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HERBAL DRUGS AS ANTI-TUBERCULAR AGENTS – A REVIEW

Linju P Thomas, Sandhya S, Kavitha M.P, Krishnakumar K*

Department of Pharmaceutical Analysis, St James College of Pharmaceutical Sciences, Chalakudy, Thrissur, Kerala, India.
St James Hospital Trust Pharmaceutical Research Centre (DSIR Recognized Centre), Chalakudy, Thrissur, Kerala, India.

ABSTRACT

Tuberculosis (TB) is a disease that has affected mankind from very ancient times.The Anti-Tuberculosis (Anti-TB) drugs are less effective because of emergence of Multi-Drug Resistance (MDR) and extensively Drug Resistant (XDR) strains of M. Tuberculosis. The use of Anti- TB allopathic medications results into side effects like hepatitis, hypersensitivity reactions, nausea, vomiting. The use of herbal medicine becoming popular due to toxicity and side effects of allopathic medicines. This review is to highlight some newly studied plants for anti-tubercular activity.

Keywords: Multi Drug Resistance (MDR), Extensively Drug Resistance (XDR).

INTRODUCTION

Herbal medicine, also called botanical medicine or phytomedicine, refers to using a plant's seeds, berries, roots, leaves, bark, or flowers for medicinal purposes. Herbalism has a long tradition of use unlike conventional medicine. It is becoming more mainstream as improvements in analysis and quality control, along with advances in clinical research, show the value of herbal medicine in treating and preventing disease [1]. In the early 19th century, when chemical analysis first became available, scientists began to extract and modify the active ingredients from plants. Later, chemists began making their own version of plant compounds. Almost one fourth of pharmaceutical drugs are derived from botanicals [2]. Recently, the World Health Organization estimated that 80% of people worldwide rely on herbal medicines for some part of their primary health care. In Germany, about 600 to 700 plant based medicines are available and are prescribed by some 70% of German physicians. In the past 20 years in the United States, public dissatisfaction with the cost of prescription medications, combined with an interest in returning to natural or organic remedies, has led to an increase in herbal medicine use [3, 4].

Treatment of illness and maintenance of health using herbal medicines is the oldest and most popular form of Healthcare practice known to humanity that has been practised by all cultures in all ages throughout the history of civilization. Herbal medicines have long earned reputation as "the people's medicines" because of their easy accessibility, safety, and the ease with which they can be prepared. This method is now gradually scorning a more mainstream method of treatment in many countries of the world, because improvements the methods of analysis and quality control of herbs and herbal drugs along with advances in clinical research their efficacy and safety are continuously bringing light to the value of herbal medicines in the prevention and treatment of diseases. In some Asian and African countries, 80 per cent of the population depends on traditional herbal medicines for primary Healthcare. In many developed countries, 70 to 80 per cent of the population have used some form of complementary or alternative medicines [CAM) composed primarily of herbal medicines. Use of herbal medicines for therapeutic purpose is now well-established and widely acknowledged to be safe and effective. Many drugs commonly used today in the developing countries are of herbal origin and about of all modern prescription drugs contain at least one active ingredient derived from plant material, either obtained from plant extracts or synthesized to mimic natural plant compound. Many of the pharmaceuticals currently available to Physicians have a long his-history of use as herbal remedies. According to the World Health Organization (WHO), approximately25

Corresponding Author:-Krishnakumar K. Email:- stjamespharmacyproject@gmail.com

per cent of modern drugs used in the United States have been derived from plants. More than 120 active compounds isolated from higher plants are widely used in modern allopathic medicine today and 80 per cent of them show a positive co-relation between their modern therapeutic use and the traditional use of the plants from which they are derived. At least 7,000 medicinal compounds derived from plants, the ingredients of herbal medicine, are included in the modern pharmacopoeia of drugs.Because of this current trend of increasing use of herbal medicines and their growing popularity all over the world, the search for drugs and dietary supplements derived from plants have accelerated in recent years. Pharmacologists, Pharmacognosists, Microbiologists, Botanists and natural-products chemists are combing the earth for phytochemicals and leads from herbs and plants that could be developed for treatment of various diseases[5].

