

REVIEW PAPER

The application of thyme as a medicinal plant in bacterial and fungal infections, as well as the investigation of its antinociceptive properties

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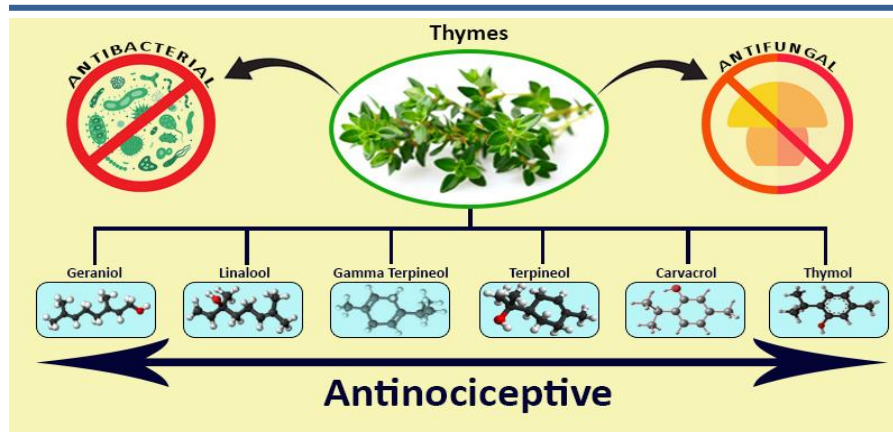
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Highlights

- Thyme is a perennial plant with dense bushes and many branches, direct roots, and many branches.
- The most important ingredients of thyme essential oil include carvacrol and thymol.
- Thyme plant has antibacterial, antifungal, anti-inflammatory, and antinociceptive features.

Graphical Abstract



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Abstract

Medicinal plants are a group of plants whose organs have effective medicinal compounds. Among the most important advantages of herbal medicines, we can mention the economic value and low cost of obtaining them, the environmental and ecological effects of their use, and the less destructive effects on natural resources. Among its disadvantages, we can mention the limited access to some plant species in all seasons and the long duration of treatment with plants. One of the common medicinal plants is thyme, which is a perennial plant with dense and branched bushes, straight roots, and many branches. Thyme essential oil is a yellow or dark reddish-brown liquid with a strong pleasant smell and a strong, persistent and cooling taste, which is extracted from the distillation of the leaves and flowering branches and is a combination of different chemicals. The volatile compounds acquired from the aerial parts of the plant include geraniol, linalool, gamma terpineol, terpineol, carvacrol and thymol. Thyme essential oil with an exact high percentage of carvacrol and thymol has substantial antimicrobial activity. Many investigations have shown the antifungal activity of thyme oil against *Candida* species. It is also known that this plant has anti-inflammatory and antinociceptive properties. The purpose of this study is to investigate the use of thyme as a medicinal plant in bacterial and fungal infections and also to investigate its antinociceptive properties.



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1. Introduction

Medicinal plants have been valuable among natural resources for a long time, and their use, either in the form of traditional medicine or in the form of preparing pure products with the help of chemical methods, has been of particular importance. Man's turning to natural and herbal substances was in pursuit of their properties in relieving pain and healing diseases. The history of using medicinal plants to treat diseases goes back centuries and herbal therapy has a history as old as human life (Sofowora et al., 2013). People who worked in the field of medicine were able to gradually gain information about the use of plants to heal patients during their experiments or by chance, and their therapeutic effects and harmlessness have been experienced over many years and it has arrived from generation to generation. Different nations and tribes have records of plants and the use of plants to treat diseases. Ancient Egyptians, Chinese, Ancient Greeks, Indians, Iranians, and other countries each have an ancient history of using herbal medicine (Petrovska, 2012).

