

Antibacterial effects of *Thymus vulgaris*, *Mentha pulegium*, *Crocus sativus* and *Salvia officinalis* on pathogenic bacteria: A brief review study based on gram-positive and gram-negative bacteria

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Abstract

Background and objective: In recent years, with the increase in resistance due to the indiscriminate use of synthetic antibiotics, it seems necessary to find alternative drugs that have both antibacterial properties and have the least side effects for humans. The purpose of this study is to review the antibacterial properties of some medicinal plants.

Material And Method In this review study, the content related to the antibacterial properties of *Thymus vulgaris*, *Mentha pulegium*, *Crocus sativus*, and *Salvia officinalis* were studied within Magiran, SID, PubMed, MEDLINE, Science Direct, Cochrane Library, Google Scholar, EMBASE, and Scopus databases from 1981 to 2019. Previously published specialized articles and systematic meta-analysis were used as a supplementary source for identifying relevant articles. Finally, data from 46 articles were pooled and analyzed.

Result: Extracts and essential oils of *Thymus vulgaris*, *Mentha pulegium*, *Crocus sativus*, and *Salvia officinalis* had a good antibacterial properties against a variety of pathogenic bacteria and their infections.

Conclusion: According to the results of this study, the studied plants can be considered as a suitable option for treating infections caused by pathogenic bacteria and helping to return the sensitivity of antibiotics in these bacteria, and this requires more comprehensive research on medicinal plants.

Keywords: Antibacterial, Medicinal plants, *Thymus vulgaris*, *Mentha pulegium*, *Crocus sativus*, *Salvia officinalis*

Introduction

The use of medicinal plants for the treatment of diseases has coincided with human history. Among the nations of the world, ancient Egypt should be considered the first nation to use herbs (1). Long before humans discovered the existence of germs, it was thought that some plants were a good cure for certain diseases (2). As such, the oils of these plants were used instead of their extracts, the most commonly used in the treatment of infections (3). Infectious diseases are among the most well-known diseases that have always affected human beings and many efforts have been made to identify the causes, treatment and control of them (4). Early in the 12th century, advances in chemistry and the discovery of sophisticated organic synthesis systems led to the development of the pharmaceutical industry and the replacement of synthetic drugs in place of herbal medicines. But as advances in the production of new chemical drugs and various antibiotics, the harmful effects of these drugs gradually began to appear and since the 1950s, numerous pathogenic bacteria have been resistant to antibiotics, which is still widespread. Therefore, the use of herbal remedies as substitutes for chemical drugs and antibiotics was investigated (5). Plants can be seen as a source of potentially useful chemicals that are only partially exploited. Herbal extracts have cases that can be used against many microorganisms (6-8). The high prevalence of resistant infectious diseases due to the increased resistance to antibiotics and the difficulties in using synthetic drugs, including the high cost of acquiring new drugs and the side effects of existing drugs, has drawn the attention of many researchers to traditional medicine (6). The purpose of this review is to investigate the antibacterial

properties of *Thymus vulgaris*, *Mentha pulegium*, *Crocus sativus*, and *Salvia officinalis* to elucidate the aim of this study was to evaluate the antibacterial properties of *Thymus vulgaris*, *Mentha pulegium*, *Crocus sativus* and *Salvia officinalis*.

Materials and Methods

In the present study, different computer-assisted searches were achieved using Magiran, SID, PubMed, MEDLINE, Science Direct, Cochrane Library, Google Scholar, EMBASE, and Scopus. Separately searches were carried out on all Persian and English language literature published through 1981 to 2019, by the key words: Medicinal herbs, Antibacterial, Traditional medicine, and Secondary compounds. Full articles related searches were saved, and articles written in English languages were translated when essential. All complete articles were saved in terms of subject matter, quality and method. The following information was collected: (1) Isolation Area; (2) Active plant compounds; (3) Effect on bacteria (type); Criteria for excluding articles included: inability to access the full text of the article and unrelated results of the articles. Duplicate articles were removed. To reduce reporting bias and data collection errors, the two researchers (Khaneshpour H and Fatemi S) independently extracted data from articles. Standard form of data collection includes: plant type, authors name, gram-positive and gram-negative. Some factors were considered to accept research articles for including within the review such as articles without data access barriers, the titles, having extraction data.

