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Review Article

Antimycobacterial Potential of Indian Spices: A Review

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ABSTRACT

Natural products and their plant-derived analogs are often a source of drugs or drug templates with limited toxicity, which has the potential to mitigate compliance issues during protracted administration. Mycobacterium tuberculosis (Mtb), the causative agent of tuberculosis (TB) infection, represents a major health problem globally. Despite the introduction of inexpensive and effective four-drug (isoniazid, rifampicin, pyrazinamide and ethambutol) treatment regimen 40 years ago, TB continues to cause considerable morbidity and mortality worldwide. Global efforts are underway to eradicate TB using new drugs with new modes of action, higher activity, and fewer side effects in combination with vaccines. Since ancient times, different plant part extracts have been used as traditional medicines against diseases including tuberculosis. This knowledge may be useful in developing future powerful drugs. In this regard this review article is an attempt to investigate the antimycobacterial activity of the spices as an alternative and highlight them for further investigation as leads for drug development. The choice of spice as an alternative is based on two basic reasons: firstly, plants have been the model source of medicine since ancient times and secondly, the increasing acceptance of herbal medicines by general population.

Keywords: tuberculosis; spices; antimycobacterial; traditional medicine.

INTRODUCTION

Tuberculosis (TB) has existed for millennia and remains a major global health problem. It causes ill health in millions of people each year and in 2015 was one of the top 10 causes of death worldwide, ranking above HIV/AIDS as one of the leading causes of death from an infectious disease[1]. Human tuberculosis is caused by infection with members of the *Mycobacterium tuberculosis* complex, which includes *Mycobacterium tuberculosis* itself, *Mycobacterium africanum*, *Mycobacterium bovis*, *Mycobacterium caprae*, *Mycobacterium microti*, *Mycobacterium pinnipedii* and *Mycobacterium canetti*[2]. TB continues to spread in every corner of the globe despite the introduction 40 years ago of the inexpensive and effective quadruple drug therapy regimen. The twenty first World Health Organization (WHO) report on the worldwide incidence of TB indicates that TB remains a global emergency. It estimates that There were 1.4 million TB deaths in 2015, and an additional 0.4 million deaths resulting from TB disease among people living with HIV. In 2015, there were an estimated 480 000 new cases of multidrug-resistant TB (MDR-TB) and an additional 100 000 people with rifampicin-resistant TB (RR-TB) who were also newly eligible for MDR-TB treatment. India, China and the Russian Federation accounted for 45% of the combined total of 580 000 cases[1].

The increase in the number of cases of TB has been associated with the infection of humans with HIV, in addition to the appearance and development of TB-resistant drugs, both multidrug-resistant (MDR), as well as extremely drug-resistant (XDR). Drug-resistant TB is caused by non-compliance with the treatment period, by prescription of an inadequate treatment regimen, by administration of inadequate drugs, *etc.* Multidrug-resistant MDR-TB is a potentially deadly disease caused by the bacilli of isoniazid (INH)-resistant TB and rifampicin (RIF)-resistant TB. Treatment for MDR-TB requires the use of at least three antibiotics, generally a combination of first- and second-line antibiotics; XDR-TB presents when, in addition to first line-drug resistance, resistance to second-line drugs is present, rendering treatment of these patients very complicated. Unfortunately, the success of curing cases of MDR-TB and XDR-TB is very low[3]. New TB drugs have begun to emerge from the pipeline, and combination regimens that include new compounds are being tested in clinical trials. Currently, two new anti-TB drugs were approved by the US Food and Drug Administration and by the European Medicines Agency: bedaquiline and delamanid[4,5]. SQ109, a 1,2-ethylenediamine, is an analogue of ethambutol is presently undergoing phase II clinical trials[6]. According to the WHO, it is estimated that by 2050, drugs and vaccines in various phases of clinical trials would help to eradicate TB. From new sources, by characterizing more antimycobacterial compounds in preclinical and clinical trials, the resistant form of bacilli emerging during the eradication programme can also be eliminated.

