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Review Article

Avicenna's Canon of Medicine and Tuberculosis: A Review on Herbal Medicine in Animal Model Research

Zakiyeh Sakhavat Nia[1,2], Mehdi Sobhani[3], and Zahra Sobhani[1*]

[1] Department of Traditional Pharmacy, Faculty of Pharmacy, Mashhad University of Medical Sciences, Mashhad, Iran
[2] Student Research Committee, Mashhad University of Medical Sciences, Mashhad, Iran
[3] Endoscopic and Minimally Invasive Surgery Research Center, Mashhad University of Medical Sciences, Mashhad, Iran

* ***Corresponding author:*** Zahra Sobhani, Department of Traditional Pharmacy, Faculty of Pharmacy, Mashhad University of Medical Sciences, Mashhad, Iran, Email: Sobhaniz@mums.ac.ir

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ABSTRACT

Tuberculosis (TB) remains a major global health challenge, highlighting the need for new and complementary therapeutic methods and strategies. The present study aimed to provide a comprehensive review of medicinal plants recommended by the renowned Persian physician Avicenna (Ibn Sina) for TB treatment, focusing on their phytochemical compounds and mechanisms of action. The present study combined a historical analysis of Avicenna's Canon of Medicine to identify medicinal plants used for tuberculosis with a systematic literature review (2000-2024) to evaluate their modern pharmacological evidence. The study targeted antimycobacterial, immunomodulatory, and symptom-relief activities using databases including PubMed, Scopus, and Science Direct. The current findings indicated that several plants, including *Artemisia absinthium* L., *Artemisia vulgaris* L., *Glycyrrhiza glabra* L., *Hyssopus officinalis* L., *Myrtus communis* L., *Thymus vulgaris* L., *Rosa damascena* Mill., *Adiantum capillus-veneris* L., *Achillea millefolium* L., *Foeniculum vulgare* Mill., *Polygonum aviculare* L., *Phoenix dactylifera* L., and *Teucrium polium* L., have multifaceted approaches against TB through potent anti-inflammatory, antioxidant, immunomodulatory, and direct antimycobacterial effects. Bioactive compounds included in these plants, such as phenolic acids, flavonoids, and terpenoids, are identified as key contributors that reduce oxidative stress, modulate immune responses, inhibit inflammatory mediators such as Interleukin-6, Interleukin-1β, and Tumor Necrosis Factor-alpha, and directly suppress *Mycobacterium tuberculosis* growth. Furthermore, these compounds help mitigate pulmonary damage and enhance host immune defenses. By integrating Avicenna's traditional knowledge with contemporary pharmacological evidence, the potential of these plants as complementary therapeutic agents for TB was noted.

1. Introduction

Tuberculosis (TB), caused by *Mycobacterium tuberculosis* (*M. tuberculosis*), is a significant global health threat, which mainly affects the respiratory system but can also impact other organs such as the kidneys and spine[1]. Transmitted via airborne particles, it is a disease of antiquity that persists as a leading infectious cause of mortality worldwide, with the World Health Organization (WHO) reporting an estimated 10 million new cases and 1.6 million deaths in 2021[2]. The emergence of multidrug-resistant tuberculosis (MDR-TB) and extensively drug-resistant tuberculosis (XDR-TB) strains presents a major challenge to treatment, underscoring the urgent need for novel complementary and alternative therapeutic strategies[3].

In response to the challenges of TB treatment, particularly drug-resistant strains, researchers are increasingly re-evaluating traditional herbal remedies. Before antibiotics, many cultures used medicinal plants to manage TB symptoms and slow disease progression, as documented in various traditional medical systems. Given the rise of drug resistance and the limitations of current treatments, the scientific study of these natural compounds may yield novel therapeutic strategies. Modern pharmacology now places significant emphasis on investigating bioactive compounds from plants with a history of medicinal use[4]. Validating these traditional

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approaches through rigorous science not only utilizes this ancient medical legacy but may also discover complementary or alternative therapies for conditions including drug-resistant TB[5].

Avicenna (Ibn Sina), the preeminent 10th-11th century Persian physician, synthesized Greek and Persian knowledge to create a comprehensive medical system based on observation and scientific analysis[6]. His seminal work, The Canon of Medicine, became a foundational text for centuries, detailing disease classification, diagnostics, and the extensive use of medicinal plants[7]. By emphasizing empirical evidence and a holistic approach, Avicenna established scientific principles that continue to hold relevance in modern medicine[6,7].

Avicenna's significant contributions to herbal medicine remain relevant today. While his principles were based on humoral theory, his detailed use of botanical treatments provides a valuable foundation for modern phytotherapy. In *The Canon of Medicine*, he identified specific plants for managing tuberculosis. Reviewing his recommendations can illuminate the potential of plant-based treatments, especially against antibiotic-resistant strains, highlighting the need for rigorous scientific research to validate their efficacy and safety for modern clinical use[8]. The study examines Avicenna's plant-based treatments for tuberculosis in The Canon of Medicine and compares them with modern scientific evidence to assess their potential value as complementary therapies.

2. Materials and Methods

2.1. Search strategy

Medicinal plants used for the treatment of TB were extracted from volume 3 of Avicenna's Canon of Medicine (Al-Qanun fi al-Tibb), specifically the tenth Treatise (Fann 10), fourth article (Maqala 4). A manual review was conducted using Arabic terms such as السّل (al-Sill), داء السل (TB disease), and علاج السل بالأعشاب (herbal treatment of TB). Identified plant names were transliterated and subsequently matched with validated modern botanical nomenclature using reference floras and an ethnopharmacological database.

