Vol.14 (4), Oct. – Dec. 2016 ISSN-0974-1550

ENVIS NEWSLETTER
MICROORGANISMS AND ENVIRONMENT MANAGEMENT
(Sponsored by Ministry of Environment, Forest & Climate Change, Government of India)

Therapeutic Potentials of Medicinal plants against *Mycobacterium tuberculosis* (MTB) infections

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ARTICLE INFO

Article history:
Received 17 January 2017
Received in revised form 15 February 2017
Accepted 17 February 2017

Keywords:
Mycobacterium tuberculosis
Medicinal Plants
Drug Resistant
MDR and XDR-TB
Anti-tubercular
Natural
Ayurveda.

ABSTRACT

Tuberculosis (TB), caused by *Mycobacterium tuberculosis* (MTB) is an infectious dreadful disease to mankind. The treatment and management of TB remains to be a constant challenge to the scientific community world-wide. TB is the cause for the second largest number of deaths globally and the death tolls remain all time high with co-infections with HIV. MTB-H37Rv is the typical MTB organism studied in many labs and in 1998 its complete genome was published. In general H37Rv are susceptible to all the first line of drugs. But emergence of Multi Drug Resistant (MDR) and Extensively Drug Resistant (XDR) strains of MTB is not uncommon and management of such clinical isolates are extremely difficult. Asian countries are known for their cultural richness in usage of several folk medicines. The use of herbal medicine is becoming popular due to less toxicity and side effects compared of allopathic medicines. Medicinal plants from Ayurveda (Indian traditional medicine system) and from foreign origin have been employed to treat TB. In this review we have addressed the merits and demerits of conventional (Allopathcic) medicine system in comparison to traditional (Ayurvedic) medicine system.

Introduction

Tuberculosis is a highly infectious disease with about one third of the world's population including 40% from India estimated to be infected[1]. However, this problem has become serious as MTB developed resistance against both the first line as also the second line of drugs. Due to this, there is an emergence of multi-drug resistant (MDR) and extensively-drug resistant (XDR) strains of MTB all over the world including India[2].The WHO intends to integrate traditional medicine into National Health systems (NHS) globally. This is an opportunity for building safe, affordable and effective NHS especially for Third world countries, rich in both medicinal plant resources and traditional medicine knowledge. It is the time for Governments to found research into holistic health models as an alternative of squandering more billions on 'health genomics', which will increase intervention and iatrogenic damages to health. The recent increase of TB is associated with the emergence of the human immunodeficiency virus (HIV) and the rapid spreads of MDR-TB strains degenerate the situation. Second-line drugs have many more adverse effects than the first-line anti-TB drugs. Medicinal plants offer a great hope to fulfill these needs and have been used for curing diseases for many centuries. These have been used extensively as pure compounds or as a crude material. Only a few plant species have been thoroughly investigated for their medicinal properties[3]. India is one of the few countries in the world which has unique wealth of medicinal plants and vast traditional knowledge of use of herbal medicine for cure of various diseases. Most healthy individuals are able to control the infection with a strong immune response, halting the progression of the disease, but not necessarily eradicating the organism[4].

Conventional anti MTB drugs

Drugs such as Isoniazid (INH or H), Rifampicin (RMP or R), Streptomycin (STM or S), Ethambutol (EMB or E) and Pyrazinamide (PZA or Z) are all considered first line of drugs to control MTB. Besides that second line and third line of drugs are being administered when drug resistance surfaced. Multi drug resistant tuberculosis (MDR-TB) or Vank's disease show resistance to isoniazid and rifampicin[5] and Extensively drug-resistant TB (XDR-TB) is a rare type of multidrug-resistant tuberculosis (MDR-TB) that is resistant to isoniazid, rifampin, plus any fluoroquinolones and at least one of three injectable second-line drugs (i.e., amikacin, kanamycin, or capreomycin)[6]. Though these drugs are in clinical practice they are known for their adverse side-effects.

Side-effects caused by conventional anti MTB drugs

Besides developing drug resistance long term administration of isoniazid can cause side effects such as nausea, vomiting, epi-gastric pain and in some cases cutaneous pruritus[7]. Similarly administration of rifampicin can cause fatigue, dizziness, headache, dyspnea, and ataxia in patient's treated. Pyrazinamide administration for longer period can develop dermatitis. Another effective anti MTB drugs is ethambutol and chronic administration can lead to Retrobulbar neuritis, nausea,

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vomiting, abdominal pain and hepatotoxicity, hematological symptoms (eosinophilia, neutropenia, and thrombocytopenia), cardiovascular symptoms (myocarditis and pericarditis), neurological symptoms (headache, dizziness, and mental confusion), hyperuricemia/ gout (due to a reduction in the excretion of uric acid by the kidney), hypersensitivity (skin rash, arthralgia, and fever) and (occasionally) pulmonary infiltrates.Treatment with streptomycin reported to cause vestibular and auditory nerve damage and occasionally renal damage[8].

