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Review Article

The importance of *Lavandula stoechas* L. in pharmacognosy and phytotherapy

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Abstract: *Lavandula stoechas* is distributed in Africa, Europe, and Asia continents, especially in the countries of Southern Europe and North Africa neighboring the Mediterranean. The use of *L. stoechas*, which has a cosmopolitan distribution, mainly in the Mediterranean region, in the treatment of rheumatic diseases and reduction of inflammatory problems in folk medicine dates back to ancient times. It has been determined that *L. stoechas* contains various bioactive phytochemicals such as flavonoids, catechic tannins, sterols, coumarins, leucoanthocyanins, and mucilages. The essential oil obtained from the leaves and flowers is widely used in pharmacy. There are ethnobotanical and phytopharmacological studies on the antimicrobial, insecticidal, antileishmanial, antioxidant, and anti-inflammatory effects of the essential oil and extracts of the plant. There are intensive studies and clinical data on its anti-inflammatory, antimicrobial, antioxidant, and anticonvulsant effects. It has been determined that *L. stoechas* has anti-inflammatory, antioxidant, antimicrobial, insecticide, larvicide, anticonvulsant, antispasmodic, sedative, hepatoprotective, nephroprotective, antidiabetic, and anticancer effects with scientific studies based on the traditional use of *L. stoechas*. This review supports that the aforementioned plant can be used as a medicine in the light of its traditional use and the data obtained as a result of scientific studies. In this review, it was emphasized that some regulations should be made on the cultivation, formulation, and marketing of *L. stoechas*.

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1. INTRODUCTION

Lavender is the common name for about 28 bushy-looking perennial plant species that do not shed their leaves in winter (İpek, 2017). Although it grows in the Mediterranean region of Turkey, it spreads almost worldwide (Gülmen, 2018).

The genus *Lavandula* consists of about 39 species, mostly of Mediterranean origin, with more than 100 varieties (Carrasco *et al*., 2015). In the *Lavandula* species, the corolla is tubular and has 5 lobes at the apex. The upper lip is 2-lobed, straight and upright. Stamens are four, and filaments are short (Baytop, 1996; Tanker *et al*., 2007).

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2. CHARACTERISTICS of *LAVANDULA STOECHAS* L.

L. stoechas, which grows naturally in Turkey and is popularly known as black pepper, is an aromatic plant belonging to the Lamiaceae family (İpek, 2017).

The flowers are gathered at the ends of the spike-shaped stems 15-20 cm long. Each spike has an average of 5 flower clusters. There are 5-15 flowers in each cluster. Two opposite leaves protect the flower clusters. Lavender flowers with very short stems; surrounded by 5 mm long sepals, gray-blue, smooth and shiny inside, hairy outside. The sepals wrap the flower like a tube and end with 4 small sharp teeth at the tip. *L. stoechas* flowers are slightly darker than other species, blackish purple. The flowers are collected in a cylindrical shape at the ends of the branches. There are 4 stamens between the petals, in colors ranging from blue to violet. The nectar gland is located under the corolla tube. Nectar secretions are particularly attractive to honeybees. Lavender seeds are 2mm tall and 1mm wide. Its shape is elongated-oval and its color is bright dark brown. 1000 of them weigh is less than 1 g (Topçu, 2008).

3. GEOGRAPHICAL DISTRIBUTION

L. stoechas has spread to three continents (Africa, Europe, and Asia) (Ez zoubi *et al*., 2020). It spreads mainly in Southern Europe and North Africa, neighboring the Mediterranean, especially in the Mediterranean and Balkan countries. There are 47 lavender species (*Lavandula* sp.), most of which are of Mediterranean origin (Gedik & Dülger, 2015). It is a plant that grows wild in regions ranging from the Canary Islands to the Mediterranean coast and India. It is cultivated extensively in France, Bulgaria, Italy, Greece, England, the USA, and North African countries (Selmi *et al*., 2018). In Morocco, this plant typically grows on calcareous soils, particularly in northern Morocco, in the middle and high Atlas and Rif Mountains. It is found in Tunisia's northern, northeastern, and Cap Bon regions at 400 to 1000 m. L. stoechas is also found in Bihar and Bengal in India (Ez zoubi *et al*., 2020).