2.2. Systematic search in scientific databases

A systematic literature search was performed across the following electronic databases: PubMed, Scopus, Science Direct, Cochrane Library, and Google Scholar as a supplementary tool to identify grey literature and articles not indexed in the core databases, covering the period from January 2000 to March 2024. The literature search was conducted by using a combination of plant names, medical subject terms, and keywords associated with therapeutic outcomes. Boolean operators (AND/OR) were used to refine the queries. The following keyword clusters were applied. Antitubercular activity, Antitubercular or Antimycobacterial or *Mycobacterium tuberculosis* inhibition, Symptom relief, Antitussive or Antipyretic or Analgesic or Antifatigue, pulmonary protective effects, Bronchodilator or Anti-asthmatic or Pulmonary fibrosis or Lung injury. For adjunctive and immunological effects, Immunostimulant, Anti-inflammatory, Antioxidant, or Antibacterial were searched. Examples of search query syntax for a single plant species were *Glycyrrhiza glabra* or Licorice and Antitubercular or Antioxidant or Immunomodulatory or Bronchodilator or Anti-inflammatory.

2.3. Inclusion criteria

Articles published in English from 2000 to 2024. *In vitro*, *in vivo*, or clinical studies evaluating the pharmacological activity of the selected plant species in the context of TB or its symptoms, studies reporting mechanisms of action, pharmacodynamics, or synergistic effects.

2.4. Exclusion criteria

Studies unrelated to tuberculosis or lung diseases, reviews without original data reports, and lacking botanical authentication.

3. Etiology and epidemiology of tuberculosis

Tuberculosis remains a highly prevalent and lethal global health challenge, disproportionately affecting low- and middle-income countries where factors such as poverty and inadequate sanitation facilitate its spread. However, it persists as a public health issue even in high-income nations. The COVID-19 pandemic exacerbated the TB crisis by disrupting essential diagnostic and treatment services globally. According to the 2024 WHO report, an estimated 10.8 million people were diagnosed with TB in 2023, a slight increase from the previous year. Although TB-related deaths dropped to 1.25 million in 2023, the disease has likely regained its position as the world's leading cause of death from a single infectious agent, surpassing COVID-19[9,10].

Tuberculosis progresses through two distinct clinical stages, including latent TB infection (LTBI) and active TB disease[11]. In LTBI, which constitutes about 90% of all TB infections, individuals harbor dormant *M. tuberculosis* bacteria, are asymptomatic, and non-infectious, though the infection can reactivate later, particularly if the immune system becomes compromised[11,12]. Active TB disease occurs when the bacteria reactivate and multiply, causing symptoms such as a chronic cough, weight loss, fever, and hemoptysis. Unlike LTBI, individuals with active pulmonary TB are contagious and can transmit the bacterium to others[11].

Pulmonary tuberculosis follows a defined pathogenic sequence transmitted through aerosol inhalation. The process initiates when immune cells phagocytose the bacteria, followed by intracellular bacterial replication. The infection may then enter a latent, asymptomatic phase, where it can persist indefinitely. Ultimately, factors such as immunosuppression can trigger reactivation to active disease, characterized by symptomatic illness and transmission potential[13].

3.1. Transmission and action mechanisms

The infectiousness of a TB patient depends on several factors. Those with smear-positive pulmonary TB are highly contagious, and the risk increases with the degree of smear positivity[14]. A study in Peru confirmed that smear-positive individuals pose a significantly higher transmission risk to household contacts than smear-negative cases, regardless of the contact's age[15,16]. *Mycobacterium tuberculosis* transmits through airborne droplets expelled by infected individuals via coughing or sneezing. When inhaled, the bacteria travel to and establish infection in the alveoli of the lungs[17]. The hostpathogen interaction in tuberculosis is complex. The initial innate immune response recruits' macrophages to contain *M. tuberculosis*, but this often fails, leading to granuloma formation. This structure, while intended to wall off the infection, paradoxically shelters the bacteria, enabling long-term persistence[17]. This homeostatic balance is vulnerable; immunosuppression, such as HIV, significantly increases the risk of active TB, highlighting the direct correlation between immune status and disease progression[18,19]. The process involves sophisticated co-evolution. After initial infection and innate response in the lungs, *M. tuberculosis* migrates to lymph nodes to prime T-cells[20,21]. These activated immune cells then travel back to the lungs, reinforcing granuloma formation where *M. tuberculosis* can establish a latent, protected state. Dendritic cells and macrophages serve as the primary defense against TB, working in concert to control bacterial replication[22,23]. Dendritic cells and macrophages form granulomas, organized structures of macrophages, giant cells, and lymphocytes, which paradoxically create a niche for *M. tuberculosis* survival. The stability of this structure is regulated by cytokines, including the pro-inflammatory ones, such as interleukin 1-β (IL-1β), interferon gamma (IFN-γ), and tumor necrosis factor-alpha (TNF-α), which enhance immune function, while anti-inflammatory ones, such as IL-10, maintain homeostasis[21,22]. In about 10% of cases, *M. tuberculosis* evades this containment, causing granulomas to break down. This marks the progression from latent infection to active, symptomatic, and transmissible disease[24].

4. Avicenna's perspective on tuberculosis

The renowned Persian physician Avicenna employed a holistic approach to treating TB, combining botanical remedies, nutritional adjustments, and other therapies to strengthen the immune system and alleviate symptoms[25,26]. Many of the medicinal plants he recommended possess direct antibacterial activity against *M. tuberculosis* while also providing relief from symptoms like fever and cough. These natural supplements are recognized for improving patient conditions and reducing disease severity. This section investigates the therapeutic impact of Avicenna's recommended herbal remedies on TB[25,26]. The summary of medicinal plants recommended by Avicenna for tuberculosis is mentioned in Table 1 and Figure 1.