Use of medicinal plants

The use of plants as the source of remedies for the treatment of many diseases dates back to prehistory period and people of all continents have practiced this old tradition. Plants contribute to be the major source of medicines throughout the human history. The World Health Organization (WHO) estimated that about 80% of world's populations rely on traditional medicinal plants for their primary health care. The uses of herbs and herbal products have been broadly being accepted in our modern way of life[9]. Plant species serve as a rich source of many novel biologically active compounds; although very few have been thoroughly investigated for their medicinal properties. About 30-40% of plants are used in today's conventional drugs and rest are used as herbal supplements, botanicals and beverages[10].

Herbal medicine is a major component in all indigenous people traditional medicine and is a common element in ayurvedic, homeopathic, naturopathic, traditional, oriental and Native American Indian medicines. WHO notes that of the 119 plant-derived pharmaceutical medicines, about 74% are used in modern medicine in ways that correlated directly with their traditional uses as plant medicines by native's culture[11]. The uses of some medicinal plants vary a lot according to regional and cultural aspects. Their use is often associated with witchcraft and superstition because the practitioners do not have the scientific insight to explain or predict the curative action of plants. One example of such an irrational concept is the Doctrine of Signatures (elements of which are found in many of the healing cultures of the world) based on the assumption that the appearance of plants may give clues to their medicinal properties[12].

The forest in India is the principal repository of large number of medicinal and aromatic plants, which are largely collected as raw materials for manufacture of drugs and perfumery products. About 8,000 herbal remedies have been codified in AYUSH systems in INDIA. Ayurveda, Unani, Siddha and Folk (tribal) medicines are the major systems of indigenous medicines. Among these systems, Ayurveda and Unani Medicine are most developed and widely practiced in India[13]. According to WHO, around 21,000 plant species have the potential for being used as medicinal plants[14].

It has been estimated, that in developed countries such as United States, plant drugs constitute as much as 25% of the total drugs, while in fast developing countries such as India and China, the contribution is as much as 80%. These countries provide two third of the plants used in modern system of medicine and the health care system of rural population depend on indigenous systems of medicine[15].

Treatment with medicinal plants is considered very safe as there is no or minimal side effects. These remedies are in sync with nature which is the biggest advantage. The golden fact is that use of herbal treatments is independent of any age groups and the sexes. Medicinal plants such as Aloe, Tulsi, Neem, Turmeric and Ginger cure several common ailments. These are considered as home remedies in many parts of the country. It is known fact that lots of consumers are using Basil (Tulsi) for making medicines, black tea, in pooja and other activities in their day to day life[16]. Now, after finding the role of herbs in medicine, lots of consumers started the plantation of tulsi and other medicinal plants in their home gardens.

Medicinal plants are considered as rich resources of ingredients which can be used in drug development pharmacopoeial, non-pharmacopoeial or synthetic drugs and play a critical role in the development of human cultures around the whole world. Moreover, some plants are considered as important source of nutrition and as a result of that they are recommended for their therapeutic values. Some of these plants include ginger, green tea, walnuts, aloe, pepper and turmeric etc. Some plants and their derivatives are considered as important source for active ingredients which are used in aspirin and toothpaste etc.[17] Apart from the medicinal uses, herbs are also used in natural dye, pest control, food, perfume, tea and so on. In many countries different kinds of medicinal plants/ herbs are used to keep ants, flies, mice and flee away from homes and offices. Now a day's medicinal herbs are important sources for pharmaceutical manufacturing[18].

Over the past two decades, there has been a tremendous increase in the use of herbal medicine; however, there is still a significant lack of research data in this field. Medicinal plants are also important for pharmacological research and drug development, not only when plant constituents are used directly as therapeutic agents, but also as starting materials for the synthesis of drugs or as models for pharmacologically active compounds[19]. Major pharmaceutical companies are currently conducting extensive research on plant materials, gathered from forests and other habitats, for their potential medicinal value[20].

