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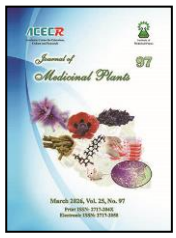

**Research Article**

# Natural treatments of Tuberculosis in Avicenna's canon: Historical insights and modern evidence

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ABSTRACT

**Background:** Tuberculosis (TB) remains a major global health concern with significant long-term complications. Avicenna, the eminent Persian physician, described various natural treatments for TB in his medical encyclopedia, The Canon of Medicine. These included not only medicinal plants such as jujube, licorice, and chicory, but also natural substances like honey and raisins, which are believed to support immune function and mitigate inflammation. **Objective:** This study aimed to examine the evidence supporting Avicenna's recommendations and assess the efficacy of these treatments. **Methods:** A comprehensive review was conducted using primary historical texts from The Canon of Medicine, alongside modern scientific literature on the pharmacological and immunomodulatory properties of the recommended natural treatments. **Results:** The findings suggest that these natural substances possess anti-inflammatory and immunomodulatory properties, which may enhance adaptive immunity and reduce inflammation. However, clinical evidence on their direct impact on TB treatment outcomes remains limited and requires further investigation. **Conclusion:** Integrating Avicenna's natural treatment strategies with modern medical approaches may offer valuable adjunct therapies for TB management. Further clinical research is needed to establish their efficacy and safety in reducing TB-related complications and to explore their role in comprehensive TB treatment protocols.

*Abbreviations:* ALT, Alanine Aminotransferase; AST, Aspartate Aminotransferase; CC14, Carbon Tetrachloride; EPO, Evening Primrose Oil; FOS, Fructo-Oligosaccharides; GSH-Px, Glutathione peroxidase; Lcn2, Lipocalin 2; LDH, Lactate Dehydrogenase; MDR, Multidrug-Resistant; $PGE_2$, Prostaglandin $E_2$; PGF2α, Prostaglandin F2alpha; PM, Persian Medicine; SCFA, Short-Chain Fatty Acids; SOD, Superoxide dismutase; TB, Tuberculosis; TCM, Traditional Chinese medicine; TM, Traditional Medicine; TNF-*α*, Tumor Necrosis Factor-*α*; TXB2, Thromboxane B2; XDR, Extensively Drug-Resistant; ZSP, *Zizyphus jujube cv. Shaanbeitanzao*

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## 1. Introduction

Tuberculosis (TB) has remained a serious disease for the global human population. According to epidemiological studies, an estimated 10 million persons have TB, while 1.5 million TB-related deaths occur annually in the world [1]. The basis of tuberculosis treatment includes the use of antibacterial drugs, nutritional support including antioxidants and B vitamins, as well as prevention and treatment of elevated liver enzymes [2 - 4].

Complementary and alternative medicines, which are based on holistic viewpoints, are becoming extremely popular worldwide these days [5]. Its various branches include diet therapy and herbal supplements, manual interventions (such as massage, chiropractic, and osteopathy), and alternative medical systems [6]. The World Health Organization considers traditional medicine (TM) as a set of health measures based on plants, minerals, and other natural products that are effective in the prevention and treatment of diseases [7].

Research indicates that complementary medicines, including homeopathy and herbal remedies, can significantly reduce the harmful impact of drugs on the liver. These treatments are particularly effective in preventing liver toxicity caused by the treatment of *Mycobacterium tuberculosis* infection. Such natural products have the potential to enhance the functionality of patients suffering from multidrug-resistant (MDR) and extensively drug-resistant (XDR) tuberculosis [8 - 10].

Persian medicine (PM) is one of the holistic schools of medicine based on the theory of humors and temperament (*Mizaj*). Its main focus is maintaining health and disease prevention based on lifestyle modification [11]. To achieve this aim, it considers “the six essentials”, most important of which include exercise, diet, and sleep management. For most diseases, PM has special preventive health measures and treatment strategies [12].

Avicenna, also known as Ibn Sina or Pur Sina (980-1037 AD), was a great Persian philosopher and physician who had a scientific insight into disease treatment over 1000 years ago. In his most famous book, the Canon of Medicine, Avicenna describes TB as a kind of wound in the lungs. Then he explains that the infected patient always sweats in addition to night fever, outflow of blood from the mouth, thin hair, and hair loss, which confirms the diagnosis of tuberculosis [13].

Avicenna has also mentioned various natural remedies for the treatment of TB, including common jujube (*Ziziphus jujube*), licorice (*Glycyrrhiza glabra*), chicory (*Cichorium intybus*), honey, and raisins [14]. It should be noted that these recommendations contain high levels of antioxidants and anti-inflammatory ingredients [15 - 18].

