

Ethnomedicinal Plants from Iraq as Therapeutic Agents against *Mycobacterium tuberculosis*: A Review

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Abstract

Mycobacterium tuberculosis is a highly infectious pathogen, which can affect both humans and animals. The metabolic products of this bacterium affect the pulmonary, nervous, lymphatic, and cardiovascular systems. The aim of this review is to provide information on certain local herbs from Iraq, which have been found to be effective against *Mycobacterium tuberculosis*. In this report, we have reviewed 13 medicinal plants and their anti-mycobacterial activities. The family, traditional medicinal uses, common local names, *in vitro* activity of the crude extract, and information about bioactive chemical composition of these plant species have been described. The crude extracts of these medicinal plants can be used to develop novel drugs against tuberculosis.

Keywords: Medicinal plants; *Mycobacterium tuberculosis*; Anti-mycobacterial activity; Iraq.

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INTRODUCTION

Mycobacterium tuberculosis is an acid-fast, Gram-positive bacterium that does not form spores; it causes a zoonotic disease known as tuberculosis (TB) in both humans and animals¹. The disease attacks several organs in the body such as the lungs, skeletal system, brain, lymphatic system, and cardiovascular system. The severity of this disease depends on certain factors, which include the genetic characteristics of the host, environmental factors, and genetic polymorphisms². Iraq is one of the countries with high incidence of TB among the countries in the Eastern Mediterranean Region³. A WHO report estimated an incidence rate of approximately 20,000 TB patients with a combined mortality of more than 4000 each year. Moreover, the estimated number of multiple drug resistance-tuberculosis (MDR-TB) cases is approximately 6.1% of all the newly reported TB cases⁴. A previous study showed the prevalence of TB in Baghdad between 2012 and 2016 and concluded that these cases occur more frequently in women than in men³. This may be due to lack of safety, low individual economic status, irregular treatment courses, and also because many cases go unreported. The incidence of the disease can be improved by detecting the disease early, implementing adequate therapy, as well as educating the people about the modes of disease transmission⁵⁻⁷.

Irrespective of whether the TB is latent or active, antibiotics are generally used for treating the infected patients. The drugs used against TB include first, second and third-line common antibiotics such as isoniazid, rifampin, pyrazinamide, ethambutol, streptomycin, amikacin, kanamycin, capreomycin, quinolone, and ethionamide⁸. However, these antibiotics have severe side-effects and *Mycobacterium tuberculosis* can easily develop resistance towards these drugs. In addition, the condition of most patients starts declining within a year of treatment due to non-compliance with the medication course, resulting in a more severe, antibiotic-resistant condition⁹⁻¹¹. Due to the resistance mechanism of *Mycobacterium tuberculosis*, it sometimes occurs along with HIV infection, and hence, there is an urgent need to develop novel therapeutic agents. Active compounds isolated from herbal sources can be effective and might be

used as substitutes for the antibiotics used against TB¹²⁻¹⁴.

METHODOLOGY

The information in this article takes the reader through the following keywords: “extract”, “medicinal plants” and “anti-mycobacterial”. We searched for these keywords using electronic databases including Science Direct, Google scholar, PubMed and Scopus. We included both *in vivo* and *in vitro* studies in our review.

Ethno-therapy for treatment of tuberculosis caused by *Mycobacterium tuberculosis*

We selected 13 plants, which have been known to have potential inhibitory effects on *Mycobacterium tuberculosis*, in this study. Between the years 2000 and 2018, the reports published in Iraq included the following medicinal plants: *Apium graveolens*, *Arachis hypogaea*, *Arganiaspinosa* L, *Camphor*, *Cinnamomum cassia*, *Commiphora molmol*, *Cuminum cyminum*, *Lepidium sativum*, *Linum usitatissimum*, *Nigella sativa*, *Pimpinella anisum*, *Piper nigrum*, and *Trigonella foenumgraecum*.

Apium graveolens

In Iraq, this plant is known as Karafs and its common English name is Celery. It is commonly cultivated in the European region as a food crop and it is also grown in Algeria, Egypt and the central region of Kingdom of Saudi Arabia (KSA)¹⁵. The seeds of *Apium graveolens* have been largely used in local and traditional medicine to treat hepatic disorders, jaundice, arthritis, high uric acids levels and many inflammatory diseases¹⁶⁻¹⁸. Previous ethnomedicinal studies have shown that celery alleviates digestible disturbances, central nervous system and cardiovascular disorders, and also has antimicrobial, anti-inflammatory, and several other pharmacological effects¹⁹⁻²¹. This study reviewed the effects of this plant on *Mycobacterium tuberculosis* using 200 mg/ml of whole-plant extract made using 70% ethanol and found that it inhibited the growth of MTB (only 20 colonies appeared after an incubation period of 4 weeks)²².

