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Antimycobacterial activity of plant compounds against extensively drug resistant (XDR-TB) *Mycobacterium tuberculosis*

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ABSTRACT

Emergence of multidrug resistant strains of *Mycobacterium tuberculosis* is globally threatening the world and creating problems for the management of tuberculosis (TB). Traditional medicine and plant secondary metabolites are playing an important role in medicine; they are also useful for developing drugs for the treatment of tuberculosis. The present study was carried out to evaluate *in vitro* anti-tubercular activity of nine isolated plant compounds (Costunolide, Eremanthine, Chrysophanol, Friedeline, Plumbagin, Lupeol, Bergenin, karanjin and Flindersine) against *M. tuberculosis* $H_{37}Rv$ and *M. tuberculosis* XDR-1 (extensively drug resistant). The antimycobacterial activity of the nine natural compounds was evaluated by broth dilution method against $H_{37}Rv$ and XDR-1strains of *M. tuberculosis*. The concentrations employed were in the range of 0.5—64.0 μg/ml. Rifampicin was used as the standard control. MIC values of all the compounds were evaluated by using dose response curve. The results showed that out of the nine compounds tested Eremanthine, chrysophanol and karanjin showed the lowest MIC value of 08 μg/ml while Costunolide, Friedeline and plumbagin showed MIC value of 16 μg/ml against $H_{37}Rv$ strain. Lupeol showed MIC value of 32.0 μg/ml while Bergenin and flindersine showed MIC value of $>$ 64.0 μg/ml. However, the tested compounds showed lesser activity against XDR-1 strain; the MIC values were in the range of 16.0 to 32.0 μg/ml. In this communication, the anti-TB activity of nine natural compounds have been reported against standard $H_{37}Rv$ strain and XDR-1 strain. The tested compounds showed appreciable activity against the standard $H_{37}Rv$ strain (MIC, 8.0 to 32.0 μg/ml). The compounds showed lesser activity towards the XDR-1 strain. Further work may be carried out on derivatives of these compounds which may lead to more potent compounds with lower toxicity.

1. Introduction

Tuberculosis (TB) is a highly infectious disease; this has been announced by the World Health Organization (WHO) as global health emergency. Worldwide, tuberculosis prevalence is very high. Nearly, one third of the world's countries is affected by *Mycobacterium tuberculosis*. Development of drug resistant strain of *M. tuberculosis* is threatening the developing countries. Pathogenic microbes are developing resistance to currently used antibiotics; this has initiated search for new drugs with potential for the management of tuberculosis.

Extensively resistant *M. tuberculosis* (Mtb) is resistant to first-line and second-line antimycobacterial drugs. In addition, currently used second-line drugs such as kanamycin, capreomycin and ethionamide used to treat MDR/XDR-TB have some safety concerns with only half percentage of cure rate (50 %) (Kumar et al., 2021). Treating MDR/XDR TB is very challenging for the researcher (Singh et al., 2023).

In India, drug resistance patterns vary widely across different parts of the country. The data on drug resistance in new cases has been variously

Abbreviations: XDR, Extensively drug resistant; MIC, Minimum inhibitory concentration; TB, Tuberculosis; WHO, World Health Organization; Mtb, *Mycobacterium tuberculosis*; MDR, Multi drug resistant; DMSO, Dimethyl sulfoxide; ADC, (bovine albumin fraction V, dextrose, catalase.

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estimated by different investigators (Paramasivan et al., 2004). An increase in the incidence of multiple-drug-resistant strains of mycobacteria has underscored the need to rapidly identify new drugs for chemotherapy.

To overcome the danger of tuberculosis, it is necessary to come up with drugs of natural origin with less side effects (Fei Huang et al., 2022). Worldwide, researchers have reported that plant molecules act as antimycobacterial agents.

