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Review Article

A mini-review on plants having *anti-tubercular* properties from northeast india and their future prospects

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Abstract

Tuberculosis (TB) is a contagious disease caused by *Mycobacterium tuberculosis*, according to WHO in 2019, around 10.0 million people were infected with TB and it is second leading cause of death among all infectious diseases after HIV. Numerous anti-TB synthetic drugs have been developed time to time for treating the disease but due to emergence of drug resistant strains most of them become ineffective after short time use. Moreover, the use of these drugs have various side effects. Therefore, to combat with deadly tuberculosis, it is urgent to search for more effective and less toxic medicines. Since pre-historic time plants have been being used in medicinal purposes and still about 80% of the world population depend on plant based traditional medicines for their health care needs. Plants are very rich source of secondary metabolites, which can be used as an alternative to synthetic drugs. Northeast India being a biodiversity hotspot rich in many indigenous floras having medicinal property most of which are yet to be explored and this region is occupied mostly by different indigenous tribes and they uses plants in medicinal and cultural purposes. In this mini-review we studied a few plant spcies of NE India having potential anti-tubercular activity.

Keywords: Medicinal plants, Secondary metabolites, Anti-tubercular, Drug resistance, Biodiversity.

Abbreviations: MIC- Minimum Inhibitory Concentration; MDR-TB- Multi-drug resistant-TB; XDR-TB- Extensive drug resistant-TB.

INTRODUCTION

Nature is the best repository of most of our needs. Besides food, cloth and habitat, one of the utmost essentials is medicines for human beings to survive in healthy condition. Plants are the rich source of different types of secondary metabolites and these secondary metabolites play key role in showing various medicinal properties to fight against various diseases (Prasad & Tyagi, 2015; Patridge et al., 2016). According to World Health Organization (WHO, 1977), “a medicinal plant” is any plant in which one or more of its organs contains substances that can be used for the therapeutic purposes or which are precursors for the synthesis of useful drugs. In contrary to having lots of side effects in synthetic medicines, plant derived medicines are less toxic in nature, therefore concern for using herbal medicines have been increasing throughout the world (Singh et al., 2003). Different types of natural products, mostly derived from plant, contain various active components and have been used for thousands of years by a major fraction

of the population, and are still used in healthcare in many parts of the world (Majeed et al., 2012). It is estimated that 80% of the total world populations depend on plant based traditional medicines, mostly from developing countries for treating various health problems (WHO report, 2001). In India about 70% of the populations depend on various medicinal plants or indigenous medicinal systems to treat various diseases (Mukherjee & Wahile, 2006). At present time extensive researches on medicines based on natural product have been increasing throughout the world. Approximately 25% of the prescribed drugs throughout the worldwide come from plants and 60% of drugs act against infectious disease either already on the market or under clinical investigations are of natural origin (Sala et al., 2011). It is well known that in *Ayurvedic* medicine system various plant based pharmacologically active compounds are used in treatment of different ailments.

Tuberculosis is a global problem and takes about 2-3 million lives in every year and over a billion people suffered from latent tuberculosis worldwide (WHO report, 2009). Different archeological reports confirm that tuberculosis is one of the oldest human diseases and has been reported in different part of the world in various civilizations. Tuberculosis is documented as "*Yakshma*" (wasting disease) in *Vedas*. In ancient Chinese and Arabic literature documentation of tuberculosis like symptoms was seen (Sharma Mohan, 2013). Tuberculosis is an air borne disease and affects lungs. In 1882 Robert Koch for the first time announced that *Mycobacterium tuberculosis* is the causative agent of TB, which belongs to MTB Complexes (Keshavjee & Farmer, 2012). Regarding treatment of TB, it was only advice to the TB patients to "*Just sleep and eat nutritious food*" in 1800s (Keshavjee Farmer, 2012). Bacillus Calmette-Guerin (BCG) was the first effective vaccine against TB, developed in the beginning of twentieth century and streptomycin is the first anti-tubercular drug which was developed in 1944 (Schatz et al., 1944). After streptomycin some other TB drugs were come into the market like isoniazid (1952), pyrazinamide (1952), cycloserine (1952), ethionamide (1956), rifampin (1957), and ethambutol (1962), but in course of time most of them became ineffective due to development of resistant strains. Due to emergence of drug resistance nature of *Mycobacterium tuberculosis* three different types of TB can be distinguished: MDR-TB (Multi-drug resistant-TB), XDR-TB (Extensive drug resistant-TB) and TDR-TB (Total drug resistant-TB) (WHO, Global tuberculosis report 2015; Horsburgh et al. 2015). And due to drug resistance nature of *M. tuberculosis* most of the presently used effective anti-tubercular drugs become ineffective in controlling TB. Therefore, we always need new effective drugs to fight against tuberculosis, hence exploration of plant resources to identify new potent phytochemicals to be used in TB medicine is all time urgent.

India is a megadiverse country that covers 2.4% of the world's total area and is habitat for 7-8% of all recorded species. More than 45,000 plant species are found in India and out of which 7500 are known for their medicinal properties. North-eastern part of India is one of the biodiversity hotspots and geographically mostly hilly in nature. It lies between 21°34'N to 29°50'N latitude and 87°32'E to 97°52'E longitude (Mao et al., 2009) and is comprises of 8 states: Assam, Arunachal Pradesh, Manipur, Meghalaya, Mizoram, Nagaland, Sikkim and Tripura. Climatic conditions of North-east India is favorable to various types of plant growth, therefore this region is great treasure of different kinds of plant resources. Demographically NE region of India is mainly occupied by tribal communities. Since this region is remote and don't have adequate modern medical facilities, hence indigenous tribes of NE India mainly depend on plant based traditional ethnic medicines to meet their healthcare needs (Syiem et al., 1999; Rosangkima et al., 2010). These indigenous tribes are very rich in traditional knowledge on various uses of plants in different types of human ailments; hence they conserve many medicinal plants for their needs. Since tuberculosis is one of the major health issues in NE region also and due to high floristic diversity, many potent anti-tubercular property bearing plant species are found in this region. Therefore, in this review we discuss some plant species showing potential anti-tubercular activities which are found in North-eastern region of India.

