mdee, M.P. Mokgotho, L.J. Mampuru and R.L. Howard, 2010. Antimycobacterial evaluation of fifteen medicinal plants in South Africa. Afr. J. Tradit. Complement. Altern. Med., 7: 34-39.

Mukherjee, P.K., N.K. Nema, S. Bhadra, D. Mukherjee, F.C. Braga and M.G. Matsabisa, 2014. Immunomodulatory leads from medicinal plants. Indian J. Tradit. Knowl., 13: 235-256.

Murthy, E.N., 2012. Ethno medicinal plants used by gonds of Adilabad district, Andhra Pradesh, India. Int. J. Pharm. Life Sci., 3: 2034-2043.

Muthuswamy, M., P. Asan and V. Kumar, 2013. Screening of antitubercular activity of some medicinal plants from Western Ghats, India. Int. J. Pharma Bio Sci., 4: 328-334.

Navarro-Garcia, V.M., J. Luna-Herrera, M.G. Rojas-Bribiesca, P. Alvarez-Fitz and M.Y. Rios, 2011. Antibacterial activity of *Aristolochia brevipes* against multidrug-resistant *Mycobacterium tuberculosis*. Molecules, 16: 7357-7364.

Nvau, J.B., P.O. Oladosu and A.T. Orishadipe, 2011. Antimycobacterial evaluation of some medicinal plants used in plateau state of Nigeria for the treatment of tuberculosis. Agric. Biol. J. N. Am., 2: 1270-1272.

Pan, J. and D. Ren, 2009. Quorum sensing inhibitors: A patent overview. Expert Opin. Therapeut. Patents, 19: 1581-1601.

Pandey, D.K., M. Tabarak and R.M. Banik, 2012. Quantitative estimation of barbaloin in *Aloe vera* and its commercial formulations by using HPTLC. Int. J. Med. Arom. Plants, 2: 420-427.

Phongpaichit, S., V. Vuddhakul, S. Subhadhirasakul and C. Wattanapiromsakul, 2006. Evaluation of the antimycobacterial activity of extracts from plants used as self-medication by AIDS patients in Thailand. Pharmaceut. Biol., 44: 71-75.

Pillars, R.B., D.L. Grooms and J.B. Kaneene, 2009. Longitudinal study of the distribution of *Mycobacterium avium* subsp. *paratuberculosis* in the environment of dairy herds in the Michigan Johne's disease control demonstration herd project. Can. Vet. J., 50: 1039-1046.

Poonam, K. and G.S. Singh, 2009. Ethnobotanical study of medicinal plants used by the Taungya community in Terai Arc Landscape, India. J. Ethnopharmacol., 123: 167-176.

Prabu, A., Prabuseenivasan and V. Kumar, 2014. Antimycobacterial activity of certain mangrove plants against multi-drug resistant *Mycobacterium tuberculosis*. Asian J. Med. Sci., 5: 54-57.

Radji, M., M. Kurniati and A. Kiranasari, 2015. Comparative antimycobacterial activity of some Indonesian medicinal plants against multi-drug resistant *Mycobacterium tuberculosis*. J. Applied Pharmaceut. Sci., 5: 19-22.

Radulovic, N.S., P.D. Blagojevic, Z.Z. Stojanovic-Radic and N.M. Stojanovic, 2013. Antimicrobial plant metabolites: Structural diversity and mechanism of action. Curr. Med. Chem., 20: 932-952.

Rajab, M.S., C.L. Cantrell, S.G. Franzblau and N.H. Fischer, 1998. Antimycobacterial activity of (*E*)-phytol and derivatives: A preliminary structure-activity study. Planta Medica, 64: 2-4.

Rajiniraja, M. and G. Jayaraman, 2014. Bioautography guided screening of selected indian medicinal plants reveals potent antimycobacterial activity of *Allium sativum* extracts-implication of non sulfur compounds in inhibition. Int. J. Pharm. Pharmaceut. Sci., 6: 671-676.

Rammanee, K. and T. Hongpattarakere, 2011. Effects of tropical citrus essential oils on growth, aflatoxin production and ultrastructure alterations of *Aspergillus flavus* and *Aspergillus parasiticus*. Food Bioprocess Technol., 4: 1050-1059.

Ramos, D.F., G.G. Leitao, F.N. Costa, L. Abreu and J.V. Villareal *et al*., 2008. Investigation of the antimycobacterial activity of 36 plant extracts from the Brazilian atlantic forest. Revista Brasileira Ciencias Farmaceuticas, 44: 669-674.

Saikia, D., S. Parveen, V.K. Gupta and S. Luqman, 2012. Anti-tuberculosis activity of Indian grass KHUS (*Vetiveria zizanioides* L. Nash). Complement. Ther. Med., 20: 434-436.

Semenya, S.S. and A. Maroyi, 2013. Medicinal plants used for the treatment of tuberculosis by bapedi Traditional healers in three districts of the Limpopo Province, South Africa. Afr. J. Tradit. Complement. Altern. Med., 10: 316-323.

Serkani, J.E., B.N. Isfahani, H.G. Safaei, R.K. Kermanshahi and G. Asghari, 2012. Evaluation of the effect of *Humulus lupulus* alcoholic extract on rifampin-sensitive and resistant isolates of *Mycobacterium tuberculosis*. Res. Pharm. Sci., 7: 235-242.

Shivkumar, A. and G. Jayaraman, 2011. Anti-tuberculosis activity of commonly used medicinal plants of South India. J. Med. Plants Res., 5: 6881-6884.