L. stoechas found in Southern Europe, Algeria, Tunisia, Canary Islands, Southwest Asia and Syria in the world, mainly Aegean Islands, Çanakkale, Istanbul-Buyukada, Izmit-Hereke, Kocaeli, Balikesir-Kazdagi, Izmir, Datça-Marmaris. Muğla, Tekirovası Antalya, between Anamur-Emirşah, İçel, Samandağı-Hatay, and Yayladağı regions in Turkey (Oraloğlu, 2018).

L. stoechas subsp. *stoechas* and *L. stoechas* subsp. *cariensis* (*L. pedunculata* Mill. subsp. cariensis) species are found in Turkey's Western and Southern regions (Selmi *et al*., 2018). *L. stoechas* is common in Mediterranean countries and Turkey, and is sold under the names of 'karabaş', 'kekik' and 'tuzla kekiği' in Izmir (Oraloğlu, 2018).

'Karabaş' grows in dry hills, open forests, limestone, and granite soils as the habitat. In addition, it is known to grow in almost any type of soil, including arid and not very acidic soils. It likes hot and dry environments, and it is known to be resistant to drought and cold between -5 and -10 °C (Öztekin Kahraman & Özoğul, 2018).

4. HISTORY

Different types of lavender were used in ancient Rome. The term lavender is derived from the Latin 'lavando' part of the infinitive 'lavare' (to bathe), as it is frequently used in baths due to its scent. The first description of the medicinal use of lavender was made in the first century AD, under the name of 'stoechas' by Dioscorides in his essential work 'De Materia Medica'. 'Stoechas' got this name because it grows on the Galatia Islands called Stoechades near Messalina. It is an herb with thyme-like twigs and filaments but with longer leaves, sharp and slightly bitter. It is boiled and used for chest pains. It can be used as an antidote. It is also called syncliopa, alcibiades, pankration or styphonia. The Egyptians called the plant 'suphlo', the 'Magi', 'oculus pythonis', and the Romans 'schiolebina' (Farsam *et al*., 2016).

Pliny, a Roman writer, naturalist, philosopher, and who lived recently with Dioscorides, stated in his encyclopedic work “Naturalis Historia” about *L. stoechas* that it only grows on the islands of the same name and because it is a fragrant plant with a bitter taste. He stated that it could be used for emmenagogue and chest pains and has antidote properties when put into a drink. Geographical clues of Dioscorides point to researchers at the site of Massalia and Galatia, the Stoechades Islands. There are only several important islands now there known as Îles d'Hyères. The only lavender species that grows there is *L. stoechas*. In short, the stoechas mentioned at the time of Dioscorides is *L. stoechas*. Galen has described stoechas as beneficial for snake bites, stomachaches, liver, kidney, biliary disorders, jaundice, and edema. Later, the use of stoechas in medieval Europe remained the same as in antiquity (Farsam *et al*., 2016).

Initially formulated by the Greeks as theriac or theriaca in the 1st century AD, this medicinal mixture was used as an antidote in countries such as Iran, China, and India through the trade links of the Silk Road. During the Renaissance, especially in Italy, the making of the theriac became an official ceremony and was prepared and sold by apothecaries until 1884. This medicinal mixture consists of 64 components, including viper meat, opium, cinnamon, gum arabic, and flowers of *L. stoechas* (Hodgson, 2001; Boulnois, 2005).

Avicenna, the leading physician of the eleventh century, wrote about the new medical effects of *L. stoechas*, whose effects were not mentioned by Galen in his book on the Law of Medicine (Farsam *et al*., 2016). Ibn Sina, in his book, stated that Osṭokudus (Karabas otu) is a red-haired, small-grained barley-like plant, and its leaves and branches are earth-colored. He wrote that cooking has therapeutic properties for joint and rib pains, it is suitable for diseases such as melancholy and epilepsy, and it is also a phlegm and bile remover (Khan, 2016).