Control strategies to prevent further spread of the disease include prompt detection, treatment and prophylactic vaccination. The only vaccine currently available against TB is Mycobacterium bovis bacille Calmett Guerin (BCG), which has been used safely for decades, but is not effective against pulmonary TB in tropical countries, and is contraindicated in people infected with HIV[7]. There are

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13 TB vaccines in Phase I, Phase II or Phase III trials. TB is exceptional among bacterial infections in that even drug-susceptible strains are difficult to treat rapidly and effectively. This challenge is, in part, because of the phenomenon of MTB persistence, a state of phenotypic drug tolerance that is attributed to a quiescent or non-

Table 1: List of spices evaluated for anti-mycobacterial activity.

S. No.	Spice	Parts used: Extract/active constituent	Mycobacterium species	Activity	Reference
1.	*Allium sativum* (garlic)	Ethanolic extract	*M. tuberculosis*	Inhibitiory effect against MDR isolates at a concentration ranged from 1 to 3 mg/ml	30
		Bulb: Methanol extract	*M. avium* *M. smegmatis*	In micro dilution assay, the extract exhibited MIC of >500 µg/ml	31
		Bulb: Aqueous extract	*M. tuberculosis*	MIC values observed for the complete inhibition of $H_{37}R_V$(susceptible strain) and $MTTRCC_{1193}$(resistant to isoniazid) were 160 and 200 µg/ml respectively in tube dilution test	32
		Leaf: aqueous extract	*M. tuberculosis*	MIC at 1:640 in broth dilution assay	33
2.	*Piper longum* (Long Pepper)	Fruits: Ethanolic extract and piperine	*M. tuberculosis*	inhibition of growth of H37Rv strain at 100µg/ml as compared with rifampicin (1µg/ml) in REMA	23
3.	*Curcuma longa* (Turmeric)	Root: DCM extract/ Curcuminoids	(i)*M. smegmatis* (ii)*M. simiae* (iii)*M. kansasii* (iv)*M. terrae* (v)*M. szulgai*	The growth of these mycobacterial strains was inhibited at a concentration of: (i) 512 µg/ ml (ii) 512 µg/ ml (iii) 128 µg/ ml (iv) 512 µg/ ml (v) 256 µg/ ml	34
		Leaf: Aqueous extract	*M. tuberculosis*	Active in broth dilution assay at MIC<1:40 dilution	33
		Leaf: Ethanol (95%) extract	*M. tuberculosis*	In tube dilution test, the activity was found against strain $H_{37}R_V$(human) at 1:80 dilution	35
		Root: Ethyl acetate extract	*M. smegmatis*	At a concentration of 115mg/ml, the turmeric root powder extract shows antimycobacterial activity	36
4.	*Juniperus excelsa* (Juniper)	Flower (i) Hexane extract (ii) Methanol extract and isolated diterpenes (iii) Juniperexelsic acid (iv) Sandracopim-aric acid (v) Sclareol	*M. tuberculosis*	MIC (µg/ml): (i) 15.5 (ii) 17.0 (iii) 14.4 (iv) 15.0 (v) 6.0 In micro broth dilution assay.	21