With the rapid progress of science on the one hand and economic issues on the other hand, the use of medicinal plants has decreased in the past and synthetic drugs have replaced plants in many cases. The experience of the last few decades has shown that synthetic drugs with all their effectiveness have many undesirable and unfortunate effects (Ekor, 2014). Today, mankind is faced with new issues and problems, such as side effects and misuse of drugs, which in some cases are more dangerous than the diseases being treated. Toxicity, sensitivity to drugs, carcinogenic and teratogenic effects, the body's resistance to drugs, and the reduction of the body's natural immune system are more prominent today. In order to avoid these problems, today man has returned to nature and turned to natural medicines and herbal remedies, and every day in Europe and other countries, people are becoming disillusioned with chemical medicines and turning to herbal remedies and natural remedies. For example, recently, scientists believe that it is better to use natural drugs such as plants to treat cancer because cancer has become resistant to synthetic drugs (Attia, 2010; Friedman et al., 2003). Proponents of the school of using medicinal plants still believe that plants with minerals, carbohydrates, organic and inorganic acids, combined with albumins or sugars, essential oils, vitamins, hormones, etc. generally have more healing power after being absorbed into the body. If instead of using medicinal plants, their effective substance is used, the desired therapeutic effect will not be achieved, because the ingredients of a medicinal plant, if taken separately, will never bring out all the therapeutic activity of the plant. On the other hand, along with the main effective substances, there are other effective substances that have therapeutic effects in plants, and these substances in most cases intensify the therapeutic effect of the plant and in many cases prevent its toxicity and unwanted effects (Bjørklund et al., 2022; Shedoeva et al., 2019).

The Lamiaceae family, which has 200 genera and approximately 4000 species, are generally herbaceous, annual plants with straight or creeping stems. Some of them have a bush-like appearance and numerous woody stems. Thyme is a member of the Lamiaceae family, which is used both in cooking and in medicine in the local Mediterranean communities, especially in Spain, Italy, France, Egypt, Greece, Lebanon, Iran, and Turkey. The name of the genus Thyme is probably derived from the Greek word Thyme, which means courage. The thyme plant has several genera, the most famous of which are Zataria, Ziziphora, Thymus, and Origanum, most of which usually have essential oils. The most important composition of the plant is its essential oil, which is present in the amount of 1 to 2.5% in its leaves. The most important ingredients of the essential oil include thymol and carvacrol, which make up 30-70% of essential oil and 15-30% of essential oil, respectively (Nieto, 2020; Raja, 2012; Salehi et al., 2018).

In traditional medicine, this plant is used as an antispasmodic, to treat whooping cough, bronchitis, lung infection, cold, and flu, and to treat bloating and muscle cramps. The modern and proven use of the thyme plant is to treat asthma, frequent dry coughs, and bronchitis. Its herbal tea is also used to treat middle ear infections, flatulence, and nausea. Patients with shortness of breath, kidney and bladder disorders, joint pain, sciatica, uterine bleeding, and abnormal secretions of women can also use the therapeutic benefits of this plant. It is prohibited to use this plant during pregnancy, but it is not prohibited during breastfeeding. Such activities are due to thymol and its structural isomer, carvacrol, which has more antibacterial activity and its antifungal

activity is less than that of phenol (Liolios et al., 2009; Younis et al., 2018). The purpose of this study is to investigate the use of thyme as a medicinal plant in bacterial and fungal infections and to investigate its antinociceptive properties.

2. Introducing the thyme plant and presenting its general characteristics

The Lamiaceae family is one of the largest plant families that have a global distribution and has about 200 genera and two to five thousand species of aromatic shrubs and short shrubs. Most of the Lamiaceae produce terpenes and other types of compounds that store these compounds mainly in the epidermal glands of leaves, stems, and reproductive organs (Uritu et al., 2018). Thyme is a plant from the Lamiaceae family. Three genera in the mint family are known as thyme, which includes *Zataria*, *Ziziphora*, and *Thymus*. The plants of the genus *Thymus* are mainly aromatic, evergreen, hardy, and shrubs, commonly found in calcareous soils and in grasslands throughout Europe and Asia. Thyme is one of the most important medicinal plants that have more than 20 known important chemical compounds. Gamma-terpinene is the key component of the essential oil in thyme, which constitutes about 30% of the essential oil and is produced by gamma-terpinene synthase (Naghdi Badi and Makkizadeh, 2003; Özgüven and Tansi, 1998).

Thyme is a perennial plant with dense and branched bushes, straight roots, and many branches. The average height of this plant is 15 to 30 cm and its width is 40 cm. The bottom of the stem is wooden, while the upper parts are green and have many branches. The leaves are small, opposite, and more or less lance-shaped and without petioles. The leaves are covered with gray hairs and contain essential oil. The flowers are small, and perfect, and can be seen in white, pink, and purple colors. The flowers appear from the second year of growth in the middle of May. In the secondary branches, the flowers are seen in the form of lateral and spiral bunches. The fruit is dark brown, 1-2 mm long, and there are four dark brown seeds inside the fruit. Thyme seeds are very small and the weight of 1000 seeds is about 300 mg. In suitable climatic conditions, they turn green 14 to 20 days after planting. The abnormal state of this plant is that some of its stems have flowers without stamens and in others, the stamens grow earlier than the pistils (Alu'datt et al., 2018; Furmanowa and Olszowska, 1992).