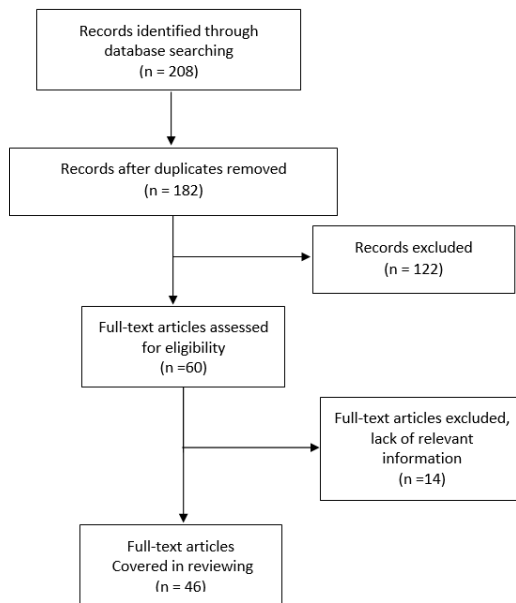


Figure 1. Flow-chart of the reviewed studies.

Result

Following the removal of articles that were not relevant to the present analysis or articles that lacked statistical information. Then, all full-text articles of relevant papers were included (n = 46). As a result, the data of this study were divided into two subgroups of gram-positive and gram-negative, respectively. The four plants studied in various studies in terms of antibacterial properties are:

Thymus vulgaris L.

Thyme by the name of science *Thymus vulgaris L* is one of the Lamiaceae family. The mint family is one of the largest globally dispersed plant families, with about 200 genera, two to five thousand species of aromatic shrubs and short shrubs (7). It has a bushy structure with a straight stem, an herbaceous or woody stem with a height of 10 to 30 cm (8). It grows in different parts of the Mediterranean and some parts of Asia. Today it is cultivated and produced in different regions of the world, including Iran (7).

Thyme contains 0.8 to 2.6% essential oil. Most of them are phenols, monoterpene hydrocarbons, and alcohols. Thymol and carvacrol are the active ingredients of thyme. *Staphylococcus aureus* is susceptible to it while gram-negative bacteria (such as *Escherichia coli* and *Klebsiella pneumoniae*) do not show any sensitivity to its essential oil (9). This plant has good antimicrobial activity against the activity of Gram-positive microorganisms and yeasts (10). Thyme contains terpene compounds (thymol and carvacrol), which have more antimicrobial properties than the total essential oils, indicating the synergistic effect of each of the compounds in the essential oil together (11-13). Thyme and cinnamon essential oil together can inhibit the growth of *Bacillus cereus* at lower concentrations (14). It is widely used in the treatment of asthma and has been used as a disinfectant in the stomach and urinary tract, as well as a diuretic and anti-inflammatory drug in traditional medicine (15). Thymol found in Thyme has anti-cumulative activity and strongly inhibits platelet adhesion and can be effective in preventing thrombosis and atherosclerosis (16). Thyme essential oil also has good effects on antibiotic-resistant bacteria such as tetracycline, erythromycin, trimethoprim, sulfamethoxazole and methicillin and can inhibit the growth of these bacteria (17). Table 1 examines the antimicrobial effect of thyme on Gram-positive and Gram-negative bacteria in several different studies.

Table 1. Evaluation of Antibacterial Properties of *Thymus vulgaris L*

Authors	Gram negative	Gram positive	References
Razavi et al.,	--	<i>L. monocytogenes</i>	17
Ahmadi et al.,	<i>E.coli</i>	<i>S.aureus</i>	18
Khodaei et al.,	<i>E.coli</i>	<i>S. aureus</i>	19
Azizi Tabrizzad et al.,	--	<i>S. aureus</i> <i>L. monocytogenes</i> <i>E. faecium</i> <i>E. faecalis</i> <i>B. cereus</i>	20
Nzeako et al.,	--	<i>S. aureus</i> <i>S. pyogenes</i>	21
Selim	<i>E.coli</i>	--	22
Carvalho et al.,	--	<i>S. aureus</i>	23
Godarzi et al.,	<i>E.coli</i>	--	24
Hanan et al.,	--	<i>B. cereus</i> <i>S. aureus</i>	25
Balkan et al.,	--	<i>Streptococcus spp</i> <i>S. aureus</i>	26
Mohajerfar et al.,	--	<i>L. monocytogenes</i>	27
Pourazar Dizaji et al	--	<i>M. tuberculosis</i>	28