In his book A New Herbal, William Turner states that the Greeks and Latins called it "stechas" or "stichas"; however, he said it was known as 'stichados' among pharmacists. It shows that the word 'osṭokudus' in Persian and Arabic texts is the Arabicized form of stichados and that Muslims or Persians before them knew stoechas through trade with Europeans through the translation of texts. Since *L. stoechas* was used for medicinal purposes in eighteenth and nineteenth-century Europe, the study proved that stoechas were imported from elsewhere than Europe (Farsam *et al*., 2016). It was used for the first time in Turkey in the fight against the cholera epidemic in the Ottoman period to eliminate the microorganism that caused cholera, and it was used to prevent the infection of wounds during the First World War (Salih *et al*., 2019).

5. ETHNOPHARMACOLOGICAL USE

5.1. Use in Turkey

L. stoechas has been widely used in Turkey since ancient times. This plant is popularly known as ‘karabas otu’, ‘gargan (Mugla)’, ‘kesisotu’, ‘coban bagirtan’, ‘kafa supuren’, ‘karan cicegi’, ‘lavanta cicegi’, ‘karahan’, ‘Mugla kekigi’, and ‘yalanci lavanta cicegi’ (Oraloğlu, 2018). The essential oil obtained from the dried flowers and aerial parts of *L. stoechas* is popularly used. ‘Karabas otu’; is widely used due to its effects such as pain reliever, antiseptic, wound healing, sedative, expectorant, relieving urinary tract inflammation, healing eczema wounds, and strengthening nerve and heart. Its effects are due to the essential oil it contains. It is generally used externally and internally as an infusion (25%). It was also known as an essential drug during the Ottoman Empire period. There is a sultan's edict dated 1848 regarding the use of black cumin in the treatment of cholera disease and its sale in pharmacies (Oraloğlu, 2018).

The flowers of this lavender species, called 'Sıttıhotuz' among the people in the Hatay region, are used as incense by being dried and burned in winter when there is a cold. It also has diuretic and rheumatic pain relief properties. The flowers are used externally as an itch reliever (Oraloğlu, 2018).

Tea prepared in the form of an infusion or decoction of the leaves and flowers of 'karabas otu' is also used to treat stomach ulcers, and unspecified cancers (Kültür *et al*., 2018; Bozyel & Merdamert-Bozyel, 2020; Bozyel *et al*., 2019). The use of 'karabas otu' as an analgesic has also been reported. For centuries, the extract obtained from the leaves and flowers of this plant has been used as a pain reliever, antimicrobial, sedative, relieving urinary tract inflammation, strengthening the heart, curing atherosclerosis, and relieving vascular occlusion in Anatolian folk medicine. *L. stoechas* flower, leaf, and aerial parts are used to treat sinusitis among the people in Anatolia. In Edremit (Balıkesir), it has been reported that the flowering branches of 'karabas otu' are used in the form of an infusion for abdominal pain, headache, cholesterol, antihypertensive, and vascular occlusion (Oraloğlu, 2018).

Antimicrobial, anti-inflammatory, and carminative properties of essential oil rich in monoterpenes have been demonstrated (İpek, 2017). It is also widely used in Anatolia to treat dental and gingival diseases (Gedik & Dülger, 2015), epilepsy, and asthma due to its sedative properties (Kalhan, 2019).

In the studies titled "Datça Peninsula (Muğla) flora and the plants used by the people in this region" and "Plants used in folk medicine in Bodrum region", it was determined that the infusion of *L. stoechas* subsp. *stoechas*, especially the flowering parts, are widely used as a cholesterol-lowering internally in these regions (Öztekin Kahraman & Özoğul, 2018).

The flowering branches of *L. stoechas* are used as a tea in cough and bronchitis, colds, headaches, ulcers, stomachaches, heart ailments, and diabetes. Leaves and stems are used in folk medicine; against rheumatism, colds, digestive system diseases, extracts wounds, eczema, urinary tract infections, and heart diseases (Gülmen, 2018).