This study aimed to examine the scientific evidence that supports the use of these natural treatments for TB treatment, given the popularity of natural products and the need for complementary treatments to improve the success rate of TB treatment.

## 2. Methods

Initially, we reviewed the "Canon of Medicine" by Avicenna to obtain relevant information regarding the TB treatment. In this regard, the chapter on lung diseases was reviewed, and the recommendations for “Sel” (tuberculosis) treatment were gathered. Then, we searched scientific databases, including PubMed, Scopus, and ScienceDirect, to explore the properties of the recommended medicinal herbs and their active ingredients without a time limit. For the keywords, the common name OR

the scientific name of the herbs AND tuberculosis were used to search the databases for the relevant evidence. Finally, the related studies were reviewed, and the main results were summarized.

## 3. Results

The main biological properties of the recommended natural substances for TB treatment have been summarized in Table 1. In the following, each herb has been explained separately.

**Table 1.** Main biological properties of medicinal herbs recommended by Avicenna for TB treatment.

| Scientific name | Common name | Activities | | | | | Results | Reference |
|---|---|---|---|---|---|---|---|---|
| | | AI | AV | AM | AA | AC | | |
| ***Ziziphus jujube*** | Jujube | + | - | + | - | + | Improve CD4, CD8, GPX, SOD | [15, 25] |
| ***Glycyrrhizin glabra*** | Licorice | + | + | + | + | + | Increase y-interferon, T- and *β*-lymphocytes | [33, 34] |
| ***Cichorium intybus*** | Chicory | + | - | + | - | + | Suppress *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Candida albicans*, and activity cytochrome P450 | [38, 43 - 48] |
| **Apis species** | Honey | + | + | + | - | + | Decreased TXB2, PGE2 and PGF2α | [54] |
| ***Vitis vinifera*** | Raisins | + | - | + | + | - | Decreased TNF- and increased Bifidobacteria, Lactobacilli, and Clostridia. | [60, 61] |

AI: Anti-inflammation; AV: Anti-viral; AM: Anti-microbial; AA: Anti-allergic; AC: Anti-carcinogen.

### *3.1. Jujube*

*Zizyphus jujuba* Mill. (Rhamnaceae), also known as red date, is distributed throughout India, Iran, Afghanistan, and China [19]. Its fruit, called jujube, is an effective herbal remedy that could improve stamina, muscular strength, and weight gain [20]. Other therapeutic effects include improvement in liver and immune system function. Dried fruits also have anticancer properties [19].

In Traditional Chinese medicine (TCM), jujube is used for the treatment of anorexia, fatigue, and loose stools [21]. It also has a high content of vitamin C, which makes it an important source of this vitamin [22]. Other vitamin contents of jujube are thiamin, riboflavin, niacin, vitamin B6, and vitamin A [21]. Compared with other edible fruits, the consumption of one fruit per day would meet the diet requirements for vitamin C and vitamin B complex for an adult man according to FAO/WHO recommendations [23].

The effect of jujube on Carbon Tetrachloride (CCl4)-induced liver injury has been previously examined to confirm its hepatoprotective activity [24]. Results of this study showed that jujube reduces the Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST), Lactate Dehydrogenase (LDH), and the hepatic malondialdehyde level in serum [21].

A study by Wang et al. in 2012 revealed that administration of jujube (at a dose of 200 or 400 mg/kg) prevents the hepatic injury in mice. In addition, using 400 mg/kg *Zizyphus jujube cv. Shaanbeitanzao* (ZSP) significantly reduced ALT, AST, and LDH. The antioxidant system with normal Glutathione peroxidase (GSH-Px)

and Superoxide dismutase (SOD) activities were also improved in the treated mice [25].

The anti-inflammatory, antimicrobial, hepatoprotective, and antioxidant activities of jujube are related to ten triterpenoid acids, including ceanothic, alphitolic, zizyberanal, zizyberanalic, epiceanothic, ceanothenic, betulinic, oleanolic, ursonic, and zizyberenolic acids in the dried fruit. In recent years, the anticarcinogenic activity of triterpenic acids has attracted researchers [21].

According to the current evidence, the flavonoids (flavonols and flavan-3-ols), triterpenic acids, and nucleoside content of jujube have key roles in the treatment of chronic disease [26]. The immunomodulatory activities of "jujube polysaccharide conjugates" have been previously investigated [27]. These compounds decrease oxidative stress because they significantly increase superoxide dismutase and glutathione peroxidase activities whilst reducing the malondialdehyde level [28]. Increasing the $CD4^+$/ $CD8^+$ T cells ratio is the other effect of jujube polysaccharide conjugates [26].

