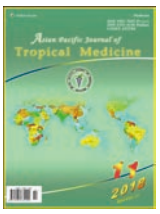

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Brucellosis: Pathophysiology and new promising treatments with medicinal plants and natural antioxidants

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ABSTRACT

Brucellosis is an old, infectious and common zoonosis whose causative agents are Gram-negative bacteria from the *Brucella* genus. Brucellosis is transmitted through direct contact with infected animals or using unpasteurized dairy products of goats, pigs, camels, sheep, buffalo and cows. Brucellosis is still the most common zoonosis in the world, with most of cases occurring in developing countries. Today, an approach to traditional medicine and medicinal plants, especially with regards to the repeated recommendations of the World Health Organization, is a necessity. One-third of chemical drugs are produced by using plants and there is a high potential to produce more drugs from plants. Medicinal plants are helpful in the management of various conditions, especially bacterial diseases. Although there is not enough scientific evidence regarding the clinical effectiveness of herbal drugs for the treatment of brucellosis, there is strong evidence on the antimicrobial effects of herbal drugs to prevent infection. Therefore, this article seeks to describe the antibacterial effects of some plant-derived essential oils or extracts, so that they can serve as promising choices to develop new anti-*Brucella* medications, as suitable alternatives to conventional antibiotics for brucellosis, as much as possible, taking into account the benefits of these herbal drugs.

1. Introduction

Brucellosis is an old, infectious and common zoonosis whose causative agents are Gram-negative bacteria from the *Brucella* genus. Brucellosis is transmitted through direct contact with infected animals or using unpasteurized dairy products of goats, pigs, camels, sheep, buffalo and cows. People working in slaughterhouses or veterinarians are at high risk of developing the disease. Brucellosis is more common in children than in adults[1,2] Non-specific symptoms of brucellosis include fever, chills, restlessness, headache, fatigue and weakness[3-5]. One of the most common symptoms of this disease is bone involvement that is seen in over half of the affected people[6]. The association between *Brucella* and brucellosis was first discovered by an army surgeon named David Bruce. He isolated bacteria from the spleen of patients in Malta from 1886 to 1887. Brucellosis is still one of the most common zoonosis in the world and more than 500 000 cases each year are diagnosed with the disease, most of whom live in developing countries. The number

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of brucellosis cases are over 10 000 000 people in some countries where brucellosis is endemic[7,8]. Centers for Disease Control and Prevention has classified brucellosis as a category B bioterrorism agent due to its easy transmission[9].

The disease cycle can be acute, sub-acute or chronic[10]. Four different *Brucella* species, *i.e.*, *Brucella suis (B. suis)*, *Brucella melitensis (B. melitensis)*, *Brucella abortus (B. abortus)* and *Brucella canis* can be pathogenic to humans[11]. Among these species, *B. melitensis* is the most contagious species, followed by *B. abortus* and *B. suis*[9]. *Brucella* species are intracellular, obligate and Gram-negative coccobacilli and are not able to produce spores[12]. *Brucella* species have no classic virulence genes encoding capsules, plasmids, pili or exotoxins, and because of factors that cause the bacteria to acquire resistance to phagocytes and increase the proliferation of phagocytic cells, they are relatively less known than other pathogenic bacteria[13].

The O-polysaccharide chain on the lipopolysaccharide layer plays an important role in pathogenicity of the bacteria. The O-polysaccharide chain of *Brucella* prevents complement accumulation on bacterial surfaces[14,15]. This is done by preventing the C1q access to the external surface of the targeted proteins; and a study led to the hypothesis that the size of the O chain acts as a protective factor against the complement system[16]. *Brucella* lipopolysaccharide protects the bacteria against antibacterial cationic peptides in addition to blocking the pathway for activation of the complement. It has been shown that brucellosis is resistant to a large variety of peptides such as defensin NP-2, lactoferrin, cecropines lysozyme, bactenecin-derived peptides, defensin-like antibiotic polymyxin B, as well as lysosomal compounds produced from polymorphonuclear leukocytes[17,18]. By controlling the adenine and guanine monophosphate systems, the bacteria prevent the integration of phagolysosomes, the release of myeloproxidase, and production of tumor necrosis factor (TNF), and thus cause the disease[19]. *Brucella* can survive inside certain macrophages in certain ways. It protects itself against the host immune system in certain ways such as stopping macrophage apoptosis, suppressing T1 specific immune responses and inhibiting TNF- α production[20-22]. *Brucella* should prevent Th1 polarization in order to protect itself against the activation of macrophages and the production of cytotoxic T cells. Polarization of the immune system is accomplished by cytokines that are rapidly produced by infected macrophages. Therefore, stopping the expression of cytokines such as TNF is one of the methods of the pathogens to fight the immune system[20,23]. Investigation of *B. suis*-infected monocytes revealed that the expression of the *A1* gene, which is one of the genes of the *bcl-2* family, increases in these cells, and contributes to the survival of the cells and, consequently, resistance to apoptosis. *B. suis*-infected cells are also resistant to the signaling of Fas ligand or apoptosis-inducing interferon gamma, which protects the host cell against different cytotoxic processes of the immune system[17].

