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Edible plants as a source of antitubercular agents

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Abstract
Tuberculosis is a chronic contagious disease caused by numerous species of mycobacterium. Due to multi-drug resistant strains of mycobacterium and to a high occurrence of tuberculosis in patients who have acquired human immunodeficiency syndrome (AIDS), the number of patients infected with the disease is rising worldwide. Thus there is an urgent need for new efficient antimycobacterial agents to replace those currently in use. Presently, Pharmaceutical and nutritional sciences have perceived a bloom in the scientific literature geared towards the use of food plants for their diversified health benefits and potential clinical applications. Health specialists now identify that a synergism of drug therapy and nutrition might deliberate optimum outcomes in the fight against diseases. The prophylactic benefits of food plants are being investigated for potential use as novel medicinal remedies due to the presence of pharmacologically active compounds. Although the availability of scientific data is rapidly growing, there is still a paucity of updated compilation of data and concerns about the rationale of these health-foods still persist in the literature.The plant kingdom is undoubtedly an important source for new anti-tubercular agents. The present review article reports the findings of edible plants that have been reported for antimycobacterial/antitubercular activity. The profiles of plants presented in this review may include information about the scientific and family name, plant parts and bioassay used, the range of activity (MIC), and the active chemical agents and extracts. The large number of plants described in this review (82 plant species belonging to 40 families) clearly demonstrated the importance of edible plants in antimycobacterial activity. This work stimulates the researchers for further research on the potential use of edible plants having antitubercular activity. An attempt has been made to highlight those promising edible plant species which are worthy of further exploration as leads for drug development. The potential challenges of incorporating these medicinal foods in the diet which offers prospective opportunities for future drug development are also discussed.

Keywords: Edible plants, tuberculosis, antimycobacterial, drug

1. Introduction
Tuberculosis (TB) (caused by *Mycobacterium tuberculosis*) remains a foremost global health problem and the second leading cause of death worldwide. In 2012 the incidence of the disease was estimated to be about 8.6 million and strikingly around 1.1 million (13%) patients were HIV-positive. India and China alone accounted for 24 and 11% of total cases, respectively [1]. Although India is the second most populous country in the world, it has more new emerging TB cases annually than any other country [2]. The current therapeutic regimens are (1) six-month regimen in which initial two months treatment is given with streptomycin, isoniazid, rifampicin, and pyrazinamide; or ethambutol replacing streptomycin and then followed by treatment with isoniazid and rifampicin for next four months and (2) eight-month regimen starting with the same four drugs in the initial phase but continuing with six months of thioacetazone and isoniazid.
With time, mycobacterium has exacerbated the problem in humans by acquiring various types of resistances [multi-drug resistance (MDR), single-drug resistance (SDR), and extensive drug resistance (XDR)] against antimycobacterial drugs [3]. The evaluation of the effectiveness of newly developed anti-tubercular agents against isolates of *M. tuberculosis* has become more important in the past few years, predominantly due to the appearance of multi-drug resistant tuberculosis [4]. There is an urgent need for new and effective anti-TB agents as an alternative to those drugs currently in use.
Plants with potential therapeutic values have been used from time immemorial to cure various ailments and infectious diseases. Of late, scientific evidences have been provided on the potential therapeutic agent exhibited by certain traditionally used vegetable extracts. The importance of edible plants may be traced to antiquity but systemic studies have not been attempted so far. Recently the exploration and exploitation of the disease fighting properties of a multitude of phytochemicals found in both food and nonfood plants have created a

renaissance in human health and nutrition research. At the same time, many opportunities for the development of novel dietary products have been created. With all new fields of study come new term knew as "Nutraceuticals" [5], a term combining the words “nutrition” (a nourishing food or food component) and “pharmaceutical” (a medical drug), is a food or food product that provides health and medical benefits, including the prevention and treatment of disease. Such products may range from isolated nutrients, dietary supplements and specific diets to genetically engineered foods, herbal products and processed foods such as cereals, soups and beverages [6].