An animal study also showed that jujube enhances the expression of evening primrose oil (EPO) and EPO receptors in ischemic/reperfusion rats [29]. The daily intake of jujube can increase the dietary iron and vitamin intake to prevent anemia in infectious diseases like TB [30]. In a clinical trial, the administration of 5 cc of jujube syrup for 4 weeks was investigated in TB patients. The liver enzyme was significantly decreased in the jujube group compared with the placebo group. This study also showed that jujube can reduce the negative effects of TB treatment on the liver [31].

### *3.2. Licorice*

Scientifically named *Glycyrrhiza glabra* L. (Fabaceae), licorice contains triterpene saponins, flavonoids, polysaccharides, pectins, simple sugars, amino acids, mineral salts, microelements, and some other substances [32]. Its other constituents, glycyrrhizic and glycyrrhetic acids, are reported to stimulate the production of antibodies, and y-interferon, and contribute to T- and B-lymphocytes production [33].

Glycyrrhizin, as one of the main active ingredients of licorice root, has many pharmacological activities such as hypocholesterolemic, antimicrobial, antiviral, preliminary free radical scavenging, antiulcer, antitumor, antiallergic, antidiabetic, anticarcinogenic, antioxidant, anti-inflammatory, hypoglycemic, and hepatoprotective properties [34]. Also, glycyrrhizic acid induces a significant reduction in serum aminotransferases and improves liver function [35].

Results of a placebo-controlled trial on 216 patients with liver toxicity due to anti-tuberculosis drugs revealed that compound glycyrrhizic injection could be a safe and effective option for such patients [36]. In another clinical trial, 84 patients with hepatitis, caused by anti-tuberculosis drugs, were randomized to receive either compound glycrrhizin or glucurolactone as a complementary treatment. Although no marked difference in symptom recovery was observed at the end of the study, the liver function and the prognosis in the glycrrhizin group were better than in the glucurolactone group [37].

### *3.3. Chicory*

*Cichorium intybus* L. (Asteraceae), commonly known as chicory, is a medicinal herb cultivated worldwide [38]. This herb originated in Europe (Mediterranean region), however, it could be cultivated in all other temperate regions [38].

Chicory contains ingredients such as alkaloids, inulin, sesquiterpene lactones, coumarins, vitamins, chlorophyll pigments, unsaturated sterols, flavonoids, saponins, and tannins [39]. The chicory leaves are good sources of phenols, vitamins A, B1, B2, B6, and C as well as potassium, calcium, and phosphorus [40, 41]. This medicinal herb has hepatoprotective, anti-inflammatory, antioxidant, sedative, immunological, cardiovascular, hypolipidemic, antidiabetic, anticancer, gastro-protective, antimicrobial [42], antibacterial, and antiviral activity [43].

In addition, its roots are rich in fiber, especially inulin (a starch-like polysaccharide) [43]. Inulin is low in calories and dietary fiber; thus, it could be used as a good replacement for sugar and an ideal component of a healthy diet [44]. Inulin also has a stimulatory effect mainly on bifidobacteria and short-chain fatty acids (SCFA) production, modulating the gut microbiota [45].

Previous research has shown the antibacterial activity of *Cichorium intybus* L. against some gram-negative bacterial pathogens, including *Escherichia coli* and *Pseudomonas aeruginosa* [46]. The antimicrobial activity of chicory seed extract against *Staphylococcusaureus*, *Pseudomonas aeruginosa*, *Candida albicans*, and *Escherichia coli* has also been reported [38].

The gene lipocalin 2 (Lcn2) mediates an innate immune response to bacterial infection. In an animal study, it was up-regulated by chicory in male and female mice; a secreted protein stimulated by toll-like receptors renders bacteria. The acute infections with *Escherichia coli* H9049 respond to this feature [43].

Another important feature made by chicory is the antioxidant effect of caffeoylquinic acids [47]. The cytochrome P450 (Cyp4a31, Cyp8b1, Cyp27a1) and flavin-containing monooxygenase (Fmo5) are key components in this regard [43, 48].

*3.4. Honey*

Various studies have shown the applicability of honey as an ointment and functional food for both nutritional and medical purposes [49]. The antimicrobial activity of honey depends on the environmental characteristics; it should be stored in a cool, dark place and freshly consumed [50, 51].