Mentha pulegium

Mentha pulegium is one of the species of *Mentha* and is a member of the Labiatae family and is a perennial plant (29). Its stems are erect, up to one and a half meters in the final stages of plant maturation. The leaves of this plant are simple and stalk-like (30, 31) and grow wild in the humid regions of central and southern Europe, western Asia and North Africa (31). *Mentha pulegium* is composed of carvacrol and thymol, which have antibacterial and antifungal properties (32). Carvacrol reduces the concentration of plasma triglycerides. The use of carvacrol stimulates the growth and proliferation of lactobacilli (33). The therapeutic properties of *Mentha pulegium* are to alleviate gastrointestinal disorders, vomiting, ulcerative colitis, and

liver disorders (34). Essential oils due to pulegone groups, Menthone and Neomenthone has antimicrobial properties because they can cause bacterial lysis by changing the permeability of cell membranes and disrupt the structure of various polysaccharides, fatty acids and phospholipids are the bacterial cell membrane (29, 35). Since essential oils of *Mentha pulegium* have an important role in preventing the growth, proliferation and spread of several bacterial species, they can be used as anti-spasm and anti-inflammatory (36, 37). Table 2 examines the antimicrobial effect of *Mentha pulegium* on Gram-positive and Gram-negative bacteria in several different studies.

Table 2. Evaluation of antibacterial properties of *Mentha pulegium*

Authors	Gram negative	Gram positive	References
Fazeli nasab et al.,	<i>E.coli</i>	<i>S.areus</i>	38
Masood et al.,	<i>Citrobacter</i> <i>E.coli</i> <i>S. typhi</i>	--	39
Hongbin Si et al.,	<i>E.coli</i>	--	40
Mahmoudi et al.,	<i>S. typhi</i>	<i>S.areus</i>	41
Gholamipour naraki et al.,	--	<i>S.areus</i>	42
Rahmani et al.,	<i>E.coli</i> <i>P.aeruginosa</i>	<i>S.areus</i>	43
Ataie et al.,	<i>Citrobacter</i> <i>E.coli</i> <i>S. typhi</i>	<i>S.areus</i>	44
Nozohor et al.,	<i>E.coli</i> <i>Kelebsiella</i> <i>P.aeruginosa</i>	<i>S.areus</i>	45
Iravani et al.,	--	<i>S.areus</i>	46
Jaber et al.,		<i>Streptococ</i> <i>ccus sp.</i>	47

Crocus sativus L

Saffron, scientifically named *Crocus sativus L.* belongs to the family (Iridaceae), mostly grown in arid and semi-arid regions of Iran ([48, 49](#)). It is a multi-stemmed plant without stem that has a tubular, spherical shape with a diameter of 5-3 cm ([50](#)). The main constituents of saffron, including crocin, crocetin, picrocrocetin and safranal, are involved in the prevention of neuronal degradation and memory enhancement ([51](#)). The therapeutic value of dried saffron stigma due to the presence of three major secondary metabolites called water-soluble crocin and its derivatives responsible for the red color of saffron, picrocrocetin the bitter taste of saffron is safranal, which is responsible for the smell of saffron ([52, 53](#)). Fat-soluble safranals and carotenoid pigments are bitter crocin, but the most important cause of bitterness is picrocrocetin saffron ([54](#)). Saffron has been shown to protect chromosomes from damage and also modulates lipid peroxidation and a potent antioxidant and a rich source of

riboflavin ([55](#)). The anticancer effects of saffron, including inhibition of tumor formation ([56](#)), anti-mutation ([57](#)), and inhibition of nucleic acid synthesis in human malignant cells have been demonstrated ([54, 58](#)). Some substances derived from saffron stigma have many therapeutic effects due to their hypolipidemic, antipsychotic, antioxidant and antidiabetic the aqueous and alcoholic extracts of saffron are protective of the heart and counteract neurodegenerative disorders. The saffron active ingredient is related to its various components such as crocetin, crocin and carotenoids and monoterpene aldehydes ([59, 60](#)). Saffron has anti-cancer properties, decreased blood bilirubin, increased oxygen in various tissues ([50](#)). [Table 3](#) examines the antimicrobial effect of *Crocus sativus L* on Gram-positive and Gram-negative bacteria in several different studies.