Table 1. Summary of medicinal plants recommended by Avicenna for treating tuberculosis

Medicinal plants	Key mechanisms of action	Reference numbers
***Artemisia absinthium* L.**	Anti-inflammatory, antioxidant, antipyretic, direct bacteriostatic/bactericidal effects against *M. tuberculosis*	(32-38)
***Artemisia vulgaris* L.**	Anti-inflammatory, antioxidant, bronchodilator, anti-asthmatic, antibacterial against *M. tuberculosis*	(39-47)
***Glycyrrhiza glabra* L.**	Anti-inflammatory, antioxidant, immunomodulatory, antitussive, anti-asthmatic, hepatoprotective, anti-fatigue, protects against lung injury	(48-65)
***Hyssopus officinalis* L.**	Anti-inflammatory, antioxidant, anti-asthmatic, modulates cytokines	(67-73)
***Myrtus communis* L.**	Anti-inflammatory, antioxidant, and direct antimicrobial activity against *M. tuberculosis*	(71, 74-81)
***Thymus vulgaris* L.**	Anti-inflammatory, antioxidant, bronchodilator, anti-asthmatic, and direct antimycobacterial activity	(82-95)
***Rosa damascena* Mill.**	Anti-inflammatory, antioxidant, bronchodilator	(96-103)
***Adiantum capillus-veneris* L.**	Anti-inflammatory, antioxidant, antipyretic, anti-apoptotic (lung protection), hepatoprotective	(104-115)
***Achillea millefolium* L.**	Anti-inflammatory, antioxidant, immunomodulatory, bronchodilator (Tracheal relaxant)	(116-126)
***Foeniculum vulgare* Mill.**	Anti-inflammatory, antioxidant, bronchodilator, direct anti-TB activity	(127-136)
***Polygonum aviculare* L.**	Anti-inflammatory, antioxidant, anti-fatigue (modulates neuroinflammation)	(137-145)
***Phoenix dactylifera* L.**	Anti-inflammatory, antioxidant, immunomodulatory, protects against lung injury and fibrosis	(146-157)
***Teucrium polium* L.**	Anti-inflammatory, antioxidant, immunomodulatory	(158-167)

M. tuberculosis: *Mycobacterium tuberculosis*

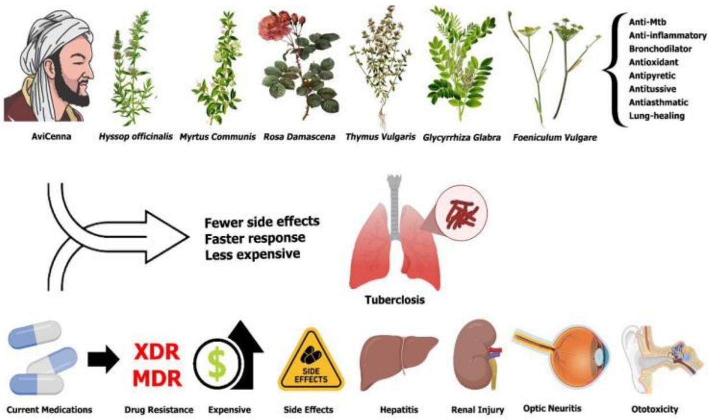

Figure 1. An overview of medicinal plants with anti-inflammatory, antioxidant, bronchodilatory, and anti-tuberculosis properties, drawing on traditional medicine and Avicenna's teachings to highlight their potential for fewer side effects, faster therapeutic response, and lower cost compared to conventional tuberculosis treatments.

4.1. Artemisia absinthium L.

Artemisia L. is a plant that grows in northern arid areas. *Artemisia* L. has 1000 genera and more than 20000 species found in different regions in the world, including Asia, Europe, and North America[29]. *Artemisia* has several active ingredients and secondary metabolites that have a wide range of bioactive activities[29]. There are some fundamental classes of bioactive compounds found in *Artemisia*, including flavonoids, phenolic acids, coumarin, and terpenes[30]. *Artemisia* is mostly used for treating malaria, hepatitis, cancer, and different diseases caused by fungi, bacteria, or viruses[29]. These diseases are treatable owing to *Artemisia*'s diverse antitumor, anti-inflammatory, and antiulcer secondary metabolites[29,30].

Artemisia absinthium L. (*Asteraceae* family) is a plant traditionally used to treat different ailments, including liver disorders, gastric pain, and wounds[29]. It exhibits broad pharmacological activities, such as antimicrobial, antioxidant, and hepatoprotective effects[30]. Notably, prolonged use of its essential oil is associated with toxicity and psychological dysfunction[31]. While the precise mechanisms of its antituberculosis activity are not fully understood, it is attributed to its diverse bioactive compounds.

4.1.1 Anti-inflammatory effects

Studies have confirmed the anti-inflammatory properties of *A. absinthium*. Amrollahi et al.[32] demonstrated that its essential oil (4-8 mg/kg) significantly reduced carrageenan-induced paw edema in mice, with efficacy similar to aspirin[32]. Furthermore, *in vitro* tests exhibited that the plant has potent lipoxygenase inhibitory activity, comparable to standard anti-inflammatory medicines such as ibuprofen[33].

4.1.2. Antioxidant activities

Artemisia absinthium L. demonstrated significant antioxidant and liver-protecting properties. Craciunescu et al.[34] indicated that flavonoid-rich extracts have potent antioxidant activity in 2,2-Diphenyl-1-picrylhydrazyl (DPPH), Oxygen Radical Absorbance Capacity (ORAC), and Trolox Equivalent Antioxidant Capacity (TEAC) assays and protect cells from oxidative stress[34]. Supporting this, Amat et al.[35] found that its aqueous extract (50-200 mg/kg) in mice reduced liver enzymes and lipid peroxidation while restoring key antioxidant enzymes such as superoxide dismutase (SOD) and glutathione peroxidase (GPx). It also suppressed pro-inflammatory cytokines (TNF-α, IL-1) and prevented liver necrosis, confirming its hepatoprotective and antioxidant effects[35].