With recent advances in medical and nutrition sciences, natural products and health promoting foods have received extensive attention from both health professionals and the public. New concepts have appeared with this trend, such as nutraceuticals, nutritional therapy, phytonutrients, and phytotherapy [7, 8, 9]. These functional or medicinal foods and phytonutrients or phytomedicines play positive roles in enhancing health, and improving immune function to prevent specific diseases and also hold great promise to reduce side effects and health care cost [10]. A good number of extracts and pure compounds obtained from plants have exhibited considerable inhibitory activity against *Mycobacterium*. It is seen that several phyto-molecules have shown anti-tubercular potency close to currently used drugs or even better than those. These phytomolecules and their semi-synthesized derivatives are under investigation for anti-tubercular activity by several research groups globally. New evidence suggests that in order to understand the health benefits of plant based supplements and foods; we will need to take into account the fact that complex mixtures of phytochemicals found in food and other botanicals may act synergistically.

The present review article describes the edible plant species from a wide range of families that have been screened for antimycobacterial activity. The different literature database search provided a total of 82 edible plant species that have been evaluated for antimycobacterial activity. Of these, 18 species which showed antimycobacterial activity can be consumed as food directly in the form of fruits and vegetables.

Table 1: Edible plant species screened for antimycobacterial activity

Family	Plant	Common Name (English)	Plant part used	Extract/ Active constituents	Evaluation against the mycobacterium species	Bioassay	Antimycobacterial activity (MIC)/IC50	References
Anacardiaceae	*Mangifera indica L.*	Mango	Leaf	Ethanol extract	MS & MT	Disc diffusion assay	1 mg/disc 50 µg /disc	[11]
Annonaceae	*Annona glabra* L.	Pond apple	Stem	Ethanol extract	MT	Radiorespirometry assay	100µg/ml	[12]
	Annona muricata L.	Prickly custard apple	Leaf	Ethanol extract	MT	Radiorespirometry assay	100µg/ml	[12]
Apiaceae	Apium graveolens L.	Celery	Leaf	Aqueous extract	MT	Broth dilution assay	1:40 dilution	[13,14]
			Seed	Methanol extract	MA and MS	Micro broth dilution assay	>500µg/ml	[15]
	Centella asiatica (L.) Urban	Centella	Whole plant	Methanol extract	MA and MS	Micro broth dilution assay	>500µg/ml	[15]
	Daucus carota L.	Wild carrot	Leaf	Aqueous extract	MT	Broth dilution assay	<1:20 dilution	[13]
Araceae	*Amorphophallus campanulatus* Blume ex Decne	Zaminknd	Stem	Ether extract	MT	Broth dilution assay	1: 5000 dilution	[16]
Arecaceae	Areca catechu L.	Betelnut palm	Fruit	Ethanol extract	MT	Tube dilution assay	1:40 dilution	[17]
Asteraceae	*Helianthus annus* L.	Sunflower	Petal	Methanol extract	MA &MS	Micro broth dilution assay	500µg/ml	[15]
	Lactuca sativa L.	Lettuce	Leaf	Aqueous extract	MT	Broth dilution assay	<1:20 dilution	[13]
	Tagetes mimuta L	Black mint	Ariel part	Methanol & Chloroform extract	MP	Agar dilution assay	1mg/ml	[18]
	Taraxacum officinale Webber	Common dandelion	Leaf & Root	Methanol extract	MA &MS	Micro broth dilution assay	500µg/ml	[15]
			Leaf, fruit &sap	Aqueous extract	MT	Broth dilution assay	1:40 dilution	[13]
	Xanthium strumarium L.	Rough cocklebur	Ariel part	Methanol &Petroleum ether extracts	MT	Broth dilution assay	1mg/ml	[19]
Berberidaceae	*Berberis vulgaris* L.	Barberry	Whole plant	Chloroform & Methanol extract	MP	Agar dilution test	100 &10.4 g/l	[20]
			Leaf	Aqueous extract	MT	Broth dilution assay	1:40 dilution	[13]
Brassicaceae	*Brassica nigra* (L.) Koch.	Black mustard	Leaf & Flower	Aqueous extract	MT	Broth dilution assay	<1:40 dilution	[13]
	Brassica rapa L.	Field mustard	Seed	Aqueous extract	MT	Disc diffusion assay	Active	[21]
	Nasturtium	Watercress	Leaf	Aqueous extract	MT	Broth dilution	<1:20 dilution,	[13,22]