		Leaf: Ethanolic extract (i) Ferruginol (ii) Sandaracopi-meric acid (iii) Hinokinol (iv) 3-β hydroxyl sandaracopimeric acid	*M. smegmatis*, *M. intracellulare* *M. chelonae* *M. xenopi*	MIC (µg/ml): (i) 5 (against each species) (ii) 32 (tested only against *M. smegmatis*) (iii) Inactive (only tested against *M. smegmatis*) (iv) Not tested	37
5.	*Foeniculum vulgare* (Fennel)	(i) linoleic acid, (ii) oleic acid, (iii) 1,3-benzenediol, (iv) undecanal, (v) 2,4-undecadienal	*M. tuberculosis* (MDR strains)	MIC in Alamar blue microassay was found to be (i) 100 µg/mL (ii) 100 µg/mL (iii) 100-200 µg/mL (iv) 50-200 µg/mL (v) 25-50 µg/mL	38
6.	*Trigonella foenum-graecum* (Fenugreek)	Seed: Protein fraction	*M. rhodochrous*	Active	39
7.	*Mentha spicata* and *Mentha piperita* (Mentha)	Ethanolic Extracts	*M.bovis*	0.39 mg/ml consistency of *M. spicata* and 100 mg/ml consistency of *M. piperita* were the least concentrations which inhibit M. bovis's growth	40
8.	*Papaver macrostomum*(Poppy seeds)	Aerial: Ethanolic extract	*M. tuberculosis*	At the concentration of >100µg/ml, 12% inhibition was observed.	41
9.	*Crocus sativus* (Saffron)	Aerial parts: Hexane, Chloroform, Ethyl acetate, Methanol and Water	*M. semegmatis* *M. tuberculosis*	Hexane extract and methanolic extract were the most active extracts producing zone of inhibition of 22 and 20 mm. respectively against both the strains. Aqueous extract of plants showed least activity by disc diffusion assay.	42
10.	*Alpinia galangal* (Galangal)	Rhizome: Ethanolic extract	*M. tuberculosis*	MIC was found to be 250µg/ml by broth microdilution method.	23
11.	*Satureja boissieri Hausskn* (Savory)	Aerial parts: chloroform (CL), Ethyl acetate (EA) and Methanol	*M. tuberculosis H37Ra*, *M. tuberculosis H37Rv* and two-positive *M. tuberculosis* clinical isolates	MIC value of CL extract was found to be 400 µg/mL against *M. tuberculosis H37Ra* strain by Microplate Alamar Blue Assay (MABA) method	43
12.	*Alium ascalonicum* (Shallot)	Bulbs: water extract that is mixed with ethyl acetate 3 times and then dissolved in methanol	*M. tuberculosis*	MIC was found to be 500µg/ml by E test.	44
13.	*Cuminum cynimum* (Cumin)	Seed oil	*M. tuberculosis* H37Rv (Isoniazid resistant)	The MIC value was found out to be 12.5µg/ml by agar disc diffusion method.	45
14.	*Cinnamomum verium* (Cinnamon)	Bark oil	*M. tuberculosis* H37Rv (Isoniazid resistant)	The MIC value was found out to be 12.5µg/ml by agar disc diffusion method.	45

15.	*Brassica nigra* (Mustard)	Leaf, Flower: aqueous extract	*M. tuberculosis*	Leaf and flower extracts were active in broth dilution assay at MIC <1:40 dilution.	46
		Ethanol (95%) extract	*M. tuberculosis* $H_{37}Rv$	Extract exhibited activity against strain (human) at 1:40 in tube dilution test.	47
		Seeds: Ethanol extract	*M. tuberculosis*	At a concentration of >100µg/ml, there was 0% inhibition.	41
16.	*Myristica fragrans* (Nutmeg)	Leaf: Aqueous extract	*M. tuberculosis*	Active in broth dilution assay at MIC <1:20 dilution	46
17.	*Pimpinella anisum* (Aniseed)	Seed: oil p-anisaldehyde	*M. tuberculosis* H37Rv (Isoniazid resistant)	The MIC value was found out to be 4.1 µg/ml	45
18.	Anethum graveolans (Dill)	Furanocoumarin, 5-[4"-hydroxy-3"-methyl-2"-butenyloxy]-6,7-furocoumarin, falcarindiol	*M. tuberculosis*	MIC observed for all the compounds ranged between 2-128 µg/ml	48
19.	*Syzygium aromaticum* (Clove)	Ethanolic extract	*M. tuberculosis* H37Ra	MIC observed was 200µg/ml	49
20.	*Zingiber officinale* (Ginger)	Rhizome	*M. abscessus and M. fortuitum*	MIC observed was 6025 µg/ml using agar dilution method	50
21.	*Salvia* species (Sage)	S.africana careulea, S.africana lutea, S.albicaulis, S.aurita, S.chamelaeagnea, S.disermas, S.dolomitica, S.garipensis, S.lanceolata, S.muirii, S.radula, S.repens, S.runcinata, S.schlechteri, S.stenophylla, S.verbenaca, carnosol, oleanolic acid, ursolic acid	*M. tuberculosis* H37Ra	Of the spices tested,11 have MIC values of 0.50mg/ml,while the MIC values of three spices are 0.10 mg/ml. Species such as S.verbenaca,S.radula and S.dolomitica displayed good antimycobacterial activity(MIC : 0.10mg/ml) also exhibited good antibacterial activity.	37
22.	*Glycyrrhiza glabra* (Liqorice)	Roots: Ethyl acetate column fraction, Glabridin	*M. tuberculosis* H37Ra and *M. tuberculosis* H37Rv	MIC observed between 29 to 118 µg/ml in BACTEC assay	51
23.	*Origanum onites* (Oregano)	Aerial parts: Methanolic extract	*M. tuberculosis* H37Rv	MIC obtained was 784µg/ml by MGIT fluorometric manual method	52
24.	*Cymbopogon citratus* (Lemon grass)	Essential oil	*M. smegmatis*	Active in agar plate assay	53