Arachis hypogaea

This plant species is a member of the Fabaceae family, which is known as **Fustik Abeed and Fustic wdani** in Arabic and its common English names are **groundnut/peanut**. It is mainly grown

in tropical countries and also cultivated in some sub-tropical areas in different parts of the world²³. The parts of this plant have several traditional medicinal uses such as the use of peanut oil to treat crust formation in certain skin diseases, for neonatal care, to relieve itching of dermal areas in cases of eczema and dry skin²⁴. Modern research on the peanut plant extract has shown its antioxidant properties and *in-vitro* studies have shown that it possesses free radical scavenging, anti-microbial, anti-parasitic and anti-inflammatory properties²⁵⁻²⁷. Further clinical research has shown that peanut skin has an anti-allergic effect as it contains large amounts of polyphenols^{28, 29}. The application of 70% ethanol extract of this plant on *Mycobacterium tuberculosis* (MTB) at 200 mg/ml concentration showed no growth of MTB²².

Arganiaspinosa L.

This plant is a small tree from the Amaranthaceae family. It grows in North African regions, especially in Morocco, and the oil-producing varieties of this plant can also be grown in jungles. In its native country, this plant is traditionally used for nutritive as well as several other purposes³⁰. On the other hand, modern uses of argan oil, produced by this plant, have shown anti-bacterial activity on diseases involving *Staphylococcus aureus* (MRSA) and *Pseudomonas aeruginosa* infections^{31, 32}. In addition, several papers have mentioned the activity of argan oil in different diseases such as cancer, heart disease, diabetes and thyroid hormone disturbances³³. The current review aims to elucidate the effects of argan oil against *Mycobacterium tuberculosis*. Its therapeutic effects depend on its rich chemical composition including oleic, linoleic, palmitic, stearic and linolenic acids and mixtures of these chemicals at concentrations of 2.5:7.5 and 3:7 yielded good inhibitory effect on *Mycobacterium tuberculosis*³⁰.

Camphor

This chemical is from a plant belonging to the Lauraceae family and it is derived from the camphor wood laurel tree. It is white in color, crystalline in texture, has a specific odor and intense taste³⁴. The tree is natively cultivated in India, Mongolia, Japan, Taiwan, and also in the Southern region of USA³⁵. The essential oil from this plant has been traditionally used to soothe muscle pain, joint conditions, dermatological

conditions, cold, and bronchial congestion³⁶. Latest studies have shown its pharmaceutical applications as an analgesic, antipyretic, anti-inflammatory, anti-spasmodic, mild expectorant and for alleviating nasal disorders^{35, 37}. The volatile oil, which has major medicinal properties, contains safrole, linalool, eugenol, and terpineol and the leaf of the plant is also a powerful source of linalool (94.9%)³⁸. The camphor plant extract showed clear activity at 200 mg/ml concentration against MTB with only 18 colonies appearing after an incubation period of 4 weeks²².

Cinnamomum cassia

This plant is classified under the Lauraceae family. It is commonly known as Chinese cassia, and it is cultured in various regions in the world. It is harvested from the inner cortex of the tree belonging to the genus *Cinnamomum*³⁹. The cinnamomum plant has been used for the oldest traditional herbal medicine used and it is also used in mouth fresheners and chewing gums for its flavor^{40, 41}. In addition, the cinnamon plant improves digestive ability and reduces colon disorder^{42, 43}. All parts of the cinnamon tree, including the leaves, bark, root, or fruits, possess medicinal properties. The bark and leaves contain the volatile oils in large amounts with chemicals having medicinal and pharmaceutical properties such as antimicrobial, antioxidant and anti-inflammatory activities^{41, 44}. Latest studies elucidating the local uses of *Cinnamomum* plants have shown that they have anti-tuberculosis activity⁴⁵.