Brucellosis is a systemic disease with a wide range of clinical symptoms so that it can be asymptomatic or cause life-threatening symptoms[24,25]. Symptoms include headache, fever, sweating, weight loss and back pain; and the most commonly observed symptoms due to the disease are meningitis, dizziness, hepatomegaly, hypoesthesia and splenomegaly[26]. Due to the specific characteristics of the bacterium, *Brucella* is one of the most important causes of fever of unknown origin[27,28]. This disease can involve various organs in the body. Bone involvement is the most commonly observed involvement in half of the people with brucellosis[29,30]. The mortality rate from brucellosis is less than 1% and the most common cause of death is heart involvement. Brucellosis also causes certain disorders such as endocarditis, pericarditis, myocarditis, and inflammation of the walls of the veins and arteries[31,32].

Nervous system disorders occur in 10% of patients and can lead to meningoencephalitis, myelitis, cerebellar involvement, cranial nerve palsy, stroke, spinal cord atrophy, chronic and acute meningitis, polyradiculoneuropathy and paraplegia. Neurological disorders, especially in the white matter, are due to immune responses to bacteria[33-35]. It can also affect the genitourinary system. Genital tract infections include testicular and epididymal inflammation, renal and testicular abscesses, prostate inflammation, glomerulonephritis and calcified nodules, which are observed in 2%-20% of the patients. The cause of epididymal inflammation is the presence of various sugars similar to erythritol in the epididymis, because bacteria need this sugar for growth[36,37]. In addition to the aforementioned disorders, this disease also causes a lot of hematologic disorders, including lymphocytosis, leukopenia, leukocytosis, thrombocytopenia, increased erythrocyte sedimentation rate and anemia; hematologic disorders are caused by hemophagocytosis, microgranuloma and hyperplasm[38]. Liver is another organ that can be involved in brucellosis. Hepatomegaly and splenomegaly have been reported in 63% and 56% of patients, respectively. Cirrhosis of the liver, hepatic parenchymal necrosis and hyperplasia of Kupffer cells are also some of the studied liver involvements[39,40].

Each year more than 500 000 people acquire brucellosis and most of them live in the Mediterranean region, the west and central Asia, certain parts of Africa and Latin America[4], as well as some Asian countries including Syria, Iraq, Iran[41] and Mongolia[42]. The overall prevalence has been reported to be high but the prevalence in China and South Korea is low[43]. However, the disease remains endemic in some areas of the two countries[44]. Brucellosis is more common in men due to their greater activity than women and children[45]. Brucellosis is an important disease in the Sub Saharan countries and has been reported in almost all African countries[46].

There is strong evidence on the antimicrobial effects of herbal drugs to prevent infection. Furthermore, oxidative stress and inflammation are involved in a lot of diseases[47-49]. Hence, medicinal plants which usually have antioxidant activity, should have more benefits in infectious diseases which mostly are associated with inflammation. This article seeks to introduce the antibacterial effects of some plant-derived essential oils or extracts, so that they can serve as promising choices to develop new anti-*Brucella* medications, as suitable alternatives to conventional antibiotics for brucellosis, as much as possible, taking into account the benefits of these herbal drugs.

2. Retrieve methods

To do this systematic review, the databases such as Web of Science, PubMed, PubMed Central, Scopus, Science Direct and Google Scholar were searched for articles on etiology, pathology and epidemiology of brucellosis, as well as the role of herbal drugs in treating undulant fever without publication time constraints. Words or keywords that were used separately in the title/keywords/abstract to retrieve articles were medicinal plant, herb, herbal medicine, traditional Chinese medicine, traditional medicine, natural medicine, phytochemical, herbal drugs and brucellosis, Malta fever, brucellosis etiology, brucellosis epidemiology and brucellosis pathology. Retrieved articles were once again analyzed. The abstracts were examined for the pre-determined inclusion and exclusion criteria. Articles without English abstract and full text were excluded from the analysis. Only the articles that mainly addressed the effect of medicinal plants and their derivatives on the control of the *Brucella* were analyzed.

A total of 155 articles were retrieved articles from databases. After analysis, 28 articles were deleted for the following reasons: repeatability and old age of publication of articles (16), lack of summaries (5) and lack of access to their full text (7). In the end, 127 articles directly affect the effect of herbs and their derivatives on the control of *Brucella* bacteria were selected for the study of cytological overview.

3. Plants used in treating brucellosis

The use of medicinal plants has increased among adults and children in recent years, so that approximately 4 per every 10 Americans use alternative therapies such as medicinal plants[50]. More than one-third of chemical drugs are produced from plants and there is a high potential to produce more effective drugs from them. Medicinal plants are used to treat various diseases such as rheumatic disorders, acquired immune deficiency syndrome, cancer, depression and bacterial diseases[51, 52]. Due to low resistance to high temperatures and the carcinogenicity of some of the synthetic compounds, today, attention has been drawn to the use of natural antioxidants. Hence, a list of the most important medicinal plants which are effective against *Brucella* and have the potential to use as anti-*Brucella* remedies are presented (Table1).