3. The natural habitat of thyme

Thyme is a plant native to the west of the Mediterranean area and south of Australia, and its cultivation is also common in other parts of the world. This plant exists in the semi-arid areas of New Zealand in the amount of several thousand hectares. Thyme grows green in hard and rocky lands and where it is well drained and grows naturally in semi-arid to moderately hot areas with high temperatures and intense sunlight. In the early stages, it has very slow growth and in the later stages of development, especially after 60 days, it has a rapid increase in dry matter accumulation compared to 40-day-old plants. The amount of soil water and light regimes significantly change the growth of thyme colonies, and an interaction effect has been observed between light conditions and soil moisture. However, in the conditions of extra light and soil moisture of 70%, the highest amount of photosynthesis and plant essential oil is observed, and the lowest amount of essential oil is also mentioned in the conditions of natural light and 50% of soil moisture. The soil of the thyme farm should be well drained and its pH should be at least 6, and if necessary, it should be amended using lime. Although it grows in very dry and rainless conditions, its yield decreases, and basically, irrigation increases the yield. *Thymus vulgaris* has not been seen wild in Iran country. Of course, thyme is cultivated every year in a large area of Spain, Germany, France, Portugal, America, the Czech Republic, Slovakia, Hungary, and North Africa (Horwath et al., 2008).

4. Harvesting and processing of thyme

Harvesting thyme is a critical point in the agricultural management of this plant. In general, the best time to collect vegetative organs including young leaves and stems containing effective substances is when the plant is in the flowering stage. The appropriate harvest time for thyme is different in different regions (Escobar et al.,

2020). Usually, thyme is dried in the sun in large quantities, but the quality of the final product is very low. Product quality can be controlled by using artificial drying. Thyme should be dried at a temperature lower than 40 degrees Celsius to reduce the loss of aroma during evaporation and keep its green color. The dried product must go through the process of separating the leaves from the stems and sieving to remove dust to produce a uniform product. Thyme essential oil can be extracted from fresh thyme aerial parts by a steam distillation system. The essential oil is stored in small glands on the leaves, the yield and quality of the essential oil vary depending on the genetic structure of the plant, the maturity stage of the plant, the time of harvesting, the environment, and the extraction operation (Doymaz, 2011; Rodríguez et al., 2014).

5. The active ingredient of thyme

The effective ingredient of thyme is an essential oil. Thyme essential oil is a yellow or dark reddish-brown liquid with a strong pleasant smell and a strong, persistent and cooling taste, which is extracted from the distillation of the leaves and flowering branches and is a combination of different chemicals. The published results show that most of the volatile compounds obtained from the aerial parts of the plant include geraniol, linalool, gamma terpineol, terpineol, carvacrol and thymol (Fig. 1). However, thyme sprigs contain essential oil, tannins, main bitter substances, saponins, and herbal disinfectants. Thyme contains 0.8 to 2.6% essential oil, most of which is made up of phenols, monoterpene hydrocarbons, and alcohols, and sometimes each of these compounds makes up to 80% of essential oil compounds. So far, 38 compounds have been identified in the essential oil of this plant, the most important of which is thymol. The compounds in the essential oil have also shown many changes during a period of 13 months. The highest levels of phenolic and carvacrol compounds have been observed in the summer season after flowering. What is important is that thyme oil grown in different regions is different in terms of color, taste, viscosity, and chemical composition (Borugă et al., 2014; Kowalczyk et al., 2020; Singletary, 2016).