Tuberculosis

Tuberculosis (TB) is an infectious disease of worldwide occurrence.Tuberculosis caused the most widespread public concern in the 19th and early 20th centuries as an endemic disease of the urban poor[6]. According to World Health Organisation (WHO), Tuberculosis is an infectious bacterial disease caused by *Mycobacterium tuberculosis*, which most commonly affects the lungs but can affect other sites as well (extra pulmonary TB). It is transmitted from person to person via droplets from the throat and lungs of people with the activerespiratory disease. Each year approximately 2 million persons world-wide die of tuberculosis and 9 million become infected. However, the probability of developing TB is much higher among people infected with HIV[6, 7]. The most common method for diagnosing TB worldwide remains sputum smear microscopy (developed more than 100 years ago), in which bacteria are observed in sputum samples examined under a microscope. However, developments in TB diagnostics in the last few years mean that the use of rapid molecular tests to diagnose TB and drug-resistant TB is increasing, and some countries are phasing out use of smear microscopy for diagnostic (as opposed to treatment monitoring) purposes[7]. In countries with more developed laboratory capacity, cases of TB are also diagnosed via culture methods (the current reference standard). Effective drug treatments were first developed in the 1940s. The most effective first-line anti-TB drug, rifampicin, became available in the 1960s. The currently recommended treatment for new cases of drug-susceptible TB is a six-month regimen of four first-line drugs: isoniazid, rifampicin, ethambutol and pyrazinamide. Treatment success rates of 85% or more for new cases are regularly reported to WHO by its Member States. Treatment for multidrug-resistant TB (MDR-TB), defined as resistance to isoniazid and rifampicin (the two most powerful anti-TB drugs) is longer, and requires more expensive and more toxic drugs. For most patients with MDR-TB, the current regimens recommended by WHO last 20 months, and treatment success rates are much lower[8].

Mycobacterium Tuberculosis

Tuberculosis is an infection caused by the rod-shaped non-spore-forming, aerobic bacterium *Mycobacterium tuberculosis* and is 0.5µm to 3µm long, are classified as acid -fast bacilli and have a unique cell wall structure crucial to their survival. The composition and quantity of the cell wall components affect the bacteria's virulence and growth rate. The peptidoglycan polymer confers cell wall rigidity and is just external to the bacterial cellmembrane, another contributor to the permeability barrier of mycobacteria. Another important component of the cell wall is lipoarabinomannan, a carbohydrate structural antigen on the outside of the organism that is immunogenic and facilitates the survival of mycobacteria within macrophage[9, 10].

Global Epidemiology of TB

According to the World Health Organization (WHO), about 8.6 million cases (8.3–9.0 million) were estimated to have occurred in 2012, approximately 2.9 of whom were women. Most cases are estimated to be in Asia and Africa (58% and 27% respectively), with the highest incidence in India (range 2.0–2.4 million) and China (0.9 −1.1 million), together accounting for 38% of the total number of cases. The global TB incidence rate slowly declined from 1997 to 2001, with an increase in 2001 (due to the rising number of cases among HIV-infected patients in Africa). Subsequently, a 1.3% per year average reduction rate has been observed since 2002, reaching 2.2% between 2010 and 2011. The absolute number of cases is also currently decreasing, though this declining trend only began in 2006 [11-16]. Based on these findings, the Millennium Development Goal 6 Target for tuberculosis (i.e. "to halt and begin to reverse the incidence") has already been achieved[17].

Twelve million (11–13 million) prevalent cases of TB were estimated in 2012, corresponding to about 169 cases per 100 000 population. TB prevalence is declining globally since the early 1990s (before incidence started to decline). This decline is largely attributed to the progressive introduction of the DOTS strategy which, by emphasizing bacteriological diagnosis and standard short-course chemotherapy with direct observation of treatment, may have significantly contributed to the reduction of chronic and untreated cases, as well as to the duration of illness [18].Nevertheless, the Stop TB Partnership target of halving the 1990 prevalence rate by 2015 will probably be missed (a reduction of 37% was registered in 2012, 169 / 100 000 compared to 263 / 100 000 in 1990), because of the delays in the African and the European WHO regions.

