

Combine effects of medicinal herbs on Multidrug-resistant tuberculosis or extensively drug-resistant–Tuberculosis

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Abstract

Extensively drug-resistant and Multidrug-resistant tuberculosis (M/XDR-TB) have been focused by different researcher in various countries, because of the big risk of this infectious disease, for its control worldwide, however, researcher faced with having difficult issues related to management, The spread of (M/XDR-TB), among community, reflect the functional state and influence of tuberculosis control program and realistic attitude of the laity toward performance of such program, medicinal herbs and other chemical drugs, management of the TB control trying to minimize the risk of (M/XDR-TB), medicinal herbs to use traditionally or scientifically for this deadly disease,

The aim of this review is to focus the combine effect of medicinal herbs on MDR or XDR tuberculosis across the globe. Recently the control of (M/XDR-TB) become a little difficult due to its combination with HIV and also due to their much expensive treatment and a particular situation like pregnancy, contraception, diabetes mellitus, substance dependence, liver disorders, psychiatric disorders, renal insufficiency, seizure disorders which lead to failure of the treatment (M/XDR-TB).

Keyword: HIV, Extensively drugs resistance, Multi-drug resistant and pregnancy, diabetes mellitus

INTRODUCTION

Since 5000 years herbs are used as drug to treat TB and other diseases in the world (R.S.kachhi; 2016). According to the estimation of WHO every years 10.4 million new cases and 1.8 million death are reported from TB (WHO; 2016) (R.S.kachhi; 2016). Tuberculosis (TB) caused by Mycobacterium tuberculosis one of the most infectious causes of death in developing countries, particularly in the Asian and African nations. (E. B. Famewo et al.; 2017). After India and china South Africa is at third number as 80% disease affected country from last 15 years among HIV/AIDS affected people (E.B.famewo;2017). India's lose (more than \$23bn) every year (£14.9bn; €20.3bn) to treat TB. Approximately 50% to 80% patients go to the private diagnostic clinic to treat TB. India have Revised National TB Control program (RNTCP) that Ayurveda is not a branch of this program. (j.samal; 2015) Tubercle bacilli can spread into the various part of the body, it can transfer from one person to another person in crowded place or face to face through air droplet from coughing and sneezing. Common sign of TB includes coughing, fever, hemoptysis, chest pain, fatigue and

weight loss. In 1993 WHO predicted worldwide emergency for TB that killed more adult people than any other infectious disease each year.

Rinne in 2001 observed done that communities in Africa have trust on ancestral sanative to treat infectious diseases (WHO, 2003). Traditional healers use medicinal plants as their primary source of medicine. (Sebua Silas Semenya* and Alfred Maroyi;2012). There are three type of M. Tuberculosis complex is more important, (M. avium, M. intracellulerae, and M. kansasii) these types are close related to the HIV patients and difficult to separate from other types (Kahaliw W et al.2017) (BMC Complementary and Alternative Medicine (2017). 9.6 million new cases of active tuberculosis were infected by TB in the year 2014, that time 1.5 million people were killed by TB among 1.1 million HIV negative and 0.4 million HIV positive in the world. Because of the slow growth of mycobacteria, combined drug also takes long time to treat TB(Kahaliw W et al.2017). Non tuberculosis mycobacteria (NTM) can cause symptoms similar to of tuberculosis sign, which is present in water and soil. Acid-fast bacilli (AFB) can be observed in sputum sample through microscopic detection. Test like Nucleic acid amplification tests such as (Xpert MTB/RIF Assay, XtracTB Assay) they do not detect ((NTM). (Vera V.et al; 2019).