3.1. Alhagi camelorum (A. camelorum)

A. camelorum is a perennial shrub with a relatively deep creeping root and is used as a traditional drug for diuresis or to remove kidney stones and pain[53]. The aqueous extract of the plant at 500 mg/mL caused an minimum inhibitory concentration (MIC) of 27 mm within 48 h under 37 ℃ [54].

3.2. Allium sativum (A. sativum)

A. sativum grows around the world depending on seasonal changes,

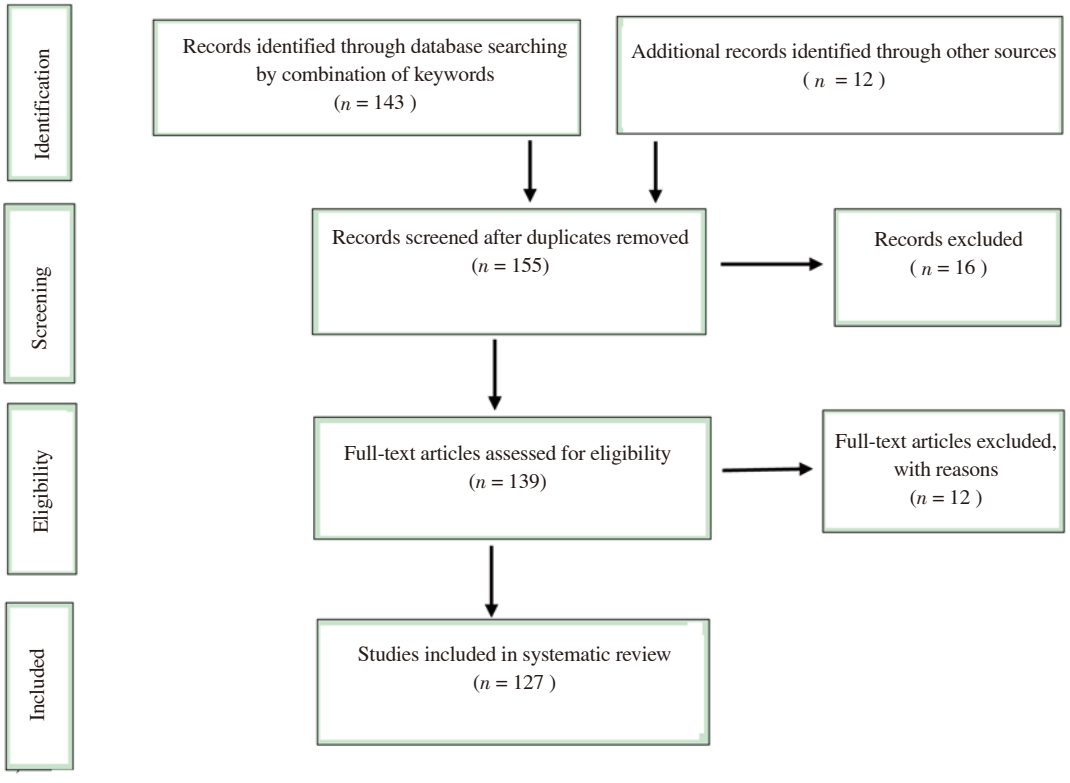

Figure 1. The criteria and the number of entry and exit articles.

however, its production is limited by the region and the type of weather. The plant is cultivated in autumn and is harvested in the summer[55]. Shapoury *et al.* reported the effect of chloroform *A. sativum* extract on *B. melitensis* (Rev1) and *B. abortus* (S19). In that study, chloroform *A. sativum* extract at dilutions of 1:10 to 1:160 could inhibit the growth of *B. melitensis* (Rev1) and *B. abortus* (S19) at 37 ℃ within 3 d. It was also found that the *A. sativum* extract could inhibit both *Brucella* species at 4 ℃ and 37 ℃ after 2 h growth[56].

3.3. Arctium lappa (A. lappa)

A. lappa, a herbaceous plant with large leaves and long root, is used orally as a medicine. In a study, the effect of *A. lappa* extracts on *B. melitensis* 16 M within 72 h was investigated. The aqueous extract of the plant at 544 mg/mL at dilutions of 1, 1:2, 1:04, 1:08, 1:16 and 1:32 caused no growth inhibition zone, but the ethanol extract of its leaf at 101.875 mg/mL and dilutions of 1, 1:2, 1:04, 1:08 and 1:16 could cause growth inhibition zones of 27.5, 16.0, 14.0, 12.0 and 4.0 mm, respectively. While the acetone extract of its leaf at 109.5 mg/mL in dilutions of 1, 1:2 and 1:4, caused growth inhibition zones of 15.5, 12.0 and 8.0 mm, respectively. Aqueous *A. lappa* extract at 259 mg/mL had no effect on inhibition of *Brucella*, but the ethanol extract of the plant at 116.25 mg/mL in dilutions of 1, 1:2, 1:04 and 1:08 caused growth inhibition zones of 24.5, 18.0, 12.0 and 10.0 mm, and the acetone extract at 200 mg/mL in dilutions of 1: 1: 2, 1: 4 and 1:8 caused the growth inhibition zones of 18.0, 12.5, 11.0 and 10 mm[57].

