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Anti-*Mycobacterium tuberculosis* Effects of Folk Medicinal Plants in Iran: A Mini-Systematic Review

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ABSTRACT

The emergence of drug resistance in *Mycobacterium tuberculosis* is a major challenge in tuberculosis treatment and control. In addition, multidrug resistance (MDR) and, more broadly, extensive drug resistance (XDR) have hampered treatment with common antibiotics. Thus, an herbal medicine containing antimicrobial capability can be a good alternative to antituberculosis drugs. In this study, we reviewed the effect of folk herbs in Iran as anti-Mycobacterium tuberculosis drugs. In this systematic analysis, keywords including medicinal plants, *M. tuberculosis* infection, Tuberculosis disease, MTB, essential oils, and extracts were searched in Science Direct, Scopus, PubMed, Ovid, Cochrane, Scientific Information Database (SID), Iran Medex, Iran Doc, Magiran, and Google scholar where articles published from 2000 to 2020 were considered. The results indicated that Iranian native herbs such as *Peganum harmala, Humulus lupulus, Capparis spinosa, Thymus vulgaris, Pulicaria gnaphalodes, Perovskia abrotanoides, Peganum harmala, Punica granatum, Digitalis sp., Citrus lemon, Rosa canina, Berberis vulgaris, Aloe vera, Mentha spp., Hypericum perforatum, Humulus lupulus, Trachyspermum copticum, Pelargonium graveolens, Levisticum officinale,* and *Dracocephalum kotschyi* were all effective antibacterial against mycobacterial infection within 0.5 ug to 200 mg. *Thymus vulgaris* was shown to be the most effective than other antibacterial agents such as Streptomycin, Cycloserin Isoniazid, and Ethambutol (0.5-40 µg/mL). Herbal remedies may be an effective therapeutic option for antibiotic-resistant tuberculosis. Potential adverse effects and antibacterial properties, along with possible synergistic interactions with other plants and drugs, require further studies to clarify.

Keywords: Folk medicinal plants, *Mycobacterium tuberculosis*, Native medicinal plants, Systematic review

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1. Introduction

Mycobacterium tuberculosis (*M. tuberculosis*, Mtb) lives inside human cells and invades them, thereby causing tuberculosis **(1)**. This disease is an ancient illness that is spread in communities by droplets. Tuberculosis has been controlled after discovering antituberculosis drugs such as ethambutol, isoniazid, streptomycin, and rifampin **(2, 3)**. However, with the evolution of drug resistance via diverse mechanisms, such as the development of drug-inactivating enzymes, changes in drug target sites, and the

emergence of isolates with multiple resistance, there has been an upsurge in new cases reported **(4, 5)**. Thus, healthcare systems worldwide confront many challenges in managing and treating these infections. According to statistics from 2010, 650000 instances of multidrug-resistant TB (MDR) were documented as attributable to *M. tuberculosis* **(6)**.

Many plants are used in traditional medicine worldwide to treat bacterial infections **(7)**. Recent research has aimed to identify herbal medicines that are simpler to obtain, have fewer adverse effects, and are less expensive to be used in conjunction with synthetic pharmaceuticals. Because of their secondary components, herbal medicines have proved to be an effective source of therapy for controlling and treating bacterial infections **(8, 9)**. In Iran, the use of traditional medicinal remedies for the treatment of infections has been widespread since ancient times. Our objective in this review is to summarize the research being done on Iranian medicinal plants as a way to tackle TB infection.

2. Materials and Methods

According to the Preferred Systematic Review Reporting (PRISMA) guidelines, relevant data were retrieved from papers in October 2021 by two authors. This systematic review was conducted by evaluating papers published in both English and Persian. Several databases, including Science Direct, Scopus, PubMed, Ovid, Cochrane, Scientific Information Database (SID), Iran Medex, Iran Doc, and Magiran, were searched using relevant keywords for papers published between 2000 and 2020. The following keywords were used to describe the study: medicinal plants, *M. tuberculosis* infection, tuberculosis, MTB, essential oils, and extracts. Two authors read the literature and then combined their findings in consultation and collaboration.

Criteria Consideration

Inclusion Criteria

The following criteria were used to select the published articles for inclusion in the discussion: studies describing the effect of Iranian native medicinal plants on *M. tuberculosis* in their entirety, including the full text of the studies written in Persian and English, studies published in reputable journals, studies with clear information, and those that only demonstrated the effect of Iranian native medicinal plants on *M. tuberculosis*.

Exclusion Criteria

Exclusion criteria included studies with no available full text, case report studies, case series, systematic reviews, abstracts of papers presented at seminars and conferences, and studies with insufficient evidence for analysis (Figure 1).