Antibiotics to treat TB

The first line therapy drugs include three or more different drugs (isoniazid, rifampin, pyrazinamide, and ethambutol).(Sameer I, et al;2017)Sonambekar et al studied about 43 patient checkup from 2008 to 2016 in the year of 2017 and cultured their (ileocolonoscopy) tissue with ITB, 10 patient showed resistance to first-line anti-TB drug, resistance to isoniazid 9 patients, rifampicin 6,pyrazinamide 5, streptomycin and ethionamide 4, ethambutol, moxifloxacin and ofloxacin 3, and p-amino salicylic acid 1 and approximately 13.9% was MDR TB need second line anti TB drugs, in high-populated country like india and similar other country 10-15% patient are resistant to isoniazid and 2-3% are MDR, (A.sonambekar et al;2017). There are two type of dugs resistance MDR and XDR, MDR is resistance to rifampicin and isoniazid, and XDR is resistance to one of the second line injectable (Jan F. et al;2018).new drugs improved against XDR-TB treatment, which is already accepted by united states food and drug administration (FDA), TB therapy per example ibuprofen, acetyl salicylic acid ,simvastatin, metformin and phenyl butyrate can concert with anti TB drugs, new drugs like valproic acid (VPA) and suberoylanilide hydroxamic acid (SAHA) therapy for increasing the effect of two main drugs of first line isoniazid and rifampicin against cell wall of mycobacterium .(M.Rao et al;2018) Group A : fluoroquinolones (Levofloxacin (Lfx), Moxifloxacin (Mfx), Gatifloxacin (Gfx).Group B : second line injectable drugs: (Amikacin (Am), Capreomycin (Cm, Kanamycin (Km), (Streptomycin) Group C: other core second line drugs (Ethionamide/Prothionamide (Eto/Pto), Cycloserine / Terizidone (Cs Trd), Linezolid (Lzd), Clofazimine (Cfz), Group D: add-on drugs: D1 Pyrazinamide, D1 Ethambutol (E, D1 High-dose isoniazid,D2 Bedaquiline (Bdq, D2 Delamanid (Dlm, D3 p-aminosalicylic acid PAS),D3 Meropenem (Mpm, D3 Amoxicillin-clavulanate (Amx-Clv, D3

Thioacetazone (T). (Kanabus,Annabel, 2016). And also one of new anti TB drug Bedaquiline (BDQ) which is approved in 2012 and still using in 105 countries, WHO also design 30 new drugs in jun 2018 for DR-TB one of them was bedaquilline (Kanabus,Annabel;2018).

Side effect of TB drugs:

Study showed that treatment of MDR-TB Recorded 256 patient between 2006 and 2011 showed 37.1% side effects contain 17.2% patient showed gastrointestinal disturbance , (18.4%), psychiatric disorder (5.5%), arthralgia (4.7%), hepatitis (3.9%), peripheral neuropathy (3.1%), hypothyroidism (2.3%), epileptic seizures (2%), dermatological effects (2%), ototoxicity (1.6%), and nephrotoxicity (1.2%). The treatment was successful in 220 (85.9%) patients with MDR-TB.(Yang et al,2017).WHO realize in 2016 that short course regimen (SCR) and long-course (LCR) regimen for the treatment of drug resistance tuberculosis both required second line injectable anti TB drugs (A.M. Ionescu, et al ,2018),

First line side to anti tuberculosis drugs are common, and include hepatitis, cutaneous reactions, gastrointestinal intolerance, hematological reactions and renal failure. These adverse effects must be recognized early, to reduce associated morbidity and mortality. (Eric J Forget & Dick Menzies,2006)Second line side effects: GI disturbance, Ototoxicity, psychiatric disorder, Arthralgia, Arthritis, central nervous system, Hepatic, Dermatologic, peripheral neuropathy. Nephrotoxicity, hyperthyroidism. (TW Yang - 2017).In children treatment of tuberculosis and also latent TB is very important through anti TB drugs rifampicin and isoniazid can show some side effects from long use of isoniazid group, T. Diallo estimated the average percentage of visits in which minor symptoms such as stomach upset, poor appetite, or fatigue were recored (T. Diallo et al;2018). Adverse effects of Anti-TB drugs: Isoniazid (Skin rash, hepatitis), Rifampicin (Abdominal pain, nausea, vomiting, hepatitis, thrombocytopenic purpura), Pyrazinamide (Arthralgia, hepatitis), Streptomycin (Vestibular and auditory nerve damage, renal damage), Ethambutol (Retrobulbar neuritis, ocular side effects), Thioacetazone (Skin rash, Exfoliative dermatitis), Paraaminosalicylic acid (Anorexia, nausea, vomiting, hypersensitivity reactions), Kanamycin (Vertigo, auditory nerve damage, nephrotoxicity), Ethionamide (Diarrhoea, abdominal pain, hepatotoxicity), Cycloserine (Dizziness, headache, depression, psychosis, convulsions) , (V. Arya;2011).