replicating population of bacilli[8]. Long treatment regimens make compliance problematic and lead to the emergence of drug resistant mutants. This situation demands development of new drugs that provide shorter treatment regimens than those currently available with existing drugs and that can overcome the increasing emergence of drug resistant strains.

Plant-based drugs have been used worldwide in traditional medicines for the treatment of various diseases. Approximately 60% of world's populations still rely on medicinal plants for their primary healthcare. According to a survey by NCI, USA, 61% of the 877 small-molecule new chemical entities introduced as drugs worldwide during 1981–2002 were inspired by natural products[9].

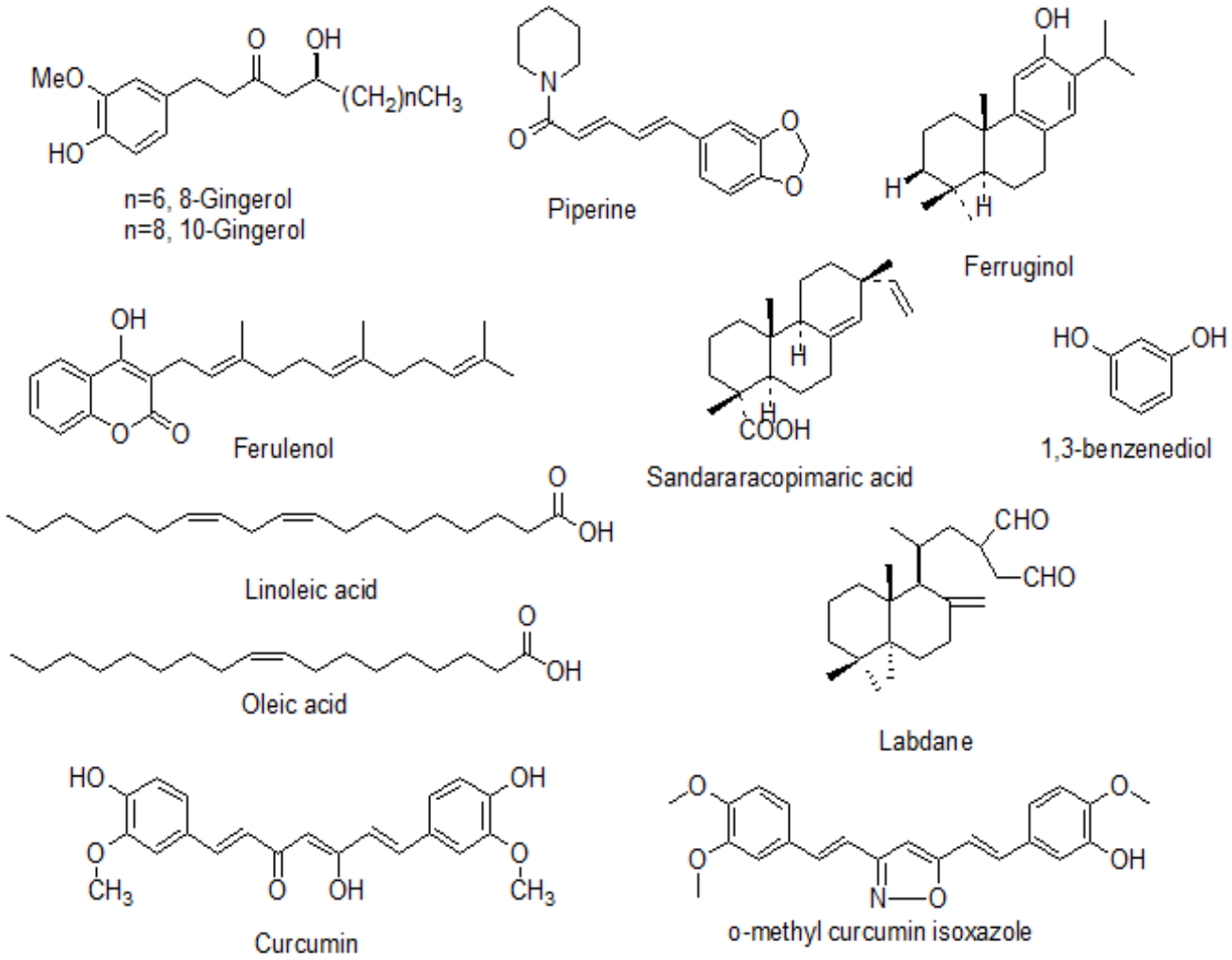

Figure 1: Chemical Structures of various phytoconstituents isolated from spices with antimycobacterial activity.

Natural products are a proven template for the development of new scaffolds for drug; and have received considerable attention as potential anti-TB agents[10]. Natural products are chemical compounds or substance produced by a living organism or found in nature that has pharmacological or biological activity[11]. Various natural compounds like alkaloids, flavonoids, terpenoids, etc., present in balanced diets orchestrate like a multidrug regimen and can maintain a healthy population. The scientific communities have given more attention towards the potential antimicrobial activities of natural products. Natural antimicrobials seems to be the most promising answer to many of the increasing concerns regarding antibiotic resistance and could yield better results than antimicrobials from combinatorial chemistry and other synthetic procedures[12].

India represented by rich culture, traditions, and natural biodiversity, offer unique opportunity for the drug discovery researchers. In ancient India, natural herbs and spices were consumed either in food, or used as medicine in order to maintain proper sanitation, health and hygiene, and to increase longevity of life[13]. There are several advantages for the use of spices (that derived from plant origins) as dietary supplement or alternative medicine manifested by reduction in the chance for developing antibiotic resistant bacteria that resulted from the frequent use of antibiotics (misuse, abuse) besides decreasing the cost of treatment (drug administration) & also minimizes the development of adverse drug reactions.

The present review article describes the Indian spices that have been screened for anti-mycobacterial activity along with their active component.