4.1.3. Antipyretic effects

Artemisia absinthium L. has demonstrated significant antipyretic (fever-reducing) properties. A study by Bhat et al.[37] induced fever in rats and treated them with a hydroalcoholic extract of the plant. The results indicated that the extract, both alone and combined with barley water, significantly reduced rectal temperature, confirming its anti-fever effects[36,37].

4.1.4. Antituberculosis effects

Given the hepatotoxicity of current TB medicines and the rise of MDR/XDR strains, exploring new agents such as medicinal plants is crucial. In one study, *A. absinthium* extracts showed dose-dependent anti-TB activity in animal models. All concentrations (20%-96%) had bacteriostatic effects, but only the 96% extract was bactericidal, highlighting its potential as a therapeutic candidate that requires further investigation[38].

4.2. *Artemisia vulgaris* L.

Artemisia vulgaris L., a prominent medicinal plant within the *Artemisia* genus, is well recognized for its essential oils, which are abundant in compounds such as α-thujone, camphor, and 1,8-cineole[39,40]. It possesses a wide range of pharmacological properties, including anti-inflammatory, antioxidant, and immunomodulatory effects, and has demonstrated significant antibacterial activity against *M. tuberculosis*[41]. These therapeutic effects are attributed to its diverse secondary metabolites, such as flavonoids, sesquiterpenes, and coumarins[39,40,42].

4.2.1. Anti-inflammatory effects

Artemisia vulgaris L. exhibits significant anti-inflammatory activity, partly attributed to its camphor content, which inhibits pro-inflammatory cytokines such as TNF-α, IL-2, and IL-4[43]. *In vivo* studies confirmed that methanolic extract (200-800 mg/mL) potently inhibited carrageenan-induced paw edema in rats by over 71%[44]. Another study found that ethanol extracts from plants in temperate regions (at 400 mg/kg) were as effective as standard anti-inflammatory medicines in a mouse model, with ethanol being a superior solvent to ethyl acetate[43].

4.2.2. Antioxidant activities

Artemisia vulgaris L. demonstrated potent antioxidant activity through both *in vitro* and *in vivo* studies. Temraz et al.[45] reported strong free radical scavenging in DPPH and Nitric Oxide assays, with treatment in rats increasing key antioxidant markers such as glutathione, ascorbic acid, and SOD[45]. Similarly, its aqueous extract effectively scavenged 2,2'-Azino-bis(3-ethylbenzothiazoline-6-sulfonic acid), superoxide, hydroxyl, and NO radicals, as shown by low IC_{50} values[46].

4.2.3. Bronchodilator effects

Artemisia vulgaris L. acts as an effective bronchodilator. A study on guinea pig tracheal tissue exhibited that its extract potently prevented contractions induced by carbachol and potassium. The mechanism involves blocking muscarinic receptors and inhibiting calcium influx, leading to tracheal relaxation[47].

4.3. *Glycyrrhiza glabra* L.

Glycyrrhiza glabra (*G. glabra,* licorice), a species rich in bioactive compounds such as the triterpenoid saponin glycyrrhizin, flavonoids, and coumarins, possesses a broad spectrum of therapeutic properties, including anti-tuberculosis activity[48,49].

4.3.1. Anti-inflammatory effects

Glycyrrhiza glabra exhibits potent anti-inflammatory effects through its flavonoid constituents. Sun et al.[50] reported that liquiritigenin reduces inflammation by modulating MAPK and Notch1/NF-κB pathways. Another study identified pinocembrin, glabranin, and licoflavanone as key anti-inflammatory compounds in *G. glabra*. In lipopolysaccharide (LPS)-stimulated macrophages, these compounds significantly decreased pro-inflammatory cytokines and COX-2/iNOS expression by inhibiting the NF-κB/MAPK pathway, with licoflavanone (IC_{50} = 37.68 μM) showing the strongest effect[51].

4.3.2. Anti-asthmatic effects

Glycyrrhizic acid, a primary active compound in *G. glabra*, demonstrated significant anti-asthmatic and immunomodulatory effects in mouse models. Studies indicated that *G. glabra* reduces key asthma indicators such as airway resistance, eosinophil count, and pro-inflammatory cytokines (IL-4, IL-5, IL-13), while boosting regulatory T cells and IFN-γ levels[52,53]. These findings suggested that *G. glabra* may be effective against TB by mitigating lung inflammation and modulating the immune response, highlighting its potential as a therapeutic agent for respiratory diseases, such as TB.

4.3.3. Antitussive effects

Glycyrrhiza glabra exhibits significant antitussive (cough-suppressing) and expectorant properties. Studies in mice and guinea pigs using different cough-inducing models (SO_2, ammonia) have demonstrated that its extract and specific compounds, such as liquiritigenin, offer cough suppression that is comparable to or exceeds the efficacy of standard medicinal treatments codeine[54-57]. These findings confirmed its potential as an effective natural cough remedy.

4.3.4. Antioxidant activities

Glycyrrhiza glabra flavonoid-rich root fractions possess potent antioxidant activity. A methanol/water extract demonstrated potent effects in multiple assays, particularly in inhibiting lipid peroxidation[58]. Furthermore, the root extract exhibits significant hepatoprotective properties. In a mouse model of CCl_4-induced liver damage, pre-treatment with the extract (300-600 mg/kg) effectively reduced oxidative stress and protected against hepatotoxicity[59].

4.3.5. Fatigue relief effects

Fatigue is a common and debilitating symptom in TB, stemming from both the disease and its long-term treatments, which severely impacts patients' quality of life. Studies suggested *G. glabra* may alleviate fatigue. In mouse models, the compound glabridin enhanced exercise endurance, reduced fatigue markers such as blood lactic acid, and promoted glycogen storage[60]. Similarly, *G. glabra* extract effectively countered signs of induced chronic fatigue stress, indicating its potential as a therapeutic agent for fatigue management[61].