Ayurvedic treatment of TB

Ayurveda treatment of tuberculosis was started in India from 1933, by the establishment of Patipukur TB Hospital, Kolkata. Drugs containing mercury, gold, calcium was prepared at the in-house pharmacy and was administered to the patients with fresh juice of herbs cultivated in the hospital garden. Formulations like *Vasantamalati*, *Kanchanabhra rasa*, *Rajamriganka rasa* were under use including *Bhallataka* (*Semicarpus anacardium*) *rasayan*, *Mallasindura*, *Vasa* (*Adatoda vasica*) *etc.*(PK Debnath et al,2012), Non-polar and polar solvent extracts of leaves, roots, seeds, flower, bark, fruit were tested against *M. TB H37RV*

or others, and minimum inhibitory concentrations (MICs) were determined by the agar-based proportion assay. Isoniazid was used as positive control to evaluate the anti-TB activity of the crude extracts of medicinal herbs. Percentage inhibition was used to evaluate the activity in L-J (Lowenstein-Jensen) medium which was calculated by mean reduction in a number of colonies on extract containing as compared to extract free controls. In BacT/ALERT also extracts of these herbs showed significant result against *Mycobacterium.Tuberculosis*. (J Samal - 2015). Plant leaves , root, bark, seed , flower,etc are collected and dried the extract with polar and non-polar solvent like water , ethanol, acetone , methanol , etc. and screened against different strain of *mycobacterium Bovis* (*M. bovis*) , H37RV, BCG, using the media for identification of effect of herbs on bacteria.(Nneka N.Ibekwe et al,2014). E.Green et al, studied Medicinal herbs in south Africa against TB on 21 herbs , four herbs were high screened to inhibit the H37Ra strain , minimum inhibitory concentration (MIC) value for *Berchemia discolor* Klotzsch Hemsl 12, 5 µg/mL, *Bridelia micrantha* Hochst. Baill (25 µg/mL), *Warbugia salutaris* Bertol. F Chiov (25 µg/mL), *Terminalia sericea* Burch ex D. F (25 µg/mL). (E.Green et al, 2010).

Selected plants for TB

Plant extracts exhibit different modes of action against different bacterial strain. They can break down the phospholipids bilayer of the cell membrane & can inhibit the entire enzyme of bacteria involved in synthesis of mycolic acid, structural components destruction, inactivation of genetic materials.

Plant name; Adhatoda vasica ,**Family name;** acanthaceae , **Common name;** vasaka.

Chemical constituentof: (Turgorins, quinazoline derivatives such as vasicine, vasicinone and b hydroxy vaccine, volatile oil, betalain and vasakin,adhatodic acid), (Sharma, Yadav; 2016). phenolic compounds (71.32mg GAE/g), total antioxidants (651% DPPH inhibition), the enzyme catalase (4716µg/g), ash content (16.72%) and pH values were formed in the Calotropis procera, whereas the total carotenoids (1987mg/100g) , superoxide dismutase (4566µg/g) and peroxidase (1322µg/g) were higher in leaves of Adhatoda vasica. The flower extract of the Adhatoda vasica have much flavonoids (0.87mg/100g) and organic matter (89.99%), also these compound used for viral diseases(Ahmed W et al; 2018).

Leaf ethanol Extracts of adhatoda vasica (AV) showed anti-tuberculosis activity in L-J medium. The proportion of inhibition is 32% for MDR isolate DKU-156 and 86% for another MDR isolate JAL-1236, whereas for sensitive *M. tuberculosis* H37Rv inhibition was found to be 70 %.(SM Kapgate - 2018). These herbs also have anticancer effect against MCF-7 cell line (R. Batool, 2017). And also used for antipyretic effect (Khan MS; 2017). This plant is very famous in field of Ayurveda&used for various treatment for respiratory tract ailments, oxytotic, abortifacient effects. (Claeson UP et al; 2000).

Plant name;Trichosanthes dioica, **Family name;**Cucurbitaceae ,**Common name;** Patola.