The Pathogen and Pathogenesis of Tuberculosis

The etiological agent *M. tuberculosis* is a rod shaped 2-6 µm long bacteria having no flagella. It is an obligate aerobic pathogen and uses human as host (Ryan & Ray, 2004). *M. tuberculosis* can stay in human body for longer period of time without showing any visible symptoms. This pathogen has some specific types of sugars and lipids in the cell envelope. Capsule possesses mycolyl-arabinogalactan-peptidoglycan (mAGP) complex that supports the upper myco-membrane and aids the viability of *M. tuberculosis* (Alderwick et al., 2015). As the pathogen is air borne, therefore, droplet released in sneezing, coughing etc. are the primary sources for TB infection and the infectious particles enter into the alveolar passage. Larger infectious particles are expelled out by the process of mucociliary clearance, on the other hand small particles can penetrate the pulmonary alveoli (Miller et al., 1966; Marais et al., 2004). After successful entering of aerosol having 1-3 bacilli into the alveoli, they must survive and encounter with alveolar macrophages and have to get access into the lymphatics or bloodstream to establish infection (Rich, 1951; Canetti, 1955; Canetti, 1965). For their survival *M. tuberculosis* adapted various techniques and discovered by many scientists time to time, some of the examples are (Balasubramanian et al., 1994; Rook & Hernandez-Pando, 1996; Orme, 2014) etc. One most common techniques of the TB pathogen survival from the interaction of host phagocytic cycle is by utilizing metabolic pathways that do not leads to phagolysosomal fusion, do not activate signaling pathways for respiratory burst or any cytocidal mechanisms (Cummings et al., 1980; Moulder, 1985).

Medicinal Plants of Northeast India Used in Tuberculosis

Northeast India is floristically very rich and inhabited by various communities and tribes. People use these plant resources for various medicinal purposes. Some of the plants found in Northeast India having anti-tubercular property are as follows:

Abutilon indicum

Abutilon indicum is an important medicinal plant. It is commonly known as "*Jopa bondha*" in Assamese. Its various plant parts such as leaves, flowers, fruits and seeds were used to treat various diseases and ailments from the ancient time. The genus *Abutilon* is one of the larger and most differed genera of the family Malvaceae with about 120 tropical and warm temperate species (Mabberley, 2017). In India, 12 species and 12 infraspecific taxa were recorded so far, of which seven species were reported from southern peninsular India (Sivarajan & Pradeep, 1996). This plant is reported in many parts of NE India and used for different purposes like food, medicine (Kar & Borthakur, 2008).

In antitubercular study,the fractions obtained after silica gel chromatography of the crude DCM- methanol (1:1) revealed the first fraction (MIC=64 mg/mL) to exert the highest inhibition against *M. tuberculosis* H37Rv. Further separation of this fraction afforded sub-fractions with moderately strong inhibitory activity against the test organism (MIC up to 64 mg/mL). Chromatographic purification of sub-fraction 1 afforded four compounds which were spectroscopically identified as β-amyrin 3-palmitate (1), squalene (2) and a 1:1 mixture of the sterols β-sitosterol (3) and stigmasterol (4). Evaluation of the antimycobacterial activity of 1–4 showed insignificant inhibitory activity against the test organism (MIC = >128 mg/mL) (Macabeo et al., 2014).

Acorus calamus

A. calamus is commonly called "*Sweet flag*" and in Assamese '*Bach*' is a perennial herb belongs to the family Acoraceae. Rhizome is the main medicinal part of the plant, used in traditional ethno medicinal system against fever, asthma, bronchitis, cough, nervous disorder, rheumatism, and various digestive problems like gas, bloating, colic, and poor digestive function. A large number of bioactive metabolites and essential oil from leaves and rhizomes of *A. calamus* have been isolated and characterized. Therefore, this plant has very great medicinal importance (Balakumbahan et al., 2010). This plant is grown throughout the India including North East India and widely used in traditional medicines in NE India (Rajput et al., 2014; Loying et al., 2019).

Webster et al. 2010 investigated antitubercular activity of *A. calamus*, for anti-tubercular activity assay plant extract were prepared by adding 1 g of ground compound to 20 mL of distilled H_2O and boiled and allowed to simmer for 3 h. After that, each extract was sterile filtered (either 0.22 or 0.45 mm), stored at –600C. When plant extract is ready they performed their assay using clear bottom 96 well microtitre plate to reduce evaporation. They used solution of rifampin as positive control. Based on their result of colorimetric microplate resazurin assay against Bacillus Calmette Guerin, *Mycobacterium avium*, and *M. tuberculosis* H37Ra they confirmed that *A. calamus* showed significantly higher anti-mycobacterial activity comparable to rifampin. Besides this several reports also shows antitubercular properties of *A. calamus*.

Adhatoda vasica

Adhatoda vasica a small, evergreen shrub belonging to family Acanthaceae is found in many regions of India as well as throughout the world. It is commonly known as '*Adosa*' and the most important part is its leaves because of its antispasmodic and expectorant effect. It is widely used in the treatment of various respiratory diseases such as asthma, chronic bronchitis, also rheumatic pain and urinary tract infections (Gangwar & Ghosh, 2014). At an altitude of 1350 m, the shrub is distributed from Indo Malayan region, to Punjab in North, and to South-east of Bengal and Manipur up toTranvacore in kerala (Singh et al., 2011). In Assam, *A. vasica* is commonly known as "*Bogabahok*".

Sharma et al. (2021) evaluated the ethanolic extract of *A. vasica* against anti-tuberculosis drug in hepatotoxic Winstar rats. Doses ranging from 200 and 300 mg/kg body weight were orally administered. A Significant increase in thiobarbituric acid, reduction of GSH levels was observed. This result suggested the tuberculosis activity of *A.vasica.*

Aegle marmelos

Aegle marmelos is a flowering plant belongs to the family Rutaceae is found in many regions of India as well as throughout the world. It is commonly known as "*bael*". *Aegle marmelos* Corr. is well known for its medicinal values rather than its edible quality. This plant is rich in bioactive metabolites like Coumarins (Marmelosin, marmesin, imperatorin), alkaloids (Aeglin, aegelenine), Tannins (skimmianine), Carotenoids and seed oils and other miscellaneous compounds and hence since ancient time it has been using as medicinal plants (Ruhil et al., 2011). This plant is reported to have wide distribution in different parts of NE India (Barbhuiya et al., 2009; Debbarma et al., 2017).