METHODS

The different literature database search provided a total number of 54 Indian spices in various forms as power/leaf/bark/stem. Out of which 24 spices which showed anti-mycobacterial activity are enumerated in table format describing plant species and common name, plant part used, type of extract and in vitro activity (MIC values), information on active compounds, if any with cross references.

Spices as Natural Antimycobacterials

Natural products are an important source of antimycobacterial compounds for leads of new drugs. In the past decade there has been renewed attention and interest in the use of traditional medicine globally. In India, 65% of the population in rural areas uses traditional medicine to help meet their primary health care needs. Plant species still serves as a rich source of many novel

biologically active compounds, as very few plant species have been thoroughly investigated for their medicinal properties[14,15]. Thus, there is renewing interest in phytomedicine during last decade and now days many medicinal plant species are being screened for pharmacological activities[16,17].

Spices and herbs have been used for many centuries by various cultures to enhance the flavor and aroma of our foods as our ancestors have recognized the usage of spices in food preservation and in treatment of clinical ailments. There are several reports on development of antibiotic resistance in diverse bacterial pathogens[18]. This shift in susceptibility of pathogens to antibiotics has adversely affected its ability to successfully treat patients and therefore shifted their attention towards herbal products. At present, it has been estimated that about 80% of the world population rely on botanical preparations as medicine to meet the needs as they are considered safe and effective against certain ailments[19]. Besides, spices are known for their unique aroma and flavor derived from compounds known as phytochemicals or secondary metabolites [20]. these are antimicrobial substances that are capable of attracting benefits and repel harmful microorganisms. The antimicrobial effectiveness of mustard, clove, cinnamon and their essential oils were reported for the first time around 1880's. Antimicrobial effectiveness of spices depend on the kind of spice, its composition and concentration, type and concentrations of the target microorganism, substrate composition, and processing and food storage conditions. Antimycobacterial potential of different spices has been studied extensively. (Table 1)