Chemical constituent ofTrichosanthes dioica :(pentacyclitriterpenes, cucurbitacins, vitamin A, vitamin C, tannins, saponins, alkaloids, mixture of noval peptides, proteins tetra),(Sharma, Yadav;2016),

Trichosanthes dioica was cultivated as vegetable, leave and water extract of these plants were used for tonic, antipyretic, in edema, alopecia, and in subacute cases of enlargement of liver but Ayurvedically leaves extract of these plant are used for antipyretic, diuretic, cardiogenic, laxative, antiulcer, etc. (kumar.N;2012). Extract of this plant also has been used against arsenic-induced toxicity on albino rat. 50-100mg/kg orally eaten by the patient for 20 days. (Bhattacharya S¹, Haldar PK; 2013). The water aqueous fruit extract of *T. dioica* has been traditionally used for the hypoglycemic effect on FBG, variable dose, 500, 750, 1000, and 1250 mg/kg body weight for normal glucose rate. (P. K. Rai et al;2013). Three different concentration of *T. dioica* (25, 50, 75 mg/ml) showed result against all five bacteria *Mycobacterium smegmatis*, *Staphylococcus aureus*, *Escherichia coli*, *Klebsiella pneumonia*, *Pseudomonas aeruginosa*. (P. K. RAI et al; 2010). Leave extract of *T. dioica* herbs also mostly used various dose 250, 500, and 750 mg/kg body weight to reduce the sub and mild diabetic rats also used for Gastric Antiulcer Activity normal dose (250 and 500 mg/kg), cholesterol lowering activity using dose (50 ml/kg), Anti-Oxidant Activity is from fruit extract of *T. dioica* its free radical scavenging property, *T. dioica* leaves extract at 200mg/kg dose showed to decrease the levels of AST, ALT, TB, ALP and increase in Total Protein, hepatoprotective activity and showed histopathological care to the liver, etc. (R. Dutta;2015).

Plant name; *Vitex negundo*, **Family name;** Verbenaceae, **Common name;** Nirgund

In this herb chemical components are different in various part of plant like seed, root, leaves, flowers, and various extract has been used for different treatment, ethanol extract of this herbs is used for hepatoprotective effect against anti-tuberculosis drugs, Chloroform extract used for cytotoxicity in human cancer cell line, anti-feedant activity, antibacterial activity, etc.

chemical component of leaves include; igninol-3,6,7,3',4'-pentamethoxyflavone 6'-p-hydroxybenzoyl mussaenosidic acid; 2'-p-hydroxybenzoyl mussaenosidic acid 5, 3'-dihydroxy-7,8,4'-trimethoxyflavanone; 5,3'-dihydroxy-6,7,4'-trimethoxyflavanone viridiflorol; β -caryophyllene; sabinene; 4-terpineol; gamma-terpinene; caryophyllene oxide; 1-octen-3-ol; globulol betulinic acid [3β -hydroxylup-20-(29)-en-28-oic acid]; ursolic acid [2β -hydroxyurs-12-en-28-oic acid]; n-hentriacontanol; β -sitosterol; p-hydroxybenzoic acid protocatechuic acid; oleanolic acid; flavonoids angusid; casticin; vitamin-C; nishindine; gluconitol; p-hydroxybenzoic acid; sitosterol Seeds 3β -acetoxyolean-12-en-27-oic acid; 2α , 3α -dihydroxyoleana-5,12-dien-28-oic acid. (CH.S.V.Praddep et al; 2017),

Ethanol leaf extract of *V. negundo* plant is used for Rheumatoid arthritis and have anti-inflammatory activity such as joint diseases (H. LAD; 2014). hepatoprotectivity may be due to their anti-oxidant activity against peroxidation and maintained glutathione status, galactosamine induced liver injuries. (N. Sharma et al;2016). leaves ethanol extract of *V. negundo* plant against bacterial activity at different zone of inhibition, for gram negative *Escherichia coli* highest ZOI was 12mm and concentration was 100mg/ml, for *Staphylococcus aureus* ZOI was 15mm and concentration 80mg/ml and for *Klebsiella pneumonia* ZOI was

11mm and concentration was 100mg/ml (M.S. Deogade,2016). The extract of *V. negundo* also has the biological ability like anti-bacterial, anti-feedant, Anti-filarial, Anti-fungal, Anti-larval, Anti-viral, Insecticidal, etc. it also display estrogen-like activity and propagate their use in hormone replacement therapy, may be water extract of *V.negundo* also have ability to inhibit the HIV type 1 reverse transcriptase enzyme, (U. Bano et al,2015). It is observed that *M. tuberculosis* H37RV is sensitive to 150 µg/ml ethanol extract of *Vitex negundo* Linn. (S. Magdum; 2011).