3.4. Berberis integerrima

Berberis integerrima is a deciduous shrub that reaches a height of 5 m, has egg-shaped leaves, yellow flowers and bark and red fruits, growing in the Middle East and central Asia[58]. In a study, the effect of the active ingredients of *Berberis integerrima* on *B. abortus* (RB-51) after 17 h incubation at 37 ℃ was investigated. Finally, the MICs of the compounds palmatine, berberine, columbamine and jatrorrhizine at 620, 500, 250 and 120 μg/mL were 6.25, 1.56, 3.12 and 0.78 mm, respectively[59].

3.5. Caraway (Carum carvi L.)

Carum carvi is an andromonoecious plant that occurs in many countries in Europe, Asia and Africa, and is traditionally used to produce oil and also is used for pharmaceutical purposes[60]. The essential oil of this plant at 0.3-2 mg/mL has been reported to inhibit the *B. abortus* isolated from the cattle[61].

3.6. Citrullus colocynthis

Citrullus colocynthis is a desert and perennial plant that spreads in African and Arab countries and India. The fruits of this plant are fleshy with dark green spots and usually yellow when they are ripened. The ethanol extract of *Citrullus colocynthis* at 25 mg/mL was able to cause a growth inhibition zone of 15 mm in diameter for 24 h under (35 ± 2) ℃[62].

3.7. Eucalyptus globulus (E. globulus)

E. globulus is a evergreen tree native to Australia that is also widely found in Spain, Portugal, Italy and India, and is used in traditional medicine for the treatment of common infections[63]. In a study, the effects of ethanol, aqueous and acetone extracts of *E. globulus* leaf on *B. melitensis* M16 and *B. abortus* S99 were examined for 5 d at 37 ℃. All extracts of the plant in a dilution of 1: 5 (for the acetone extract at 166 mg/mL and for the ethanol extract at 162.4 mg/mL) caused growth inhibition zones of 25, 30 and 30 mm in diameter and the aqueous extract in a dilution of 1: 320 produced no effect, but the ethanol and acetone extracts caused growth inhibition zones of 15 and 10 mm in diameter for the 16 M strain.

The aqueous, ethanol and acetone extracts of this plant at 1: 5 dilution caused growth inhibition zones of 22.5, 27.5 and 27.5 mm and the ethanol and acetone extracts at the dilution 1: 320 growth inhibition zones of 10 and 14 mm for *B. abortus* S99, but its aqueous extract at this dilution was ineffective. The aqueous extract of this plant at a dilution of 1:40 (21.62 μg/mL) caused a growth inhibition zone of 20 and 17 mm for the 16M and S99 species. Ethanol extract of *E. globulus* produced the greatest effect on both *Brucella* strains followed by the acetone and aqueous extracts[64].

3.8. Humulus lupulus (H. lupulus)

H. lupulus grows in the northern hemisphere, with its best growing conditions in moderate humid climates. *H. lupulus* has crossed leaves with leaf-stalk up to 7-12 cm in size. Male and female flowers of this plant grow on separate plants and the antimicrobial properties of the plant are mainly due to its acids[65]. Shapouri *et al.* have shown that *B. abortus* and *B. melitensis* were more susceptible to the flower or cone extract of *H. lupulus*. Various forms of the *H. lupulus* extract (aqueous, ethanol and acetone) have had more than 3 mm of inhibition zone in dilutions of 1:10 to 1: 320 for both species of *Brucella* and the ethanol extract had the greatest effect. The aqueous extract of *H. lupulus* in dilutions of 1:10 to 1: 640 affected *B. abortus* and *B. melitensis* within 24 hours, while the acetone and ethanol extracts of the plant have been found to affect in dilutions of 1:10 to 1: 1 280 within 24 h[66].

3.9. Juniperus oxycedrus L.

The MIC of the methanol extract of *Juniperus oxycedrus* leaf at 300 μg/disc was determined to be 8-13 mm at 37 ℃ within 24 h, indicating a strong anti-*Brucella* effect relative to the MIC of 12 mm determined for the antibiotic sulbactam used as a control. However, the aqueous *Juniperus oxycedrus* extract was ineffective[67].

3.10. Mentha piperita, Origanum majorana, Myristica fragrans, Cinnamomum verum and Citrus limon (C. limon)

In a study, the effects of different plants such as *Mentha piperita*, *Origanum majorana*, *Myristica fragrans*, *Cinnamomum verum* and *C. limon* on *B. abortus* 544 were investigated. The inhibitory effect of 1% essential oil of the bark of *Cinnamomum verum* persisted after 24-144 h following infection[68]. This plant is an evergreen plant belonging to the Lauraceae family, has anti-allergic and antipyretic properties, and grows in the tropical regions of Africa and Asia[69]. *Mentha piperita* is a perennial plant and native to Europe, northern America and Canada, has a variety of colors, with fragrant leaves and can grow up to 30-90 cm[70]. It was observed to reduce bacterial growth within 4-144 h. *C. limon* is a tree of 3-6 m, and its 1% essential oil is able to inhibit bacterial growth within 48-96 hours[68]. *Origanum majorana* is a perennial and resistant plant that grows wildly in Egypt, eastern Mediterranean region, and northern Europe with mulching materials. The 1% essential oil of its leaf, along with 0.1% essential oil of cinnamon, was able to reduce bacterial growth within 24-144 h[71]. The 1% essential oil of *Myristica fragrans*, an evergreen that is native to tropical region such as Indonesia, along with *C. limon*, produces a synergistic effect to inhibit *B. abortus* 544[68].