Table 3. Evaluation of antibacterial properties of *Crocus sativus L*

Authors	Gram negative	Gram positive	References
Talei et al.,	--	<i>S. aureus</i>	4
Gandomi Nasrabadi et al.,	--	<i>B. cereus</i> <i>L. monocytogenes</i>	48
Barani karbasaki et al.,	--	<i>Lactobacillus</i> <i>S. mutans</i> <i>C. albicans</i>	61
Tayel et al.,	--	<i>B. subtilis</i>	62
Mohamadian et al.,	--	<i>S. areus</i> <i>B.subtilis</i>	63
Azami et al.,	<i>S. typhimurium</i>	--	64
Vahidi et al.,	<i>E.coli</i>	<i>S. areus</i>	65
Abbasvali et al.,	--	<i>S. areus</i>	66
Asgarpanah et al.,	<i>S. typhimurium</i> <i>S. dysentery</i>	<i>B. cereus</i> <i>S. areus</i>	67
Parray et al.,	<i>P. aeruginosa</i>	<i>S. areus</i>	68
Hashemi et al.,	<i>E.coli</i> <i>Salmonella</i>	<i>S. areus</i>	69
Pintado et al.,	<i>Salmonella</i>	--	70

Salvia officinalis

Salvia officinalis is one of the important genera of the Lamiaceae family (71). With more than 900 varieties of ornamentals, medicines and spices spread worldwide (72-73). It is found in the natural arena, in the Mediterranean, in parts of Europe and Iran (74, 75). About 58 species of this genus are known in Iran, 17 of which (29%) are endemic to Iran (72). Plants of this genus have significant essential oils with more than 100 active compounds, including hydrocarbon monoterpenes, oxygenated monoterpenes, sesquiterpene hydrocarbons, sesquiterpene oxygenated terpenes and diterpenes which exhibit many biological activities (76, 77). *Salvia officinalis* contains bitter and diterpene flavonoid substances, phenolic acids and tannins (78, 79). *Salvia officinalis* essential oil is used in the perfumery, food and pharmaceutical industries (72). Biological activities of this plant such as antibacterial, antioxidant, anti-inflammatory, anti-Alzheimer's, gastric ulcer and lipid-lowering agents have been reported (80, 81). *Salvia*

officinalis has been used in traditional and modern medicine as an effective herbal medicine to heal inflammation and heal skin wounds. *Salvia officinalis* extract also reduces blood sugar in healthy and diabetic patients but does not affect insulin dependent patients (78). Recent studies have confirmed the plant's antibiotic, antispasmodic, anxiolytic, antifungal, antioxidant, hypoglycemic, tonic, antiperspirant and estrogenic properties (82). It is rich in antioxidants of calcium, potassium, magnesium and zinc and is a vasodilator (78). *Salvia officinalis* has an effect on the central nervous system. It is calming and hypnotic, skeletal muscle relaxant, analgesic, memory enhancer, anticonvulsant, neuroprotective and anti-infarct protection as well as inhibiting ethanol and morphine withdrawal syndrome (74). Two substances in the extract, including camphor and alpha thujene essence, are used for health benefits (83). Traditional medicine has been used for the treatment of inflammatory bowel disease and wound healing in traditional medicine. Nowadays, a new ointment of *salvia officinalis* extract is

effective in healing wounds (84, 85). Studies have shown that methanol extract of *Salvia officinalis* is effective for anti-cell growth activity against cervical cancer, skin cancer and post-cancerous cancer. *Salvia officinalis* extract can play a role in the inhibition of cancer of the large intestine (83). Other studies have shown that *Salvia officinalis* extract inhibits the growth and proliferation of colorectal cancer cells in cell culture medium (86). Also, in another study it has been shown that some of the compounds extracted from *Salvia officinalis* have cytotoxic and deleterious effects on the DNA of cancer cells of the colon and liver cultured in cell culture medium (87, 88). Research has shown that the combination of alpha terpineol, which is one of the major compounds in salvia officinalis, can inhibit tumor cell growth and thus inhibit the release of CE, thus inhibiting its effects (89). *Salvia officinalis* extract, especially

alpha-terpineol, Togen monoterpenes, beta-pyrene, synovol and essential fatty acids, prevent the destruction of healthy cells and prevent tumorigenic activity in these cells. The CEA marker is in the blood serum. On the other hand, although the molecular mechanism associated with the metastasis of some cancers is unclear, however, the production of CEA has been both clinically and empirically identified as an effective factor in metastasis (90). Studies have shown that there is a close relationship between serum CEA level and colorectal head metastasis to the liver (91), since *salvia officinalis* extract has anti-metastatic effects, reducing its effect on CEA. The prospect needs approval (88). Table 4 examines the antimicrobial effect of *Salvia officinalis* on Gram-positive and Gram-negative bacteria in several different studies.