4.3.6. Treatment of lung injury

Lung damage, a hallmark of TB, ranges from acute inflammation and abscesses to chronic fibrosis, leading to permanent respiratory impairment. Glycyrrhizin, a key compound in *G. glabra*, demonstrated notable protective effects against such injury. In mouse models of LPS-induced acute lung injury, glycyrrhizin treatment suppressed key inflammatory mediators (IL-6, TNF-α, IL-1β) and inhibited the NF-κB/NLRP3 inflammasome pathway, thereby reducing lung inflammation and damage[62,63]. These findings suggested its potential to mitigate TB-associated lung injury.

4.3.7. Antituberculosis effects

Several studies demonstrated the direct therapeutic potential of *G. glabra* against TB. An inhalable liposomal powder of licorice extract was effectively deposited in mouse lungs, significantly reducing bacterial counts in the lungs and spleen over 56 days[64]. Furthermore, a clinical trial on TB patients found that adding licorice as an adjunct therapy for eight weeks improved sputum conversion rates by 10%, resolved fever more effectively, provided more effective cough relief, and resulted in fewer gastrointestinal side effects compared to the placebo group[65].

4.4. *Hyssopus officinalis* L.

Hyssop, a perennial herb belonging to the *Lamiaceae* family, has been historically valued for its diverse applications in both medicine and culinary practices. Extracts and essential oils derived from hyssop are used for anti-inflammatory, antioxidant, antibacterial, antiviral, expectorant, antiseptic, carminative, tonic, diuretic, and cardiovascular effects[66].

4.4.1. Anti-inflammatory effects

Hyssop exhibits significant anti-inflammatory activity. An ethanolic extract reduced inflammation in a rat paw edema model by lowering phagocyte levels and nitrite/nitrate[67]. Another study found that a methanol extract (200 mg/kg) inhibited paw edema as effectively as indomethacin. *In vitro*, the extract potently inhibited the COX-2 enzyme, comparable to celecoxib. Molecular modeling identified chlorogenic acid and rosmarinic acid as key compounds with strong binding affinity to COX-1 and COX-2, surpassing ibuprofen[68].

4.4.2. Anti-asthmatic effects

Hyssop demonstrated remarkable anti-asthmatic potential. In an ovalbumin-induced asthma model in mice, hyssop treatment effectively normalized key asthma indicators. It reduced elevated eosinophil and immunoglobulin E (IgE) levels, increased IgG, and decreased excessive airway mucus secretion[69]. Furthermore, the treatment reduced levels of matrix metalloproteinase-9 and its inhibitor, mitigating collagen deposition and mucus hypersecretion, which supports its role in preventing airway remodeling in asthma[70].

4.4.3. Antioxidant activities

Hyssop exhibits notable antioxidant activity across its flowers, leaves, and stems. Studies using DPPH radical scavenging and lipid peroxidation assays confirm this effect, with one methanolic extract showing 40% inhibition of lipid peroxidation[71,72]. This antioxidant capacity is directly correlated with the plant's phenolic content[73].

4.5. Myrtus communis L.

Myrtus communis L. (myrtle), an aromatic evergreen shrub, has been used in traditional medicine to treat coughs, diarrhea, and for its antimicrobial properties[74,75]. Its specific mechanisms of action against TB are discussed next.

4.5.1. Anti-inflammatory effects

Myrtus communis L. possesses potent anti-inflammatory properties. In a rat model of colitis, both its hydroalcoholic extract and essential oil effectively reduced inflammation, as shown by improved ulcer index, colitis index, and myeloperoxidase activity[77]. The activity is attributed to specific compounds, such as myrtucommulone, which directly inhibits key enzymes (COX-1, 5-lipoxygenase) in the inflammatory pathway[78]. In mice, myrtucommulone reduced inflammation by lowering leukocyte infiltration, myeloperoxidase activity, and pro-inflammatory cytokines (TNF-α, IL-1β)[79].

4.5.2. Antioxidant activities

Myrtus communis L. exhibits strong antioxidant activity, primarily attributed to its high phenolic content. Methanolic extracts from its leaves, stems, and flowers indicated superior antioxidant effects compared to essential oils, with leaves being the most potent part[80,81]. The main antioxidants identified are gallotannins in leaves and flowers, and catechin in stems[80]. Methanol is the most effective solvent for extracting these antioxidant compounds[81].

4.5.3. Antituberculosis effects

The essential oil of myrtle demonstrated significant and selective antimicrobial activity. It is effective against *M. tuberculosis* strains, such as H37Rv, H37Ra, and multi-drug resistant clinical isolates, with a low MIC of 0.17% (v/v). In contrast, myrtle was far less effective against *M. paratuberculosis* (MIC of 2%)[81]. The anti-bacterial mechanism against gram-positive bacteria is reported to involve cell wall destruction.

4.6. Thymus vulgaris L.

Thymus vulgaris L. (*T. vulgaris,* thyme), a fragrant shrub from the *Lamiaceae f*amily, is traditionally used to treat respiratory ailments such as bronchitis, coughs, and sore throats[82]. Its essential oil possesses broad antimicrobial, antiviral, and antioxidant properties[83]. These effects are primarily due to phenolic monoterpenes, including thymol and carvacrol, which are also potent antifungals. Other constituents may act synergistically to enhance the oil's overall efficacy[84-86].

4.6.1. Anti-inflammatory effects

Thyme essential oil and its constituents, thymol and carvacrol, exhibit anti-inflammatory activity, but their effects vary. In a pleurisy model, both thymol and carvacrol inhibited leukocyte migration. However, in a topical ear edema test, only carvacrol was effective, while thymol caused irritation, possibly by triggering prostanoid and histamine release[87]. Additionally, both thyme and thymol can modulate inflammation by suppressing the gene expression and production of key pro-inflammatory cytokines, including IL-6, IL-1β, and TNF-α[88].