	officinale R. Br.					assay	100µg/ml	
Caricaceae	*Carica papaya* L.	Papaya	Leaf	Aqueous extract	MT	Tetrazolium microplate assay	100µg/ml	[21,23]
Caryophyllaceae	*Stellaria media (L.) Vill.*	Chickweed	Leaf	Aqueous extract	MS	Broth dilution assay	<1:20 dilution	[13]
Chenopodiaceae	*Beta vulgaris* L.	Beet root	Leaf	Aqueous extract	MT	Broth dilution assay	<1:20 dilution	[13]
	Chenopodium album L.	Melde	Leaf	Aqueous extract	MT	Broth dilution assay	<1:20 dilution	[13]
	Spinacia oleracea L.	Spinach	Leaf	Aqueous extract	MT, MA	Broth dilution assay	<1:20 dilution, 59µmol/L	[13,24]
Clusiaceae	*Mammea americana* L.	Mammee	Leaf	Ethanol extract	MS & MT	Disc diffusion assay	25 µg/disc &50 µg/disc	[11,25]
Combretaceae	*Terminalia catappa L.*	Indian almond	Stem	Ethanol extract	MT	Broth dilution assay	100µg/ml	[12]
Cucurbitaceae	*Citrullus colocynthis* Schrad.	Desert gourt	Fruit	Ethanol extract	MT	Tube dilution assay, Radiometric BACTEC 460TB system	1:80 dilution, 31.2µg/ml	[17,26]
	Cucumis sativus L.	Cucumber	Fruit	Aqueous extract	MT	Broth dilution assay, Radiometric BACTEC 460TB system	<1:40 dilution, 7.8µg/ml	[13,27]
	Cucurbita maxima Duchesne	Pumpkin	Fruit	Aqueous extract	MT	Broth dilution assay	<1:20 dilution	[13]
	Cucurbita pepo L.		Fruit	Ethanol extract	MP	Disc diffusion assay	Active	[21]
	Luffa cylindrica (L.) Roem.	Smooth luffa	Aerial parts	Ethanol extract	MS	Agar dilution assay	1mg/ml	[28]
	Momordica charantia L.	Bitter gourd	Leaf	Ethanol extract	MT	Disc diffusion assay	500 µg/disc	[11]
Elaeagnaceae	*Hippophae rhamnoides* L.	Common sea-buckthorn	Fruit	Ethanol extract	MP &MS	Agar diffusion assay	50µl	[29]
Euphorbiaceae	Chrozophora tinctoria Hook. f.	Giradol	Ariel part	Ethanol extract	MS	Agar dilution streak method	1mg/ml	[28]
	Croton tiglium L.	Jamalgotha	Whole plant	Ethanol extract	MT	Tube dilution assay	1:40 dilution	[17]
Fabaceae	*Glycyrrhiza glabra* L.	Liquorice	Active constituent	Lico-isoflavone	MT &MS	Broth dilution assay	25 &50 µg/ml	[30]
			Root	Methanol extract	MA &MS	Micro broth dilution assay, Radiometric BACTEC 460TB system	250 &500 µg/ml, 29.16 µg/ml	[15,31]
	Trigonella foenum-graecum L.	Fenugreek	Seed	Protein fraction	MR	Disc diffusion assay	Active	[32]
Labiateae	*Mentha spicata* L.	Spearmint	Leaf	Aqueous extract	MT	Broth dilution assay	1:40, 300 µg/ml	[13,33]
	Salvia officinalis L.	Sage	Whole plant	Choloroform extract	MP	Agar dilution assay	2.3g dried plant /l	[20]
Lamiaceae	*Lamium album* L.	White nettle	Whole plant	Chloroform extaact	MP	Agar dilution assay	17g dried plant /l	[20]
	Lamium amplexicaule L.	Henbit deadnettle	Whole plant	Ethanol extract	MI	Agar diffusion assay	20mg/ml	[34]
	Melissa officinalis L.	Lemon balm		Ethanol extract	MT	Tube dilution assay	1:80 dilution	[17]
	Mentha piperita L.	Peppermint	Leaf	Methanol extract	MA &MS	Micro broth dilution assay	500µg/ml	[15]
	Ocimum basilicum L.	Basil	Whole plant	Chloroform extract	MP	Agar dilution assay	22.7g/l, 6.25 µg/ml	[20,35]
			Seed	Aqueous extract	MT	Disc diffusion assay	Active	[21]
	Ocimum sanctum L.	Holy basil	Leaf	Ether extract	MT	Broth dilution assay	80µg/ml	[36]
			Leaf	Aqueous extract	MT	Broth dilution assay	1:1 dilution	[37]
			Leaf	Aqueous extract	MT	Broth dilution assay	1:80dilutions	[13]
	Thymus vulgaris L.	Thyme	Leaf	Aqueous extract	MT	Broth dilution assay	1:40 dilution, 25 µg /ml	[13,38]
Lauraceae	*Cinnamomum*	Cinnamon	Leaf	Aqueous extract,	MT	Broth dilution	1:640, 12.5 µg/mL	[13,39]

