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REVIEW ARTICLE

Time Need of Plant Medication: A Case Study Review on Tuberculosis

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Abstract

Tuberculosis is a deadly disease mainly caused by *Mycobacterium tuberculosis*. Its treatment has proven a difficult task for humanity. More than 20 allopathic medicines are used for the treatment of tuberculosis. Almost all the drugs cause adverse effects like hypersensitivity reactions, hepatitis, vomiting, nausea etc. Due to these side effects of allopathic medication, the demand of use of herbal medication is increasing day by day. The demand of herbal medicines is also increasing due to the fact that *M. tuberculosis* showing much resistance against traditional allopathic drugs and attaining the condition of Multidrug-resistant tuberculosis (MDR-TB) and Extensively Drug Resistant-Tuberculosis (XDR-TB). This particular review is aimed at importance of anti-TB medicinal plants. About 15 plants are addressed in this review work, which have the potential to treat the tuberculosis. This review will stimulate researchers to conduct research on the anti-tubercular activity of different medicinal plants.

Key words: *Mycobacterium tuberculosis*, Allopathic Medication, Medicinal Plants, Drug Resistance, Anti-TB

Introduction

Right from the beginning, humans have been facing much kind of diseases mainly caused by bacteria. With the increase in diseases, the man introduced antibiotics to tackle the problem of infections (Livermore, 2003; Tenover, 2001). But with the passage of time, bacteria became resistant to antibiotics. This increase in the resistance of bacteria is because of excessive use of antibiotics and social changes. This situation demands that the measures should be taken to stop the spread of already existing strains and the emergence of new ones (Okeke et al, 2005). Recent studies in the fields of human and veterinary medicine (Blackman, 2002; Barbosa and Levy, 2000), aqua-culture (Reilly and Kaeferstein, 1997) and agri-culture (Angulo et al, 2004) have supported that bacteria have become more resistant to antibiotics due to use and misuse of antibiotics. An increasing number of bacteria are practically resistant to all antibiotics available in the market. Multidrug resistance has been shown in *Salmonella enterica* serovar Typhimurium, *Escherichia coli*, *Entero-coccus faecium*, *Shigella dysenteriae*, *Staphylo-coccus aureus*, *Haemophilus influenza*, *Mycobacte-rium tuberculosis*, *Klebsiella pneumoniae*, *Pseudo-monas aeruginosa*, *Stenotrophomonas maltophilia*, *Acinetobacter baumannii*, *Burkholderia* and *Xanthomonas* (Betina, 1994). This work will focus on the disaster caused by the *Mycobacterium tuberculosis*, the adverse health effects of allopathic medicines for the treatment of tuberculosis and the need and use of herbal medicines to treat the deadly disease.