4.6.2. Anti-asthmatic effects

Thyme oil demonstrates significant anti-asthmatic and antioxidant effects. In an ovalbumin-induced asthma model in rabbits, thyme oil treatment normalized lung tissue, reduced signs (wheezing, sneezing), and lowered key Th2 cytokines (IL-4, IL-5, IL-13), IgE, and reactive oxygen species (ROS)[89]. The antioxidant properties of thyme and its constituent thymol have been further confirmed by their ability to reduce free radicals in mice[90].

4.6.3. Antioxidant activities

As reported in the previous section, thyme exhibits therapeutic activity against bronchial asthma through various mechanisms, particularly through its antioxidant properties[89,90]. Additionally, *T. vulgaris* silver nanoparticles demonstrated significant DPPH radical scavenging activity in a study by Aldosary et al.[91].

4.6.4. Antituberculosis effect

Thymus vulgaris L. exhibits potent and direct activity against *M. tuberculosis*. Its extracts and essential oil demonstrated notable growth inhibition, with studies reporting low MIC values (0.5 mg/ml for acetone extract and as low as 0.5-40 μg/ml for essential oil)[92,93]. Notably, the essential oil indicated bactericidal effects at a concentration of 1 μg/ml[94], and its efficacy has been found comparable to, or even surpassing, that of standard anti-TB medicines such as isoniazid and streptomycin in some assays[95].

4.7. Rosa damascena L.

Rosa damascena L. (*R. damascena*) is one of the most important aromatic species of the *Rosaceae* family. Its essential oil is highly valued in perfumery and cosmetics. Numerous therapeutic activities of *R. damascena* have been reported, including its analgesic properties, anti-muscle cramp effects, anti-inflammatory actions, anti-cough properties, antioxidant activity, and anti-cancer effects[96].

4.7.1. Anti-inflammatory effects

Rosa damascena essential oil exhibited remarkable anti-inflammatory and antioxidant properties. In a rat model of sepsis-induced inflammation, pre-treatment with the oil (50-100 mg/kg) prevented hepatotoxicity by reducing oxidative stress, lipid peroxidation, and modulating key inflammatory mediators, such as COX-2 and PGE2[97,98]. These findings suggested its potential as an alternative to conventional anti-inflammatory medicines.

4.7.2. Antioxidant activities

Rosa damascena demonstrated potent antioxidant activity, primarily attributed to its high content of phenolic compounds, flavonoids, anthocyanins, quercetin, and kaempferol[99]. This is confirmed by strong performance in standard assays, including DPPH, Ferric Reducing

Antioxidant Power (FRAP), ABTS, with significant activity observed across different plant accessions[100]. The petal extract is notably more potent than the receptacle extract, showing effectiveness at much lower concentrations[101].

4.7.3. Bronchodilator activity

Rosa damascena L. acts as an effective bronchodilator. Its extracts and essential oil induce dose-dependent relaxation of tracheal smooth muscle in animal models. The mechanism is multi-faceted, involving potential stimulation of β-adrenoceptors, blockade of histamine (H1) receptors[102], and the inhibition of multiple potassium channels (voltage-gated, ATP-sensitive, and calcium-activated)[103].

4.8. Adiantum capillus-veneris **L.**

Adiantum capillus-veneris L., an evergreen fern, is traditionally used to treat respiratory ailments. Its essential oil, containing compounds such as carvacrol and thymol, exhibits documented antibacterial and antifungal properties[104-106].

4.8.1. Anti-inflammatory effects

Adiantum capillus-veneris L. demonstrated significant anti-inflammatory and hepatoprotective effects. In rat models of colitis, both its aqueous and hydroalcoholic extracts reduced inflammation in a dose-dependent manner, an effect attributed to their phenolic and flavonoid content[107]. Similarly, a methanolic extract notably reduced carrageenan-induced paw edema in mice[108]. Furthermore, the extract exhibited hepatoprotective properties in rats exposed to a toxic fungicide, reducing liver damage by lowering oxidative stress and pro-inflammatory cytokines (TNF-α, IL-6)[109].

4.8.2. Antioxidant activities

Adiantum capillus-veneris L. is a valuable source of antioxidants. Its activity is attributed to flavonoids, such as rutin and isoquercetin, which boost endogenous antioxidants (glutathione, catalase, SOD) and scavenge free radicals[107,109]. The essential oil, rich in carvone, carvacrol, and thymol, also exhibited strong DPPH radical scavenging ability[110]. Studies confirmed that methanol and ethyl acetate extracts have more potent antioxidant and enzyme-inhibitory effects than aqueous extracts[111,112], collectively underscoring the plant's significant antioxidant potential.

4.8.3. Antipyretic effects

Adiantum capillus-veneris exhibits significant antipyretic (fever-reducing) activity. In a mouse model, a methanolic extract (600 mg/kg) reduced yeast-induced fever more effectively than a standard dose of paracetamol, lowering rectal temperature from 38.63°C to 37.09°C within three hours[108]. This effect is likely due to a variety of phytochemicals, including flavonoids, terpenoids, and alkaloids present in the plant[108].

4.8.4. Treatment of lung injury

Adiantum capillus-veneris extract demonstrated protective effects against exercise and hypoxia-induced lung cell apoptosis. In trained rats under hypoxic conditions, the extract (500 mg/kg) modulated key apoptotic regulators (P53, TNF-α, Bax/Bcl-2 ratio) and increased respiratory surface area[113,114]. Additionally, in interval-trained rats, an ethanol extract (200 mg/kg) acted as a pulmonary oxidative stress modulator by beneficially regulating metallothionein levels[115].

4.9. Achillea millefolium L.

Achillea millefolium L. (yarrow), a medicinal plant from the *Asteraceae* family, has been used for centuries to treat a wide range of ailments. These include liver disorders such as hepatitis, jaundice, respiratory issues including cough, pneumonia, fever, and inflammatory conditions, including rheumatoid arthritis, highlighting its broad pharmacological potential[116, 117].