Scientific name: *Plectranthus amboinicus***Kingdom:** Plantae

Family: Lamiaceae**Higher classification:** Spurflowers

Actually different extract of *P. amboinicus* like leaves, essential oil, decoction use for many purpose such as Antibacterial activity, antifungal activity, antiviral activity, activity against Respiratory diseases, Oral Diseases, Digestive diseases (Diarrhea, Constipation, dyspepsia, indigestion & as carminative), Antitumor activity etc.with different MIC values (Greetha Arumugam, et al,2016). Combine effect of *P.amboinicus* with other medicinal plant like *Lippia alba*, *Lippia sidoides*, *Cymbopogon citrates*, and *Cinnamomum zeylanicum* essential oil extract against mycobacterium tuberculosis H37Rv, inhibit MT with different MIC, for *P.amboinicus* ($351.6 \pm 39.06 \mu\text{g/mL}$), *lippia alba* showed no inhibitory activity against TB, for *l.sidoides* is ($299.5 \pm 117.2 \mu\text{g/mL}$), for *C. citrates* is ($1,250 \mu\text{g/mL}$), for *C. zeylanicum* is ($286.5 \pm 130.2 \mu\text{g/mL}$), (Motaet al, 2018).

Mostly TB infection occurs early with current HIV infection, In the presence of HIV other part of the body can get this infection, about 90% cases is related to pulmonary TB which have chest pain and 15-20% active TB infection recorded out of lung which is called extra pulmonary TB, chronic cough, night sweats and weight loss, 25% people does not have any sign, more than 50% cases of extra pulmonary TB recorded with HIV and young people, pulmonary active infection can be analyzed by chest X-RAY and latent infection of TB can be analyzed the skin test or blood test.

Since a few years TB become again the global health problem, particularly drugs resistance emergency, this infectious disease become the second grade when it is combined with HIV, death for human around the world, three herbs which have aromatic compound wereresearched about Genus *Cymbopogon* (Family Poaceae), *Cymbopogon citratus* (leaves), *C. nervatus* (inflorescences) and *C. proximus* (leaves and inflorescences) are operate in vitro, anti TB reaction of essential oil of these medicinal herbs was observed. These oils are used against nine clinical isolated for their activity in vitro and sensitive strain H37RV of TB, (Laboratory – Sudan National Public Health Laboratory).

Tuberculosis is one of the deadly infectious diseases worldwide. Collection of information that In India about 40% out of the one third of world population has been infected with TB. Actually many medicinal plant have much active compound which have the ability to cure the TB, and the medicine which is extracted from the plant are very effected worldwide, They are accepted green drugs are safe and more dependable then synthetic drugs which is more expensive now a days and also have more side effects to the body,

Table 1: Nine selected herbs which are ascertained by the Department of pharmacognosy and phytochemistry, KBIPER, Gandhinagar, Gujarat.

Plant name	Botanical source	Family	Part used
Amla	Emblica officinalis	Euphorbiaceae	Fruits
Baheda	Terminalia bellerica	Combretaceae	Fruits
Harde	Terminalia chebula	Combretaceae	Fruits
Ashwagandha	Withaniasomnifera	Solanaceae	Roots
Long pepper	Piper longum	longum Piperaceae	Fruits
Tulsi	Ocimum sanctum	Liliaceae	Leaves
Vasaka	Adhatoda vasica	Acanthaceae	Leaves
Nagarmoth	Cyperus rotundus	Cyperaceae Rhizomes	Rhizomes
Rasna	Alpinia galanga	Zingiberaceae	Rhizomes

Approximately *mycobacterium smegmatis* have many similarities with other virulent pathogens that are also mycobacteria, nine medicinal herbs tested on the basis of two model which three herbs A. vasika, O. sanctum and A. galanga showed the maximum anti TB activity at the MIC (100 µg/ml, 250 µg/ml and 250 µg/ml

(K. Jethva et al, 2016).