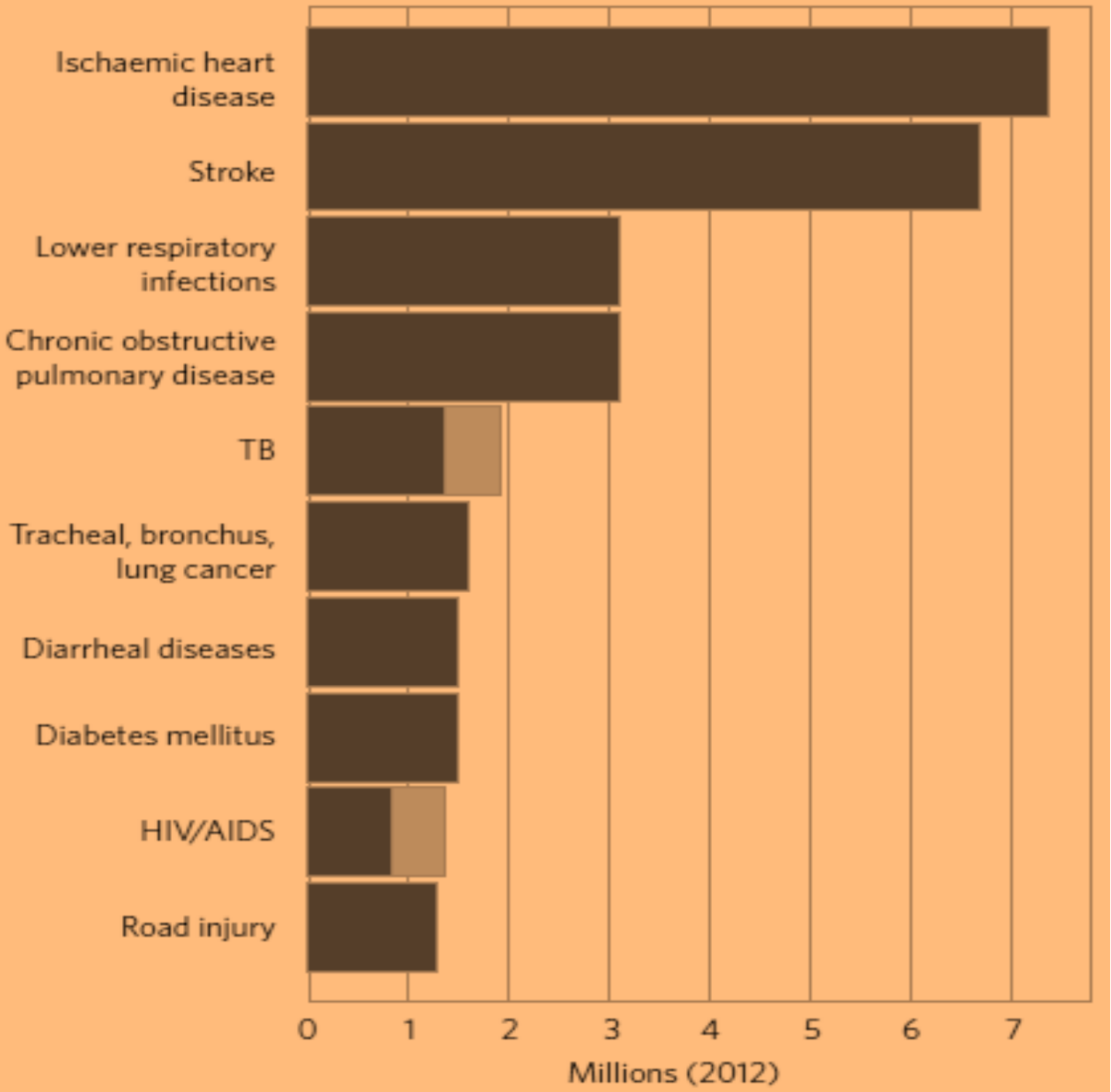

Figure 1: Top causes of death worldwide in 2012 (Deaths from TB among HIV positive people are shown grey) (WHO, 2016)

Tuberculosis (TB): A Case Study

In 1882, Robert Koch discovered *Mycobacterium tuberculosis*, which is the causative agent of airborne infectious disease called (TB). Even in 2016, one of the main causes of morbidity and mortality is tuberculosis, mainly in middle and low-income countries (WHO, 2015). *M. tuberculosis*, the pulmonary pathogen can cause disease in whole body. Moreover, TB is an asymptomatic infection to a life-taking disease (Esmail et al, 2014; Barry et al, 2009). From a clinical perspective, patients with an asymptomatic and non-transmissible state are classified as having latent TB infection (LTBI), and others having active TB disease, which is transmissible (in active pulmonary TB). General symptoms of patients having active

TB disease are such as fever, lack of appetite with weight loss, and fatigue, continual cough and haemoptysis (coughing up blood) (Esmail et al, 2014; Barry et al, 2009).

Estimated Incidences of TB in 2015

In 2015, worldwide there were 10.4 million incident cases of TB (ranging 8.7-12.2 million) estimated which was equivalent to 142 cases out of 100 000 population. Most of the incident cases estimated for 2015 happened in Asia (61%) and the WHO African Region (26%); while smaller ratios of incidences were from the Eastern Mediterranean Region (7%), the European Region (3%) and the Region of the Americas (3%). 87% of all estimated incident cases reported from worldwide were happened in 30 high TB burden countries. The six countries having the highest number of incident cases were India, Indonesia, China, Nigeria, Pakistan and South Africa combining 60% of the global total. Out of these, India, Indonesia and China alone were having 45% cases of global total in 2015. Estimated 11% of the incident cases of TB were among those people who were co infected with HIV/AIDS. The higher proportion of TB co infected with HIV/AIDS was estimated from WHO African Region with more than 50% in parts of southern Africa (WHO, 2016).

