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Review Article

NATURAL PRODUCTS AS AN IMPORTANT LEADS FOR DISCOVERY OF NEW ANTITUBERCULAR AGENTS: A REVIEW

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ABSTRACT

There is a very much need for a discovery of new molecules a potent molecule that can cure tuberculosis and prevent the recurrence. A multidisciplinary approach is required to procure a potent bioactive compound and this includes expertise in the fields of ethnobotany, ethnopharmacology and Phytochemistry. The present communication acts as a bioprospecting source for the drug discovery against tuberculosis, including several anti tubercular agents which is used by used by tribal people and prescribed by THPS which showed a good inhibition rate. Therefore, this review strives to describe the literature on the traditional plants/potent molecules those have been proved to have antimicrobial activity and to provide essential discussion and accelerate the research.

Keywords: Tuberculosis, Antitubercular drug discovery, Traditional healers, Drug discovery.

INTRODUCTION

Global status and current scenario of tuberculosis

Tuberculosis TB remains a global public health threat. In India, it accounts for nearly one third of prevalent cases worldwide and remains a major cause of morbidity and mortality [1]. A fixed dose combination FDC containing rifampicin R, isoniazid I, and pyrazinamide Z is the mainstay of the treatment of TB. Although FDC products provide many advantages, poor and variable bioavailability of antitubercular treatment ATT drugs produce a challenge to successful antitubercular program [2, 3]. Indiscriminate use of these drugs has led to the development of multidrug resistant MDR, making the treatment difficult. Many pathologists described the Co-existence of carcinoma and TB [4, 5]. A hypothetical pathway has been postulated based on *in vitro* and *in vivo* experiments to explain Co-existence of carcinoma and TB. Production of ROS, prostaglandins, leukotrienes LT, cytokines due to cell mediated response by macrophages infected with *Mycobacterium tuberculosis* leads to damage to DNA, inhibition of apoptosis of cells with damaged DNA by enhancing the synthesis of B-cell lymphoma 2 family of apoptosis regulator proteins [6, 7]. These results in mutagenesis of progeny cells, and extensive fibrosis associated with recurrent infection eventually causing tumourigenesis [8].

Table 1: List of the indian medicinal plants used for treatment of tuberculosis

S. No.	Vernacular name and family	Parts used	Extract	Type of organism tested/MICμg/ml	Ref. No.
1	*Cassia sophera* (Caesalpinaceae)	Aerial parts	Methanolic extract	M. smegmatis 125	[13]
2	*Solanum auaraniticum* (Solanaeceae)	Aerial parts	Ethanolic extract	M. smegmatis 312	[14]
3	*Diospyros Montana* (Acanthaceae)	Leaves	Methyl ether extract	M. aurum <0.10	[15]
4	*Phaseolus vulgaris* (Fabaceae)	Seeds	Alcoholic extract	M. smegmatis 50	[16]
5	*Goniothalamus Gitingensis* (Annonaceae)	Leaves	Pet. ether extract	M. aurum 17	[17]
6	*Alpinia galanga* (Zingiberaceae)	Aerial parts	Ethanolic extract	M. smegmatis 250	[18]
7	*Allium cepa* (Liliaceae)	Bulb	Aqueous extract	M. smegmatis 100	[19]
8	*Allium sativum* (Liliaceae)	Bulb	Aqueous extract	M. tuberculosis 50	[19]
9	*Prunus armeniaca* (Rosaceae)	Fruits	Ethanolic extract	M. tuberculosis 100	[20]
10	*Adhatoda vasica* (Acanthaceae)	Leaves	Ethanolic extract	M. smegmatis <0.10	[21]
11	*Lantana camara* Verbenaceae	Leaves	Chloroform/ Methanol extract	M. tuberculosis 50	[22]
12	*Acacia Senegal* (Mimosaceae)	Stem bark	Alcoholic extract	M. smegmatis <0.10	[22]
13	*Vitex negundo* (Verbenaceae)	Leaves, seeds	Ethanol extract	M. aurum 100	[23]
14	*Taxus baccata* (Taxaceae)	Leaves	Aqueous extract	M. fortuitum 150	[24]
15	*Andrographis paniculata* (Acanthaceae)	Leaves	Aqueous extract	M. smegmatis 100	[24]