Commiphora molmol

This plant is classified under the Burseraceae family and its common name **myrrh** is derived from the Arabic word **Mur**. Various species of the Commiphora plant are cultivated in different regions of the world⁴⁶. The traditional medicinal use of this genus Commiphora includes treatment of headache, wound care, joint pain, bone fractures, and diarrhea⁴⁷. Latest research shows that the active compound of commiphora extract has anti-cancer activity and *in vitro* experiments have shown its anti-microbial activity^{48, 49}. Latest studies on the application of *Commiphora molmol* in treating tuberculosis have shown its activity against clinical isolated TB sample at 200 mg/ml concentration, resulting in no growth of MTB²².

Cuminum cyminum

This plant species is a member of the Apiaceae family, which is known as Kamoun in Arabic and as Cumin in English⁵⁰. It is cultivated and grown in the MENA regions - Middle East and North Africa. In addition, the plant is also grown in the United States of America, India and China^{50,51}. The traditional medicinal uses of cumin include as a treatment for diarrhea and jaundice, and it also has diuretic and astringent properties. The oil of the cumin plant is used in food manufacturing for making cheese and soups⁵². The extract of the cumin seed has anti-microbial and bactericidal properties, as shown by *in vitro* experiments⁵³. Through phytochemical analysis of the parts of this plant, the phenolic content in the methanol extract was evaluated and found to exhibit anti-oxidant and anti-inflammatory activities^{54, 55}. The crude plant extract made using 70% ethanol at 200 mg/ml concentration completely inhibited the growth of MTB after an incubation period of 4 weeks²².

Lepidium sativum

This species of herbs is a common garden plant. It is classified under the Brassicaceae family and is found in countries like Africa and Ethiopia. However, it can also be found in different parts of the world such as Southwest Asia⁵⁶. The plant has several names including garden pepper cress, pepperwort and El Rashad⁵⁷. It is used in the Arabic countries as traditional medicine to treat asthma, cough, bronchitis and as an expectorant^{57, 58}. The chemicals found in this plant, such as oleic acid, stearic acid, linoleic acid and ascorbic acid, have several pharmaceutical effects. All of the chemicals have significant diuretic, anti-inflammatory, anti-diarrheal, anti-microbial, analgesic and laxative activities⁵⁹⁻⁶¹. Through whole plant extraction using 70% ethanol solvent, its activity against MTB was shown; at 200 mg/ml concentration, it completely suppressed MTB growth (no colonies seen)⁹.

Linum usitatissimum

This particular plant species has been cultivated for its oil since a long time. Its common name is flax or linseed and it belongs to the Linaceae family⁶². The flax plant is native to Egypt and it is commonly distributed between the Arabic gulf and Red Sea. However, it can also be found in certain other countries like India, Pakistan, and Afghanistan⁶³. There are quite a few traditional medicinal uses of *Linum usitatissimum*

and it has several therapeutic benefits such as an anti-tussive, laxative, expectorant, and diuretic⁶⁴. The linseed shell is characterized by its shape, which is hard with different colors. Its chemical composition is as follows: 41% fat, 28% fiber, and 20% protein with high internal polyunsaturated fatty acids content⁶⁵. In modern therapy, there are abundant data available on the properties of flaxseed such as its anti-coagulant, anti-diabetic, anti-microbial, anti-oxidative activities as well as its nephro-, hepato- and cardio-protective effects⁶⁶⁻⁶⁸. The ethanol extract of flax plant showed anti-tuberculosis activity at 200 mg/ml concentration and only 25 MTB colonies grew after the 4-week incubation period²².

Nigella sativa

This plant is commonly known as black seed in Arabic and its common English name is black cumin⁶⁹. It is a herb belonging to the Ranunculaceae family⁷⁰. *Nigella* seeds have been used to improve human health, particularly in the Middle Eastern countries. This plant species is cultivated in many areas in the world, especially in Arabic countries. It has been, in fact, mentioned by Prophet Mohammed as having the property to enhance physical power and health^{71, 72}. *Nigella sativa* is commonly used in traditional medicine as a diuretic, and as a cure for liver disorders, digestive system problems, fever, and jaundice^{72, 73}. Different studies describing the modern applications of the black nigella seeds have shown that it has therapeutic activity against several conditions such as bacterial, fungal, parasitic, and viral infections as well as in metabolic disorders, hypertension, diabetes, gastrointestinal disease and hepatic disorders^{69, 72}. The published articles on the black seed plant show chemical composition consisting of high oil content of approximately 28 to 36% as well as different bio-active chemicals such as flavonoids and saponins. The pharmaceutical benefits exerted by these phytochemicals include anti-cancer, anti-microbial, anti-inflammatory, anti-oxidant and detoxifying activities^{73, 74}. This plant is also effective against *Mycobacterium tuberculosis* and it showed significant inhibitory effect at a concentration ratio of 2.5:7.5 and 3:7 after completion of the incubation period⁷⁵.