Actually Tuberculosis is more infectious deadly world global disease which is called commonly as TB, and treatment of this deadly worldwide disease is also very big challenge for health community to produce active effective compound against it,

However the drugs which are used to cure TB, nowadays *M.tuberculosis* bacteria get resistance to these drugs so that it's called Multidrug-resistant tuberculosis (MDR-TB), that can be treated with second line drugs and another type is extensively drug resistant tuberculosis (XDR-TB). Actually these types of resistance TB are great challenges for global health community to produce new types of anti-tuberculosis drugs,

Nowadays medicinal herbs are also used to treat common diseases by ancienttime due its active compound which is very important for treatment, but know the main focus is on two types of resistance MDR-TB and XDR-TB among our ecosystem, approximately in this review of paper 25 different herbs selected for treatment TB and also 23 worldwide herbs has been selected between 2011- 2015 to treat MDR-TB through

new technological way and 16 effective herbs selected in India for treatment against MDR-TB, study showed that all these types of medicinal herbs are very effective against MDR-TB,

Table 2: Reported between (2011-2015) all selected Indian medicinal herbs and other countries herbs having the ability against MDR-TB.(R. Pandit et al, 2015).

Plant name (Botanical)	Family	Part Used	solvent used for extraction	Chemical constituents	Anti-TB activity/MIC values
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 H37Rv and Tuberculosis H37Ra is 0.25 and 0.125mg/mL respectively in ethyl acetate fraction
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 μ g/mL whereas for the hexane fraction it is 50 μ g/mL against M tuberculosis H37Rv
Withania somnifera (Linn.)	Solanaceae	Fresh leaves and roots	Water	Need to be identify	1.0 mg/mL - 64.47% and 0.01mg/mL - 17.88% inhibition of Tuberculosis H37Rv
Piper nigrum L.	Piperaceae	Seeds	Acetone, ethanol and distilled water	Piperine	MIC of acetone extract is 100 μ g/mL and combination of acetone and ethanol extracts is 50 μ g/mL against M. tuberculosis H37Rv
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 μ g/mL respectively against M. tuberculosis H37Rv
Acacia catechu (L.) Willd	Mimosaceae	Roots	Sequentially extracted in water, ethanol,	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) agains M.tuberculosis H37Rv
Ailanthus excels Roxb	Simaroubaceae	Roots	chloroform and hexane	Compound-1: 13-hydroxy-5(10), 14-halimadien-6-one	
Aegle marmelos Corr	Rutaceae	Leaf	Cold methanol followed	Compound-2: 6 α ,7 α -diacetoxy-	
Andrographispaniculata Nees	Acanthaceae	Leaf	by fractionation in hexane, chloroform and	13-hyd	

Datura metel L	Solanaceae	Leaf	n-butanol	roxy-8(9),14-labdadiene	MIC for compound 3 and 4 is 100 and 25 µg/mL respectively against M. tuberculosis HRv (ATCC27294)
Vitex trifolia L. (syn. Vitex rotundifolia)	Verbenaceae	Leaves		Compound-3: 9-hydroxy-13(14)-labde n-15, 16-olide) and Compound-4: Isoambreinolide	
Allium sativum	Amaryllidaceae	Bulb	Petroleum ether, ethyl acetate and chloroform	Either fats and fixed oils or phenol and aryl amine derivative	MIC of Acalypha indica, Adhatodavasica and Allium sativum is 5, 10 and 1.25 mg/mL respectively (80 mg/mL of garlic oil against M. tuberculosis HRv37)
Acalypha indica	Euphorbiaceae	Leaves			
Adhatoda vasica	Acanthaceae	Leaves			
Actinopteris radiata Linn	Actiniopteridaceae	Whole plant	n-Hexane, chloroform and ethanol	Need to be identify	MIC of n-Hexane, chloroform and ethanolic extracts 25µg/mL respectively against M. tuberculosis H37RV

(Gautam.A.H et al, 2012)

Botanical name of plant	Family name	Part Used	solvent used for extraction	Chemical constituents	Anti-TB activity/MIC values
Lantana camara L	verbenaceae	Leaf	Methanol, ethanol	α -Copaene, β -Elemene, α -humulene, Aromadendrene II oxide, β -Selinene, α -Selinene, Caryophyllene II oxide, Spathulenol, Delta-Cadinene, (S. Murugesan et al, 2016)	For Three different strain of anti-TB/and also for other diseases like skin itches, antiseptic, tumor etc
Morinda citrifolia	Rubiaceae	Leaf	Ethanol	Moisture-Ash, Crude fat, Crude fibre, Crude protein, Carbohydrate, Calorific value, Alkaloid, Cyanide, Flavonoid, Oxalate, Saponin (Muhammad Bini Etsuyankpa et al, 2017)	Same activity as rifampicin and also used for others diseases to treat like asthma, stomach ulcer, E.coli etc.