4.9.1. Anti-inflammatory effects

Achillea millefolium L. exhibited potent anti-inflammatory properties through multiple mechanisms. *In vitro*, its extract suppresses key pro-inflammatory mediators (NO, iNOS, COX-2, IL-6, IL-8) in immune and skin cells, likely by inhibiting the NF-κB and p38 MAPK pathways[118,119]. *In vivo*, the extract effectively alleviated dermatitis signs in mice[118]. Its protective effect was further confirmed against toxins from *Clostridium difficile*, highlighting its broad anti-inflammatory and cell-protective potential[120].

4.9.2. Antioxidant activities

Achillea millefolium L. demonstrated significant antioxidant activity. Both its hydrodistilled essential oil (IC_{50} = 1.83 mg/mL in DPPH assay) and hydroalcoholic extracts indicated potent free radical scavenging ability across multiple assays (DPPH, ABTS, CUPRAC, FRAP)[121,122]. Decoction extracts exhibit the highest activity, and the effects are largely attributed to bioactive compounds such as thymol and carvacrol[122,123].

4.9.3. Bronchodilator activity

The hexane extract from the aerial parts of *A. millefolium* L. demonstrated significant tracheal smooth muscle relaxant effects in rats (EC_{50} = 412.0 μg/mL). The mechanism involves muscarinic receptor antagonism, activation of the NO/cGMP pathway, and inhibition of calcium influx into smooth muscle cells. The compounds leucodin and achillin are identified as the key active constituents responsible for this bronchodilatory effect[124].

4.9.4. Immunomodulatory Effect

Achillea millefolium L. exhibited remarkable immunomodulatory properties. A methanolic extract increased lymphocyte and monocyte counts in mice, indicating an immunostimulatory effect attributed to its alkaloids, tannins, and flavonoids[125]. Conversely, the polysaccharide fraction of an aqueous extract demonstrated a more complex immunoregulatory role in human monocytes. It promoted the secretion of both pro- and anti-inflammatory cytokines (e.g., TNF-α, IL-10) while simultaneously inhibiting key signaling pathways, such as NF-κB, ERK1/2, and Akt[126].

4.10. Foeniculum vulgare Mill

Foeniculum vulgare Mill. (fennel), an *Apiaceae* family plant used as a spice is traditionally employed to relieve respiratory symptoms. It possesses broad pharmacological activities, including antibacterial, antioxidant, and hepatoprotective effects[127,128].

4.10.1. Anti-inflammatory effects

Foeniculum vulgare Mill exhibits significant anti-inflammatory activity. Its coumarin compounds, particularly imperatorin, inhibit pro-inflammatory cytokines (IL-6, TNF-α, IL-1β) and COX-2 expression in both cellular and mouse models[129]. Similarly, a fennel extract suppressed IL-6 and TNF-α production in LPS-induced mice. The mechanism also involved modulation of NO levels, LDH activity, immune cell infiltration, and phosphorylation of the ERK signaling pathway[130].

4.10.2. Antioxidant activities

Foeniculum vulgare Mill. is a well-established source of antioxidants. Its coumarin compounds exhibit free radical scavenging activity in DPPH and ABTS assays[129]. Comparative studies on fennel seeds confirm significant antioxidant capacity across various assays (beta-carotene/linoleic acid, reducing power, DPPH), with some variation in potency observed between different geographical sources[131,132].

4.10.3. Bronchodilator effects

Foeniculum vulgare Mill. demonstrated bronchodilatory properties. Both its ethanolic extract and essential oil induce relaxation of guinea pig tracheal smooth muscle[133]. The compound fenchone, present in fennel, acts as a potent bronchodilator. Its mechanism primarily involves the activation of potassium (K^+) channels, with additional contributions from phosphodiesterase inhibition and calcium (Ca^{2+}) channel blockade[134].

4.10.4. Antituberculosis effect

Foeniculum vulgare Mill. exhibited direct antimicrobial and anti-tuberculosis activity. Different leaf extracts (petroleum ether, chloroform, methanol) showed efficacy against *M. tuberculosis*, with the chloroform extract being active in a TB-specific assay[135]. Furthermore, a hexane extract from *Foeniculum vulgare vardulce* was effective against MDR *M. tuberculosis* strains. Bioassay-guided fractionation identified 2,4-undecadienal as the most active compound, with a promising MIC of 25–50 μg/mL[136].

4.11. Polygonum aviculare L.

Polygonum aviculare L. (knotgrass), a climbing plant from the *Polygonaceae* family, is traditionally used for its astringent (against diarrhea), diuretic, and healing properties[137,138]. Its activity is attributed to compounds, such as avicularin, myricitrin, and different diterpenes[137,138].

4.11.1. Anti-inflammatory effects

Polygonum aviculare L. demonstrated significant anti-inflammatory activity. Its isolated flavonol glucuronides potently inhibit ROS production and elastase release in human neutrophils at low concentrations (0.5-10 μM)[139]. Furthermore, the extract reduces DNA damage (γH2AX formation) and modulates transcription factor activity, confirming its role as a potent inflammatory regulator[140].

4.11.2. Antioxidant activities

Polygonum aviculare L. is rich in phenolic antioxidants. An optimized deep eutectic solvent extraction method yielded extracts with strong DPPH and FRAP activity[141,142]. Comparative analysis shows that the methanolic extract of the stems possesses the highest antioxidant capacity, followed by the roots and leaves[143].