3.11. Lavandula pubescens (L. pubescens)

In a study, the effect of raw extracts of *L. pubescens* aerial parts, which has almost oval leaves and is found mostly in the Middle East, on *B. abortus* (CMCC 210101) was studied. The MICs of the ultrasonic-microwave extract of *L. pubescens* at concentrations of 10 and 20 mg/mL were (4.11±0.30) and (7.12 ± 0.40) mm, respectively. The MICs of the ultrasonic-homogenizer extract of the plant at concentrations of 10 and 20 mg/mL were (11.3 ± 0.3) and (12.3 ± 0.4) mm, respectively; and finally, the MICs of the maceration extracts at concentrations of 10 and 20 mg/mL were (10.9 ± 0.4) and (11.9 ± 0.5) mm at 37 ℃ within 22 h[72].

3.12. Nepeta cataria (N. cataria)

N. cataria is a perennial plant with white to pink flowers and spreads in the eastern Mediterranean regions, western Himalayas, central Asia, southern Siberia and China. The essential oil of *N. cataria* at 10 μL caused a 10 mm growth inhibition zone diameter within 24 h under 37 ℃[73].

3.13. Nigella sativa (N. sativa)

N. sativa is from the Ranunculaceae family and is found in abundance in the Mediterranean region and southern parts of Asia, India, Egypt and Syria, and grows up to 20-30 cm. It has large fruits, each containing 3-7 follicles that contain a large number of seeds[74]. Due to the ability of *Brucella* to grow at low temperatures, Alsawaf *et al.* examined the growth rate of the bacteria in the presence of *N. sativa* in white cheese in freezer [(2 ± 5) ℃]. In that study, *N. sativa* oil and seed were found to be able to inhibit *B. melitensis*, and the oil produced a more potent effect. After two days, cheese with 1% of seed (1% of the total cheese content), cheese with 0.3% oil (percentage of total cheese content) were able to reduce *B. melitensis* growth[75].

3.14. Oliveria decumbens

Oliveria decumbens occurs in south and southwest Iran, is endemic in Iran and is traditionally used to treat diarrhea and fever[76]. The MICs of the ethanol and methanol extracts of this plant at 50, 100, 200 and 400 mg/mL were 8, 10, 13 and 16 mm and 9, 12, 14 and 17 mm, respectively[71].

3.15. Origanum acutidens (O. acutidens)

O. acutidens that grows mostly in calcareous and non-calcareous stones at an altitude of 1 000-3 000 m is an important genus of the Lamiaceae family, includes about 900 species and spreads across the globe. Sökme *et al.* evaluated the effect of this plant on *B. abortus* A77. The essential oil of this plant was highly able to eliminate *B. abortus* (A77), and an MIC of 250 mm was recorded for 10 μL of its extract that was approximately four times higher than the MIC of the antibiotic sulbactam (62.50 mm)[77].

3.16. Origanum syriacum (O. syriacum) and Thymus syriacus (T. syriacus)

T. syriacus is used as a herbal tea and spice, and to treat cough and respiratory disorders, and grows in the eastern Mediterranean region[78, 79]. *O. syriacum* can grow up to 90 cm in vast regions of the eastern Mediterranean region, southern Turkey, Syria and Cyprus, and is used in Syria to treat respiratory and digestive disorders[79]. The essential oil of *T. syriacus* aerial parts at 50 mg/mL caused a moderate growth inhibition zone (22.6 mm in diameter), while the *O. syriacum* essential oil was able to cause a growth inhibition zone of 16.2 mm in diameter[80].

3.17. Peganum harmala L.

Peganum harmala is a perennial and flowering bush, and grows up to 30-100 cm. The plant spreads in northern Africa, the Mediterranean region, the Middle East, Pakistan, India and Iran[81]. The effects of the extracts of the seed, leaf, flower and root of the plant within 24 h under 37 ℃ on *B. melitensis* were investigated. In that study, the concentrations of 50, 100, 200 and 400 mg/mL of seed and leaf extracts caused growth inhibition zones of 5, 21, 24 and 26 mm and 6, 6, 6 and 7 mm in diameter, and its flower extract at all concentrations caused a growth inhibition zone of 6 mm in diameter. Finally, the root extract of the plant at 50, 100, 200 and 400 mg/mL was able to cause growth inhibition zones of 14, 19, 22 and 23 mm in diameter, respectively[82].