Anti MTB agents derived from the ayurvedic literature

Ayurveda, means the science of life (Ayur = Life, Veda = Science), it is an ancient medical knowledge which was developed in India thousands of years ago and describes numerous plants to treat several diseases. When we particularly talk about TB, more than 250 medicinal plants from India have been reported[17]. The comprehensive safety, toxicity and clinical studies are needed for these plants before using them effectively as curative and/or preventive medications against TB. List of plants from Ayurveda has been discussed in Table 1.

Anti-tubercular plants from foreign origin

Anti-tubercular plants are found all over the world such as South Africa, New Zealand, Malaysia, Nigeria, Tibet etc. A list of anti-tubercular plants from foreign origin is shown in Table 2.

Table 1: Common anti-tubercular plants from Ayurveda[3,21-32]

Botanical/ family name	Ayurvedic name	Part used	Chemical constituents	Other biological activities
Acalypha indica, **Euphorbiaceae**	Kuppi	Leaves	Kaempferol, acalyphamide and other amides, quinone, sterols, cyanogenic glycoside	Antibacterial, used in bronchitis, asthma
Adhatoda vasica, **Acanthaceae**	Vaasaa	Leaves	Quinazoline alkaloid	Expectorant (used in bronchial asthma)
Allium cepa, **Liliaceae**	Palaandu	Bulbs	Volatile oil with sulphurous constituents, including allylpropyl disulphide, sulphur containing compounds, including allicin, alliin, flavonoids, phenolic acids and sterols	Antibiotic, antibacterial, antisclerotic, anticoagulant
Allium sativum**, Liliaceae**	Lashuna	Bulbs	Sulphurcontaining amino acids known as alliin	Antibiotic, bacteriostatic, fungicide, anthelmintic, antithrombic, hypotensive, hypoglycaemic, hypocholesterolaemic
Aloe vera, **Liliaceae**	Ghritkumaarika	Leaves, gel from leaves	Anthraquinone glycosides, known as aloin	Purgative
Vitex negundo**, Verbenaceae**	Nirgundi	Leaves, seeds	Iridoid glycosides, isomeric flavanones and flavonoids	Anti-inflammatory, analgesic
Trichosanthes dioica, **Cucurbitaceae**	Patola	Roots, fruits	Free amino acids, nicotinic acid, riboflavin, vitamin C, thiamine, 5-hydroxytryptamine	Cathartic, febrifuge
Tinospora cordifolia**, Menispermaceae**	Guduuchi	Stem, leaves	Alkaloidal constituents, including berberine; bitter principles, including columbin, chasmanthin, palmarin, tinosporon, tinosporic acid and tinosporol	Antipyretic, antiperiodic, anti-inflammatory
Caesalpinia pulcherrima**, Caesalpiniaceae**	Padangam	Leaves, flowers	Flavonoid, myricitroside	Laxative, antipyretic
Prunus armeniaca, **Rosaceae**	Peetaalu	Kernels	Salicylic acid,organic acids tannins, potassium salts, protocatechuic, *p*coumaric, ferulic and diferculic acids	Antitussive, antiasthmatic
Ocimum sanctum**, Labiatae**	Tulasi	Leaves, flowers, Seeds	Ursolic acid, apigenin, orientin luteolin, apigenin -7- Oglucuronide, luteolin-7-Oglucuronide	Carminative, stomachic, antispasmodic, antiasthmatic, antirheumatic, expectorant, hepatoprotective, antiperiodic
Morinda citrifolia**, Rubiaceae**	Ashyuka	Leaves, roots, fruits	Anthraquinonesalizarin and its glycosides, *nor*damnacanthol. Ursolic acid, β-sitosterol. asperuloside and caproic acid	Antileucorrhoeic, antidysenteric emmenagogue
Myrtus communis**, Myrtaceae**	Muuraddaan	Fruits	Tannins (pyrogallol derivative), flavonoids (including myricetin, kaempferol, quercetin glycosides; volatile oil containing α-pinene, cineole, myrtenol, nerol, geraniol and dipentene	Antimicrobial, antiparasitic, antiseptic
Canscora decussate, **Gentianaceae**	Daakuni	Roots	β-amyrin, friedelin,genianine mangiferin, Xanthones	Anticonvulsant, CNS depressant, antiinflammatory, hepatoprotective.
Piper species**, Piperaceae**	Pippali	Fruits	Aristolactams, dioxoaporphines long chain isobutyl amide, lignans, longamide, pluviatilol, methyl pluviatilol (fargesin), sesamin, asarinine, piperine	Digestive, appetizer and carminative
Vitex trifolia**, Verbenaceae**	Sinduvaara	Leaves, roots, fruits	Flavonoids-artemetin, luteolin, orientin, casticin; and iridoid glycosides, aucubin and agnuside. alkaloid, vitricin	Febrifuge, antibacterial, anthelmintic, cytotoxic
Mallotus philippensis**, Euphorbiaceae**	Kampillaka	Gland, hair of fruit	Phloroglucinol derivatives; rottlerin, isorottlerin, iso allorottlerin	Purgative, anthelmintic, styptic
Colebrookea oppositifolia**, Lamiaceae**	Binda	Leaves, fruits, roots	Flavonoids	Antiinflammatory
Rumex hastatus**, Polygonaceae**	Katambal	Root and bark	Tannins	Astringent
Mimosa pudica**, Mimosaceae**	Laajavanti	Leaves, roots	Mimosine and turgorin	Astringent, antiseptic, styphic, blood purifier

