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>
<thead>
<tr>
<th>S. No.</th>
<th>Vernacular name and family</th>
<th>Parts used</th>
<th>Extract</th>
<th>Type of organism tested/MICµg/ml</th>
<th>Ref. No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cassia sophera (Caesalpinaceae)</td>
<td>Aerial parts</td>
<td>Methanolic extract</td>
<td>M. smegmatis 125</td>
<td>[13]</td>
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<td>2</td>
<td>Solanum auraniticum (Solanaceae)</td>
<td>Aerial parts</td>
<td>Ethanolic extract</td>
<td>M. smegmatis 312</td>
<td>[14]</td>
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<td>3</td>
<td>Diospyros Montana (Acanthaceae)</td>
<td>Leaves</td>
<td>Methyl ether extract</td>
<td>M. aurum -0.10</td>
<td>[15]</td>
</tr>
<tr>
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<td>Phaseolus vulgaris (Fabaceae)</td>
<td>Seeds</td>
<td>Alcoholic extract</td>
<td>M. smegmatis 50</td>
<td>[16]</td>
</tr>
<tr>
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<td>Goniolahtamus Gittingensis (Liliaceae)</td>
<td>Leaves</td>
<td>Pet. ether extract</td>
<td>M. aurum 17</td>
<td>[17]</td>
</tr>
<tr>
<td>6</td>
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<td>Aerial parts</td>
<td>Ethanolic extract</td>
<td>M. smegmatis 250</td>
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<td>Allium cepa (Liliaceae)</td>
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<td>Aqueous extract</td>
<td>M. smegmatis 50</td>
<td>[19]</td>
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<td>8</td>
<td>Allium sativum (Liliaceae)</td>
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<td>Aqueous extract</td>
<td>M. tuberculosis 100</td>
<td>[19]</td>
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<tr>
<td>9</td>
<td>Prunus armeniaca (Rosaceae)</td>
<td>Fruits</td>
<td>Ethanolic extract</td>
<td>M. tuberculosis 100</td>
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<td>Leaves</td>
<td>Ethanolic extract</td>
<td>M. smegmatis 100</td>
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<td>Chloroform/ Methanol extract</td>
<td>M. tuberculosis 50</td>
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<tr>
<td>12</td>
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<tr>
<td>13</td>
<td>Vitex negundo (Verbenaceae)</td>
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<td>M. aurum 100</td>
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<tr>
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<td>Taxus baccata (Taxaceae)</td>
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<td>Aqueous extract</td>
<td>M. fortuitum 150</td>
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<td>15</td>
<td>Andrographis paniculata (Acanthaceae)</td>
<td>Leaves</td>
<td>Aqueous extract</td>
<td>M. smegmatis 100</td>
<td>[24]</td>
</tr>
</tbody>
</table>

Table 1: List of the indian medicinal plants used for treatment of tuberculosis
A field survey was carried out with the traditional health practitioners THPS in south India are analyzed in this review. Terpenoids, Flavanoids [41].

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 antitymocobacterial 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 spectabilis (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, Flavonoids [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-obluate, 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, punicaglin, terflavin A, ellagitannin, tercheulin, terchebin. The tree yields a gum. It contains tannic acid up to 40% and Chebulic Myrobalan in carious teeth and bleeding gums. Fruit pulp used in dentifrices [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. Myrobalsan 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, yellow, seeds are closely packed, ovoid, oblong, and compressed in the ground and it produces small, self-fertile, off-white flowers.
The green flowers are arranged in panicles and have a distinct odor.

**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, Aphrodisiac [46].

**Major chemical constituents**
Phenols and terpenes, tannins, mucilage, trace amounts of coumarin.

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

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. Berries ready 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 Clove 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 white, small, sessile, covering a tubular spadix; fruits globose, 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**
It benefits the general weakness, dyspepsia, impotency, dysentery, diarrhea, dysentery, epilepsy, neuralgia, rheumatic pain, skin disorders, TB, urinary disorders, vomiting, wasting [53].

b. *Guduchi* (Menispermaceae)

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

b. *Guggul* (Burseraceae)

**Description**
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 tree produces 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 tuberculare, 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, grey-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, anti-diabetic, anticancer, antiulcer, antioxidant, antiinflamatory, 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 (Solanaceae)

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, steroids, 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 serratte. Flowers monocious, 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 compounds needed for the development of plant derived anti-tuberculosis drugs.

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CONFLICT OF INTERESTS

Declared None
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