Table 2: List of the Indian Plants used by the tribal people for tuberculosis

S. No.	Vernacular name and family	Tribe name	Parts used	Ref no
1.	*Adhatoda vasica* (Acanthaceace)	Gond tribe, A. P	Leaves	[25]
2.	*Ziziphus mauritiana* (Rhamnaceace)	Used locally in TN, U. P	Fruit, Leaves, seed	[26]
3.	*Euphorbia hirta* (Euphorbiaceae)	Shivalik hills of Himalayas	Whole plant	[27]
4.	*Ziziphus abyssinica* (Rhamnaceace)	Irula tribes, Nilgiris	Tree bark	[28]
5.	*Cyphomandra betacea* (Solanaceae)	Irula tribes, Nilgiris	Fruit	[28]
6.	*Oroxylum indicum* (Bignoniaceae)	Gadaba tribe	Root, flower, Stem, Bark	[29]
7.	*Chenopodium album* (Amaranthaceae)	tinsukia community	Tender shoots	[30]
8.	*Argyreia speciosa* , (Convolvulaceae)	Kondar and Saur tribe	Root	[31]
9.	*Phyllanthus fraternus* (Euphorbiaceae)	Mizoram tribe	Whole plant	[32]
10.	*Leptadenia pyrotechnica* (Asclepiadaceae)	Bhiloda tribe, Gujarat	Stem	[33]
11.	*Curculigo orchioides* (Hypoxidaceae)	Ethnic People of Western Himalaya	Roots	[34]
12.	*Malaxis acuminate* (Orchidaceae)	Ethnic People of Western Himalaya	Bulb	[34]
13.	*Solarium Torvum* (Tubiflorae)	Kattunayakan in Tamilnadu	Roots	[35]
14.	*Nerium oleander* (Apocynaceae)	Adilabad District, Andhra Pradesh	Leaves	[36]
15.	*Azadirachta indica* (Meliaceae)	Hingoli District, Maharashtra	Fruit	[37]
16.	*Bambusa arundinacea* (Poaceae)	Tribes of Dantewada, Chhattisgarh	Whole plant	[38]
17.	*Nelumbium nucifera* (Nelumbonaceae)	Tribes of Dantewada, Chhattisgarh	Stem, Root	[38]
18.	*Agave americana* (Agavaceae)	Bargarh District, Orissa	Whole Plant	[39]
19.	*Celosia argentea* (Amaranthaceae)	Bargarh District, Orissa	Whole Plant	[39]
20.	*Polygonum molli* (Polygonaceae)	Badaga Community, Nilgiris, Tamilnadu	Root	[40]

Chen-Yi Wu, et al. [9] and few cohort studies [10, 11]suggested that TB is associated with an increased risk of lung cancer. These studies were conducted in high-risk populations, such as heavy smokers, asbestos-exposed workers, or populations with a high indoor exposure to coal smoke. Andrzej Pawlowski, et al. [12] studied that there even chances for co-infection of TB and HIV.

Glimpses on indian medicinal plants as antitubercular aids or sources for new antitubercular leads

The list of Indian medicinal plants listed below are few most active natural products exhibits antimycobacterial activity done by literature survey, systematic search of scientific literature for data and also by the survey conducted with traditional health practitioners THPS in south India are analyzed in this review.

A field survey was carried out with the traditional health practitioners THPS in South India and collected information in regard with medicinal plants/medication commonly prescribed in case of tuberculosis. The objective of the survey was to provide an important data base of anti tubercular plants used by THPS, where the scientific validation is lacking still, so these plants can be an important source of discovery of new leads against tuberculosis.

In siddha system

The few medicinal plants prescribed by the Siddha practitioner during the survey are listed below, which are usually used for cough, Tuberculosis and upper respiratory tract infections.

a. *Abies spectablis* (Pinaceae)

Description:

Tree height of 60 m. Branches horizontally spreading. Bark dark gray, rough and scaly. Shoots red-brown, deeply grooved, pubescent in the grooves. Needles on the upper side of the shoot arranged in several ranks, leaves with emarginated apex; upper surface dark green and glossy, with 2 broad stomata bands beneath. It is found in China, Afghanistan, North India, Kashmir, Nepal.

Major constituents

Terpenoids, Flavanoids [41].

Pharmacodynamic uses

The leaf juice used in the treatment of asthma, bronchitis, astringent, carminative, expectorant, stomachic and tonic. An essential oil obtained from the leaves is used to treat colds, rheumatism and nasal congestion. The leaf juice is antiperiodic [42].

b. *Terminalia chebula (*Combretaceae)

Description

It is a much branched, medium sized tree. Leaves elliptic-obovate, densely woolly beneath, with 2 basal glands. All flowers yellowish-white, in axillary spikes. Drupe obovoid, orange-brown hermaphrodite in terminal spikes, glabrous, more or less 5–ribbed when dried.