TB mortality was estimated at 1.3 million deaths (1.0–1.6 million) in 2012, including 320 000 (300 000 – 340 000) HIV-associated cases. A 45% drop in TB mortality rate has been observed globally since 1990.The traditional case detection rate (CDR), defined as the proportion of notified cases among the estimated number of new and relapse TB cases, thought to have occurred in a given year, is a problematic indicator in TB epidemiology, though it could potentially provide very useful information on the "diagnostic capacity" of a TB control program [19, 20]. The denominator consists of an estimate: significant efforts are currently ongoing to obtain reliable estimates through the performance of costly prevalence surveys but coverage is still limited. In 2012, 6.1 million TB cases were notified by the National TB Programs (NTPs). 5.4 million were new cases, and 0.3 million were relapses (with India and China showing the highest notification rates: 39% overall); 0.4 million cases of retreatment (excluding relapses) were also reported. Most newly diagnosed patients had pulmonary TB, and more than half of them were sputum smear positive. CDR reached 66% (64–69%) in 2012 with several regional differences. In other words, one-third of cases, corresponding to an estimated 3 million cases, were missed that year. This implies that a significant proportion of TB patients remain either unrecognized and untreated or not notified. The former actively contribute to further transmission of the disease. The latter may be detected outside of national programs and managed inappropriately, also contributing to further transmission and creation of drug resistance. Further improvements in diagnostic capacity and surveillance system are needed in some Regions such as South-East Asia, Africa, and Eastern Mediterranean [21].

Treatment outcome represents a useful process indicator to be closely monitored, being a measure of progress in expanding access to quality-assured care. Approximately 22 million lives are estimated to have been saved since 1995, when the DOTS strategy was introduced. The proportion of successfully treated patients, currently reaching 87% at global level, is significantly lower than the average, in some WHO regions, like the European one (probably due to the high failure rate associated to MDR-TB) and in the African one (due to the high rate of deaths or defaulting linked to HIV co-infection) [22].

Transmission

M. tuberculosis is carried in airborne particles, called droplet nuclei, of 1– 5 microns in diameter. Infectious droplet nuclei are generated when persons who have pulmonary or laryngeal TB disease cough, sneeze, shout, or sing. Depending on the environment, these tiny particles can remain suspended in the air for several hours. *M. tuberculosis* is transmitted through the air, not by surface contact. Transmission occurs when a person inhales droplet nuclei containing *M. tuberculosis*, and the droplet nuclei traverse the mouth or nasal passages, upper respiratory tract, and bronchi to reach the alveoli of the lungs[23].

Pathophysiology

Infection occurs when a person inhales droplet nuclei containing tubercle bacilli that reach the alveoli of the lungs. These tubercle bacilli are ingested by alveolar macrophages; the majority of these bacilli are destroyed or inhibited. A small number may multiply intracellularly and are released when the macrophages die. If alive, these bacilli may spread by way of lymphatic channels or through the bloodstream to more distant tissues and organs (including areas of the body in which TB disease is most likely to develop: regional lymph nodes, apex of the lung, kidneys, brain, and bone). This process of dissemination primes the immune system for a systemic response. After transmission into immune system, mycobacteria interfere with different immunological mediators [24]. The interaction of T cells with infected macrophages is central to protective activity against M.tuberculosis and depends on the interplay of cytokines produced by each cell. TNF-α, IL-12 and IFN-γ, which activates alveolar macrophages to produce a variety of substances involved in growth inhibition and killing of mycobacteria. Macrophages also secrete IL-2, amplifying this pathway in a positive feedback loop[25]. TNF-α is believed to play multiple roles in the immune and pathological responses in tuberculosis. M.tuberculosis induces TNF-α secretion by macrophages dendritic cells and T-cells. The production of anti-inflammatory cytokines such as IL-4,IL-10 and TGF-β in response to M.tuberculosis may down –regulate the immune response and limit tissue injuiry, but excessive production of these cytokines may result in failure to control the infection[26]. Macrophages are the part of the innate immune system and provide an opportunity for the body to destroy the invading mycobacteria and prevent infection. The complement system also plays a role in the phagocytosis of the bacteria. The complement protein C3 binds to the cell wall and enhances recognition of the mycobacteria by macrophages[27]. The subsequent phagocytosis by macrophages initiates a cascade of events that results in either successful control of infection, followed by latent tuberculosis, or progression to active disease called primary progressive tuberculosis[28]. After being ingested by macrophages, the mycobacteria continue to multiply slowly, with bacterial cell division occurring every 25-32hrs. Initial development of TB involves production of proteolytic enzymes and cytokines by macrophages in an attempt to degrade the bacteria. Released cytokines attract T- lymphocytes to the site, the cells that constitute cell-mediated immunity. In fact, M. Tuberculosis organisms can change their phenotypic expression, such as protein regulation, to enhance survival. Leisons in persons with less effective immune systems progress to primary progressive tuberculosis. In patients infected with M. tuberculosis, droplets can be coughed up from the bronchus and infect other persons. Bacilli can also

drain into the lymphatic system and collect in the trachea-bronchial lymph nodes of the affected lung, where the organisms can form new caseous granulomas [29-31].