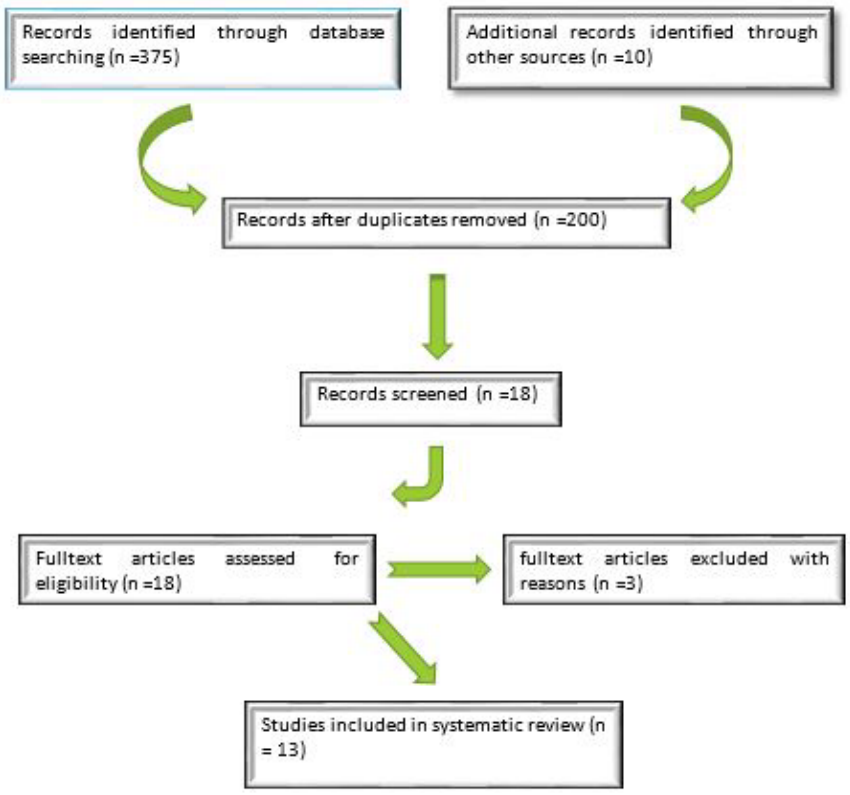

Figure 1. PRISMA graph of data retrieved from various databases based on inclusion and exclusion criteria

Data Extraction

The required information was extracted from articles, including plant name and its family, concentration, positive control dose, and treatment period by two researchers and then merged with consultation as well as consensus.

3. Results

Selected studies

Data details, including their herbal family, used organs of the plants, and place of occurrence, are reported in Table 1. According to these results, 13 medicinal plants were detected with anti-*M. tuberculosis* effects in Iran include *Peganum harmala, Humulus lupulus, Capparis spinosa, Thymus vulgaris, Pulicaria gnaphalodes, Perovskia abrotanoides, Peganum harmala, Punica granatum, Digitalis sp., Citrus lemon, Rosa canina, Berberis vulgaris, Aloe vera, mint, Hypericum perforatum, Humulus lupulus, Trachyspermum copticum, Pelargonium graveolens,* and *Levisticum officinale Dracocephalum kotschyi*.

Table1. List of medicinal plants affecting *Mycobacterium tuberculosis*

Scientific name	Herbal family	Organ	Native	Zone(mm)	MIC	Ref
Peganum harmala	Nitrariaceae	Root and seed	North of Iran	18.7±3.5	-	(10)
Humulus lupulus	Cannabaceae	stems, leaves and roots	Iran	-	4 and 8 mg/mL	(11)
Capparis spinosa	Caper bush	fruit	Iran	-	25 mg/mL	(12)
Thymus vulgaris	Lamiaceae	oil	Tehran, Iran	-	0.5-40 µg/mL	(13)
Pulicaria gnaphalodes	sunflower	oil	Iran	-	640 µg/mL	(14)
Perovskia abrotanoides	Salvia	oil	Iran	-	640 µg/mL	(14)
Peganum harmala	Nitrariaceae	seed	North of Iran	18.7	50 mg/mL	(15)
Punica granatum	Lythraceae	peel	North of Iran	18.8	25 mg/mL	(15)
Digitalis sp.	Plantaginaceae	leaf	North of Iran	12.5	100mg/mL	(15)
Citrus lemon	Rutaceae	fruit	North of Iran	12.5	200mg/mL	(15)
Rosa canina	Rosaceae	fruit	North of Iran	0	0	(15)
Berberis vulgaris	Berberidaceae	fruit	North of Iran	0	0	(15)
Aloe vera	Asphodelaceae	leaves,	Iran	60	-	(16)
mint	Lamiaceae	leaves	Iran	0	-	(16)
Hypericum perforatum	Hypericaceae	leaves	Iran	41	-	(16)
Humulus lupulus	Cannabaceae	Petals	Iran	-	15.7 µg/mL(Aqueous) 31.2 µg/mL(ethanol)	(17)
Trachyspermum copticum	Apiaceae	oils	Iran	-	19.5 µg/mL	(18)
Pelargonium graveolens	Pelargonium graveolens	oils	Iran	-	78 µg/mL	(18)
Levisticum officinale	Apiaceae	roots	Iran	-	32 and 64 µg/mL	(19)
Dracocephalum kotschyi	Lamiaceae	leaves	Iran	-	640 µg/mL	(20)