India is one of the mega biodiversity centers for plants. Since ancient times, crude plant extracts, herbal drugs and traditional medicine were widely consumed by the people for the management of different ailments such as bacterial infections and viral diseases; they were also used as antioxidants. Worldwide, researchers have reported many plant molecules as potentially useful against the M. *tuberculosis* H37Rv, and multi drug resistant *M. tuberculosis*. Natural products from plant sources are very useful and play a crucial role in the development of new antimycobacterial agents. Secondary metabolites isolated from traditional medicinal plants have been explored for their biological properties against TB pathogens; they significantly decreased the growth of microbes. The traditionally used medicinal plants such as leaves of *Lantana camara*, stem bark of *Zanthoxylum leprieurii* and roots of *Cryptolepis sanguinolenta* were tested against rifampicin-resistant *Mycobacterium tunerculosis* and *M. smegmatis*. The results showed that those plant extracts significantly inhibited the tested bacteria at a low concentration of 45 µg/ml (Tuyiringire et al., 2022). Earlier reporst showed that aqueous extract of ten Namibian traditionally used medicinal plants' crude extracts exhibited significant antimycobacterial activity against *Mycobacterium tuberculosis* H37Rv-GFP strain with lowest MIC ranging from 9.9 to 86.8 µg/mL (Raidron et al., 2022).

From traditional medicinal plants, 350 natural products have been reported to have potential anti- TB activities (Newton et al, 2002). Several plant molecules have been reported for their significant anti-TB properties against TB causing pathogens through *in silico* method by targeting their respective enzymes and protein sites. Many plant compounds such as alkaloids (Miryala et al., 2021), terpenoids (Houghton et al., 1990), and chalcones and flavonoids (Lin et al., 2002) have shown *in vitro* antimycobacterial activity.

There is an urgent need to develop new potential antimycobacterial agents to control resistant *M. tuberculosis*, with low toxicity. The aim of the present study was to evaluate nine plant compounds from traditional medicinal plants for antimycobacterial activities against standard and drug resistant *M. tuberculosis.*

2. Materials and methods

Isolation of Plant compounds

The natural products reported in this communication for which anti-TB activity has been studied, have already been reported from our laboratory: Costunolide (1) (Eliza et al., 2009), Eremanthine (2) (Eliza et al., 2009a), Chrysophanol (3) (Sheeba Rani et al., 2010), Friedeline (4) (Antonisamy et al., 2011), Plumbagin (5)(Sunil et al., 2012), Karanjin (6), Lupeol (7) (Rajiv Gandhi et al., 2016), Bergenin (8) (Karunai Raj et al., 2012), and Flindersine (9) (Duraipandiyan et al.2009) (Fig. 1). Table 1. gives the list of the traditional medicinal plants from which these compounds were isolated and their medicinal properties.