Estimated Mortality of TB in 2015

In 2015, there were 1.4 million (range 1.2-1.6 million) deaths were estimated in HIV-negative people with TB with addition of 0.39 million (range 0.32 to 0.46 million) deaths were estimated among HIV-positive people with TB. TB is one among the top 10 reasons of mortality worldwide, and has caused more deaths as compared to HIV/ AIDS in 2015. Nearly 84% of TB deaths among HIV-negative patients happened in WHO African Region and South-East Asia Region in 2015; both of these regions have estimated 86% of the combined total of TB deaths in HIV-positive and HIV-negative patients. India and Nigeria have 48% of global TB mortality rate in HIV-negative people and 43% of the combined total TB mortalities in HIV- positive and HIV- negative patients. Universally, the ratio of TB mortality HIV-positive people was 24 per 100000 population and among HIV-negative people it was 19 per 100000 population.

The variation among countries was very obvious, ranging from more than 40 deaths per 100000 population in five Asian countries with high TB burden (Papua New Guinea, Bangladesh, Myanmar, the Democratic People's Republic of Korea and Cambodia) and in many of the WHO African Region countries to less than one TB mortality per 100000 population in many high-income countries (WHO, 2016).

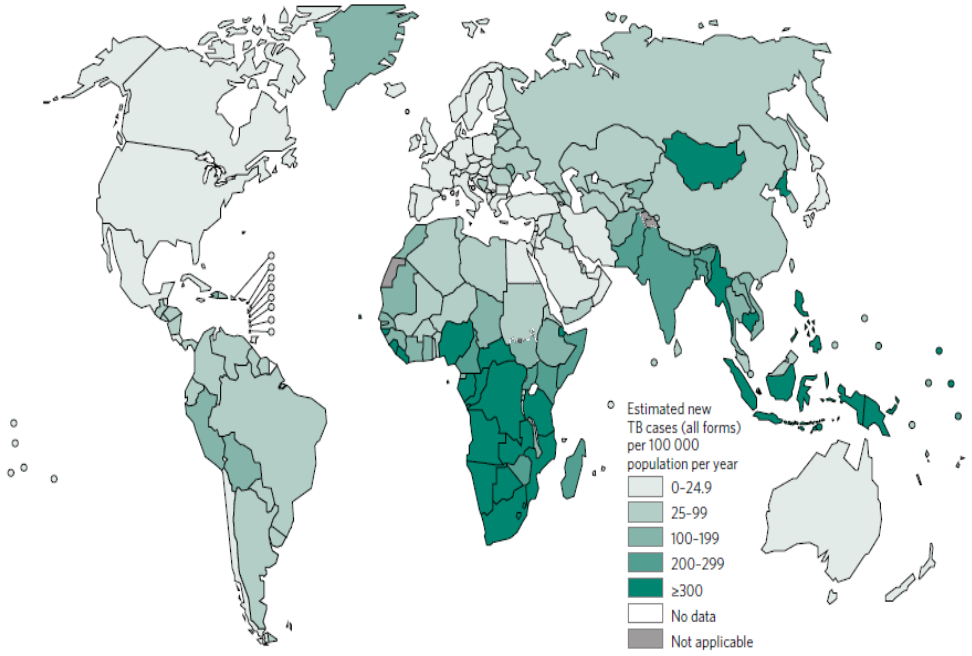

Figure 2: Estimate of TB incidences rates, 2015 (WHO, 2016)