3.18. Prunus mahaleb & parsley (Petroselinum crispum)

Prunus mahaleb, a small tree with a height of 2-8 m, occurs in the central and southern Europe, and parsley is a turnip-rooted plant and grows more frequently in the cold and northern regions, especially in Europe and west Asia. The study of Seyyednejad *et al.* showed that the ethanol extract of *Prunus mahaleb* at 1.0 mg/mL could inhibit *B. melitensis* after 24 h incubation at 37 ℃, with a minimum inhibitory concentration of 11 mm, but at higher concentrations, namely, 0.2 mg/mL, did not produce any effect. Ethanol parsley (*Petroselinum crispum*) seed extract at 0.1-0.2 mg/mL concentrations was also effective on *B. melitensis*, with a growth inhibition zone diameter of 7 and 9 mm after 24 h incubation, whereas at higher concentrations, did not produce any effect[83].

3.19. Quercus brantii (Q. brantii)

Q. brantii, spreading in west Asia and the Middle East, is a tall tree with a height of 20 m with oval leaves[84]. The study of Safary *et al.* showed that the methanol and ethanol extracts of *Q. brantii* fruit had a tremendous effects on *B. melitensis*, with an MIC of 30 and 26 mm for ethanol and methanol extracts at 0.44 g/mL, while the MIC of the studied antibiotic was 25 mm. Both ethanol and methanol extracts at 0.1, 0.2, 0.3, 0.4 and 0.5 g/mL were effective on bacteria, with MICs of 20, 25, 27, 30 and 15 mm and 20, 22, 25, 26 and 16 mm for 24 h at 37 ℃[85].

3.20. Radix paeoniae Rubra, Coptis chinensis, Galla chinensis (G. chinensis) and Cortex phellodendrim

In a study, the effects of ethanol extract of various plants at 30 mg/mL on different species of *B. melitensis* including 16M, 293, 183, and 4611 were investigated. Overall, these plants showed anti-*Brucella* effects. *Coptis chinensis*, as a traditional drug called Huanglian, has been widely used in Chinese and other Asian countries for the treatment and prevention of cancer and inflammation for centuries[86-88]. The whole dried root of *Radix paeoniae* is used as a traditional drug in China to treat blood stasis syndrome and to reduce pharygeal pain and pharyngitis[89]. and its MICs for the 16M, 293, 183, and 4611 species were 18, 14, 18 and 16 mm, respectively[90]. Different parts of the *G. chinensis* are used to treat various diseases in traditional Chinese medicine[91]. The MICs of the *G. chinensis* on species 16M, 293, 183 and 4611 were 39, 32, 33 and 40 mm, respectively[90]. *Cortex phellodendrim*, known as Huangbai, is used as a herbal drug in several regions of China and to treat diseases such as diarrhea and cancer[87]. The MICs of the *Cortex phellodendrim* on species 16M, 293, 183 and 4611 were 13, 12, 12 and 15 mm, respectively. Among the plants mentioned, *G. chinensis* produced the greatest effect against *Brucella*, so that the MIC of the antibiotic clavumox for the *B. melitensis* species M16 was 44 mm[90].

3.21. Saffron (Crocus sativus L.)

Crocus sativus belongs to the Iridaceae family and is found in the southern and central Europe, northern Africa, southwest Asia and west China[92]. The MICs of the ethanol and methanol extracts of the plant at 50, 100, 200 and 400 mg/mL were 8, 10, 12 and 14 mm and 8.9, 10.0, 12.0 and 14.0 mm, respectively[71].

3.22. Salvia sclarea

Salvia sclarea is a plant native to southern Europe with a height of 100 cm that is cultivated in France, Russia and the United States. The MICs of the ethanol and methanol extracts of the plant at 50, 100, 200 and 400 mg/mL were 7, 8, 10 mm and 12 and 6, 6, 9 and 14 mm, respectively[71].

3.23. Scrophularia deserti

Scrophularia deserti is found in Iran, Egypt, Palestine, Jordan and Saudi Arabia, grows up to 10-50 cm and has thick leaves[93]. The ethanol extract of the aerial parts of this plant showed various effects on *Brucella* at different concentrations. Ethanol extract of the plant at concentrations of 12, 24, 36, 48 and 60 μg/mL, caused growth inhibition zones of 6, 7, 7, 8 and 9 mm in diameter after 24 h, 6.5, 7.5, 7.5, 8.5 and 9.5 mm in diameter after 48 h, and 6.6, 7.7, 8.9, 9.0, and 9.7 mm in diameter after 72 h, respectively[94].

3.24. Teucrium polium

Teucrium polium is found in abundance and is used as a traditional drug in Iran. The plant has pink to white flowers[95]. The MICs of the ethanol and methanol extracts of this plant at 50, 100, 200 and 400 mg/mL were 6.0, 9.5, 10.0 and 12.0 mm, and 6, 8, 9 and 11 mm, respectively[71].