Tested organisms

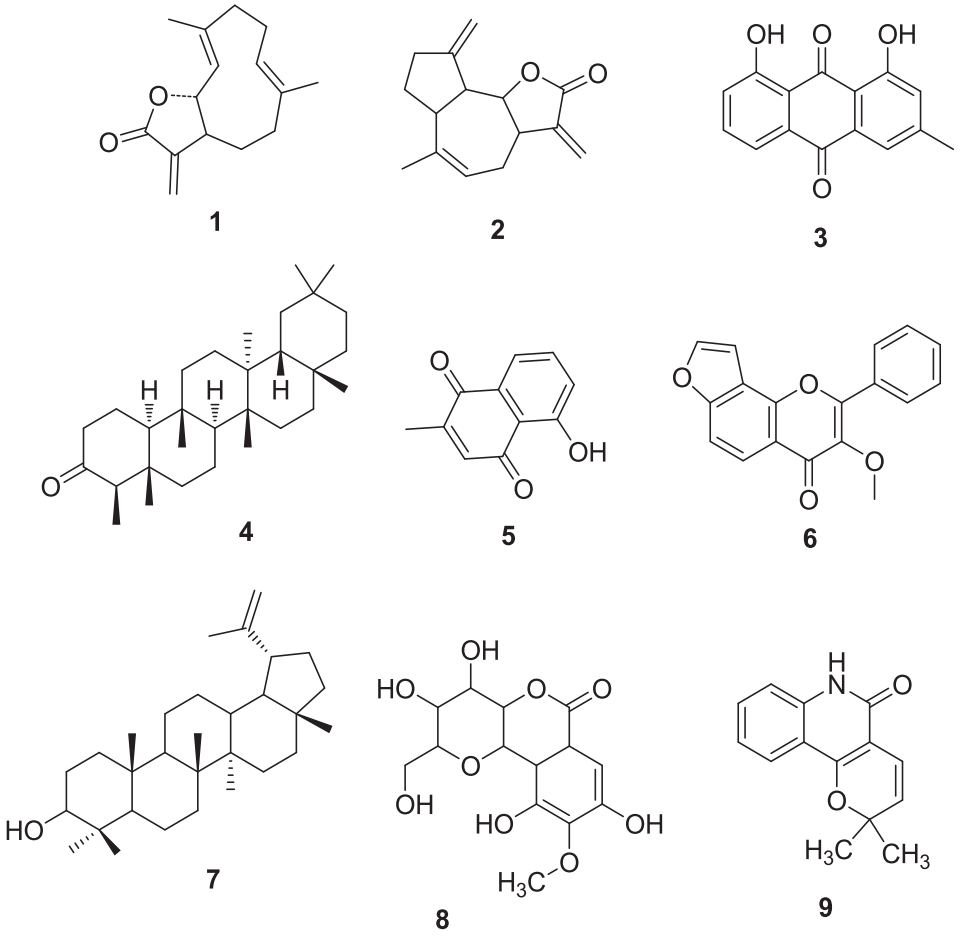

Fig. 1. Tested compounds. Costunolide **(1)**, Eremanthine **(2)**, Chrysophanol **(3)**, Friedeline **(4)**, Plumbagin **(5),** Karanjin **(6)**, Lupeol **(7)**, Bergenin **(8)**,and Flindersine **(9)**.

Table 1
Compounds Isolated from traditional medicinal plants with their medicinal properties.

S. N	Compounds	Botanical source	Medicinal properties
12	Costunolide Eremanthine	*Costus speciosus*	*Rhizome:* used to fever, cough, asthma, leprosy, bronchitis, inflammation, constipation, skin diseases, anthelmintic and other respiratory diseases (Eliza et al., 2009)
3	Chrysophanol	*Cassia occidantalis*	*C. occidentalis*leaves used to skin diseases, heal wounds, fever, throat infection, sores and bone fracture (Sheeba et al., 2010).
4	Frideline	*Azimatetracantha*	Different parts of *A. tetracantha*used to treatment of several ailments; the roots are useful as dyspepsia, diuretic, chronic diarrhoea, rheumatism; stem bark is used to expectorant and astringent; leaves are used for treating Asthma, Ulcer and TB (Antonisamy et al., 2011).
5	Plumbagin	*Plumbago zeylanica*	Plumbagin showed different type of biological properties such as bronchial infection, anti-asthma, anti-tuberculosis, antimicrobial, antimalarial and anticancer and also showing that as insecticidal agent, hyperglycaemic, arteriosclerosis (Tokunaga et al., 2004).
6	Karanjin	*Pongamiapinnata*	An Different parts of *P.pinnata* radiantly used to antioxidant, antimicrobial, ant antilipidperoxidative, antioxidants and antidiabetic and Cough (Fugare et al., 2021).
7	Lupeol	*Aegle marmelos*	This plant has traditional uses are antipyretic,haemostatic, antidiabetic, antidiarrheal, antiscourbuticand antidote against snake venom (Rajiv Gandhi et al.,2016).
8	Bergenin	*Peltophorumpterocarpum*	Bark of *Peltophorum* spp. to treat muscular pain, antimicrobial, sores, dysentery and eye troubles (Karunai Raj et al.2012).
9	Filindersine	*Toddalia asiatica* (L) Lam. (Rutaceae)	This plant traditionally consuming by tribal people for various ailments such as fruits of *T. asiatica* to use for the cough, malaria and root are used to influenza and digestion problem (Duraipandiyan et al., 2011).

The antimycobacterial activities of isolated compounds were evaluated against *M. tuberculosis* sensitive strain H37Rv and *M. tuberculosis* multidrug resistant strain XDR-1. All the compounds were initially screened against the M. *tuberculosis* H37Rv at the concentration of 0.5–64.0 μg/ml.