According to Suja et al. (2017), root extract of this plant has been used against pulmonary tuberculosis in Ayurvedic medicine system. The organic solvent extract of the fruit is used for this anti-mycobacterial study and based on MIC value determined by Resazurin Microtiter Assay (REMA) of purified molecules on virulent laboratory strain *M. tuberculosis* H37Rv they suggested anti-tubercular properties. The hexane extract of *A. marmelos* fruits inhibited the growth of *M. tuberculosis* at an MIC of 50µg/mL. From column chromatography they separated the

molecules imperatorin, β-sitosterol, plumbagin, marmesin, marmin, and stigmasterol, these all compounds has ability to inhibit *M. tuberculosis*.

Allium cepa

Allium cepa is commonly known as Onion, is a herbaceous biennial plant grown for its edible bulb. This plant is belongs to the family Liliaceae. *A. cepa* contains many sulfur containing compounds in the form of cysteine derivatives like S-alkyl cysteine sulfoxides which decompose by the action of an enzyme allinase into a variety of thiosulfinates and polysulfides on extraction. In addition to free sulfoxides nonvolatile sulfur-containing peptides and proteins are also present and therefore it has great therapeutic value (Augusti, 1996). This species is present throughout the India including North East India.

Anti-tubercular activity was observed from water extract of the *A. cepa*, against two MDR strains of *M. tuberculosis.* The antimicrobial assay was performed in Lowenstein Jensen (L-J) medium and Middlebrook 7H9 broth in BacT/ALERT 3D system. These MDR strains were resistant to 1st line and some 2nd line TB drugs like refampin, isoniazid. But this plant extract can inhibit growth of *M. tuberculosi*. In this study for the 1st time it was reported that *A. indica* and *A. cepa* shows activity against susceptible *M. tuberculosis* H37Rv as well as MDR isolates of *M. tuberculosis* (Gupta et al., 2010).

Allium sativum

Allium sativum commonly known as Garlic, belongs to family Liliaceae. The bulb of the plant is the most commonly used part. Garlic has been used as medicines since long ago in different folk medicines. Since garlic is a rich source of bioactive compounds therefore it shows diverse biological activities including antitubercular, antidiabetic, anticancer, antithrombotic etc. (Agarwal, 1996). The genus *Allium* is distributed widely over the warm-temperate and temperate zones of northern hemisphere and it occurs in boreal zone. *Allium sativum* is widely distributed in NE India and used in various traditional medicines (Devi et al., 2014).

Dibua et al. 2013 studied antimycobacterial activity of garlic oil by colony count method. Sterile drug solutions and extracts were prepared by dissolving in sterile water and then filtering through 0.22 µm nylon filter. For this study they used 1.5 x10^{7} CFU/ml of bacteria by diluting the suspension to 1:10. The diluted bacterial suspension is inoculated and spread on Middlebrook 7H11 agar plates. Maintaining aseptic conditions, empty sterilized discs were impregnated with 30 µl of varying concentrations of rifampicin solution (3 mg/ml) and garlic oil (10, 50 and 80 mg/ml) and impregnated disks were placed on the seeded agar plate. Under appropriate growth condition, at first plates were kept in room temperature for 30 min after that at 37° C incubated for 14-21 days. Based on the MIC value comparison of garlic oil to standard antimycobacterial drugs (rifampicin, isoniazid and ethambutol), it was confirmed that garlic extract shows higher antimycobacterial properties than isoniazid and ethambutol (Viswanathan et al., 2014).

Aloe vera

Aloe vera is a succulent perennial plant and grown abundantly in tropical and subtropical areas. It belongs to the family Asphodelaceae (Liliaceae). Due to presence of large varieties of enzymes, amino acids, vitamins and other bioactive metabolites, *Aloe vera* is widely used in different medicinal purposes since long ago. *A. vera* provides several health benefits, some of them are wound healing, minimizing frost bite damage, protection against skin damage from x-rays, lung cancer, intestinal problems, increasing high density lipoprotein (HDL) etc. (Ahlawat & Khatkar, 2011). *A. vera* is widely grown and used in various medicinal purposes in different parts of NE India (Mehrotra & Srivastava, 2010; Sonowal & Barua, 2011).

The hepatoprotective effect of *A. vera* against anti-tuberculosis drug side effect was investigated by Mawarti et al. 2017 in rats treated with anti-tuberculosis drug with ethanolic *A. vera* extract dose of 40; 80; and 120 mg/kg body weight. They found that rats with only anti-tuberculosis drug increase the TNF-α level initiating an immunological response due to toxic effect of drug in liver. However, rats with *A. vera* extract reduce the level of TNF-α level indicating that *Aloe vera* can be used as an alternative to anti-tuberculosis drug to suppress side effect.

Andrographis paniculata

Andrographis paniculata commonly known as Kalmegh belonging to family Acanthaceae is an annual herb. *A. paniculata* contains diterpenes, lactones, and flavonoids. Flavonoids mainly exist in the root, but have also been isolated from the leaves (Singh et al., 2017). It shows various pharmacological activities, therefore it is an important medicinal herb and used in different part of the world; some common therapeutic uses are: antipyretic, antimalarial, anti-inflammatory, anti-thrombogenic, hepatoprotective effect (Abu-Ghefresh et al., 2009; Saxena et al., 2010; Bardi et al., 2014).

Antimycobacterial assay was carried out by Mishra et al. (2013) in LJ medium with or without plant extract by indirect proportion method. 75% Methanol extract of the plant leaf was applied in the range of 0.25-08 mg/ml agar plate and agar plate without plant extract used as control plate. The minimum inhibitory concentration (MIC) was calculated and based on that it was confirmed that *A. paniculata* leaf extract has anti-tubercular potentiality.