***Peganum harmala*:** Based on the results of the antimicrobial and antioxidant properties of Davoodi *et al.* and Jahanpour *et al.* studies, it was found that *Peganum harmala* leaves and seeds have potential as complementary medicine for the treatment of *M. tuberculosis*, even against resistant strains **(10, 15)**.

Humulus lupulus: Serkani *et al*. described the antimicrobial effect of stems, leaves, and roots of *Humulus lupulus* on rifampin-sensitive and resistant isolates of *M. tuberculosis* in different concentrations of hop ethanol extract (4 and 8 mg/mL) **(11)**. In Rafiee *et al.* study, the MIC levels of aqueous and ethanol extracts of *Humulus lupulus* were reported as 7.8 µg/mL and 15.7 µg/mL, respectively. The amount of MBC was 15.7 µg/mL and 31.2 µg/mL, respectively. Therefore, the results indicated strong antimicrobial activity of aqueous and ethanolic extracts of *Humulus lupulus* against *M. tuberculosis* **(17)**.

Capparis spinosa: In the study of Ehsanifar *et al.*, the antimycobacterial effect of the methanolic extract of the *Capparis spinosa* at a concentration of 25 mg/mL was reported in clinical isolates sensitive to rifampin **(12)**.

Thymus vulgaris: Pourazar Dizaji reported the MIC values of isoniazid, ethambutol, streptomycin, and cycloserine less than 10 µg/mL and MIC values for rifampicin and kanamycin 40 µg/mL. In addition, they reported MIC of *Thymus vulgaris* essential oil between 0.5 and 40 µg/mL (P<0.05). Therefore, they showed that thyme essential oil has antibacterial activity against *M. tuberculosis* **(13)**.

Pulicaria gnaphalodes: The results of Hozoorbakhsh *et al.* showed that the essential oil extract of *P. gnaphalodes* has strong inhibitory effects on MTB up to about (70.9%) **(14)**. In Jahanpour *et al.* study, the ethanol extract of Punica granatum bark showed an average inhibition zone of 18.8 mm at a concentration of 200 mg/mL against *M. tuberculosis* isolates, while the average inhibition zone around isoniazid and rifampin was 19.2 and 18.8 mm. The results indicated a potential activity against *M. tuberculosis* isolates **(15)**.

Perovskia abrotanoides: The results of Hozoorbakhsh *et al.* showed that the essential oil extract of *Perovskia abrotanoides* has strong inhibitory effects on *M. tuberculosis* up to about (86%) **(14)**.

Digitalis sp: In Jahanpour *et al.* study, the Ethanol extract of Digitalis sp. has a mild antimycobacterial effect at concentrations of 200 and 100 mg/mL showed that in this study, isoniazid and rifampin antibiotics inhibited non-MDR *M. tuberculosis* isolates, so the results indicate the potential efficacy of *Digitalis sp* ethanolic extract against *M. tuberculosis* **(15)**.

Citrus lemon: The results of the Jahanpour *et al.* study showed that the ethanolic extract of *Citrus lemon* could prevent the growth of non-MDR *M. tuberculosis* in concentrations of 200 and 25 mg/mL **(15)**.

Rosa canina* and *Berberis vulgaris: In investigating the antimicrobial activity of *Berberis vulgaris* and *Rosa canina* fruit extracts, it was found that the extracts of these fruits do not have antimicrobial activity against *M. tuberculosis* isolates **(15)**.

Aloe vera: In investigating the antimicrobial properties of *A. vera* against *M. tuberculosis* isolates by disc diffusion method, the inhibition zones of *A. vera* extract of 60 mm were reported. Also, based on the results, 50% of the cells were killed in 24 hours and 20% in 10 minutes when exposed to Aqueous *A. vera* extract **(16)**.

Mint: Antimicrobial effects of mint on *M. tuberculosis* isolates showed that the zone of inhibition of mint extract was 0 mm, also, the time to kill 95% of cells in contact with the aqueous extract of mint was reported for a week **(16)**.