***Assay of Antimycobacterial activity*.**

The antimycobacterial activity of nine plant compounds was tested against TB causing standard strain of $H_{37}Rv$ (*M. tuberculosis*) and extensively drug resistant XDR-1 strain *M. tuberculosis*. The method of broth microdilution assay was used to determine the minimum inhibitory concentration (MIC) (CLSI, 2008; Maccari et al., 2002; Wallace et al., 2008). The *M. tuberculosis* cultures were grown in sterile Middlebrook 7H9 broth with supplemented 10 % ADC (BD Biosciences, USA). The tested bacteria were grown in mid-log phase at 37 °C (10–12 days), in the incubator. The stock solutions of the tested compounds were prepared at 1 mg/ml in DMSO. From the stock solution, each compound was added to each well so that the final concentrations were 64.0 μg/ml, 32.0, 16.0, 8.0, 4.0, 2.0, 1.0 and 0.5 by double dilution method. The culture turbidity was adjusted to 1 McFarland turbidity standard and further diluted to a 1:10 ratio so that each well contained 1×10^5 cells. Rifampicin was used as reference standard at the concentration of 0.06 and 0.2 for standard H37Rv and XDR strain respectively. Peripheral wells were filled with sterile distilled water to prevent evaporation of media. The plates were incubated for three weeks at temperature of 37 °C under 5 % CO_2. Bacterial growth inhibition was determined both visually and with spectrophotometer at OD_{600nm} (Multiskan spectrum; Thermo Scientific, USA). The lowest concentration at which no growth was observed was taken as MIC value. The experiment on antimycobacterial activity was conducted at the Clinical Microbiology Division, Indian Institute of Integrative Medicine, Jammu, 180 001, India.

3. Results

The search for new antimycobacterial agents from traditional medicinal plants is continuing worldwide since many newly drug resistant *M. tuberculosis*is have emerged. The traditionally used medicinal plants of tribal and local people have many advantages for isolating novel molecules for management of tuberculosis. In the present investigation, anti-TB activities of nine natural products were evaluated against standard *M. tuberculosis* H37Rv and XDR-1 strain by broth micro dilution method. The tested compounds were already reported for different biological properties by us. The *in vitro* test results for these compounds are given in Table 2 as minimum inhibitory concentrations. The activity ranged from 8.0 to > 64.0 μg/ml. Among the compounds tested, most of them displayed potent inhibitory activity with low MIC values against H37Rv and XRD-1 *M. tuberculosis*. The compound Eremanthin (2), Chrysophanol (3) and Karanjin(6) showed the lowest MIC values of 8 μg/ml against standard H37Rv. The above three compounds showed MIC values of 16.0, 32.0 and 32.0 μg/ml respectively against to XDR-1 strain. The compounds Costunolide **(1)**, Friedeline (4), and Plumbagin (5) showed MIC value of 16 μg/ml against standard H37Rv strain; the MIC values of > 64 μg/ml for compounds 1 & 4 and 32.0 μg/ml for plumbagin (5) were recorded. The MIC values against H37Rv strain for lupeol (7), Bergenin (8) and flindersine were 32.0 μg/ml, >64 μg/ml and > 64 μg/ml respectively. Rifampicin showed MIC value of 0.06 μg/ml for standard H37Rv strain and 0.2 μg/ml for XDR-1 strain. Over all, the studies confirmed that the compounds Eremanthin (2),

Table 2
Antimycobacterial activity (MIC) of isolated compounds against *M. tuberculosis.*

S. No	Tested compounds	MIC μg/ml	
		Mycobacterium tuberculosis $H_{37}Rv$	*Mycobacterium tuberculosis* XDR-1
1	Costunolide	16	>32
2	Eremanthine	8	16
3	Chrysophanol	8	32
4	Friedelin	16	>32
5	Plumbagin	16	32
6	Karanjin	8	32
7	Lupeol	32	>32
8	Bergenin	>64	>64
9	Flindersine	>64	>64
10	Rifampicin	0.06	0.2

1–9: Isolated compounds.
10: Rifampicin- Standard antimycobacterial agent.