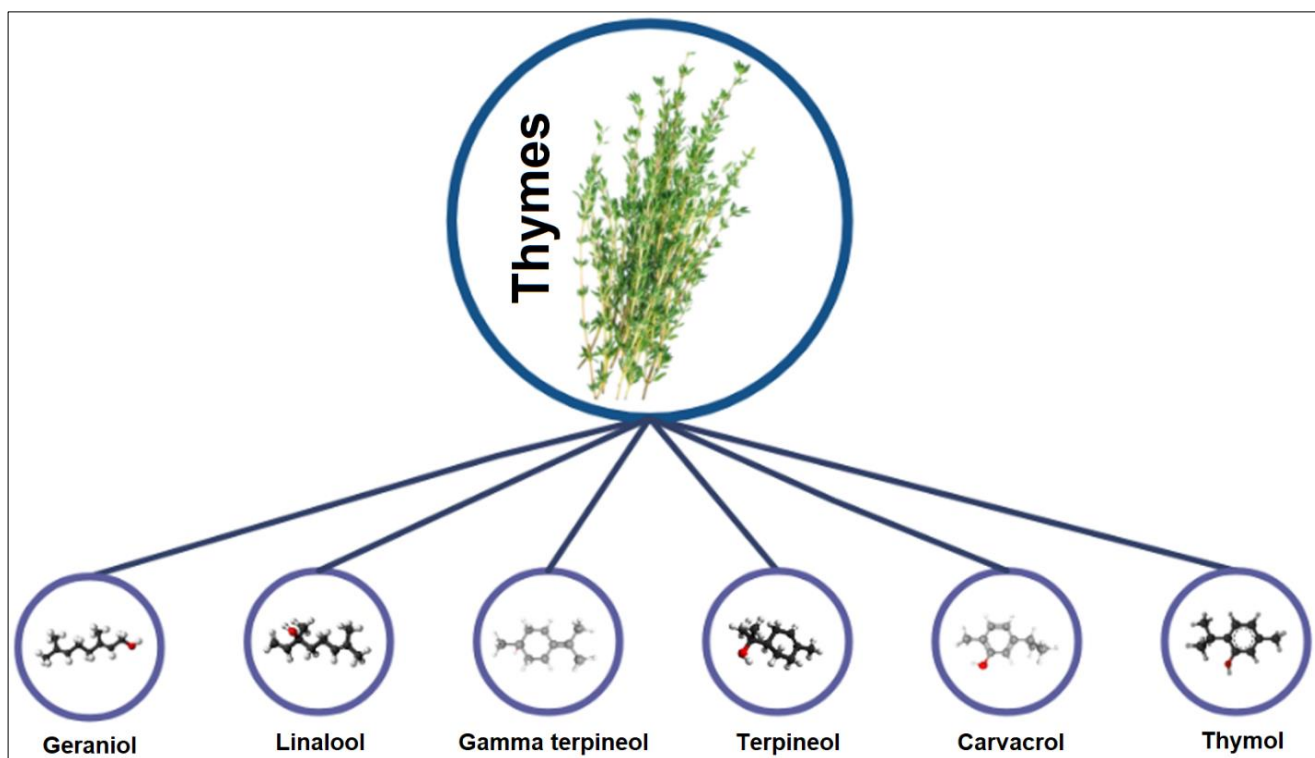


Fig. 1. Compounds obtained from the aerial parts of thyme. The published data illustrated that most of the volatile compounds obtained from the aerial parts of the plant include geraniol, linalool, gamma terpineol, terpineol, carvacrol and thymol.

6. Food applications and medicinal properties of thyme

This plant is widely used in traditional medicine due to its properties such as expectorant, antitussive, anti-bronchitis, anthelmintic, and diuretic. The thymus is a Greek word that means brave, and ancient Greek women used to sew this plant to the clothes of their husbands who were going to war. Because they believed that thyme gives them courage and as a result, they win in war. The aromatic and medicinal properties of *Thymus* have made it one of the most famous plants in the world (Jiang et al., 2014; Wang et al., 2012). *Thymus* species are generally used as herbal teas as well as seasonings and medicinal plants. Thyme is used in all kinds of foods, including cooked foods, meat and meat products, spices and seasonings, etc. Thyme white oil, tincture, and its liquid extract are used as aromatic compounds in most important food products, including frozen dairy desserts, gelatins, and desserts containing rice flour, etc. (Franz et al., 2007).