Table 2: List of Anti-Tubercular plants of foreign origin[16,33-47]

Botanical name	Family	Extract	Chemical constituents
Clavija procera	Theophrastaceae	Ethanolic	Oleanane triterpenoid (aegicerin)
Rhodomyrtus tomentosa	Myrtaceae	Alcoholic	Rhodomyrtone
Aristolochia taliscana	Aristolochiaceae	Hexane	Neolignans
Astraeus pteridis	Astraeaceae	Ethanolic	Lanostane triterpenes and phenylalanine
Byrsonima crassa	Malpighiaceae	Chloroform	Triterpenes:α-amyrin, β-amyrin and their acetates, lupeol, oleanolic acid, ursolic acid and α-amyrinone
Galenia africana	Asteraceae	Ethanolic	Flavonoids
Gentianopsis paludosa	Gentianaceae	Ethanolic	1,7,8-Trihydroxy-3-methoxyxanthone, luteolin-7-O-glucoside
Cryptocarya latifolia	Lauraceae	Acetone, water	Coumarins
Euclea natalensis	Ebenaceae	Acetone, water	Naphthoquinones
Helichrysum melanacme	Asteraceae	Acetone, water	Essential oils
Nidorella anomala	Asteraceae	Acetone, water	Naphthoquinones
Thymus vulgaris	Lamiaceae	Acetone, water	Flavonoids, essential oils
Buddleja saligna	Scrophulariaceae	Alcoholic	Non-cytotoxic triterpenoids oleanolic
Leysera gnaphalodes	Asteraceae	Alcoholic	Non-cytotoxic triterpenoids oleanolic
Laggera pterodonta	Asteraceae	Methanolic	Flavonoids
Laggera aurita	Asteraceae	Methanolic	Flavonoids
Salvia hypargeia	Lamiaceae	Alcoholic	Diterpene
Salvia sclarea	Lamiaceae	Alcoholic	Diterpene
Angiopteris evecta	Marattiaceae	-	Lactones, coumarins
Costus speciosus	Costaceae	-	Flavonoids
Pluchea indica	Asteraceae	-	Phenolics
Tabernaemontana coronaria	Apocynaceae	-	Alkaloids
Pelargonium reniforme	Geraniaceae	Ethanolic, acetone	Phenolics
Pelargonium sidoides	Geraniaceae	Ethanolic, acetone	Phenolics
Quinchamalium majus	Santalaceae	Methanolic	Triterpenes
Senecio chionophilus	Asteraceae	Hexane, dichloromethane	Sesquiterpenoids
Evodia elleryana	Rutaceae	Hexane, ethyl acetate, methanol	Alkaloid, quinoline

Conclusion

Natural products as crude materials with efficacy against various diseases have been selected by humans over many generations of practical experience. However many effective medicines such as morphine, aspirin, atropine, ephedrine, reserpine and digitoxin were developed from natural products. Medicinal plants, since times immemorial have been used in virtually all cultures as a source of medicine. The widespread use of herbal remedies and health care preparations described in ancient texts such as the Vedas and the Bible, obtained from commonly used traditional herbs and medicinal plants, traced to the occurrence of natural products with medicinal properties.

Conventional (allopathic) medicines are indeed effective until the emergence of MDR and XDR isolates but are known to cause side-effects. In contrast, ayurvedic and other traditional medicine appear to be promising not only by inhibition of MTB and XDR isolates but also are hardly known to cause any side effects. Ayurvedic and other traditional medicine have shown inhibition of MTB and XDR strains *in-vitro*. However their overall *in-vivo* efficacy, toxicity and Maximum tolerated dose to be administered are required to be extensively studied before in enters in to human usage.

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