Chrysophanol (3) and Karanjin (6), significantly inhibited the growth of *M. tuberculosis* at lowest concentration of 8.0 μg/ml. Further studies may be carried out for synthetic derivatives for Eremanthin, Chrysophanol and Karanjin. The above results indicated that some of the tested compounds significantly inhibited the growth of *M. tuberculosis* at lowest concentration; this will be useful to pharmaceutical industry to work further.

4. Discussion

The present study revealed that the traditionally used plant secondary metabolites inhibited the TB causing *M. tuberculosis* significantly. Nine isolated compounds were screened against standard strain $H_{37}Rv$ and XDR-1 strain. The rhizome of *C. speciosus* is widely used in Ayurveda system of medicine to treat bronchitis, asthma, inflammation, and cough (Moosmannand Behl, 2002); from this, two tested compounds Costunolide and Eremanthine were isolated. This indicates that traditionally used medicinal plants possess reliable biological properties.

The compound chrysophanol significantly inhibited the growth of standard strain of *M. tuberculosis* at 08 μg/ml concentration. This compound was isolated from *Cassia occidentalis* leaves. Traditionally, this plant is used for treatment of fever, tuberculosis and liver complaints (Kritikarand Basu, 2009).

The compound Friedeline isolated from *A. tetracantha* leaves inhibited the growth of *Mycobacterium tuberculosis* $H_{37}Rv$ at concentration of 16 μg/ml. This is very low concentration which is useful to develop new antimycobacterial agent.

Phillips et al. (2012), reported that the compound oleanolic acid isolated from Lantana hispida was subjected to antimycobacterial activity. It inhibited the growth of M. tuberculosis H37RV at the concentration of 25 μg/ml. Our compound friedelin inhibited *M. tuberculosis* at low concentration of 16 μg/ml.

Newton et al (2002) reported that when the seed extract of *P. corylifolia* was subjected to bioassay guided fractionation, it yielded bakuchiol and meroterpene; they were tested against *M. tuberculosis.* Previous researchers had reported that *Terminalia phanerophlebia* ethanolic leaf extract at 3.90 μg/mL (Madikizela et al., 2014), and *Zanthoxylum capense* methanolic root extract at 1.6 μg/ml showed activity against M. tuberculosis H37RV (Luo et al., 2013).

Many of the plants used in our study are distributed worldwide; they are also used in traditional medicine. Plant secondary metabolites such as terpenoids, alkaloids, anthraquinones, terpenes, sterols and saponins have been reported by researchers as having moderate to high anti-TB activities (Newton et al.,2000).

Jimenez-Arellanes et al. (2003) studied the anti-TB activity of different polar solvent extracts of 22 medicinal plants against TB causing pathogen *M.* tuberculosis H37Rv and M. avium at different concentrations ranging from 50 to 200 μg/mL.

The present study showed lowest MIC values ranging from 8.0 to 64.0 μg/ml. Active plant compounds can be pursued further for developing a useful antimycobacterial drug.

5. Conclusion

Currently, researchers are trying to produce potential novel antimycobacterial agents from natural sources with low toxicity and less side effects as alternate for the currently used drugs. The present study revealed that the plant molecules isolated from traditionally used medicinal plants can inhibit the growth of standard and drug resistant *M. tuberculosis*. Tested molecules Eremanthine and chrysophanol inhibited the growth of standard strain of *M. tuberculosis* at lowest concentration of 8 μg/ml. Also, the same compounds inhibited the growth of drug resistant *M. tuberculosis* at lowest concentrations with Eremanthin at 16 μg/ml and Chrysophanol at 32 μg/ml. In particular, the compound Eremanthin inhibited the rifampicin drug resistant *M. tuberculosis*. This may help develop novel antimycobacterial agents.

CRediT authorship contribution statement

Veeramuthu Duraipandiyan: . **Savarimuthu Ignacimuthu:** . **Inshad Ali Khan:** Validation, Methodology, Investigation, Formal analysis. **Hissah Abdulrahman Alodaini:** Writing – review & editing, Validation, Funding acquisition, Formal analysis. **Ashraf Atef Hatamleh:** Writing – review & editing, Validation, Software, Investigation, Formal analysis. **Antony Stalin:** .

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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