	zeylanicum			essential oil		assay		
Liliaceae	Allium sativum L.	Garlic	Leaf	Aqueous	MT	Micro broth dilution	1:1640	[13]
			Bulb	Methanolic extracts	MA and MS	Micro broth dilution	>500µg/ml	[15]
			Bulb	Allicin isolated from water extract	MT	Agar-dilution test	1670µg/ml	[40]
			Bulb	Aqueous extract	MT	Tube dilution test	160µg/ml	[41,42]
	Allium schoenoprasum L	Chives	Leaf	Ethanol extract	MS	Agar-diffusion test	13–18mm zones of inhibition were found at 50µl of extract	[29]
	Aloe vera Mill.	Aloe vera	Leaf	Ethyl acetate & Aqueous extract	MT	Disc diffusion assay	Active	[43,44]
	Asparagus officinalis L.	Garden asparagus	Leaf	Aqueous extract	MT	Broth dilution assay	<1:20 dilution	[13]
Malvaceae	*Abelmoschus esculentus* L.	Okra	Leaf	Aqueous extract	MT	Broth dilution assay	<1:20 dilution	[13]
Moraceae	*Morus alba* L.	White mulberry	Leaf	Methanol extract	MP	Agar dilution assay	1mg/ml	[18]
	Artocarpus lakoocha Roxb.	Monkey jack	Root	Lakoochin A and B	MT	Microplate alamar blue assay	12.5 µg/ml 50 µg/ml	[45]
Moringaceae	*Moringa oleifera* Lam.	Drumstick tree	Seed	4-(α-L-Rhamnosyloxy) benzyl isothiocynate, isolated from aqueous extract	MP	Tube dilution assay	17.5 µg/ml	[46]
Myristicaceae	*Myristica fragrans* Houtt.	Nutmeg	Leaf	Aqueous extract	MT	Broth dilution assay	<1:20 dilution	[13]
Myrtaceae	*Psidium guajava* L.	Guava	Stem	Ethanol extract	MT	Broth dilution assay	100µg/ml	[12]
	Myrtus communis L.	Myrtle	Leaf	Methanol & Chloroform extract	MP	Agar dilution assay	0.25mg/ml	[18]
	Eugenia uniflora L.	Pitanga	Leaf	Aqueous extract	MT	Agar diffusion assay	10mg/ml	[47]
	Syzygium jambos (L.)	Watery rose apple	Leaf	Ethanol extract	MT	Agar dilution assay	500µg/ml	[11]
Piperaceae	*Piper betle* L.	Piper betle	Leaf	Essiential oil	MT	Broth dilution assay	1:5000 dilution	[48]
	Piper cubeba L. f.	Cubeb	Whole plant	Ethanol extract	MT	Tube dilution assay	1:80 dilution	[17]
	Piper nigrum L.	Black Pepper	Whole plant	Ethanol extract	MT	Tube dilution assay	1:80 dilution	[17]
Plantaginaceae	*Plantago psyllium* L.	Psyllium	Whole plant	Ethanol extract	MS	Agar dilution assay	1mg/ml	[28]
Poaceae	*Zea mays L.*	Maize	Leaf	Aqueous extract	MT	Broth dilution assay	<1:20 dilution	[13]
Portulacaceae	*Portulaca oleracea* L.	Pigeweed	Leaf	Ethanol extract	MT	Broth dilution assay	100µg/ml	[12]
Punicaceae	*Punica granatum* L.	Pomegranate	Whole plant	Ethanol extract	MT	Tube dilution assay	1:50 dilution	[49]
Ranunculaceae	*Nigella sativum* L.	Fennel	Seed	Methanol extract	MA & MS	Broth dilution assay	500µg/ml	[15]
Rhamnaceae	*Ziziphus mauritiana Lam.*	Common jujube	Root	Methanol extract	MP	Disc diffusion assay	2g/ml	[50]
Rosaceae	Eriobotrya japonica Lindl.	Loquat	Leaf	Aqueous extract	MT	Disc diffusion assay	Active	[21]
	Fragaria vesca L.	Wild strawberry	Leaf	Methanol extract	MT	Disc diffusion assay	50 µg extract/disc	[51]
	Prunus domesticata L	Plums	Leaf	Aqueous extract	MT	Broth dilution assay	<1:40 dilution	[13]
	Prunus persica Batsch	Peach	Stem	Aqueous extract	MT	Disc diffusion assay	Active	[21]
	Pyrus malus L.	Pear	Leaf & Peel	Aqueous extract	MT	Broth dilution assay	<1:20 dilution	[13]
	Rubus fruticosus L.	Blackberry	Aerial part	Methanol extract	MP	Agar dilution assay	1mg/ml	[18]
Rutaceae	Angle marmelos	Bengal	Fruit	Methanolic	MA and MS	Micro broth	>500µg/ml	[15]