Examples of the spices which appear to be among the most active include *Allium sativum* (Fam. Liliaceae), *Foeiniculum vulgare* (Fam. Apiaceae), *Curcuma longa* (Fam. Zingiberaceae) *Juniperus excelsa* (Fam. Cupressaceae), *Trachyspermum ammi* (Fam. Apiaceae), *Piper longum*, *Piper nigrum* (Fam. Piperaceae) and *Nigella sativa* (Fam. Ranunculaceae). In some cases, compounds have been isolated which have antimycobacterial activities, for example 5-hydroxy furanocoumarin has been isolated from *Foeiniculum vulgare* and Ferruginol, Sandaracopimeric acid, Hinokinol, 3-β hydroxyl sandaracopimeric acid were isolated from ethanol extract of *Juniperus excels*[21]. Semi purified fractions of *Crocus sativus* (Saffron) were found to inhibit the growth of clinically isolated MDR strains of *Mycobacterium*[22]. (Fig. 1)

Deepthi et al has also reported better antimycobacterial activity of piperine isolated from *Piper longum*[23]. Piperine, a trans-trans isomer of 1-piperonyl-piperidine, is an antimycobacterial agent which at 128µg/mL completely inhibits the efflux pump of *M. smegmatis* mc2[24]. This compound is commonly found in plants belonging to the family Piperaceae (*Piper nigrum*). *Curcuma amada* Roxb., Zingiberaceae, used in Ayurveda and Unani systems of medicine in the Indian subcontinent, is effective against various respiratory disorders. From its chloroform extract a diterpene dialdehyde, labdane, exhibited much less antimycobacterial activity (500 µg/mL), but two semisynthetic analogues, diol and dioxime, had MICs of 250 and 500 µg/mL, respectively[25]. Linoleic acid, oleic acid, and other organic compounds such as 1,3-benzenediol, undecanal, and 2,4- undecadienal from the isolates of *Foeniculum vulgare* Mill., Apiaceae, had activity against MDR forms[26]. Curcuminoids form the major constituents in the plant *Curcuma longa* L., Zingiberaceae. The curcuminoid constituents were structurally modified to 55 analogs and the antimycobacterial activity of each compound was evaluated. An isoxazole analog, mono-O-methylcurcumin isoxazole, showed potent activity against sensitive and MDR clinical isolates. The activity was found to be 1131-fold more than the parent compound curcumin[27]. (Fig. 1)

Investigations on ginger rhizome (*Zinziber officinale*) afforded three gingerol analogs, 6-gingerol, 8-gingerol and 10-gingerol. The lipophilic analogs 8-gingerol and 10-gingerol were found to be more active, with MIC values of 25-50 µg/mL towards *M. tuberculosis* H37Rv[28]. The rhizomes of *Ferula communis* yielded a range of antibacterial phenolic functionalized antibiotics including ferulenol and ferchromone. While ferulenol exhibited strong growth inhibitory activity towards a range of mycobacteria including *M. cellulare*, *M. xenopi*, *M. chelonei* and *M. smegmatis* with an MIC of 1.25µg/mL, ferochromone was found to be less active with an MIC of 50µg/mL against the same range of bacteria[29]. Extracts of *Juniperus excelsa* are used in Saudi Arabia, yemen and Oman as a traditional remedy for tuberculosis and jaundice. Bioassay guided fractionation of an extract of the leaves showed the diterpenes ferruginol and sandararacopimaric acid to be antimycobacterial constituents.

CONCLUSION

Plant product drugs and herbal remedies have been employed since prehistoric times to treat human and animal diseases and several countries still rely on plants and herbs as the main source of drugs. With the increasing awareness of people towards natural food and natural therapies, spices might act as the most obvious alternative. In developing countries like India, where spices are produced and used as food additives, their use as antimycobacterial agents can be extremely useful. This review illustrates that extracts of spices 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. These finding may help the scientist to take up new projects in search of new antimycobacterial compound.

CONFLICTS OF INTEREST

All authors have none to declare.

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