Artocarpus lakoocha

Artocarpus lakoocha belongs to the family Moraceae. It is found in India, Nepal, Bhutan, Bangladesh, Myanmar and Malaysia (Hari et al., 2014). Species of *Artocarpus* in South-East Asia, Indonesia, Western part of Java and India are use as food and traditional medicine (Jagtap et al., 2010; Konwar

et al., 2020) recorded that Ahom tribe of Chengalijan village use juice of *A. lakoocha* for treating dysentry. It is use for anti-inflammatory therapy and as well as an anti-skin aging agent by traditional *Thai* peoples (Hari et al., 2014).

Boonyaketgoson et al. (2020), evaluated the anti-tuberculosis activity of *A. lakoocha* against *M. tuberculosis* H37Ra. They found 12 compounds from acetone extract of *A. lakoocha.* Compound 7 (cyclocommunin) showed most active antimycobacterial activity with MIC value of 12.3 µM against *M. tuberculosis* H37Ra.

Caesalpinia pulcherrima

Caesalpinia pulcherrima is an exotic, hardy, shrub or a small tree belonging to family Caesalpinacaea. It is found throughout India and is use for treating ulcers, fever, tumors, asthma and skin diseases (Hedge et al. 2020). *C. Pulcherrima* possess numerous phytoactive constituents such as glycosides, retinoids, flavones, chalcones, flavanols and sterols (Vivek et al., 2013). It is commonly known as "*Peacock's flower*" or "*Peacock's Pride*". In Northeast, it has been reported from Assam (Bordoloi et al. 2014) and also it has been reported as an exotic species from Papum pare district of Arunachal Pradesh (Kalita et al. 2015)

Promsawan et al. (2003), evaluated the anti-tubercular activity of two furanoditerpenes compounds namely 6β-benzoyl-7β-hydroxyvouacapen-5α-ol and 6β-cinnamoyl-7β-hydroxyvouacapen-5α-ol isolated from the roots of *C. pulcherrima* via activity guided fractionation at 6.25 µg/ml, 6**β**-cinnamoyl-7β-hydroxyvouacapen-5**α**-ol displayed strong anti-tubercular activity with low MIC (Minimum Inhibitory Concentration) whereas 6**β**-benzoyl-7**β**-hydroxyvouacapen-5**α**-ol displayed less active at MIC 25 µg/ml. This result suggested the anti-tuberculosis activity of *C. pulcherrima*.

Camellia sinensis

Camellia sinensis is one of the most economic plant of North-East India especially Assam, whose leaves and leaf buds are used to produce tea. This plant is belong to the family Theaceae. It is commonly known nas "*Chaa*". It is a widely used medicinal plant by the trials throughout India, China and popular in various indigenous system of medicine like Ayurveda, Unani and Homoeopathy (Baibado et al., 2011; Namita et al., 2012).

Screening of antitubercular activity was performed by Yeragamreddy et al. 2013 against *M. tuberculosis H37Rv* using microplate alamar blue assay (MABA). The methanolic extract for *Camellia sinensis* were selected and subjected to column chromatography according to increasing polarity of solvents in the order of n-hexane, ethyl acetate and a mixture of methanol and ethyl acetate (50:50% v/v). From their study they observed that *C. sinensis* exhibit considerable antitubercular activity. Glucoronide saponin from *Camellia sinensis* showed good antibacterial activity and mild antitubercular activity. Therefore, this plant has great potentiality to develop anti-tubercular drugs by further study.

Capsicum annuum

Capsicum annuum belongs to family Solanaceae which is native to South America, Central America and Galapagos (Walsh & Hoot, 2001). It is commonly known as "Chilli Pepper" in english and in Assamese it is known as "*Jalakia*". India is the largest producer of dry chillies and pepper (FAO, 2019). In Northeast India, *C. annuum* is found in Arunachal Pradesh, Assam Nagaland, Meghalaya, Manipur, Tripura, Mizoram and Sikkim (Yatung et al., 2014). Capsaicin present in *C. annuum* is used for the treatment of muscles and lower back joint pains, chronic disorders, nonallergic Rhinitis (Bhutia et al., 2019).

Famewo et al. (2017) studied the anti-mycobacterium tuberculosis activity of *C. annuum* liquid extract against H37Rv. They found that *C. annuum* showed MIC against *M. tuberculosis* at 25 µg/ml. da Silva Gebara et al. (2020) evaluated the antimicrobial activity of *C. annuum* against Candida and *M. tuberculosis*. Six fractions (F1, F2, F3, F4, F5, F6) of *C. annuum* was obtained by reverse phase chromatography. Fraction F2 displayed highest antimycobacterial effect with an MIC_{50} value of 39.2 ± 1.6 µg mL−1. This result suggests the anti-tuberculosis activity of *C. annuum.*

Cassia occidentalis

Cassia occidentalis is a shrub belonging to Fabaceae. It is commonly known as "*Hat-tenga*" in Assamese. It grows throughout the tropics and subtropics. It is used for landscape purposes, as food and medicinal and leaf extracts have broad spectrum antibacterial, antimalarial, antifungal, antimutagenic, antiplasmodial, anticarcinogenic, and hepatoprotective activity (Murugan et al., 2014). There are several reports on the distribution of this plant in NE India including Assam (Banik et al., 2010; Sikdar & Dutta 2008).

For anti-mycobacterial study the petroleum ether extract for *C. occidentalis* were selected and subjected to column chromatography according to increasing polarity of solvents in the order of n-hexane, ethyl acetate and a mixture of methanol and ethyl acetate (50:50% v/v). In this study total 15 column fractions were collected for plant and tested by TLC technique for the presence of chemical constituents. Flavones of *C. occidentalis* exhibited considerable antitubercular activity and by further study it can be a potent antibacterial drug (Yeragamreddy et al., 2013).

Catharanthus roseus

Catharanthus roseus is an evergreen plant belonging to family Apocynaceae and indigenous to Madagascar (Mishra et al., 2017). 7 species of genus *Catharanthus* is endemic to Madagascar and 1 species in India and Sri-lanka (Nejat et al. 2015). It is commonly known as "*Cayenne jasmine*", "*old maid*", "*periwinkle*" in English. In Assam it is called as "*Piralikunwori*" or "*Nayantara*".