Hypericum perforatum: In a study, the inhibition zones of the aqueous extract of *Hypericum perforatum* against *M. tuberculosis* were reported 41 mm. 50% of the cells were killed in 24 hours and 20% in 10 minutes when exposed to Aqueous *Hypericum perforatum* **(16)**.

Trachyspermum copticum: In Kardan *et al.*, study the MIC values for *Trachyspermum copticum* against *M. tuberculosis* isolates were from 19.5 µg/mL to 78 µg/mL **(18)**. Therefore, the antimicrobial properties of *Trachyspermum copticum* against *M. tuberculosis* were reported.

Pelargonium graveolens: In Kardan *et al.* study, the MIC values for *Pelargonium graveolens* against *M. tuberculosis* isolates was 78 µg/mL **(18)**. As a result, this essential oil was effective against *M. tuberculosis isolates.*

Levisticum officinale: Monsefesfahani *et al.*'s study of phytochemical isolation of *Levisticum officinale* extract and investigation of their antimicrobial properties showed that Falcarindiol and oxypeucedanin have moderate antimicrobial activity against MDR *M. tuberculosis* with MIC values = 32 and 64 µg/mL **(19)**.

Dracocephalum kotschyi: In the study, it was found that the methanolic extract of *Dracocephalum kotschyi* at a concentration of 640 µg/mL was significantly effective against *M. tuberculosis* sensitive and resistant to isoniazid **(20)**.

4. Discussion

The emergence of multidrug-resistant *M. tuberculosis* (MDR) and extended drug-resistant *M. tuberculosis* (XDR) are the most important challenges in TB control. The mechanisms of drug resistance are attributed to the inappropriate use of anti-TB drugs.

Thus, the long-standing prevalence of TB in various communities and the lack of novel drugs that may be used to treat it has exacerbated concerns. In this regard, scientists worldwide attempt to create new treatments that might eliminate TB. According to the findings, herbal medicines are sought for development as alternative pharmaceuticals to manage TB cases since they are less costly and have fewer adverse effects than chemical drugs. *Peganum harmala, Humulus lupulus, Capparis spinosa, Thymus vulgaris, Pulicaria gnaphalodes, Perovskia abrotanoides, Peganum harmala, Punica granatum, Digitalis sp., Citrus lemon, Rosa canina, Berberis vulgaris, Aloe vera, Mentha spp., Hypericum perforatum, Humulus lupulus, Trachyspermum copticum, Pelargonium graveolens,* and *Levisticum officinale Dracocephalum kotschyi* have been reported as Iranian native plants affecting tuberculosis infection. *Humulus lupulus* was effective against susceptible and resistant Mycobacterium isolates, with *Humulus lupulus* also exhibiting antibacterial efficacy against rifampin-resistant Mycobacterium isolates at a MIC value of 8 mg/mL **(11)**. Also, Thymus vulgaris showed effects on *M. tuberculosis*. It was observed that T. Vulgaris essential oil had a substantially lower MIC value than typical medications, including ethambutol, isoniazid, streptomycin, and cycloserine, which are often used for the treatment of infections **(13)**. Another study evaluated the inhibitory effect of alcoholic extracts of *Berberis vulgaris, Rosa canina, Peganum harmala, Punica granatum, Digitalis sp, and Citrus lemon* on *Mycobacterium* isolates. The findings indicated that extracts of *Peganum harmala*, *Punica granatum*, *Digitalis* sp, and Citrus lemon exhibited inhibitory effects against non-MDR bacteria at various doses, with *Punica granatum* showing the maximum inhibition zone (19.5 mm) against isoniazid and rifampin-resistant isolates. On the other hand, neither *Berberis vulgaris* nor *Rosa canina* inhibited *M. tuberculosis* isolates **(18)**.

These findings revealed that various natural Iranian plants might effectively inhibit *Mycobacterium* isolates. However, *in vitro* and *in vivo* experiments are required to obtain further insight into antimycobacterial mechanisms.

5. Conclusion

There are promising results regarding the antibacterial efficacy of Iranian medicinal plants that have been studied recently. However, further investigation into their metabolites will be required to corroborate these claims. Additionally, a combination treatment, including using these herbs in conjunction with one another or with standard antibiotics, may effectively reduce antibiotic resistance in *M. tuberculosis*.

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Author's Contributions

Conceptualization, Shakib. P; methodology, Marzban. A & Lashgarian. H.E; investigation, Saki. R; writing—original draft preparation, Ramazanzadeh. R; writing—review and editing, Khalili Fard Ardali. J; supervision, Shakib. P.

Conflict of Interest

The authors declared no conflicts of interest.

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