Shrivastava, A. and H.K. Garg, 2014. Effect of andrographolide on proliferation of *Mycobacterium canetti*. Int. J. Pharmaceut. Res. Scholars, 1: 410-413.

Sibanda, T. and A.I. Okoh, 2007. The challenges of overcoming antibiotic resistance: Plant extracts as potential sources of antimicrobial and resistance modifying agents. Afr. J. Biotechnol., 6: 2886-2896.

Sikkema, J., J.A. de Bont and B. Poolman, 1995. Mechanisms of membrane toxicity of hydrocarbons. Microbiol. Mol. Biol. Rev., 59: 201-222.

Simoes, M., R.N. Bennett and E.A.S. Rosa, 2009. Understanding antimicrobial activities of phytochemicals against multidrug resistant bacteria and biofilms. Nat. Prod. Rep., 26: 746-757.

Singh, A.V., S.V. Singh, P.K. Singh and J.S. Sohal, 2010. Genotype diversity in Indian isolates of *Mycobacterium avium* subspecies *paratuberculosis* recovered from domestic and wild ruminants from different agro-climatic regions. Comp. Immunol. Microbiol. Infect. Dis., 33: e127-e131.

Singh, R., S. Hussain, R. Verma and P. Sharma, 2013. Anti-mycobacterial screening of five Indian medicinal plants and partial purification of active extracts of *Cassia sophera* and *Urtica dioica*. Asian Pac. J. Trop. Med., 6: 366-371.

Singh, S.V., J.S. Sohal, N. Kumar, S. Gupta and K.K. Chaubey *et al*., 2014a. Recent approaches in diagnosis and control of mycobacterial infections with special reference to *Mycobacterium avium* subspecies. Adv. Anim. Vet. Sci., 2: 1-12.

Singh, S.V., P.K. Singh, A.V. Singh, J.S. Sohal and N. Kumar *et al*., 2014b. Bio-load and bio-type profiles of *Mycobacterium avium* subspecies *paratuberculosis* infection in the domestic livestock population endemic for Johne's disease: A survey of 28 years (1985-2013) in India. Transboundary Emerg. Dis., 61: 43-55.

Sinhababu, A. and A. Banerjee, 2013. Ethno-botanical study of medicinal plants used by tribals of Bankura districts, West Bengal, India. Indian J. Med. Plants Stud., 1: 98-104.

Stabel, J.R., 1998. Johne's disease: A hidden threat. J. Dairy Sci., 81: 283-288.

Suhitha, S., S.K. Devi, K. Gunasekaran, H.C. Pakyntein, A. Bhattacharjee and D. Velmurugan, 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. Curr. Top. Med. Chem., 15: 21-36.

Tangmouo, J.G., A.L. Meli, J. Komguem, V. Kuete and F.N. Ngounou *et al*., 2006. Crassiflorone, a new naphthoquinone from *Diospyros crassiflora* (Hien). Tetrahedron Lett., 47: 3067-3070.

Tiwari, R., S. Chakraborty, K. Dhama, S. Rajagunalan and S.V. Singh, 2013. Antibiotic resistance-an emerging health problem: Causes, worries, challenges and solutions: A review. Int. J. Curr. Res., 5: 1880-1892.

Trombetta, D., F. Castelli, M.G. Sarpietro, V. Venuti and M. Cristani *et al*., 2005. Mechanisms of antibacterial action of three monoterpenes. Antimicrob. Agents. Chemother., 49: 2474-2478.

Uc-Cachon, A.H., R. Borges-Argaez, S. Said-Fernandez, J. Vargas-Villarreal and F. Gonzalez-Salazar *et al*., 2014. Naphthoquinones isolated from *Diospyros anisandra* exhibit potent activity against pan-resistant first-line drugs *Mycobacterium tuberculosis* strains. Pulmonary Pharmacol. Therapeut., 27: 114-120.

Ulrich-Merzenich, G., D. Panek, H. Zeitler, H. Wagner and H. Vetter, 2009. New perspectives for synergy research with the omic-technologies. Phytomedicine, 16: 495-508.

Van der Kooy, F., J.J.M. Meyer and N. Lall, 2006. Antimycobacterial activity and possible mode of action of newly isolated neodiospyrin and other naphthoquinones from *Euclea natalensis*. South Afr. J. Bot., 72: 349-352.

Venkitanarayana, K., 2014. The potential for plant derived antimicrobials for controlling zoonotic and food-borne diseases. Proceedings of the 2nd International Conference on Animal and Dairy Sciences, September 15-17, 2014, Hyderabad International Convention Centre, India.

Webster, D., T.D.G. Lee, J. Moore, T. Manning and D. Kunimoto *et al*., 2010. Antimycobacterial screening of traditional medicinal plants using the microplate resazurin assay. Can. J. Microbiol., 56: 487-494.

Wink, M., 2008. Evolutionary advantage and molecular modes of action of multi-component mixtures used in phytomedicine. Curr. Drug Metab., 9: 996-1009.

Zazueta-Beltran, J., N. Leon-Sicairos, S. Muro-Amador, A. Flores-Gaxiola, J. Velazquez-Roman, H. Flores-Villasenor and A. Canizalez-Roman, 2011. Increasing drug resistance of *Mycobacterium tuberculosis* in Sinaloa, Mexico, 1997-2005. Int. J. Infect. Dis., 15: e272-e276.