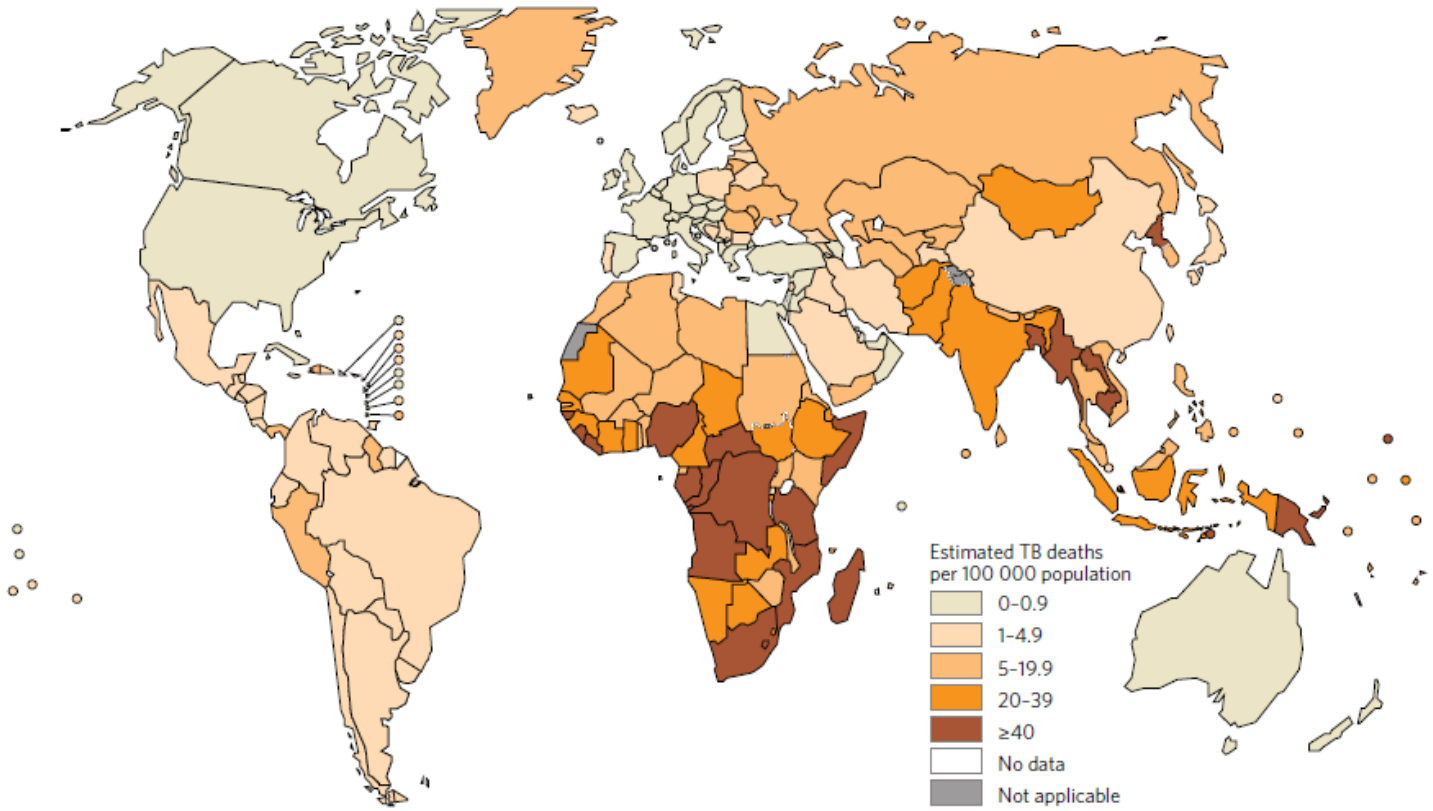

Figure 3: Estimated TB mortality rates in HIV negative people, 2015 (WHO, 2016)

Current Tuberculosis Therapy and Duration

For treatment of tuberculosis those antibiotics are used which are equally beneficial for the treatment of other bacterial diseases (Kishore et al, 2009). Standard anti-TB course of therapy consists of rifampicin, isoniazid, ethambutol, plus pyrazineamide should be taken daily in the initial two months of treatment (intensive phase) and followed by daily dose of isoniazid and rifampicin for four months in continuous phase (Huang et al, 2009; Kishore et al, 2009; Kingkaew et al, 2009).