3.25. Tortille leptophylla (T. leptophylla)

T. leptophylla grows in Europe, North Africa, Southeast Asia and Iran with a height ranging from 20 cm to 70 cm. Maleki *et al.* reported that among the studied concentrations of ethanol *T. leptophylla* fruit extract, only 0.2 g/mL of the extract could affect *B. melitensis* within 24 h under 37 ℃ with a growth inhibition zone diameter of 8 mm, while the bacteria showed resistance to the dilutions of 0.3 and 0.1 g/mL[96].

3.26. Vitex pseudo-negundo

Vitex pseudo-negundo is found in different regions of the world from the Mediterranean region to central Asia and is used in Iran as a herbal drug[97]. The MIC of the ethanol extract of this plant at 50, 100, 200 and 400 mg/mL was 6 mm and those of the methanol extract 8, 8, 7 and 11, respectively[71].

3.27. Zataria multiflora Boiss (Z. multiflora), sumac and Ocimum basilicum L.

The effect of ethanol extracts of *Z. multiflora*, sumac and *Ocimum basilicum* on *B. melitensis* (Rev1) at 37 ℃within 48 h was investigated. The first three plants showed anti-*Brucella* effects. Among the plants mentioned, *Z. multiflora* exhibited the strongest effect. Lamiaceae is a highly valuable medicinal plant and is found in large quantities in Iran, Pakistan and Afghanistan[98]. This plant is locally called *Saatar*, has small, egg-shaped and almost rounded leaves with a large number of small flowers[89,99]. The plant at dilutions of 10, 20 and 40 mg/mL caused MICs of 11.11,18.88 and 28.77 mm, respectively[100]. Sumac is widely used in Turkey and the Middle East. The plant has red fruits with a single kernel, and the height of its tree reaches 1-4 m[101]. The plant also has had MICs of 6.77, 15.72, and 22.55 mm at dilutions of 10, 20 and 40 mg/mL, respectively[100]. The plant at concentrations of 20 and 40 mg/mL caused MICs of 6.66 and 7.5 mm[100].

3.28. Ziziphus spina-christi

Ziziphus spina-christi is a mountain shrub that grows widely and reaches a length of 5-10 m in the Mediterranean region, Africa, Australia and the tropical regions of the Americas[102]. Motamedi *et al.* showed that the ethanol and methanol extracts of *Ziziphus spina-christi* leaf had a strong effect on *B. melitensis*. The MICs of the ethanol and methanol extracts at concentrations of 0.1, 0.2, 0.3, 0.4 and 0.5 g/mL were 9, 10, 11, 15, 9 mm and 11, 11, 13, 15, 9 mm, respectively within 24 h[103].

4. Conclusion

Perhaps the oldest human medicines for the treatment of undulant fever that still retain their place in modern medicine are herbal

Table 1
Plants and their most important active ingredients that are potentially effective to prevent undulant fever.

Herb(s)	Main ingredient	Molecular formula	Herb(s)	Main ingredient	Molecular formula
Allium sativum[55]	Allicin	$C_6H_{10}OS_2$	*Galla chinensis* Sumac[91]	Gallotannin	$C_{76}H_{52}O_{46}$
Prunus mahaleb[83]	Alpha-Eleostearic acid	$C_{18}H_{30}O$	*Teucrium polium*[95]	Germacrene D	$C_{15}H_{24}$
Coptis chinensis *Cortex phellodendrim* *Berberis integerrima* Bunge [58,59,86,87]	Berberine	$C_{20}H_{18}NO_4$	*Vitex pseudo-negundo*[97]	Hexadecanoic acid (Palmitic acid)	$C_{16}H_{32}O_2$
Radix paeoniae Rubra[89]	Butylidenephthalide	$C_{12}H_{12}O_2$	*Ocimum basilicum* *Salvia sclarea*[100]	Linalool	$C_{10}H_{18}O$
Peganum harmala[82]	Carboline	$C_{11}H_8N_2$	*Mentha piperita*[70]	Menthol	$C_{10}H_{20}O$
Origanum acutidens *Lavandula pubescens* *Origanum syriacum*[72,77]	Carvacrol	$C_{10}H_{14}O$	*Petroselinum crispum*[83]	Myristicin	$C_{11}H_{12}O_3$
Quercus ilex[84,85]	Catechin	$C_{15}H_{14}O_6$	*Juniperus oxycedrus* *Scrophularia deserti*[67,93,94]	Pinene	$C_{10}H_{16}$
Eucalyptus globulus[63,64]	Cineole	$C_{10}H_{18}O$	*Arctium lappa* *Quercus brantii* *Galla chinensis* Sumac *Alhagi camelorum* Fisch [53,57,84,91]	Tannin	$C_{76}H_{52}O_{46}$
Cinnamomum verum[69]	Cinnamaldehyde	C_9H_8O	*Origanum majorana*[77]	Terpinen-4-ol	$C_{10}H_{18}O$
Crocus sativus[92]	Crocin	$C_{44}H_{64}O_{24}$	*Zataria multiflora* Boiss *Oliveria decumbens* *Satureja hortensis* *Nepeta cataria* *Thymus syriacus* [73,76,78,79,89]	Thymol	$C_{10}H_{14}O$
Citrullus colocynthis[62]	Cucurbitacin	$C_{30}H_{42}O_6$	*Nigella sativa*[74,75]	Thymoquinone	$C_{10}H_{12}O_2$
Torilis leptophylla[96]	Gallic acid	$C_7H_6O_5$	*Lavandula pubescens*[72]	Xanthohumol	$C_{21}H_{22}O_5$

medicines. Three main properties of herbal drugs, including anti-inflammatory, antimicrobial and antioxidant, are often observed in the presented plants extracts and may be due to the presence of several compounds or a single compound. This is closely associated with some important issues in the treatment of brucellosis, such as the emergence of resistant microbial species to conventional antibacterial drugs. Medicinal plants have a wide range of active ingredients that can be used for specific treatment[104-108].