Raja et al. (2015) evaluated the methanol extract of *C. roseus* against *M. tuberculosis*. Phytochemicals from *C. roseus* was analyzed by GCMS. They found that antibiogram of *C. roseus* showed active antimycobacterial property against *M. tuberculosis* and maximum inhibition zone of 22 ± 1.63 mm. Also, the MIC of *C .roseus* phtyochemicals displayed positive inhibitory at 50 µg/ml. These results suggest the anti-tuberculosis property of *C. roseus.*

Costus speciosus

C. speciosus is a small plant resembling ginger plant and rhizome is the main medicinally used part. This plant is belong to the family Zingiberaceae and shows many pharmacological activities like pneumonia, dropsy, rheumatism, urinary diseases, jaundice, skin diseases and leaves are used to treat mental disorders. This plant is widely found in various part of North East India and used in different medicinal purposes (Bhuyan & Zaman, 2008; Barbhuiya et al., 2009).

Anti-tubercular activity against *M. tuberculosis* H37Rv of the different solvent partitions of the plant materials was determined by tetrazolium colorimetric microdilution assay. The n-hexane partition of *C. speciosus* shows highest antitubercular activity with minimum inhibitory concentrations (MICs) of 100–200 µg/mL and minimum bactericidal concentration (MBC) of 200 µg/mL. Due to their destructive effects on the integrity of the mycobacterial cellular structure anti-TB activity was proved (Mohamad et al., 2013).

Couroupita guianensis

C. guianensis is a large deciduous tropical evergreen tree belonging to the family Lecythidaceae. It is commonly known as Cannonball tree because of its fruit appears like cannonball. It has been reported to contain volatile oils, keto-steroids, glycosides, couroupitone, indirubcin, isatin and phenolic substances in various part of the tree. Therefore it is traditionally used by different tribes for various ailments. This plant is reported in Assam and different parts of NE India (Gogoi et al., 2019).

For anti-tubercular activity plant extract with methanol solvent is used and by calculating the zone of inhibition by agar plate well diffusion assay. The chloroform extract of leaves of *C. guianensis* is subjected to TLC for determining the phytochemicals present in the extract. After TLC other techniques like Gas chromatography and mass spectroscopy is used and it is found that bis (2-ethylhexyl) phthalate or di (2-ethylhexyl) phthalate (DEHP) was found as a major component with 94% of abundance and retention time (rt) of 44.84. Based on zone of inhibition study it was found that this plant has great potentiality in anti-tubercular drug development (Priyadarshini & Veeramani, 2020).

Curcuma longa

Curcuma longa is a medicinal plant belonging to family Zingiberaceae. It is found in tropical and subtropical countries mostly cultivated in India and China (Araujo et al., 2001). It is commonly called as "*Haldi*" in India. Sarma et al. 2005 reported that Northeast India contains the highest species of Curcuma. The rhizome of *C. longa* called "*Turmeric*" is used in food for flavor and has many medicinal values (Sabale et al., 2013). In Tamenglong distrct of Manipur, Rhizome and leaves of *C. longa* is used for various ethnobotanical uses such as for Antiseptic, vermifuge, blood purifier, cancer, cut, dyes, flavoring agent, food wrapper, vegetables (Daimei & Kumar, 2014).

Ogudo et al. 2014 evaluated the antimycobacterial activity of *C. longa* (Turmeric) methanol, n-hexane and dichloromethane extracts against 4 species of Non-tubercular mycobacteria. They found that Methanol and n-hexane extract of *C. longa* showed most active inhibition zone of 16 ±0.5 and 20 ±0.0 mm for *M. abscessus* with MIC and MBC of 25 mg/mL and 75 mg/mL. These results suggest the anti-tuberculosis activity of *C. longa*.

Glycyrrhiza glabra L.

This plant is belongs to the family Fabaceae, an small perennial herb. It is widely distributed in NE India and commonly known as *Jesthimadhu* in Assam and some parts of NE India. Rhizomes and roots are the main medicinal part of this plant. This plant is very rich in different phytochemicals like Glycyrrhizin, licoflavonol, glycyrol, licoricone, formononetin, phaseollinisoflavan, hispaglabridin A & B, 3-hydroxy glabrol, 3 -methoxy glabridin. Therefore, this plant is widely used as in various traditional medicines (Gupta et al., 2008).

Antimycobacterial activity of acetone extract of *G. glabra* is compared by determining minimum inhibitory concentration (MIC) value with standard anti-tubercular drugs rifampicin (RIF), ethambutol (ETH) and isoniazid (INH) by (Nair et al., 2015). From their experiment they observed that acetone extract of *G. glabra* showed significantly lower MIC (0.97 - 1.95 µg/mL) against MTBH as compared to standard drugs INH (7.81 - 15.62 µg/mL) and ETH (15.62 - 31.25 µg/mL) ($p < 0.0001$), whereas, MIC of RIF was significantly lower than MIC observed for acetone extract of G. glabra ($p < 0.0001$). Therefore, *G. glabra* has potential ability to develop anti-tubercular drugs.

Mallotus philippensis

Mallotus philippensis is an evergreen plant belonging to family Euphorbiaceae, which is popular in *Ayurveda* due to its anthelmintic property (Buha and Acharya 2020). It is distributed throughout North America and East Asia up to Northern Indo-Pak (Afzal et al. 2013). Buha et al. 2020 reported that *M. philippensis* is used by 18 states of India including Assam, Manipur and Mizoram for medicinal purpose. It is commonly known as '*Kamala*' tree and in Assam it is known as *Gangai, Puddum, Lochan*.

Hong et al. (2010) studied about the anti-tuberculosis compounds of *M. philippensis* through Bioassay-directed fractionation of organic extract against H37Rv. They found

5 compounds, of which compound 1 (mallotophilippen F) showed the highest effect against *M. tuberculosis* strain with an MIC of 16µg/mL. Gupta et al. 2010 evaluated the ethanolic extract of *M. philippensis*. They found out that the MIC of ethanolic extract against virulent and avirulent strains H37Rv and H37Ra were 0.25 and 0.125 mg ml g ml^{-1}. These results suggest that *M. philippensis* has anti-tuberculosis property.