	Corr)	quince		extracts		dilution		
			Root	Methanolic extracts	MP	Disc diffusion assay	>300µg/ml	[52]
Rubicaeae	*Morinda citrifolia* L.	Noni	Leaf	Ethanol & Hexane extract	MT	Broth dilution assay	100µg/ml	[53]
			Leaf	*E*-phytol	MT	Broth dilution assay	34 µg/ml	[53]
			Leaf	cycloartenol	MT	Broth dilution assay	64 µg/ml	[53]
			Leaf	stigmasta-4-en-3-one	MT	Broth dilution assay	2 µg/ml	[53]
			Leaf	stigmasta-4-22-dien-3-one	MT	Broth dilution assay	2 µg/ml	[53]
			Leaf	β-sitosterol	MT	Broth dilution assay	128 µg/ml	[53]
			Leaf	stigmasterol	MT	Broth dilution assay	32 µg/ml	[53]
			Leaf	campesta-5,7,22-trien-3β-ol	MT	Broth dilution assay	2.5 µg/ml	[53]
Solanaceae	*Solanum tuberosum L.*	Potato	Leaf	Aqueous extract	MT	Broth dilution assay	1:20 dilution	[13]
Typhaceae	*Typha elephantina Roxb.*	Coltsfoot	Leaf	Aqueous extract	MT	Broth dilution assay	1:40 dilution	[13]
			Whole plant	Chloroform, Ethanol & Petroleum ether extracts	MS	Broth dilution assay	1g/ml	[54]
	Typha latifolia Edgew.	Bulrush	Leaf	Aqueous extract	MT	Broth dilution assay	<1:20 dilution	[13]
Umbelliferae	*Foeniculum vulgare* Mill.	Fennel	Seed	Methanol extract	MA & MS	Micro broth dilution assay	500µg/ml	[15]
Zingiberaceae	*Alpinia galanga* Willd.	Greater galanga	Rhizome	Oil	MT	Broth dilution assay	30µg/ml	[55]
	Curcuma longa L.		Leaf	Aqueous extract	MT	Broth dilution assay	1:40, 0.09 µg/ml	[13,56]
	Zingiber officinale Rosc.	Ginger	Rhizome	Dichloromethane extract	MA &MT	Broth dilution assay	100µg/ml	[57]