Acacia Senegal L	Mimosace ae	Bark	phenolics, condensed tannin and phlobatannin, gallic acid, protocatechuic acid pyrocatechol, (+)- catechin, (-) epigallocatechin-7-gallate, and (-) epigallocatechin-5,7- digallate, (-) epicatechin, (+) dicatechin, quercetin, (+) leucocyanidin gallate, sucrose and (+) catechin-5-gallate.(Mariyam Roqaiya et al,2015)	Anti-microbial activity
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Actually TB is one of the old disease formed thousand years ago, but still now people are infected with this disease, at the start this infectious diseases was treated by the herbs by traditionally method, many people died that time, but by the development of medicinal technology percentage of death has been decreased. India is also one of the country in world, in which more people are affected by tuberculosis so approximately one third of the people are infected with TB in the world, the cause of increasing incidence of this diseases is the resistance of organism with drugs, called MDR-TB, Rajiv rai studied this research in three different area (Gond, Korku and Bhatra) state of Madhya Pradesh and Chhattisgarh India in the year between (2004-2006),

by the survey method he collected information among seven hundred elderly people about 443 person (63.2%) were suffering from TB infectious diseases, so Gonad tribes peoples were using root and leaves powder of Muskdana (*Abelmoschus esculentus*) herbs to treat their TB infection, but the Korku region people used root and leaves powder of Adusa (*Adhatoda vasica*), and the Bhatra tribe people also were using the powder of any part of the plant of Van Tulsi (*Ocimum basilium*) to cure TB, out of 700 people 307 (69.3%) peoples were using continuously herbal medicine for five month through locally treatment in their region, these herbs are also recognized by the WHO to treat TB, actually it's not possible that you should replace these home treatment with modern medicine, (Rajiv Rai; 2016).

Actually (Ngadino et al, 2018) studied in vitro to estimate antimycobacterial activity of the ethanolic extract of *Curcuma xanthorrhiza* herbs. *Curcuma xanthorrhiza* was collected from Surabaya estate, Indonesia, made 1kg powder after drying the plant, then mixed in 95% ethanol (5L) incubated just one week at 37°C and filter to separate the supernatant and evaporate with a vacuum rotary evaporator at 45°C. In this study two methods were used broth microdilution and disc diffusion to recognize the MIC and MBC, so ethanolic extract of *C. xanthorrhiza* is used for H37RV strain of TB bacteria.

MIC of *Curcuma xanthorrhiza* ethanol extract against *M. tuberculosis* H37Rv on resazurin microtiter plate assay method was 1600 µg/ml. Serial two-fold dilutions rifampicin (10 µg/ml) and *C. xanthorrhiza* ethanol or acetone extract (0 µg/ml, 200 µg/ml, 400 µg/ml, 800 µg/ml, 1600 µg/ml, and 3200 µg/ml).