Although clinical evidence, in its current meaning, does not exist on all medicinal plants that are used traditionally, plants like *Q. brantii* fruit, *O. acutidens* seed, *A. sativum*, *Peganum harmala*, *A. camelorum* and some other plants have experimentally well established and their action mechanisms have been well explained pharmacologically[110, 110]. Physicians should not overlook the use of herbal drugs, but they should know the indications and ways of their administration, as well as the risks and limitations of their use. Herbal drugs in acute and severe diseases may often not comprise an adequate treatment, but they are nevertheless useful as complementary drugs. For example, the antimicrobial effects of medicinal plants as complementary drugs will be effective to control the acute infections that need to be treated with more potent drugs.

There is often no scientific evidence for the clinical effectiveness of herbal drugs, and more research is needed to confirm the effectiveness of medicinal plants. There is strong evidence on the antimicrobial effects of herbal drugs to protect the body against infection, but this is only very partially related to medical treatment and mostly includes dietary advice. However, a variety of plant extracts (ethanol, methanol, acetone, aqueous, *etc.*) and essential oils can be used to treat, control or increase the efficacy of the treatment.

Research on medicinal plants is always accompanied by identification of active ingredients. Plants reported in this article produce different antimicrobial effects, which is probably due to the difference in the active ingredients in the plants or the concentration of the active ingredient. For example, carvacrol is the main compound of plants such as *O. acutidens*, *L. pubescens* and *O. syriacum*. Carvacrol is a monoterpenoid phenol with a tangy taste. Carvacrol is produced by the plant's aerial organs, and is stored in the subcuticular storage cavity[111]. The antibacterial action mechanism of carvacrol involves eliminating the membrane integrity, proton and potassium outflow from the cell by increasing the permeability of the membrane and changing pH gradient in the cells[112]. This substance can also depolarize the membrane by using its hydroxyl groups[113]. According to studies on the toxicity of this substance, the Caco-2 cells did not get damage in the short-term exposure to carvacrol[114]. Also, carvacrol has no significant effect on lymphocytes and indices of blood growth[115]. In addition, thymol is the main compound of plants such as *Z. multiflora*, *Oliveria decumbens*, *Sylvia hortensis*, *N. cataria* and *T. syriacus*. Thymol is the main identified phenol in the essential oils of the plants belonging to the Lamiaceae family[116]. Thymol is the product of *p*-cymene hydroxylation and *p*-cymene is the product of γ -terpinene aromatization[117,118]. The essential oils rich in thymol are used in the food industry as a flavoring and preservative agent[119]. Thymol has also been used as an insect-repellent and for medical purposes from ancient times[120,121]. It has a phenolic hydroxyl in different sites on the phenol ring and, by virtue of its hydrophilicity, dissolves and destroys the organisms, and also can lead to the depolarization of the bacterial membrane. Thymol produces no destructive effect on Caco-2 cells in the short term[114]. The main compound of some plants such as *A. lappa*, *Q. brantii*, *G. chinensis*, sumac and *A. camelorum* is tannin. Tannins are water-soluble polyphenols which can be detected in higher herbaceous and woody plants and are divided into two groups: Hydrolysable and non-hydrolysable. They are found in many foodstuffs such as tea, cocoa seed and grapes[122,123]. Because of the presence of hydroxyl groups, they are able to bind to proteins and other macromolecules[124]. Tannins destroy bacteria through various mechanisms, including inhibition of bacterial enzymes through the formation of a complex with them, exerting destructive effect on the membrane of the organism, forming complex with iron ion, depriving the organism of its essential nutrients, and affecting the metabolism of the bacteria directly by inhibiting oxidative phosphorylation[125]. Other plants that have effective ingredients, such as berberine, possess many pharmaceutical and biological properties, such as anti-inflammatory, anti-tumor, viral, and bacterial, and stop bacterial growth by inhibiting DNA and protein synthesis, while causing very low toxicity[126,127]. Therefore, the active ingredients of the herbal drugs can be used to make the best use of them. However, it is noteworthy that herbal remedies have different compounds that may lead to synergistic effects by inducing different mechanisms in the living organism and may be more effective than the constituents isolated from them.

5. Recommendations

More clinical, controlled trials using extracts and other products are needed to determine the efficacy and risks of plant products in the treatment of brucellosis, as well as to examine the long-term safety and tolerability of plant medicines used in food supplements.

Conflict of interest statement

We declare that we have no conflict of interest.

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