Abbreviations of Mycobacterium species—MT: *Mycobacterium tuberculosis*; MP: *Mycobacterium phlei*; MS: *Mycobacterium smegmatis*; MA: *Mycobacterium avium*; MI: *Mycobacterium intracellulare*; MR: *Mycobacterium rhodochrous*;

Discussion

The data suggests that amongst all the plants. 12 most active plant species, are *Allium sativum*, *Alpinia galanga*, *Artocarpus lakoocha*, *Cinnamomum camphora*, *Citrullus colocynthis*, *Glycyrrhiza glabra*, *Morinda citrifolia*, *Moringa oleifera*, *Ocimum sanctum*, *Piper cubeba*, *Portulaca oleracea*, *Zingiber officinale* which are widely distributed in India from tropics to alpine Himalayas. All these plant species exhibited significant in vitro antimycobacterial activity (extracts showed MIC values ranging from 2 to 500 µg/ml) and from 5 of these species the active compounds have been isolated with MIC values ranging from 2 to 500 µg/ml. Lakoochin **A** and **B** (stilbene derivatives) isolated from *Artocarpus lakoocha* exhibited MIC value of 12.5 and 50 µg/ml, respectively. Licoisoflavone isolated from *Glycyrrhiza glabra* showed MIC value of 25 µg/ml. Active compounds, E-phytol(MIC 34 µg/ml), cycloartenol (64 µg/ml), stigmasta-4-en-3-one (2 µg/ml),stigmasta-4-22-dien-3-one (2 µg/ml),β-sitosterol (128 µg/ml), stigmasterol (32 µg/ml),campesta-5,7,22-trien-3β-ol (2.5 µg/ml). The Feruginol (5 µg/ml). 4-(α-l-rhamnosyloxy) benzyl isothiocynate (MIC 17.5 µg/ml) were identified as the active compound from *Moringa oleifera*. Active constituents of *Gingiber officinale* namely 10-gingerol (MIC 25 µg/ml) and 8-gingerol (MIC 50 µg/ml) were found to be active. Thus, the active extracts of these 25 species may prove to be useful agents for treatment of TB and the isolated active compounds may be considered as lead compounds for new anti-TB drug development. The past decade has witnessed an explosion of clinical research to show specifically what health benefits individual foods can offer, identifying the various nutrients and phytochemicals associated with these benefits and how they can be incorporated in the diet. One of the major issues of the WHO was to thoroughly investigate the plants as a promising source of therapies for human disease management [58]. Rationally designed polyherbal preparations are progressively being developed as alternative for multitarget therapeutic and prophylactic usage. This has resulted in growing lines of evidence to show that old molecules are finding new applications through a better understanding of traditional knowledge and clinical observations [59]. Till date, a miscellany of phytochemicals has been identified in medicinal plants to have versatile profile of effectiveness [60]. One sole plant may, for example, contain bitter substances that stimulate digestion, anti-inflammatory compounds, polyphenols that can act as an antioxidant, and venotonics, antibacterial, and antifungal tannins that perform as natural antibiotics [59]. In certain cases, when a combination of medicinal foods or extracts is consumed at the same time or mixed in appropriate formulation, the therapeutic effects could be a result of total sum of different classes of compounds present within the foods [61]. Indeed, there have been reports highlighting that intake of whole medicinal food which have resulted in significantly better outcomes compared when an equivalent dose of single isolated active ingredient was given. Thus, it can be argued that synergism can occur when two or more compounds interact in ways that mutually enhance, amplify, or potentiate each other's effect [62].

Conclusion

It is clearly evident from the data presented in Table 1 that edible plants have great potential to be used as anti-TB agents. The data illustrates that extracts of plant species from wide range of families and genera have exhibited significant in vitro antimycobacterial activities and a number of active plant-derived compounds belonging to different chemical classes have been isolated. There is a strong positive correlation between the antimycobacterial activity results and the traditional knowledge on plants used for TB and TB-related diseases in Ayurveda and the ethnomedicine. In the light of modern science, the efforts should be made to identify and characterize the active constituents from these plants. As mentioned earlier, globally around 2 million people die annually due to TB therefore these findings may help the researchers to further explore the main actives from nature and may lead to development of newer anti-TB drugs.

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