Table 1: First-Line and Second-Line Medicines Recommended by WHO

Group		Drug
First-Line Drugs (Oral)		Rifampicin, Isoniazid, Pyrazinamide, Ethambutol, Rifapentine, and Rifabutin
Second-Line Drugs	**Fluoroquinolones**	Moxifloxacin, Levofloxacin, Ofloxacin and gatifloxacin
	Injectables	Kanamycin, Streptomycin, Capreomycin and Amikacin
	Bacteriostatic anti-TB drugs (Oral)	Prothionamide, Ethionamide, Terizidone, Cycloserine, p-Aminosalicylate sodium and p-Aminosalicylic acid

Drug Resistance in Tuberculosis

Resistance can be defined as the ability of an organism and its offspring to multiply and remain viable under specific conditions that would inhibit or destroy other members of the strain (Cloete, 2003). When bacteria are least threatened by the antibacterial drug, this condition is defined as

bacterial resistance. For the assessment of TB control planning and TB epidemiological trends, identification of drug resistance in *M. tuberculosis* is very important (Shamaei et al, 2009). If *M. tuberculosis* shows *in vitro* resistance to both first line drugs i.e. rifampicin and isoniazid, this condition is defined as Multidrug-resistant tuberculosis (MDR-TB) (Park et al, 2009). Extensively drug-resistant tuberculosis (XDR-TB) is defined as resistance to rifampicin and isoniazid, plus resistance to any one fluoroquinolone and to one of three second-line injectable drugs (e.g., kanamycin, capreomycin, or amikacin) (Ani et al, 2009; Shamaei et al, 2009; Ruttoh et al, 2009).

The global health security has been greatly affected by the emergence of XDR-TB and it has derailed the efforts which were made to reduce the incidence of TB (WHO, 2015). For example, over one hundred countries are affected by XDR-TB as compared to 83 countries which were reported by WHO in 2013 (WHO, 2015; WHO, 2014). This increase in XDR-TB cases is because of improper TB treatment (Gandhi et al, 2010), HIV co-infection, poverty and poor observance of anti-TB treatment (Dheda et al, 2014; Matteelli et al, 2014). Globally, despite the poor reporting of TB incidences, an estimate of 480,000 new cases of MDR-TB was reported in 2013. Over 50% of these cases were reported from India, Russian Federation and China (WHO, 2014). It is noted that nearly 10% of people having MDR-TB are also affected by XDR-TB over 100 countries (WHO, 2015). Global Tuberculosis Report of 2015 showed that the expenditure of treating XDR-TB per patient were ranging from nearly US$ 21,000 in upper middle-income countries to US$ 7,000 in low-income countries (WHO, 2015).

The treatment of tuberculosis by chemical drugs is much costly and has adverse effects. A survey results conducted in India showed that adverse reactions from drug treatment of MDR-TB range from 57.14% to 94.3% and the most common adverse effect was gastrointestinal problem (71.7%) (Akshata et al, 2015). On the other hand, herbal medicines have naturally occurring chemical compounds which can be derived from the whole plant or from its particular part. Herbal medicines have more advantages as they have fewer side effects, cheaper and effective in curing multiple diseases. Because of above mentioned advantages, the demand to use herbal medicines for the treatment of tuberculosis is increasing. A number of medicinal plants are being suggested for the treatment of tuberculosis after anti-mycobacterial activity across the globe (Newton et al, 2000; Mohamad et al, 2011; Babalola et al, 2012; Robles-Zepeda et al, 2013; Balcha et al, 2014; Njeru et al, 2015).

Table 2: Adverse Effects Caused by Anti-TB Drugs

Group	Drug	Adversarial Effects
First-Line Oral Drugs	Rifampicin	Hepatotoxicity, Nausea, Exanthema, Anorexia, Immunological Reactions, Fatigue, Abdominal Pain, Headache, Ataxia, Dyspnea etc.
	Isoniazid	Hepatotoxic, Vomiting, Nausea, Epigastric Pain, Coma etc.
	Ethambutol	Nausea, Hepatotoxicity, Retrobulbar Neuritis, Hypersensitivity etc.
	Pyrazinamide	Severe Exanthema, Kidney Failure, Pruritus, Acute Arthritis etc.
Second-Line Drugs	Fluoroquinolones	Affects central nervous system, gastrointestinal, cardiovascular and endocrine system, urinary tract etc.
	Injectables	Neurotoxic, ototoxic, nephrotoxic, hypersensitivity etc.
	Bacteriostatic anti-TB drugs (Oral)	Psychiatric and neurological adverse effects.