Honey contains fructose and glucose as its main sugar content. Its other ingredients include minerals, proteins, phenolic acids, free amino acids, enzymes like glucose oxidase, catalase, flavonoids (e.g., quercetin, luteolin, kaempferol, apigenin, chrysin, and galangin), and vitamins such as phyllochinon (K), thiamin (B1), riboflavin (B2), pyridoxin (B6), and niacin (B3), and [52]. A daily supplemented diet with a honey serving of 1.2 g/kg body weight increases the body antioxidant agents like blood vitamin C concentration by 47 %, $\beta$-carotene by 3 %, uric acid by 12 %, and glutathione reductase by 7 % [53].

A study by Al-Waili and Boni investigated the anti-inflammatory effects of honey in humans after ingestion of 70 g of honey [53]. The mean plasma concentration of thromboxane B2 (TXB2) was reduced by 7 %, 34 %, and 35 %, and that of prostaglandin $E_2$ (PGE2) by 14 %, 10%, and 19 % at one, two, and three hours after honey ingestion, respectively. The level of prostaglandin F2alpha (PGF2$\alpha$) was also decreased by 31 % at 2 hours and by 14 % at 3 hours. At day 15, plasma concentrations of TXB2, PGE2, and PGF2$\alpha$ decreased by 48 %, 63 %, and 50 %, respectively. In an animal model of inflammatory bowel disease, honey intake decreased the inflammation [54].

In an *in vitro* study, Mycobacteria did not grow in cultures with higher percentages (such as 10 %

and 20 %) of honey in contrast with cultures containing lower percentages (i.e., 5 %, 2.5 %, and 1 %). Another *in vitro* study revealed the efficacy of a high concentration of honey on MDR TB [55]. Due to its antimicrobial and antioxidant effects, in addition to the beneficial mineral content, honey boosts the immune system, making it an ideal antimicrobial agent [56].

*3.5. Raisins*

Dried grapes or raisins (*Vitis vinifera* L.) were a common part of the human diet in the past because of their energetic value and specific nutritional compounds [57]. Raisins are rich in sugars (fructose and glucose), minerals (magnesium, iron, potassium, phosphorus, zinc), vitamins (ascorbic acid, pyridoxine, riboflavin, and thiamin), dietary fiber, prebiotics (3.3-4.5 g per 100 g), and other active molecules including flavonoids, hydrocinnamic acids, epicatechins, and resveratrol [58]. The possible effects of raisins are: contribution to body weight control and reduction of systolic blood pressure, total cholesterol, and LDL-cholesterol [57, 58].

Raisins also have antioxidant and anti-inflammatory properties [59]. A study showed that Tumor Necrosis Factor-$\alpha$ (TNF-$\alpha$), which is an important cell signaling protein involved in inflammation, was lowered significantly from 3.5 to 2.1 ng/L in the group receiving raisins [60]. The phenolic acids (caftaric and coutaric acid), flavonols (quercetin and kaempferol), glycosides, rutin, and anthocyanins have also been identified in raisins in large amounts [57].

According to the evidence, the high amounts of fructo-oligosaccharides (FOS) in raisins increase Bifidobacteria, Lactobacilli, and Clostridia. By increasing the colonization of beneficial bacteria, raisins positively affect the gut microbiota and improve gastrointestinal health [61].

## 4. Discussion

The treatment of tuberculosis (TB) remains a significant challenge worldwide, with the persistent prevalence of multidrug-resistant (MDR) and extensively drug-resistant (XDR) strains further complicating management. While conventional pharmaceutical approaches primarily focus on antimicrobial therapy, there is increasing interest in complementary and alternative treatments that might offer supportive benefits, especially in terms of immune modulation, reducing drug toxicity, and improving overall health. Persian Medicine (PM), as an ancient and holistic medical system, offers valuable insights into the treatment of TB, especially through its emphasis on the use of medicinal herbs and nutritional strategies.

*4.1. Immune-modulatory effects of herbal treatments*

A key aspect of Avicenna's therapeutic approach was the activation and modulation of the immune system, which is crucial in combating TB. The inflammation associated with TB can often lead to long-term complications, including tissue damage, diabetes, and other chronic conditions due to the pro-inflammatory cytokine storm it induces. Many of the herbs recommended by Avicenna, including jujube, licorice, and chicory, possess strong anti-inflammatory properties that could mitigate these complications by reducing inflammatory markers and enhancing immune responses.

Jujube, for example, has been shown to modulate immune cell activity, particularly through its polysaccharides, which enhance the activity of superoxide dismutase and glutathione peroxidase, reducing oxidative stress [62]. These properties are particularly beneficial for TB patients, as oxidative stress can exacerbate tissue damage and hinder immune response.