Mimosa pudica

Mimosa pudica is an annual or perennial herb, belonging to family Mimosaceae. It is found to be native in tropical America and to tropical and subtropical parts of India (Ahmad et al., 2012). It is commonly known as "*Touch me not*" plant. *M. pudica* is used in the treatment of various diseases due to its antiasthmatic, aphrodisiac, analgesic and antidepressant properties (Ahmad et al., 2012). Debnath et al. (2015) found out that the local inhabitants residing near Trishna Wildlife Sanctuary in Tripura used fresh root of *M. pudica* for treating tooth problems and leaf and bark for piles problems.

Gupta el al. (2010) found out that the ethanolic extracts of *M. pudica* showed active MIC of 0.25–0.5 mg ml^{-1} against *M. smegmatis.* This result suggests the anti-tuberculosis activity of *M. pudica*.

Moringa oleifera

M. oleifera commonly known as "*Drumstick*" or *"horse raddish tree*" belongs to family Moringaceae. It is found in tropical and subtropical countries and native to Himalayan regions of North west India, Africa, Arabia, South east Asia, the Pacific, Caribbean islands and South America (Abdul Razis et al., 2014). Tag et al., 2012 reported that pod of *M. oleifera* is used as herbal medicine to treat diabetes mellitus in Arunachal Himalaya region. Chhetri 2006 reported that *M. oleifera* is cultivated in Nongpoh, Umroi and Mawiong regions of Meghalaya as kitchen garden.

Hepatoprotective activity of *M. Oleifera* ethanol leaves extract and Silymarin (SM) against anti-tubercular drugs was evaluated. Oral administration of ethanol extract of *M. oleifera* leaves (150, 200 and 250 mg/kg body weight) and SM (200 mg/kg body weight) in male winstar rats was evaluated for 45 days. It was observed a significant reduction in (Aspartate transaminase) AST, (Alanine aminotransferase) ALT, and (**alkaline phosphatase)** ALP level. (Pari et al., 2002).

Nyka et al. (2014) evaluated the petroleum ether, ethyl acetate and methanol extracts from roots, stem bark, leaves and seeds of *M. oleifera* against *Mycobacterium indicus pranii* (MIP) and *Mycobacterium madagascariense*. They found out that ethyl acetate extract of *M. oleifera* leaf showed most active activity against *M. Madagascariense* with MIC of 0.37381 mg/ml. This result suggests the anti-tuberculosis activity of *M. oleifera*.

Ocimum sanctum

Ocimum sanctum, a perennial shrub distributed up to an altitude of 6000 ft in Himalayas (Namsa et al. 2011). It belongs to the family Lamiaceae. The common name of *O. sanctum* is "*Holy Basil*" and in India it is popularly known as "*Tulsi*". It is a very important traditional medicine for the Hindus of Indian Sub-continent (Gupta et al., 2002). Shankar et al. (2011) reported six species for malarial treatment in Northeast India, out of which *O. sanctum* was used. Das et al. (2009) found out that the ethnic communities of fringe village near Manas National Park used *O. sanctum* as medicinal plant.

Jayapal et al. (2021) evaluated the in-vitro anti-tuberculosis activity of *O.sanctum* oil extracted via hydro distillation against H37Rv and nine *M. tuberculosis* clinical isolates with BD BACTEC MGIT instrument. They found that the MIC of *O. sanctum*oil against H37Rv was 3 µl (2.931 µg) whereas for the *M. tuberculosis* clinical isolates, the MIC was 1.5 µl (1.4655 µg) to 6µl (5.862 µg). Thus, this indicates the anti-tuberculosis activity of *O.sanctum*.

Oroxylum indicum

Oroxylum indicum is a deciduous evergreen plant belonging to family Bignoniaceae growing up to a height of 12 m (Singh et al., 2017). It has been found in the areas of Bangladesh, India, Malacca, Sri Lanka, Malay Islands, and China (Gokhale et al., 2006). It has been found in the areas of Manas national Park and is used for treatment of various ailments including diarrhea, dysentery, gout, vomiting, rheumatoid arthritis, fever (Laloo et al., 2016).

More et al. (2017) evaluated the hepatoprotective activity of *O. indicum* against anti-tubercular drugs. Ethanol and aqueous extract of *O. indicum* (500 mg/kg) was orally administered in Winstar rats for 90 days. A significant reduction in serum enzymatic levels (ALT, AST, LDH, T Bil) was observed. These results suggest the anti-tuberculosis activity of *O. indicum*.

Piper longum

Piper longum belongs to family Piperaceae and is found in tropical and subtropical regions of world including Indonesia, Malayasia, Singapore, Srilanka, South Asian regions, India in Assam, Arunachal Pradesh and Tamil Nadu (Zaveri et al., 2010; Barua et al., 2014).

Barua et al. (2014) evaluated the antioxidant and antimycobacterial activity of *P. longum* seed via comparison extracted by chloroform, ethyl-acetate, hexane, ethanol, hydro-ethanol and aqueous extract against *M. smegmatis.* They found that out of 6 extracts, chloroform extract showed MIC of 8 mg/mL indicating its most active anti-tuberculosis effect against *M. smegatis*.

Orally administered aqueous extract in Swiss albino mice against anti-tuberculosis drugs for 45 days revealed reduced glutathione levels and decreased lipid peroxidation

(Gurumurthy et al., 2012). These results suggest the anti-tuberculosis activity of *P. longum.*

Piper nigrum

Piper nigrum is a medicinal plant belonging to family Piperaceae. It is considered as a highly economic spice crop found in Western Ghats of India and also cultivated in Vietnam, Malaysia, Indonesia, China, and Brazil, Sri Lanka and West Indies (Hao et al., 2012; Sen et al., 2016). It is commonly called as Black pepper and known as "*Jhaluk"* in Assam. Purkayastha et al. (2004) found that the ethnic communities of Dibru-Saikhowa Biosphere reserve used the fruit of *P. nigrum* for treating abdominal pain, irregular menstruation, sterility, hydrophobia, jaundice, piles, pneumonia. Immature *P. nigrum* fruit is used for hepato-protective purpose in Assam (Borthakur et al., 2004).