Medicinal Plants Screened for Anti-TB Activity

1. ***Piper nigrum L.***

Botanical Name: *Piper nigrum* L.
Part Used for Extract Formation: Seeds
Chemical Used for Extract Formation: Ethanol, acetone and distilled water
Chemical constituent: Piperine
Anti-Tubercular Activity (MIC Value):
MIC against *M. tuberculosis* H37Rv is 50µg/mL for combination of ethanol and acetone extract and 100µg/mL for acetone extract (Birdi et al, 2012).

2. ***Allium sativum, Acalypha indica, Adhatoda vasica***

Botanical Name: *Allium sativum, Acalypha indica, Adhatoda vasica*
Part Used for Extract Formation: *Allium sativum* (bulb), *Acalypha indica* (leaves), *Adhatoda vasica* (leaves).
Chemical Used for Extract Formation: Ethyl acetate, petroleum ether and chloroform
Chemical constituent: Either fixed oils, fats or derivatives of aryl or phenol amine
Anti-Tubercular Activity (MIC Value):
MIC of *Allium sativum, Acalypha indica* and *Adhatoda vasica* is 1.25, 5 and 10 mg/mL respectively against HRv37 strain of *M. tuberculosis* (Rajiniraja and Jayaraman, 2014).

3. ***Mallotus philippensis (L) Muell Arg.***

Botanical Name: *Mallotus philippensis (L) Muell Arg*.
Part Used for Extract Formation: Leaves
Chemical Used for Extract Formation: Crude extracts formation using 95% ethanol than fractionation using methanol, chloroform, hexane and ethyl acetate
Chemical constituent: *β*-sitosterol and Ursolic acid
Anti-Tubercular Activity (MIC Value):
MIC of ethyl acetate fraction is 0.125 mg/mL against *M. tuberculosis* H37Ra and 0.25 mg/mL against *M. tuberculosis* H37Rv (Gupta et al, 2011).

4. ***Actiniopteris radiate (L)***

Botanical Name: *Actiniopteris radiate Linn.*
Part Used for Extract Formation: Whole plant
Chemical Used for Extract Formation:
Chloroform, n-Hexane and ethanol
Chemical constituent: identification is needed
Anti-Tubercular Activity (MIC Value):
MIC of extracts of chloroform, n-Hexane and ethanolic is 3.125, 12.5 and 25 µg/mL respectively against H37RV strain of *M. tuberculosis* (Munna et al, 2014).

5. ***Allium sativum***

Botanical Name: *Allium sativum*
Part Used for Extract Formation: Cloves
Chemical Used for Extract Formation: 70% ethanol
Chemical constituent: Identification is needed
Anti-Tubercular Activity (MIC Value):
MIC of ethanolic extract of garlic against 5 non-MDR and 15 MDR-TB isolates of *M. tuberculosis* is ranged from 1 to 3 mg/mL (Hannan et al, 2011).

6. ***Humulus lupulus***

Botanical Name: *Humulus lupulus*
Part Used for Extract Formation: Whole plant
Chemical Used for Extract Formation: Alcohol
Chemical constituent: Not identified
Anti-Tubercular Activity (MIC Value):
MIC against resistant and sensitive strains of *M. tuberculosis* is 8 and 4 mg/mL respectively (Serkani et al, 2012).

7. ***Chamaedorea tepejilote* and *Lantana hispida***

Botanical Name: *Chamaedorea tepejilote* and *Lantana hispida*
Part Used For Extract Formation: Ariel parts
Chemical Used for Extract Formation: Hexane
Chemical constituent: Oleanolic acid and ursolic acid
Anti-Tubercular Activity (MIC Value):
MIC of both compounds ranged from 12.5µg/mL to 50µg/mL for *M. tuberculosis* H37Rv and four mono-resistant strains of *M. tuberculosis* H37Rv measured by Microplate Alamar Blue Assay (MABA) (Jimenez-Arellanes et al, 2013).