Among the medicinal uses of this plant, it can be mentioned as stomach strengthening, anticonvulsant, remedy for various diseases of the respiratory system, laxative, remedy for weakness of the digestive system, flatulence, chronic cough, and menstrual pain relief. Recent studies show that thymus species have antibacterial, anti-viral, anti-fungal, anti-parasitic, and antioxidant properties. Essential oils have an inhibitory effect on fungi, and the fungicidal effect of plant essential oils is weaker than their bactericidal effect (Hassanpouraghdam et al., 2022; Petran et al., 2020). The antimicrobial effect of the essential oil is related to thymol and carvacrol components, especially its thymol. This essential oil can be the basis for future studies in order to make disinfectants and food supplements to control human and animal diseases. Since thymol is an anthelmintic, it is used as an anthelmintic medicine. Red thyme oil has been officially considered as a germicide since the 16th century, and its antimicrobial properties are due to thymol and carvacrol, and it is widely used in mouthwashes, gargle solutions, toothpastes, soaps, cleaners, and various disinfectant medical products (Botelho et al., 2007). It is also recommended in the treatment of whooping cough, tuberculosis, and bronchitis. Red thyme oil also has the properties of preventing sensitivity, itching, and sun damage for human skin, but when it is used undiluted, it causes severe burning and itching for the skin. Thyme extract liquid is one of the ingredients of thick anti-cough syrups which is also used as a flavoring agent. Its essential oil in the form of alcoholic solutions is sometimes used to cure some indigestion and simple diarrhea (Wang et al., 2014).

7. Antibacterial properties of thyme

Essential oils of plant are appropriate sources of oxygenated monoterpenes, especially carvacrol and thymol, with noteworthy antimicrobial features (Fig. 2). It is well known that genetics, as well as the environmental conditions of the plant, can affect the performance, the essential oils composition, and therefore the antimicrobial features. The antimicrobial action of many essential oils is correlated with their phenolic monoterpenes. Shirazi thyme essential oil with a high level of carvacrol and thymol had noteworthy antimicrobial action (Chouhan et al., 2017; Swamy et al., 2016). Research has shown that these substances are naturally lipids, operate on cellular membranes, and result in significant morphological injury, leading to changes in penetrability and release of cellular mediators. Para-cymene is considered as another oil element. Nevertheless, conflicting information has been observed about the antimicrobial function of para-cymene. Investigations have illustrated an antagonistic interaction between carvacrol and thymol, phenolic monoterpenes, and para-cymene. Instead, other investigations revealed that para-cymene alone was an ineffective antimicrobial factor and its mixture with carvacrol produced an agonistic activity, leading to destabilization of the microbial membrane. Shirazi thyme leaf essential oil is stable at a wide range of pH and high temperatures. Moreover, the proteolytic treatment of the oil could not influence its antibacterial function. Therefore, it is acceptable that non-protein complexes are accountable for the observed antibacterial features of this herb. This plant extracts revealed a weaker antibacterial action rather than its essential oil. Antibacterial features of polar extracts can too be attributed to the existence of various kinds of complexes including flavonoids and more polar phenolic compounds sensitive to heat or stable against heat. In addition, the

existence of rosemary in the extract could be another effective factor contributing to the antibacterial action of plant parts (Dib and El Alaoui-Faris, 2019; Karki and Birukov, 2018; Sajed et al., 2013; Serhan et al., 2015).

Shirazi thyme essential oil is active against a wide range of clinical strains of *Klebsiella pneumoniae*-producing beta-lactamase. Thyme extract could prevent DNase enzyme release and enterotoxin production in *Staphylococcus aureus* and verotoxin production in *Escherichia coli*. The essential oil of this plant can also be used as an effective food preservative because it has been revealed that it can prevent the food pathogens growth including *Listeria monocytogenes*, *Bacillus cereus*, *Escherichia coli*, *Salmonella typhimurium*, and *Staphylococcus aureus* bacteria. In addition, it is suggested that the extract of this plant is efficient as a mouthwash due to its significant effect against oral streptococci. Shirazi thyme essential oil is effective in destroying *Enterococcus faecalis* and thus cleans the root canal in dentistry. The inhibitory properties of ethanolic, methanolic, hexane and chloroform extracts of Shirazi thyme *vs.* multiple drug-resistant *P. aeruginosa* were investigated. The outcomes showed that while all the tested extracts were effective, the most antibacterial activity was observed in the methanol extract. In addition, an extract combinations had a variable antagonistic or synergistic influence (Ginting et al., 2021; Nzeako et al., 2006; Zygadlo et al., 2017).