Zodape et al. (2021) evaluated the anti-tuberculosis activity of ethanolic seed extract of *P. nigrum* and anti-tuberculosis drugs Ethionamide (ETH), Para amino salicylic acid (PAS) against H37Rv strains. They found that ethanolic extract had shown no effect either independently or in combination but displayed anti-tuberculosis activity against H37Rv strains. These results suggest anti-tuberculosis property of *P. nigrum*

Piper sarmentosum

This plant is a perennial herb, creeping along the ground or erect, growing up to 50–60 cm and belongs to the family Piperaceae. Phytochemical investigation of this plant reveals that it produces several classes of bioactive metabolites such as alkaloids, amides, pyrones, dihydrochalcones, flavonoids, phenylpropanoids, lignans and neolignans (Rukachaisirikul et al., 2004). This plant is widely distributed in tropical and subtropical region of the world. This plant is native to NE India (Sim et al., 2009; Mohd Zainudin et al., 2013).

Anti-tubercular activity is assessed by Rukachaisirikul et al. 2004 from fruit extract by using hexane and methanol as solvent. Microplate Alamar Blue Assay (MABA) is used to determine anti-mycobacterial activity of the extract against *Mycobacterium tuberculosis* H37Ra strain. Based on the MIC value of the separated compounds it was observed that out of 9 compounds assayed for anti-tubercular property 7 compounds (pellitorine, guineensine, sarmentine, brachyamide B , 1-piperettyl pyrrolidine, 3 ,4 ,5 -trimethoxycinnamoyl pyrrolidine, sarmentosine) showed good result. Therefore it is confirmed that this plant has great potentiality in anti-tubercular drug development.

Plumbago zeylanica

P. zeylanium is a herbaceous plant belonging to the family Plumbaginaceae. This plant is grown in tropical and sub-tropical regions of the world. *Plumbago zeylanica* is widely distributed in India and used in various medicinal purposes. The root of the plant and its constituents has potential therapeutic values including anti-atherogenic, cardiotonic, hepatoprotective and neuroprotective properties (Tilak et al., 2004). This plant is used by various tribes of North East India, for example in preparation of "*Jou"* by Boro tribe of Assam (Basumatary et al., 2014).

For the study of anti-tubercular activity by Nayak et al. 2014, plant compounds were synthesized and tested by treating Plumbagin with 1-Naphthoyl chloride, 2-Naphthoyl chloride and Hexanoyl chloride. Further the synthesized Plumbagin derivatives were condensed with antitubercular drugs-Isoniazid, Pyrazinamide, and Ethionamide. By determining logP value it was confirmed that Ethionamide analogs of Plumbagin possess best antitubercular activity among all synthesized compounds. The compounds were screened in both standard H37Rv and clinical isolate S, H, R, and E sensitive **M. tuberculosis** strain with taken Rifampicin as a standard drug. From their experiment they conclude that 1-Naphthoyl chloride-Ethionamide derivative of Plumbagin was the most effective in clinical isolate: S, H, R and E sensitive **M. tuberculosis.**

Stephania hernandifolia

Stephania hernandifolia is flowering plants in the family Menispermaceae, It is commonly known as Jabong. These plants are available around the region of Jaintia Hill (Meghalaya), and the most important part is its stems and roots because of its antimicrobial property. This plant is used in many traditional medicines.

Like the *Strophanthus wallichii,* it has been also used in traditionally in the treatment of tuberculosis by different tribes like Jaintia tribes of NE India. Molecular docking study also supports their anti-tubercular properties. Phytochemical analysis and characterization identified the compound DL tetrahydropalmatine, which has many report to have anti-tubercular activity (Suhitha et al., 2015). This proved anti-tubercular activity of this plant.

Strophanthus wallichii

Strophanthus wallichii is a flowering plants in the family Apocynaceae, is found in many regions of India as well as throughout the world. It is commonly known as 'Tylle sanein'. These plants are being used by the local herbal practitioners only for the local people to cure psoriasis, tuberculosis (TB), tumor, cancer, viral diseases, kidney stone, diabetes, etc. (Suhitha et al., 2015). This plant is reported in many part of NE India including Assam (Borah et al., 2020)

This plant is being used for treating tuberculosis since long ago by various traditional herbalists. Molecular docking study also proved their anti-tubercular properties. The compounds 2-hydroxy-4-methoxy- Benzaldehyde from methanolic extract of *Strophanthus wallichii* has been confirmed after determining their molecular structures, since this compound is reported to have anti-tubercular activity. Therefore, this plant has potentiality to develop anti-tubercular drugs (Suhitha et al., 2015).

Tinospora cordifolia

Tinospora cordifolia is a climbing shrub belongs to the family Menispermaceae and commonly known as "*Guduchi*". From different parts of the plant body *viz.* root, stem or whole body various types of bioactive metabolites like alkaloids, steroids, diterpenoid lactones, aliphatics, and glycosides are synthesized (Saha & Ghosh, 2012). This plant is native to India and used in Indian Ayurvedic medicinal system against jaundice, diabetes, and rheumatoid arthritis and many other diseases also. This plant has reported in various parts of North East India (Yadav & Agarwala, 2011;Sultana & Handique, 2013).

Gupta et al. (2016) investigated the immunomodulatory effects of G1-4A, a polysaccharide obtained by ethanol extract followed by acetone prcipitation from *T. cordifolia* against *Mycobacterium tuberculosis* (MTB) infected mice. A significant reduction of bacillary burden was seen in the lungs of MTB infected BALB/c mice treated with G1-4A. Also increase expression of TNF-α, INF-γ and NOS2 were observed in mouse lungs along with increased Th1 cytokines levels like IFN-γ, IL-12 and decreased Th2 cytokine levels like IL-4 in the serum. This result suggested the tuberculosis activity of *T. cordifolia*.

Tithonia diversifolia

T. diversifolia is an annual or perennial shrub belongs to the family Asteraceae. It is commonly known as "*Mexican sunflower*". is a valuable source of various bioactive compounds are extracted from **T. diversifolia**, hence it has used in different traditional medicine system for treating different health problems (Tagne et al., 2018). This plant is native to Mexico and Central America which later introduced into Africa, Australia, Asia and South America. This plant is cosmopolitan in distribution. There are several reports of its existence in NE India (Singh & Theunuo, 2018).