Tuberculosis Types

Tuberculosis (TB) is divided into two categories: pulmonary and extra pulmonary

Pulmonary Tuberculosis Types:

- Primary Tuberculosis Pneumonia
- Tuberculosis Pleurisy
- Cavitary Tuberculosis
- Miliary TB
- Laryngeal Tuberculosis [32]

Primary Tuberculosis Pneumonia

This uncommon type of TB presents as pneumonia and is very infectious. Patients have a high fever and productive cough. It occurs most often in extremely young children and the elderly. It is also seen in patients with immunosuppression, such as people with HIV/AIDS, and in patients on long term corticosteroid therapy[33].

Tuberculosis Pleurisy

This usually develops soon after initial infection. A granuloma located at the edge of the lung ruptures into the pleural space, the space between the lungs and the chest wall. Usually, a couple of tablespoons of fluid can be found in the pleural space.

Once the bacterium invade the space, the amount of fluid increases dramatically and compresses the lung, causing shortness of breath (dyspnea) and sharp chest pain that worsens with a deep breath (pleurisy). A chest x-ray shows significant amounts of fluid. Mild- or low-grade fever commonly is present. Tuberculosis pleurisy generally resolves without treatment; however, two-thirds of patients with tuberculosis pleurisy develop active pulmonary TB within 5 years[34].

Cavitary TB

Cavitary TB involves the upper lobes of the lung. The bacteria cause progressive lung destruction by forming cavities, or enlarged air spaces. This type of TB occurs in reactivation disease. The upper lobes of the lung are affected because they are highly oxygenated (an environment in which *M. tuberculosis* thrives). Cavitary TB can, rarely, occur soon after primary infection.

Symptoms include productive cough, night sweats, fever, weight loss, and weakness. There may be hemoptysis (coughing up blood). Patients with cavitary TB are highly contagious. Occasionally, disease spreads into the pleural space and causes TB empyema (pus in the pleural fluid)[35].

Miliary TB

Miliary TB is disseminated TB. "Miliary" describes the appearance on chest x-ray of very small nodules throughout the lungs that look like millet seeds. Miliary TB can occur shortly after primary infection. The patient becomes acutely ill with high fever and is in danger of dying. The disease also may lead to chronic illness and slow decline.

Symptoms may include fever, night sweats, and weight loss. It can be difficult to diagnose because the initial chest x-ray may be normal. Patients who are immunosuppressed and children who have been exposed to the bacteria are at high risk for developing miliary TB[36].

Laryngeal TB

TB can infect the larynx, or the vocal cord area. It is extremely infectious[37].

Extra pulmonary Tuberculosis

This type of tuberculosis occurs primarily in immunocompromised patients.

- Lymph Node Disease
- Tuberculosis Peritonitis
- Tuberculosis Pericarditis
- Osteal Tuberculosis
- Renal Tuberculosis
- Adrenal Tuberculosis
- Tuberculosis Meningitis [38]

Lymph Node Disease

Lymph nodes contain macrophages that capture the bacteria. Any lymph node can harbor uncontrolled replication of bacteria, causing the lymph node to become enlarged. The infection can develop a fistula (passageway) from the lymph node to the skin.

Tuberculosis Peritonitis

M. tuberculosis can involve the outer linings of the intestines and the linings inside the abdominal wall, producing increased fluid, as in tuberculosis pleuritis. Increased fluid leads to abdominal distention and pain. Patients are moderately ill and have fever.

Tuberculosis Pericarditis

The membrane surrounding the heart (the pericardium) is affected in this condition. This causes the space between the pericardium and the heart to fill with fluid, impeding the heart's ability to fill with blood and beat efficiently.

Osteal Tuberculosis

Infection of any bone can occur, but one of the most common sites is the spine. Spinal infection can lead to compression fractures and deformity of the back.