Pimpinella anisum

Pimpinella anisum is one of the oldest herbal medicinal plants that belongs to the

Umbelliferae family. It is grass-like in shape and is about 50 cm in length. Its common English name is **anise**⁷⁶. *Pimpinella anisum* is grown and cultivated in various areas such as Asia, Middle Eastern regions like Iran and Egypt. It has also been reported to grow in Europe and Mexico⁷⁷. Every year, the anise fruit is harvested between August and September. Its traditional medicinal uses include alleviation of various conditions such as digestive disorders, GIT spasms, and constipation and also to increase the breast milk production in women^{76, 77}. The secondary metabolism products of this plant consist of various chemicals with anti-microbial and anti-oxidant activities [78-80]. Several studies in the medical field have shown that the essential oils of this plant have many positive health benefits such as anti-inflammatory, analgesic, anti-convulsant and hepatoprotective activities⁸¹⁻⁸³. The 70% ethanol whole-plant extract along with distilled water showed significant inhibitory activity at 200 mg/ml concentration against MTB growth in the 4-week incubation period as only 3 colonies were seen²².

Piper nigrum

Piper nigrum is commonly known as black pepper and it is considered to be the oldest medicinal herb in the world. It is grown in different regions like Asia, Europe and Africa⁸⁴. In Arabic, it is known as Filfil Aswad and it belongs to the Piperaceae family⁸⁵. It has several important uses in traditional medicine and has been used to treat preclinical cases such as asthma, skin disorder, sore throat, snake bite and as an antipyretic medication⁸⁶. The black pepper seed contains several potent chemicals. Many studies have shown that it has anti-bacterial, anti-diarrheal, anti-colic, anti-fungal and anti-inflammatory activity against various infectious diseases^{87, 88}. In this review, we have shown the anti-mycobacterial activity of *Piper nigrum*, which has potent inhibitory activity at 200 mg/ml concentration and suppresses the growth of MTB with only 4 colonies seen after the 4-week incubation period²².

Trigonella foenum-graecum

This medicinal plant, commonly known as fenugreek, is considered to be one of the oldest plants used in traditional medicine. It belongs to the Papilionaceae family⁸⁹. It is cultivated throughout the world due to its adaptive behavior⁹⁰. Although it is grown worldwide under various climatic

conditions, it is especially found in Asia and Africa. Due to its widespread distribution, its medicinal role has been well documented. For instance, in Iran, the extract of this plant is used to lower blood sugar level⁹¹. In China, its seeds are used to treat digestive disorders, gastritis, and gastric ulcers and also, in food manufacturing⁹⁰. Several studies have reported the bioactive chemicals found in this plant and have shown their applications in the medical field. Furthermore, it has many pharmacological activities such as hypoglycemic, anti-diabetic, anti-lipidemic, anticancer, anti-microbial and anti-inflammatory activities^{92, 93}. The plant has clear anti-mycobacterial effect as after completion of the entire incubation of 4 weeks, no MTB growth was seen when it was used at 200 mg/ml concentration²².

CONCLUSION

It is evident that the aforementioned herbal medicinal plants from Iraq exhibit anti-mycobacterial activity and hence, can be used against *Mycobacterium tuberculosis*. There is a significant positive correlation between the traditional used of medicinal plants and their anti-mycobacterial activity. Further research in the field of modern pharmaceutical science should be conducted to isolate and identify the bioactive chemical compounds from these plants. We expect that these findings will encourage the researchers to engage in drug discovery and develop novel natural products that may eventually facilitate the development of a novel anti-TB drug.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

FUNDING

None.

DATA AVAILABILITY

All datasets generated or analysed during this study are included in the manuscript.

AUTHORS' CONTRIBUTION

All authors have made substantial, direct and intellectual contribution to the work and approved it for publication.

ETHICS STATEMENT

This research article does not contain any studies involved with human participants or animals.

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