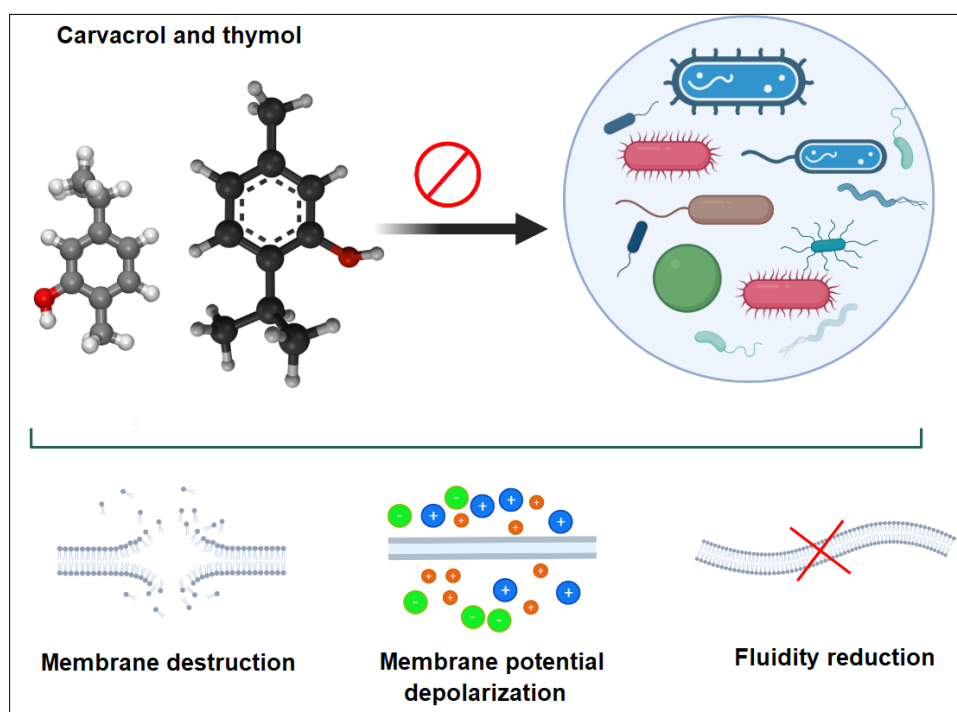


Fig. 2. Antibacterial effects of thyme. The thyme has antibacterial effect and this may arise from carvacrol and thymol compounds in thyme. These together with Nano compounds or alone can cause some disturbances in the membrane.

8. Antifungal properties of thyme

Many studies have investigated the antifungal action of Shirazi thyme oil *vs.* *Candida* species. Candidiasis is a primary or secondary infection caused by *Candida* species, especially *Candida albicans*. The infection may be confined to the mouth, skin, vagina, nails, larynx, gastrointestinal tract, and trachea, or it may be systemic and cause endocarditis, septicemia, and meningitis. The pathological reaction is different and varies from simple inflammation to a granulomatous or chronic reaction. The causative agent of the disease is *Candida albicans* in most cases and this fungus is usually isolated from the skin, mucous membrane, mouth, vagina, and feces of normal people. Therefore, this infection has an endogenous origin and the original disease manifests itself as an opportunistic infection (D'Enfert et al., 2021; Mayer et al., 2013).

Most of the lesions are formed in moist areas of the body, such as the folds under the breast, the skin around the anus, and other wrinkled areas. Fruit peelers, canners, dishwashers, and people who are in constant contact

with water because of their job are prone to *Candida* infection of the hands because the moisture leads to wetting and crushing of the skin. *Candida albicans* is part of the natural and resident flora of the oral mucosa, the mucosa of the digestive system, and the reproductive system of women. In these places, if the fungus multiplies a lot and overcomes other organisms and there are no limiting factors, it can cause disease, which has been observed in some studies that living alone in tropical areas or having contact with infected patients increases *Candida albicans* in the skin. Diseases such as diabetes mellitus are the basis for the development of candidiasis, immunosuppressive and cytotoxic drugs disrupt the body's natural defenses, and immune deficiencies are the basis for the development of *Candida* infections. Iron deficiency is also a predisposing factor for candidiasis, because iron is one of the necessary substances in cell-mediated immune responses, and therefore, due to iron deficiency, cell-mediated immunity is impaired and causes an increase in candidiasis (Nobile and Johnson, 2015; Talapko et al., 2021; Trofa et al., 2008).