Renal Tuberculosis

This can cause asymptomatic pyuria (white blood cells in the urine) and can spread to the reproductive organs and affect reproduction. In men, epididymitis (inflammation of the epididymis) may occur.

Adrenal Tuberculosis

TB of the adrenal glands can lead to adrenal insufficiency. Adrenal insufficiency is the inability to increase steroid production in times of stress, causing weakness and collapse.

TB Meningitis

M. tuberculosis can infect the meninges (the main membrane surrounding the brain and spinal cord). This can be devastating, leading to permanent impairment and death. TB can be difficult to discern from a brain tumor because it may present as a focal mass in the brain with focal neurological signs.Headache, sleepiness, and coma are typical symptoms. The patient may appear to have had a stroke.

HERBAL DRUGS: NEED OF THE DAY

The current therapy for TB include antibiotics such as rifampicin, ethambutol, isoniazid and pyrazinamide, but the emergence of problem of multiple drug resistant (MDR) and (XDR) strains of mycobacterium is very common with anti TB drugs. The adverse effects of anti-TB drugs are given in table 1. The presences of "cross resistance" cause no single drug or combination therapy was able to control TB fully and such drug resistance is developed only against purified chemical compounds. Any single purified compound will produce resistance in pathogens. The Mycobacteria are self-equipped to digest the drug by modifying their receptor structure according the chemical structure of the drug. Thus the Mycobacteria slowly adapt and develop resistance against modern drugs. Herbal drug whether extract or decoction used against any pathogen will not cause the problem of drug resistance. Hence an effective and appropriate drug therapy as an anti-tuberculosis drug need to be discovered which will solve the problem of cross resistance as well as drug resistance. List of natural products as Anti-TB agents are given in table 2 [39].

Table 1. Adverse Effects of Anti-TB Drugs

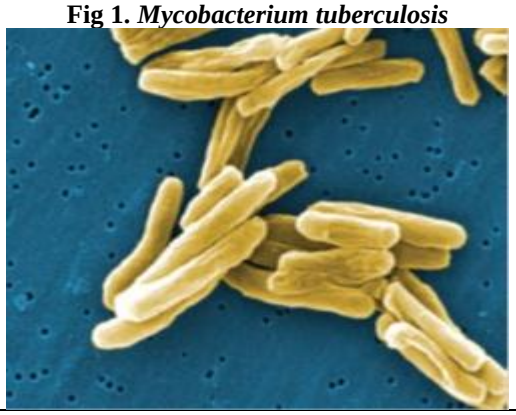
Drug	**Adverse effects**
Isoniazid	Hepatitis
Rifampicin	Pain, hepatitis, thrombocytopenia, nausea, vomiting
Pyrazinamide	Arthralgia, hepatitis.
Streptomycin	Vestibular and auditory nerve damage, renal damage
Ethambutol	Ocular side effects, retro bulbar neuritis
Thioacetazone	Skin rash, exfoliate dermatitis
Para-amino salicyclic acid	Anorexia, hypersensitivity, nausea, vomiting
Kanamycin	Vertigo, nephrotoxicity, auditory nerve damage
Pethionamide	Diarrhoea, hepatotoxicity, abdominal pain [40-44]

Table 2. Common Anti-Tubercular Plants

Sl.no	**Botanical/family name**	**Part used**	**Chemical Constituent**	**Activity**
1	*Acalypha indica*, Euphorbiacaeae	Leaves	Kaempferol, Acalyphamide, Quinine, Sterols Cyanogenic glycosides	Anti bacterial, Bronchitis, Asthma
2	*Aloe vera*, Liliaceae	Leaves, gel from leaves	Anthraquinone glycosides(aloin)	Purgative, anthelminthic, Emmenagogue
3	*Allium cepa*, Liliaceae	Bulbs	Volatile oil, Sulphur containing compounds -allicin, alliin	Antibacterial, pneumonopathy, asthma , bronchitis.
4	*Allium sativum*, Liliaceae	Bulb	Sulphur containing compounds –alliin,	Antibacterial, antifungal, Bronchitis, asthma, Pulmonary and laryngeal Tuberculosis.
5	*Ocimum tenuiflorum*, Lamiaceae	Whole plant	Ursolicacid, Apigenin Orientin,Apigenin-7-Oglucuronide, Luteolin-7-O-glucuronide	Febrifuge, Useful in asthma, Bronchitis Skin diseases
6	*Morinda citrifolia***,**	Leaves,	Ursolic acid, Asperuloside,	Anti-inflammatory, Gout,