Anti-tubercular activity was studied from leaf extract in methanol solvent in terms of zone of inhibition by agar well diffusion assay. *T. diversifolia* showed significant anti-mycobacterial activity, and further characterization showed that the major antimycobacterial component of TD plant was ZGB ($C_{15}H_{24}$), a monocyclic sesquiterpene (Priyadarshini & Veeramani, 2020).

Vitex negundo

Vitex negundo is a large aromatic shrub belongs to the family Lamiaceae. It is commonly known as '*Chinese chaste tree'* and reported to produce wide variety of bioactive metabolite and widely used in traditional medicines as analgesic, antioxidant and anti-inflammatory. *V. negundo* is widely distributed in different areas of NE India including Assam (Dolui et al., 2004; Tandon et al., 2008; Borah et al., 2012).

Evaluated the hepatoprotective effect of *V. negundo* ethanolic leaf extract against anti-tuberculosis drug causing hepatotoxicity in Winstar rats. Doses of 100, 250 and 500 mg/kg of *V. negundo* ethanolic leaf extract was administered orally for 35 days. Doses of 250 and 500 mg/kg showed a significant reduction in TB, Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT) and Alkaline Phosphatase (ALP) levels, thus proving that *V. negundo* can be used as an alternative against anti-tuberculosis drug causing hepatotoxicity (Tandon et al., 2008).

Vitex trifolia

The plant species belonging to family Verbenaceae, is a deciduous shrub native to Southeast Asia, Australia, East Africa and Micronesia. It produces a variety of diterpenoids and iridoids due to which they shows medicinal properties like antioxidant properties. It has been reported that methanol extract of this plant possesses strong antioxidant activity (Ono et al., 1998). *Vitex trifolia* is abundantly reported in various part of North-East India (Khumbongmayum et al., 2005; Shah et al., 2013).

Anti-tubercular activity against H37Rv strain of *M. tuberculosis* was studied by in BACTEC-460 assay. This assay uses MIC values in µg/ml of compounds from the *Vitex trifolia* leaf extracted with cold methanol. Based on TLC and HPLC result brought out a new halimane diterpenoid, 13-hydroxy-5(10),14-halimadien-6-one and two new labdane diterpenoids, 6,7-diacetoxy-13-hydroxy8(9),14-labdadien and 9-hydroxy-13(14)-labden-15,16-olide molecule for the first time from hexane extract of *Vitex trifolia* leaves. These newly identified compounds by further study may have potentiality in development of anti-tubercular drugs (Tiwari et al., 2013).

Withania somnifera

Withania somnifera, a wonder herb of family Solanaceae. It grows in India, Pakistan and parts of Africa and it has multiple medicinal properties. It is commonly known as '*Ashwagandha*'. *W. somnifera* is a very rich source of various types of bioactive metabolites and has been extensively used for its medicinal properties. These include anti-cancerous, antioxidant, antiepileptic, antidepressant, anti-anxiety, anti-inflammatory, antiarthritic, and antimicrobial. It also has neuroprotective, spermatogenic, hepatoprotective, hypoglycemic and hypolipidemic properties (Mehmood et al., 2020). This plant is very common in North East India and is used widely in medicinal purposes (Tiwari et al., 1979; Deka & Deka 2007).

W. somnifera is an immunity enhancer and hence act as adjuvant for anti-tuberculosis drugs used as DOTS. For this root extract of *W. somnifera* is used and got very effective response (Kumar et al., 2018). Again Adaikkappan and his coworker in 2012 studied the anti-tuberculosis activity of *W. somnifera* against *M. tuberculosis* H37Rv. They studied MIC value of the aqueous extract of the plant against the test pathogen and found that *W. somnifera* extract shows very promising result as anti-tubercular agent (Adaikkappan et al., 2012).

Ziziphus oenoplia

Ziziphus oenoplia is a thorny shrub belonging to family Rhamnaceae found in the temperate warm regions and sub-tropical of the world (Thirugnanasampandan et al., 2017). Eswari et al. 2013 reported that *Z. oenoplia* is native to India and Southeast Asia. Taran and Deb 2019 reported 39 species in which *Z. oenoplia* was found in Tripura. The plant has antidysenteric and antidiarrhoeal properties (Yadav et al., 2016).

Rao et al. (2012) evaluated the hepatoprotective potential of *Z. oenoplia* against male Wistar albino rats treated with anti-tubercular drugs. Dose of 150 and 300 mg/kg ethanolic extract of *Z. oenoplia* with silymarin of 100 mg/kg were administered orally for 21 days. They found out that dose dependent manner of *Z. oenoplia* ethanolic extract restored the elevated serum enzymatic levels serum levels of glutamic oxaloacetic transaminase (SGOT), glutamate pyruvate transaminase (SGPT), alkaline phosphatase (SALP), and bilirubin. Also, dose dependent extract inhibited the hepatic melondialdehyde formation in the liver of rats. This result suggests that *Z. oenoplia* has anti-tuberculosis activity and can be used as an alternative to anti-tuberculosis drugs.

CONCLUSION

Tuberculosis is a global problem, and causes infections and death of millions of people in every year; it is so serious that in 1993 it was declared as Global emergency. Since the first anti-tubercular drug Streptomycin, large number of drugs have come into the market but after applying short time most of them became ineffective due to development of drug resistant strains of *M. tuberculosis*. Multidrug resistant strains (MDR), Extensively drug resistant strains (XDR) and Total drug resistant strains (TDR) are very difficult to treat, as most of the 1st and 2nd line TB drugs are not effective to treat them. Moreover excessive use of synthetic drugs may cause different types of side effects also. Therefore, interest towards plant based medicines have been increases throughout the world as they cause less or no side effects on human health.

Northeast India is rich in biodiversity, many endemic plant species are found in this region which are widely used in traditional medicine system. Different parts of various plants which possess variety of bioactive metabolites are used against different diseases. In this mini-review we have discussed 37 plant species from Northeast India which have anti-tubercular properties. It is not possible to discuss all plant species showing anti-tubercular properties, we just tried to focus some plants having potential anti-tubercular activity. Further research and development can explore more and more plants having tremendous medicinal value like anti-tubercular. Exploration of the unexplored plant resources of NE India can open a new door for pharmaceutical industries to develop new life saving drugs for betterment of human life in future.

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