8. ***Ranunculi Ternati Radix***

Botanical Name: *Ranunculi Ternati Radix*
Part Used for Extract Formation: Whole plant (Leaves stem and roots)
Chemical Used for Extract Formation: Water and 70% ethanol extracts and water and 70% ethanol

eluted part of Ethanol extract from macro porous resin (WEPMR and EEPMR)
Chemical constituent: Need to be identify
Anti-Tubercular Activity (MIC Value):
70% ethanol eluted part of Ethanol extract from macro porous resin (EEPMR) showed great anti-tubercular activity with MIC 1.0 mg/mL on MDR2314-2 and XDR1220 strain of *M. tuberculosis* (Zhang et al, 2015).

9. Withania somnifera (L)

Botanical Name: *Withania somnifera (L)*
Part Used for Extract Formation: Roots and leaves
Chemical Used for Extract Formation: water
Chemical constituent: need identification
Anti-Tubercular Activity (MIC Value):
The highest anti-mycobacterial activity was found 64.47% of 1.0 mg/mL and least inhibition activity was 17.88% of 0.01 mg/mL dose against *M. tuberculosis* H37Rv (Adaikkappan et al, 2012).

10. Alstonia scholaris

Botanical Name: *Alstonia scholaris*
Part Used for Extract Formation: Leaves, fruit, flower and bark
Chemical Used for Extract Formation: Water, Butanol and ethyl acetate
Chemical constituent: Not identified
Anti-Tubercular Activity (MIC Value):
Butanol extracts of bark and flower showed good anti-TB activity with MIC at 100 and 500 µg/mL respectively against *M. tuberculosis* H37Rv (Antony et al, 2012).

11. Kaempferia galanga

Botanical Name: *Kaempferia galanga*
Part Used For Extract Formation: Rhizome
Chemical Used for Extract Formation: Ethanol
Chemical constituent: Ethyl p-methoxycinnamate
Anti-Tubercular Activity (MIC Value):
MIC of Ethyl p-methoxycinnamate (EPMC) is 0.242–0.485 mM against *M. tuberculosis* H37Rv, H37Ra, multidrug resistant (MDR) and drug susceptible clinical isolates measured by resazurin microtitre assay (REMA) (Lakshmanan et al, 2011).

12. Andrographis paniculata

Botanical Name: *Andrographis paniculata*
Part Used For Extract Formation: Whole plant
Chemical Used for Extract Formation: Methanol and hexane (5:1)
Chemical constituent: Andrographolide
Anti-Tubercular Activity (MIC Value):
MIC of methanolic extract of *A. paniculata* was 250µg/mL against H37Rv, MDR and drug sensitive clinical isolates of *M. tuberculosis* (Prabu et al, 2015).

13. Plumeria bicolor

Botanical Name: *Plumeria bicolor*
Part Used For Extract Formation: Bark
Chemical Used for Extract Formation: Chloro-form
Chemical constituent: Plumericin and iso-Plumericin
Anti-Tubercular Activity (MIC Value):
Plumericin showed better anti-TB activity than isoplumericin with MIC values of 1.3 ± 0.15, 1.5 ± 0.13, 2.0 ± 0.07, 2.1 ± 0.12 and 2.0 ± 0.14 µg/mL and MBC values of 2.5 ± 0.18, 2.9 ± 0.20, 3.8 ± 0.27, 3.6 ± 0.22 and 3.7 ± 0.32 µg/mL, respectively against all four sensitive as well as MDR clinical isolates of *M. tuberculosis* (Kumar et al, 2013).

Conclusion

The review proposes that there is an increase in demand of phyto-pharmaceuticals all over the globe, firstly because of the adverse health effects of the allopathic medicines and secondly the unique ability of many plants to counter the deadly tuberculosis pathogen. Many plants showed very low MIC value against MDR clinical isolates of *M. tuberculosis*. Solid steps surely must be chosen to translate this knowledge into preventive or curative measures for anti-TB therapies.

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