Studies have shown that essential oil is effective against *Candida albicans*. This substance can also work against vaginitis produced by *Candida albicans*. Alshaikh et al study provide a collection of the experimental evidence on the treatment efficiency of thyme essential oil *vs.* drug-resistant clinical isolates of *Candida albicans*. Their results could be employed in the development of a novel antifungal compounds (Alshaikh and Perveen, 2021). Another study showed that thymol has a fungicidal impact on *Candida* species and a synergistic influence in combination with nystatin (De Castro et al., 2015). Another study found that thyme oil and thymol alone or in combination with antifungal compounds could act as a hopeful antibiofilm agent *vs.* drug-resistant strains of *Candida* species, and additional studies are needed for its synergistic therapeutic effect, especially inside the body (Jafri and Ahmad, 2020).

9. Anti-pain properties of thyme

Pain is a defense mechanism of the body and occurs when any tissue suffers a defect and causes a person to react and eliminate the cause of pain. Most diseases are accompanied by pain. Even simple activities such as sitting for a long time cause tissue destruction due to a lack of oxygen caused by reduced blood flow. When the skin becomes painful, a person naturally shifts his weight unconsciously. But in a person who has lost his sense of pain due to spinal injuries, this pain has not gone away and as a result, he does not move. As a result, this pressure causes a wound in that area (Crofford, 2015; Raffaelli and Arnaudo, 2017). It is one of the biological characteristics is to protect a person against danger, which causes a person to react and distance herself from the danger factor or run away. All the pain receptors in the skin and other tissues are free nerve endings and are widespread in the surface layers of the skin, mucous membrane, as well as some internal tissues including bone lining, artery walls, joint surfaces, etc. These receptors have different types such as thermal, mechanical, chemical, and silent type. These receptors are divided into two types, peptidergic and non-peptidergic (Dubin and Patapoutian, 2010).

In a study, the anti-inflammatory, antinociceptive properties of ethanolic and aqueous extracts of Shirazi thyme aerial portions were investigated in rats and mice. Analgesic action was performed by writhing and hot plate examinations. Intraperitoneal injection of both extracts in mice showed analgesic activity, which was dose-dependent. In the study, it was concluded that Shirazi thyme has an analgesic effect and this might be mediated through opioid receptors. Also, the extracts revealed anti-inflammatory influences *vs.* chronic and acute inflammation (Hosseinzadeh et al., 2000). Another study showed that *T. spicata* extract, thymol, extract nanopolymer and thymol nanopolymer are effective in decreasing drug withdrawal symptoms. The therapeutic potential and mechanism of action may be similar to that of clonidine. Another study showed that the simultaneous use of thyme formulations leads to the intensification of the depressant effects of diazepam and pentobarbital on the central nervous system. The thyme formulation probably exerts its effect by interfering with their metabolic pathways and altering the concentration and pharmacological effects with conventional drugs tested (Rašković et al., 2021).

10. Conclusion

The effective substance of thyme is an essential oil, which is a yellow or dark reddish-brown liquid with a strong pleasant smell and a strong, persistent and cooling taste, which is extracted from the distillation of the leaves and flowering branches and is a combination of different chemicals. Most of the volatile compounds obtained from the aerial parts of the plant include geraniol, linalool, gamma terpineol, terpineol, carvacrol and thymol. However, thyme sprigs contain essential oil, tannins, main bitter substances, saponins, and herbal disinfectants. The aromatic and medicinal properties of *Thymus* have made it one of the most famous plants in the world. Thyme is used in all kinds of foods, including cooked foods, meat and meat products, spices and seasonings, etc. Among the medicinal uses of this plant, it can be mentioned as stomach strengthening, anticonvulsant, remedy for various diseases of the respiratory system, laxative, remedy for weakness of the digestive system, flatulence, chronic cough, and menstrual pain relief. *Thymus* species have anti-bacterial, anti-viral, anti-fungal, anti-parasitic, anti-inflammatory, anti-pain, and antioxidant properties. Essential oils have an inhibitory effect on fungi, and the fungicidal effect of plant essential oils is weaker than their bactericidal effect. The antimicrobial effect of the essential oil is related to thymol and carvacrol components, especially its thymol. This essential oil can be the basis for future studies in order to make disinfectants and food supplements to control human and animal diseases.

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