Major constituents

Flowers contain chebulin, a glycoside. Fruits contain phenolic compounds, punicalagin, terflavin A, ellagitannin, tercheulin, terchebin. The tree yields a gum. It contains tannic acid up to 40% and Chebulic acid. Gallic and anthraquinone like principle [43].

Pharmacodynamic Uses

The dried fruits constitutes the drug known as Chebulic Myrobalan or Harra. This Myrobalan can be applied externally on chronic ulcers, wounds and scalds or used as a gargle in inflammation of the mucous membrane of mouth. Myrobalans are used as laxative; they also have some effect on blood pressure as cardiac tonics. The powder of the fruit is used as a dentifrice in carious teeth and bleeding gums. Fruit pulp used in dentifrices [43].

c. *Mukia Scrabella (*Cucurbitaceae)

Description

It is a perennial herb with simple tendrils. Stems are climbing, long, slender, much-branched, and covered with bristly hairs, with the young parts densely covered with white hairs. Flowers are yellow, seeds are closely packed, ovoid, oblong, and compressed in the pulp.

Major constituents

Coumarins, amino acids, flavonoids, tannins, triterpenes and glycosides [44].

Pharmacodynamic uses

Antimycobacterial, hepatoprotective, anti-inflammatory, anti-arthritic, immuno modulatory properties [44].

d. *Lepidium meyenii* (Brassicaceace)

Description

Lepidium meyenii is also called as Maca. Its scalloped leaves lie close to the ground and it produces small, self-fertile, off-white flowers.

The tuberous root, which looks like a large radish which is usually off-white to yellow in color. It is grown as an annual; seven to nine months is required to produce the harvested roots.

Major constituents

Isothiocyanates, beta-ecdysone, saponins, sitosterols [45].

Pharmacodynamic uses

Used for tuberculosis, anemia, energy, fertility, food, impotence, memory, menopause, menstrual disorders [45].

e. *Cinnamomum verum* (Lauraceae)

Description

Cinnamon is the inner bark of a tropical evergreen tree. The light brown, papery bark and leathery leaves are ovate-oblong in shape. The green flowers are arranged in panicles and have a distinct odor. The tree bears purple berries with a single seed. Cinnamon has a fragrant perfume and a sweet and aromatic taste. The spice is known as dal-chini in Hindi.

Major constituents

Phenols and terpenes, tannins, mucilage, trace amounts of coumarin [46].

Pharmacodynamic uses

Anti mycobacterial, anticancer, antidiabetes, Aphrodisac [46].

f. *Syzygium aromaticum* (Myrtaceae)

Description

Small evergreen tree, leaves are pinkish to dark green, with pungent odor when young. Flowers are red in color. Fruit dark red, fleshy drupe. Buds readily exude oil when pressed or scratched with a fingernail.

Major chemical constituents

The major constituent up to 20% is an essential oil, which is characterized by the presence of eugenol 60–95%, eugenol acetate 2–27%, and α-and β-caryophyllene 5–10%.

Pharmacodynamic uses

Clove's anesthetic and anti-inflammatory properties are helpful in alleviating joint aches and pains. It is a potent platelet inhibitor, preventing blood clots in the body. Studies have shown that Cloves stimulate insulin activity up to three times in the body, combating diabetes effectively [47].

g. *Piper nigrum* (Piperaceae)

Description

It is a plant of 20 feet. It is a perennial with a round, smooth, woody stem; color dark green and attached by strong sheath-like foot-stalks to joints of branches. Flowers are small, white, sessile, covering a tubular spadix; fruits globular, red berries. The berries are collected as soon as they turn red and before they are quite ripe. Pepper has an aromatic odour, pungent and bitterish taste.

Major chemical constituents

The fruit contains volatile oil, resin, alkaloids and terpenoids [48].

Pharmacodynamic uses

In Siddha, the infusion is used as a stimulant, carminative and attractive and is more powerful than black pepper. It is an aphrodisiac and emmenagogue and externally acts as a rubefacient. Powdered long pepper administered with honey will relieve cough, cold, bronchitis, asthma hoarseness and hiccup [49].

h. *Ferula asafoetida* (Apiaceae)

Description

Ferula asafoetida is an herbaceous, perennial plant which has carrot-shaped roots. It is an oleo gum resin obtained from the rhizome and root of the plant. A milky juice exudes from the cut surface. After some days, the exudates are scraped off and a fresh slice of the root cut when more latex exudes; sometimes the resin is removed along with the slice.