Similarly, licorice has been reported to stimulate both the production of antibodies and the activation of T- and B-lymphocytes, key players in adaptive immunity [63]. In TB, where the immune system's ability to clear *Mycobacterium tuberculosis* is compromised, these immune-modulatory effects could enhance the body's defense against the infection and promote quicker recovery.

Chicory, another herb recommended by Avicenna, is rich in inulin, which can improve gut microbiota composition by promoting the growth of beneficial bacteria. This, in turn, could enhance systemic immune responses, a vital factor in managing infections like TB. The immunological benefits of these herbs underscore the relevance of Avicenna's recommendations in modern therapeutic contexts, particularly in adjunctive treatments for TB.

*4.2. Hepatoprotective properties*

In addition to modulating the immune system, Avicenna's recommended herbs also offer significant hepatoprotective properties, which are especially pertinent given the liver toxicity associated with anti-TB drugs. Jujube has been shown to reduce liver enzyme levels and prevent liver damage induced by toxic substances like carbon tetrachloride [64]. Its antioxidant content, including triterpenoid acids, plays a crucial role in protecting hepatic cells from oxidative damage. Similarly, licorice, through its active compound glycyrrhizin, has demonstrated hepatoprotective effects by reducing serum aminotransferases and improving liver function [65].

For TB patients, who often experience liver toxicity from long-term anti-TB drug regimens, the inclusion of jujube and licorice in their diet could provide valuable support in protecting liver function, thus enhancing the overall treatment experience. The clinical trials examining glycyrrhizin's efficacy in mitigating liver toxicity [66] provide compelling evidence for the incorporation of licorice into complementary TB treatment protocols.

*4.3. Antioxidant and anti-microbial properties*

Oxidative stress is a major factor in the pathogenesis of TB, leading to tissue damage and exacerbation of the disease. Both jujube and chicory possess strong antioxidant properties, which help neutralize free radicals and reduce cellular damage. Honey, renowned for its high antioxidant content, has also demonstrated significant antimicrobial activity against various pathogens, including *Mycobacterium tuberculosis* [67]. The high phenolic content of honey contributes to its antibacterial and anti-inflammatory effects, supporting immune function and aiding in the reduction of TB symptoms.

Raisins, too, with their high concentration of antioxidants, such as flavonoids and resveratrol, have been shown to reduce inflammatory cytokines like TNF-α [68], further complementing the anti-inflammatory effects of other herbs. Additionally, raisins' prebiotic content may enhance gut health, which is vital for overall immune function. This is particularly beneficial for TB patients, as gastrointestinal health is often compromised due to malnutrition or antibiotic side effects.

*4.4. Nutritional support in TB management*

Beyond their medicinal properties, the herbs recommended by Avicenna also provide essential nutrients that can support the overall health of TB patients. Jujube, rich in vitamins C, B complex, and essential minerals, serves as a vital source of nutrition [69]. These nutrients are crucial for

maintaining energy levels and supporting immune function, both of which are often impaired in TB patients. Raisins, with their high sugar content, provide a rapid source of energy, while also supplying important vitamins and minerals that can aid in recovery [68].

Honey's nutritional profile further supports the immune system by providing essential amino acids, vitamins, and minerals, while also acting as a natural energy booster. As a food with both therapeutic and nutritional benefits, honey stands out as an excellent adjunct in TB treatment.

## 5. Conclusion

The use of herbal remedies in the treatment of tuberculosis, as proposed by Avicenna, provides a valuable perspective on integrating ancient wisdom with modern scientific research.

The evidence presented in this study suggests that jujube, licorice, chicory, honey, and raisins exhibit multiple therapeutic properties, including immune modulation, anti-inflammatory effects, antioxidant activity, hepatoprotection, and antimicrobial action. These herbs, when incorporated into TB treatment regimens, could help alleviate some of the side effects associated with conventional TB therapies, particularly liver toxicity, while enhancing the overall immune response and supporting recovery.

As the burden of TB continues to challenge global health systems, it is crucial to explore all avenues for improving treatment outcomes. Avicenna's holistic approach, combining medicinal herbs and nutritional strategies, offers a promising adjunct to conventional treatments, emphasizing the need for a multifaceted approach to TB care. Further clinical studies and trials are warranted to confirm the efficacy and safety of these herbal remedies in contemporary TB management.

## Author contributions

MAHK: Methodology, Investigation, Writing Original Draft, AA: Investigation, Reviewing; BD: Investigation, Writing Original Draft, Editing; PT: Reviewing; HRJ: Reviewing.

## Conflict of interest

There is no conflict of interest to be declared.

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