4.11.3. Fatigue relief effects

Polygonum aviculare L. extract demonstrated significant anti-fatigue effects. In a mouse model of stress-induced fatigue, treatment with the extract (100 mg/kg) reduced lethargy and modulated key physiological markers. Knotgrass lowered stress hormones, including corticosterone, epinephrine, neurotransmitters (serotonin), and pro-inflammatory cytokines (TNF-α, IL-1β, IL-6) in the brain, indicating that its anti-fatigue action works through the modulation of neuroinflammation[144,145].

4.12. Phoenix dactylifera L.

Phoenix dactylifera L. (date palm) is cultivated for its nutritious fruit, which possesses several health benefits, including anti-inflammatory, antioxidant, and antimicrobial properties, attributed to bioactive compounds, such as phenolics, carotenoids, and phytosterols[146-148].

4.12.1. Anti-inflammatory effects

Phoenix dactylifera L. exhibited significant anti-inflammatory activity. An Algerian date extract (50 mg/kg) reduced paw edema and inflammatory markers, such as C-Reactive Protein (CRP) and homocysteine, in mice[149]. Furthermore, methanolic extracts from Moroccan date seeds and fruits demonstrated potent effects in multiple models, reducing paw and ear edema in rodents. This activity is directly linked to their high phenolic and flavonoid content, with specific compounds, including rutin, quercetin, and caffeic acid, identified as key contributors[150,151].

4.12.2. Antioxidant activities

Phoenix dactylifera L. demonstrated notable and varied antioxidant potential. A hydroethanolic extract protected against oxidative stress by activating antioxidants, reducing ROS, and suppressing pro-apoptotic genes (p53, Bax)[152]. However, antioxidant capacity varies considerably among different date fruit and seed varieties, as shown by differences in polyphenol, flavonoid, and tannin content and their performance in FRAP, DPPH, and ABTS assays[153,154]. This highlights the need to evaluate each variety individually for specific applications.

4.12.3. Immunomodulatory effects

Phoenix dactylifera L. exhibited potent antioxidant, anti-inflammatory, and immunomodulatory properties. In a rat model of aluminum chloride-induced toxicity, a date fruit extract (500 mg/kg) effectively reversed oxidative stress by increasing glutathione, SOD, and catalase levels, while also decreasing pro-inflammatory cytokines (TNF-α, IL-6), NF-κB, and lipid markers peroxidation[155].

4.12.4.Treatment of lung injury

Phoenix dactylifera L. demonstrated significant protective effects against chemical-induced lung injury. In rats, an ethanolic extract of Ajwa date pulp mitigated benzopyrene-induced damage by restoring antioxidant enzymes (SOD, catalase, GPx) and reducing pro-inflammatory cytokines (TNF-α, IL-6, IFN-γ), CRP, and angiogenesis markers[156]. Similarly, date palm sap protected against bleomycin-induced lung fibrosis in rats by reducing lipid peroxidation, modulating hydroxyproline and antioxidant enzymes, and preventing morphological lesions, an effect attributed to its phenolic and vitamin content[157].

4.13. Teucrium polium L.

Teucrium polium L., a wild plant from the *Lamiaceae* family, is used in traditional medicine for its diverse therapeutic properties. These include treating diabetes, gastrointestinal disorders, inflammation, and rheumatism[158,159]. Its bioactivity is attributed to compounds, such as flavonoids, terpenoids, sterols, and saponins[160].

4.13.1. Anti-inflammatory effects

Teucrium polium L. exhibits significant anti-inflammatory activity through multiple mechanisms. Its hydroalcoholic and aqueous extracts reduce key pro-inflammatory cytokines (IL-6, TNF-α, IL-1β) and markers (CRP, MCP-1) in rodent models of inflammation[161-163]. One study also indicated that can increase the anti-inflammatory cytokine IL-10[163]. These effects are consistently attributed to its polyphenol and flavonoid content[161, 162].

4.13.2. Antioxidant activities

Teucrium polium L. is a rich source of natural antioxidants. Studies consistently show that its methanolic extract possesses the highest antioxidant activity, correlating with its superior phenolic and flavonoid content[164]. Key antioxidant compounds identified include luteolin glycosides and pelargonin[165]. The plant's efficacy has been confirmed across multiple assays (DPPH, ABTS, FRAP, β-carotene bleaching), demonstrating significant free radical scavenging and reducing power[164-166].

4.13.3. Immunomodulatory effects

Teucrium polium L. exhibited selective immunomodulatory and cytotoxic effects. A methanolic extract promoted the proliferation of healthy human immune cells, increasing CD14+, CD3+, and CD20+ subsets with CD25+ activation markers, while inducing apoptosis in hepatitis C virus (HCV)-infected cells. This immunostimulatory effect was consistent in healthy cells but was only observed in infected cells at the highest extract concentration, demonstrating its potential as a targeted immunomodulatory agent[167].

5. Conclusion

The present study validated Avicenna's traditional use of medicinal plants for tuberculosis (TB) by aligning it with modern scientific evidence. The plants exhibit multi-targeted therapeutic potential through four key mechanisms, including direct antimycobacterial activity, anti-inflammatory effects by suppressing TNF-α, IL-6, and IL-1β, potent antioxidant action, and immunomodulation. These properties support their role as promising adjunctive therapies to conventional TB treatment. While the findings are compelling, further *in vivo* and clinical research is necessary to fully determine their efficacy, safety, and best integration into modern anti-TB regimens for better patient outcomes.

Declarations

Competing interests

The authors declared that there is no conflict of interest.

Authors' contributions

Zakiyeh Sakhavat Nia wrote the draft of the manuscript. Mehdi Sobhani and Zahra Sobhani revised the manuscript draft and reviewed the final edition of the article. All authors have reviewed and approved the final edition of the manuscript before publication in this journal.

Ethical considerations

The authors declare that the present manuscript is original and is not being considered elsewhere for publication. The authors have reviewed additional ethical concerns, such as research misconduct, data fabrication, and redundancy.

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Availability of data and materials

All data from the current study are available upon reasonable requests from the authors.

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