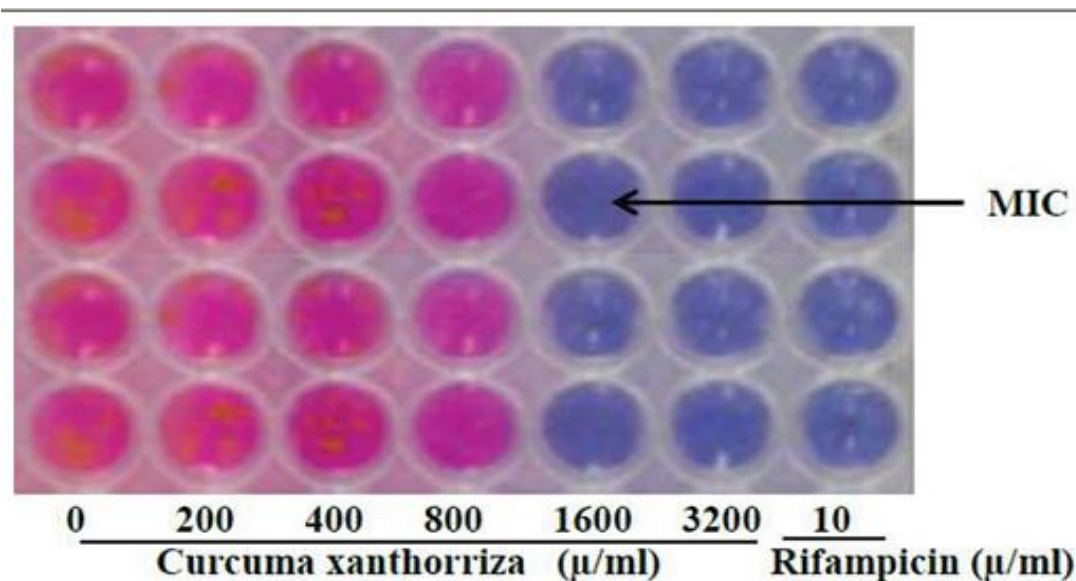


Figure 1: Resazurin microtiter plate assay method

Ethanol extract of *C. xanthorrhiza* has an antibacterial effect in vitro against H37RV strain of TB and, increasing concentration of ethanol extract can potentially affect the bacteria. (Ngadino et al, 2018).

Worldwide study showed about usage of anti-TB drugs which is less effective to treat tuberculosis because of their resistance to allopathic medicine like MDR-TB and XDR-TB, so when bacteria become resistance then again this would not have any effect as anti-TB drugs, these drugs also have many side effects like hepatitis, hypersensitivity reaction, nausea, vomiting, intestinal disorders etc, (Gautam.A.H et al,2012).

Table 3: Common Signs and symptoms by which TMPs Identified mycobacterium tuberculosis in patients, (J.R.S. Tabuti et al,2010)

Sign/symptom	Frequency
Cough lasting more than 2 months	18
Weight loss	12
Fast/labored breathing	9
Wheezing cough	8
Standing body hair	6
Slimy sputum	5
Bloody cough	5
Chronic fever	3
Cough with vomiting	3

Sweating	2
Dehydration	2
Dry cough	1
Coiled hair	1
Loss of appetite	1
Frequent spitting	1
Malaise	1
Smelly breath	1
Tonsillitis	1
Darkening skin	1
Bone and muscle pain	1
Spiritual powers	1

Biographical detail when we interviewed with 33 TMPs, recognized common sign of TB infection include Contaminated utensils, Congested living conditions, Un-boiled milk, meat and blood, Excessive drinking of alcohol, Social smoking, Contaminated food and beer, Smoking, Congenital, Drinking dirty water, Poor hygiene, Air contamination due to poor hygiene, Carrying heavy loads, Associated with fevers, Eating fried food, Eating raw foods like vegetables, Eating too much hot pepper, Untreated cough, administration of drugs especially medicine of vomiting to children,

88 plants were recorded from three district which is used to treat TB, However seven plant out of 88 plant species were mentioned by three or more TMPs, the following seven plant which are more effective than other identified medicinal plants, *Eucalyptus* spp, *Warburgia salutaris* (G. Bertol.) Chiov, *Ocimum suave* Willd, *Zanthoxylum chalybeum* Engl, *Momordica foetida* Schum, *Persea Americana* Mill. and *Acacia hockii* DeWild.), Actually TB drugs were made from combine preparation of these plant or mono preparation of plant decoction and infusion to make the dosage, different doses were used orally at different time, that time TMPs did not know how to keep the drugs for a long time and package the drug into the water plastic bottle, symptoms and sign to identify the TB are shown in table 3 by the TMPs, actually they know that TB is a transmissible diseases and spread among poor hygiene and crowding.

Local people used local treatment of TB in district surveyed, so this local method of treatment was not favorable, TMPs still struggling and experimenting to find new species of plant for treatment of TB, so these methods are needid to screen which species is important, recently technology of processing and packaging of drugs are very basic need to develop these technology for having good medicine, (J.R.S. Tabuti et al,2010).

Conclusion

Research on HIV related M/XDR-TB is a little difficult, also so much expensive and is challenging in a particular condition like diabetes mellitus, renal insufficiency, liver disorders, pregnancy, breastfeeding, contraception, psychiatric disorders which lead to the failure of the treatment, further research should be done for finding the combine medicinal herbs for cure.

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