Major chemical constituents

Ferula asafoetida contains about 40-64% resin, 25% indigenous gum, 10-17% volatile oil, and 1.5-10% ash. The resin portion is known to contain asareninotannols 'A' and 'B', Ferulic acid, umbelliferone and four unidentified compounds [50].

Pharmacodynamic uses

Asafoetida is used as carminative, nerve stimulant, or in intestinal flatulence. It is also used an expectorant in chronic bronchitis and is administered with honey as an electuary in chronic cough and asthma [51].

In ayurveda system

The few medicinal plants prescribed by the Ayurvedic practitioner during the survey are listed below, which are usually used for cough, Tuberculosis and upper respiratory tract infections.

***a. Adhatoda vasica* (Acanthaceace)**

***Description*:** Adhatoda is a shrub with lance-shaped leaves. They are oppositely arranged, smooth-edged, and borne on short petioles. They are bitter-tasting. Trunk has many, long, opposite, ascending branches, where the bark is yellowish in color. Flowers are usually white and the inflorescence shows large spikes. Fruits are pubescent, and are with club-shaped capsules.

Major chemical constituents

The leaves of Adhatoda vasica contain phytochemicals such as alkaloids, tannins, saponins, phenolics and flavonoids [52].

Pharmacodynamic uses

Adhathoda is used in Asthma, bleeding, bronchitis, cough, diabetes, diarrhea, dysentery, epilepsy, neuralgia, rheumatic pain, skin disorders, TB, urinary disorders, vomiting, wasting [53].

***b. Guduchi* (Memispermaceae)**

Description

Guduchi is a glabrous climbing shrub with a papery bark that is creamy white to gray in color. The shrub shoots out aerial roots. It bears heart-shaped leaves. The yellow flowers are axillary and long-stalked racemes. The fruit is pea-sized, subglobose drupe and red colored on maturity. Guduchi is found in deciduous and dry forests throughout India.

Major chemical constituents

Its main constituents are terpenoids, alkaloids, lignans, steroids [54].

Pharmacodynamic uses

It benefits the general weakness, dyspepsia, impotency, dysentery, secondary syphilis, tuberculosis, jaundice, constipation, leprosy, general debility, cutaneous rashes and condylomata [54].

***c. Guggul (*Burseraceae)**

Description

This is a soft water soluble myrrh resin harvested from the tree, Commiphora Mukul. It is of great importance in Ayurvedic medicine as a rejuvenating ingredient. The resin is collected from cut branches and incisions in t*h*e trunk of the tree and dried to a solid.

Major chemical constituents

The oleo resin contains essential oils, diterpene alcohol such as E and Z, guggulsterol-I, II, III, cholesterol, Sesamin and camphorene [55].

Pharmacodynamic uses

Guggul has been used in the traditional Ayurvedic medical system for centuries. Commercial products are promoted for use in tuberculosis; however, clinical studies do not substantiate this

claim. Anti-inflammatory and cardiovascular effects are being evaluated, as well as use in cancer, obesity, hyperlipidemia and diabetes [56].

***d. Myristica fragrans (*Myristicaceae)**

***Description*:** It is a small evergreen tree, flowers are bell-shaped, pale yellow, waxy and fleshy. The trees produce smooth yellow ovoid or pear-shaped fruits. The fruit has a fleshy husk. When ripe the husk splits into two halves along a ridge running the length of the fruit. Inside is a purple-brown shiny seed, with a red or crimson covering an aril.

***Major chemical constituents*:** Nutmeg's essential oil, which has a sharp taste and a peppery smell, is composed mainly of camphene and pinene, but also contains myristicin which is toxic [57].

***Pharmacodynamic Uses*:** Nutmeg and mace, widely accepted as flavoring agents, have been used in higher doses for their aphrodisiac, skin problems, muscle spasm, rheumatism and psychoactive properties [58].

In homeopathy system

The few medicinal plants prescribed by the Ayurvedic practitioner during the survey are listed below, which are usually used for cough, Tuberculosis and upper respiratory tract infections.

a. *Acalypha Indica* (Euphorbiaceae)

***Description*:** It is an erect annual herb. Stems are ribbed and pubescent. Leaves veined from the base, hairless to finely velvety on both surfaces; margin toothed. Flowers in axillary spikes, very small, yellowish-green. Fruits are tuberculate, pubescent.

***Major chemical constituents*:** It mainly contains alkaloids "acalypus" and "acalyphine", cyanogenic glycoside, inositol, resin and volatile oils [59].