	Rubiaceae	roots, fruits	Carproic acid	Wounds Febrifuge, Boils
7	*Vitex trifolia*, Verbenaceae	Root,fruits,leaves	Flavonoids-Artemetin Luteolin Orientin, vitricin	Febrifuge,Cytotoxic Anti bacterial, Anthelminthic, Tuberculosis, Painful inflammation, Bronchitis.
8	*Mallotus philippensis*, Euphorbiaceae	Glandular hairs of fruit	Phloroglucinol Isorottlerin, Isoallorottlerin	Purgative, Styptic Anthelminthic
9	*Coscinium fenestratum*, Menispermaceae	Stem	Flavonoids	Anti-inflammatory, Antiseptic, Skin diseases, Jaundice, Diabetes.
10	*Hydnocarpuslaurifolia, Flacourtiaceae*	Roots, bark, Seeds	Chaulmoogric fatty acids	Anti-leprotic and Anti –TB
11	*Mimosa pudica*, Mimosaceae	Roots ,leaves	Mimosine Turgorin	Astringent,Antispasmodic,Inflammations, Smallpox, Haemorrhoids.
12	*Kalanchoe pinnata*, Crassulaceae	Leaves	Triterpenoids-friedelin, Taraxerol, Glutinol	Anti-inflammatory, Disinfectant, Tonic, Used in burns boils
13	*Flacourtia ramontchi*, Flacourtiaceae	Bark, fruits Roots, Leaves	Phenolic glucoside, Ramontoside, Flacourtin, β-sitosterol&its β- D-glucopyranoside	Anticholerin, Useful in poisonous bites, Skin diseases.
14	*Myristica fragrans* **,** Myristicaceae	Seed,aril	Tannins, Flavanoids, kampherol, Volatileoil, Geraniol, Quercetin, glycosides	Anti-inflammatory, Anthelmintic, Febrifuge, Useful in asthma, cough, skin diseases, impotency.
15	*Canscora deccusata*, Gentainaceae	Roots	Friedelin, Genianine, Xanthones	Anti-inflammatory, Anticonvulsant, CNS depressants, Anthelminthic, Leprosy, Tuberculosis, Skin diseases.
16	*Piper betle*, Piperaceae	Whole plant	Lignans, Piperine, Sesamin, Asarinine, Isobutyl amides, Pluviatilol, Aristolactums	Anthelmintic, Febrifuge, Asthma, Bronchitis, Leprosy, Fever.
17	*Vitex negundo*, verbenaceae	Leaves, seeds	Iridoidglycosides, Isomeric flavones, flavanoids.	Anti- inflammatory, Analgesic,Anthelmintic, arthritis, leprosy.
18	*Prunus cerasoides*, Rosaceae	Heartwood	Salicylic acid, Tannins, Ferulicacid,Potassium salts diferulic acid	Useful in wounds, ulcers, leprosy, asthma, sprains**.**
19	*Trichosanthes lobata*,Cucurbitaceaee	Whole plant	Free amino acids, Nicotinic acid, Riboflavin, Thiamine, Vitamin C,	Anthelmintic, Anti-inflammatory, Antipyretic, Useful in leprosy, Leucoderma
20	*Tinospora cordifolia*, Menispermacea	Stem	Alkaloids, Columbin, Palmarin, Tinosporon, Tinosporol, Berberine	Anthelmintic, Anti-spasmodic, Anti-inflammatory, Useful in chronic fevers, gout, skin diseases, leprosy.
21	*Caesalpinia bonduc***,** Caesalpiniaceae	Leaves, seeds, root bark	Flavanoids, Myricitroside	Febrifuge, Anthelmintic, Anti-inflammatory, Useful in asthma, leprosy, skin diseases, intestinal worms, diabetes [45-53].

Fig 1. *Mycobacterium tuberculosis*



CONCLUSION

There has been an increase in demand for the herbal medicine all over the world .The side effects associated with allopathic drugs are remarkably necessities the need of herbal drugs. This review makes an attempt to compile some of the anti-tubercular plants. Various phytoconstituents like alkaloids, glycosides, Flavanoids, tannins, quinones present in plants are responsible for its anti-TB activity.

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CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

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