Table 4. Evaluation of antibacterial properties of *Salvia officinalis*

Authors	Gram negative	Gram positive	References
Salimpour et al.,	<i>E.coli</i> <i>K.pnemuniaie</i>	--	5
Moshafi et al.,	<i>Ecoli</i>	<i>B.subtilis</i> <i>S.areus</i> <i>S.epidermidis</i>	73
Batooli et al.,	--	<i>P. vulgaris</i>	92
Ahmady-asbchin et al.,	<i>L.monocytogenes</i> <i>E.coli</i>	<i>S.areus</i>	93
Mitić-ćulafić et al.,	--	<i>B.subtilis</i> <i>S.areus</i>	94
Iravani et al.,	--	<i>B subtilis</i> <i>S.areus</i> <i>S.epidermidis</i>	95
Omidpanah et al.,	<i>E.coli</i>		96
Javidnia et al.,	--	<i>B.subtilis</i> <i>S.areus</i>	97
Gharenaghdeh et al.,	<i>E.faecalis</i>	<i>B.subtilis</i>	98
Rasoli et al.,	--	<i>S.areus</i>	99
Arben et al.,	<i>L.monocytogenes</i> <i>E.coli</i>	<i>S.areus</i>	100
Ghezelbas et al.,	--	<i>B. anthracis</i> <i>S. areus</i>	101

Discussion

Infectious diseases are among the most well-known diseases that have always affected human beings and many efforts have been made to identify the causes, treatment and control of them (102). Due to the drug resistance and side effects of antibacterial chemical drugs, the scientific research approach to natural resources has become very popular in recent decades (103). The discovery of new antimicrobial metabolites from plants is an important alternative to overcome the decrease in the level of drug resistance by human pathogens. Due to the urgent need of the world for new antibiotics, there is a growing interest in the research of the chemistry of medicinal plants (104). Antibacterial herbal medicines inhibit the progression of the disease and in some cases relieve the disease (105). Different parts of medicinal plants such as, roots, stems, flowers, leaves have different antimicrobial properties (106). Antibacterial herbal medicines have various therapeutic properties that have little or no side effects (107). In general, some of the properties of plant essential oils that lead to antibacterial properties are: the hydrophobic property that penetrates the lipids of the bacterial cell membrane, disrupting cellular structure, causing the outflow and saturation of ions and others. Contains cellular contents (108). Phenolic substances in plant essential oils, including carvacrol, eugenol and thymol, which damage the cell's cytoplasmic membrane and coagulate cellular contents (109, 110). Binding of the carbonic group of essential oils to cellular proteins and preventing the role of amine acid and decarboxylase, which is mainly due to the presence of cinnamaldehyde in the essential oils (111). Reactions of aldehydes with -SH groups are effective in fungal growth and

prevent the growth of microorganisms (17). Cinnamaldehyde, carvacrol, caron and thymol appear to have no significant or marginal effects in vivo, whereas in vitro they exhibit mild to moderate toxic effects on the cell (112). There appear to be no complications in this regard (113). However, studying and understanding the substances present in these plants and their proper use can overcome many problems, such as the prevalence of antibiotic resistance or the chemical side effects of certain drugs

Conclusion

Proper use of medicinal plants requires accurate scientific information and knowledge of the chemical compounds in them, because the presence of chemical compounds causes the therapeutic effect of the plant. Therefore, it is necessary to study the antimicrobial effects of plant extracts. Oils and compounds isolated from them are of great importance. One of the important reasons for the tendency of medical societies to use herbal compounds is their low side effects to chemical drugs that have been proven over the years in traditional medicine. As the world health organization warns of the overuse of common antibiotics and serious concerns about increased resistance to pathogenic microorganisms, research into the discovery of effective antimicrobial agents on these microorganisms Resistance has begun seriously. The main active ingredients of the essential oils and extracts of these herbs can be potential candidates for use as antibacterial substances. However, confirmation of the antimicrobial efficacy of these plants should be thoroughly investigated.

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