***Pharmacodynamic Uses*:** It is used in the treatment of pneumonia, Bronchitis, asthma, and rheumatism. Promotes the removal of mucous secretion from the bronchial tubes. Also used to promote the flow of urine. To expel worms from the body [60].

b. *Aegle Marmelos* (Rutaceae)

***Description*:** The bael fruit tree is slow-growing, flaking bark. A clear, gummy sap, exudes from wounded branches and hangs down in long strands. It is sweet initially, later irritating to the throat. The fruit, round, or oblong, hard, woody shell, gray-green or yellowish. Inside, there is a hard central core and 8 to 20 triangular segments, dark-orange walls, filled with aromatic, pale-orange, pasty, sweet, astringent, pulp. Pulp is embedded with 10 to 15 seeds, flattened-oblong, bearing woolly hairs and each enclosed in adhesive sac, transparent mucilage that solidifies on drying.

***Major chemical constituents*:** Main chemical components are the essential oils limonene, α-phellandrene, E-β-ocimene, α-pinene, E-caryophyllene, β-elemene and germacrene B. And the major constituents are namely α-phellandrene, limonene, E-β-ocimene and α-pinene [61].

Pharmacodynamic Uses: It is mainly used as antibacterial, antidiabetic, anticancer, antiulcer, antioxidant, antimalarial, analgesic, hepatoprotective agent [62].

c. *Ocimum sanctum* (Lamiaceae)

Description

It is a branched, fragrant and erect herb. Its leaves are nearly round and long entire or toothed. Flowers are small purple to reddish color, present in small compact clusters or cylindrical spike. The fruits are small and yellow to reddish in color. Different parts of the plant are traditionally utilized in the Ayurveda and Siddha systems for treatment of several ailments.

Major chemical constituents

The major components present in the leaves of Ocimum sanctum were Eugenol, Caryophyllene, Cyclopentane, Cyclopropylidene, Cyclohexane, 1,2,4-triethenyl, octadecane, 1,1-dimethoxy and Benzene methanamine, N, N, a, 4-tetramethyl [63].

Pharmacodynamic uses

It is mainly used for its antimicrobial, antioxidant, wound healing, hepatic disorder, antidote for snake bite and scorpion sting [64].

d. *Solanum xanthocarpum* (Solanaceace)

Description

It is a spiny diffused herb. The young branches are densely covered with minute star-shaped hair, while the mature branches are zigzag, covered with yellow, sharp shining prickles and spread close to the ground. The flowers are purple in color that can be seen in small bunches. The plant bears glabrous, globular drooping berries as fruits, yellow or pale in color, with green veins.

Major chemical constituents

Solanum xanthocarpum plant contains alkaloids, sterols, saponins, flavonoids and their glycosides and also carbohydrates, fatty acids, amino acids [65].

Pharmacodynamic uses

It is used for its anti-inflammatory, antiasthamatic, antifertility, antihyperlipidaemic, hepatoprotective activity [66].

e. *Castanea vesca* (Fagaceae)

Description

It is the lofty chestnut-tree, and valued for its sweet nuts. Its alternate leaves are long, smooth, coarsely serrate. Flowers monoecious, without corollas; long sterile; the fertile in clusters of three, the fruit when ripe becomes thick and leathery, beset with prickles, and becoming a burr enclosing from one to three nuts.

Major chemical constituents

Chestnut major constituents are tannins, triacylglycerols, tocopherols, to cotrienols and fatty acids [67].

Pharmacodynamic uses

The plant is taken in small doses internally for the treatment of a wide range of venous diseases, including hardening of the arteries, varicose veins, phlebitis, tuberculosis and hemorrhoids. The seeds are decongestant, expectorant and tonic. They have been used in the treatment of rheumatism, and neuralgia [68].

CONCLUSION

The concept of this review focuses on two important aspects. First, the medicinal properties of the plants, when researched through modern scientific methods, may prove to have enormous potential in the discovery of newer and more efficacious anti tubercular medicines. Second, a few numbers of the plants used by the THPS are the functional food ingredient used in daily life, if validated by scientific research, can prove a cost-effective way of minimizing diseases and keeping the population healthy without the necessity of using costly drugs or Nutraceuticals. Such validation can prove to be immensely useful for poverty-stricken populations of many developing countries throughout the world. This is an indication of the potential value of the documented medicinal plants as sources of compounds needed for the development of plant derived anti-tuberculosis drugs.

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CONFLICT OF INTERESTS

Declared None

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