It is essential because of its analgesic, antiseptic, and anti-irritant effects and is used in perfumery and cosmetology due to linalool and linalyl acetate in its essential oil. The essential oil obtained from the 'karabas otu' in Turkey with an average yield of 0.5-0.7% mainly contains camphor, fenchone, borneol, terpinol, and cineol; these compounds are used in pharmacy. Its essential oil is known to treat headaches, nervous tensions, and rheumatism and is also used against colitis, poor diet, and spasms by inhalation. It is recorded in the literature that flowers are used to heal breast, liver, spleen, and some cancer types (Ayral, 1997).

In various regions of Turkey, especially in the Aegean and Mediterranean, patients suffering from high blood pressure prefer 'karabas otu' because of its blood pressure-lowering effect. In addition, its oil is used in the treatment of skin blemishes and as a massage oil. It can also be used for the sterilization of open wounds (Salih *et al*., 2019).

5.2. Use in Other Countries

Ethnobotanical data show that the plant in question is used as an antispasmodic, analgesic, and anti-inflammatory agent in the treatment of rheumatic diseases in north Africa (Morocco). Many researchers are interested in the antimicrobial, insecticidal, antileishmanial, antioxidant, and anti-inflammatory properties of L. stoechas essential oil and extracts (Ez zoubi *et al*., 2020).

In Tunisia, Algeria, and Morocco, it is used in traditional pharmacopeia to treat rheumatic diseases, diabetes, depression, and headaches (Ez zoubi *et al*., 2020).

Known locally as 'Ustu khuddoos', *L. stoechas* is native to Asia Minor. It is an imported product in Pakistan and is traditionally used for various central nervous system diseases such as epilepsy and migraine. It has been called the 'brain cleaner'. It is also used in folk medicine as an antispasmodic in colic pains. For medicinal purposes, the aerial- parts are used (Gilani *et al*., 2000).

6. PHYTOCHEMICAL CONTENT

In a study conducted in 2020, various chemical groups such as flavonoids, catechic tannins, sterols, coumarins, leucoanthocyanins, and mucilages were detected in the aqueous-alcoholic extract of the aerial parts of *L. stoechas* (Ez zoubi *et al*., 2020).

6.1. Essential Oil

The most crucial active ingredient of lavender flowers is the colorless and slightly yellow essential oil. The essential oil rate in lavender flowers varies between 1-3%. According to the codex, the genuine lavender flower should contain at least 1% essential oil (Topçu, 2008). 'Karabas otu' essential oil (Oleum Lavandula) is an essential oil obtained by steam distillation from the aerial parts of *L. stoechas*. It is known that the essential oil obtained by steam distillation from the aerial parts of *L. stoechas* contains compounds such as camphor, fenchone, borneol, terpinol, and cineol. It is used externally and internally as an antiseptic. It is also used externally as a wound healer and a good antiseptic (Öztekin Kahraman & Özoğul, 2018). The essential oil obtained from its leaves is used for headaches, withdrawal syndrome, burn injuries, and expectorants (Oraloğlu, 2018).

The essential oil of *L. stoechas* grown in Turkey contains camphor, fenchone, borneol, terpinol, cineol, linalool, linalyl acetate, bornyl acetate, and cadinene. Since it contains 30% camphor and 18% fenchone, half of the essential oil is a ketone and differs from the species found in Europe with this feature. Again, since the rate of linalool is 0.6%, it is not a source of linalool, but a source of camphor, unlike the species found in Europe (Kalhan, 2019). Oxygenated monoterpenes make up the bulk of the essential oil (46.19-92.93%) isolated from the flowers of *L. stoechas* (Aprotosoaie *et al*., 2017).

In a different study, the essential oil content of *L. stoechas* was between 0.77-1.2%. 51 compounds, including fenchone, pinocaryl acetate, camphor, eucalyptol, and myrtenol, were detected in the essential oil (Gilani *et al*., 2000). Variable results were obtained in the essential oil ratios of *L. stoechas* grown in different Mediterranean countries. In a study by Carrasco *et al*. (2015), 1,8-cineole, camphor, and fenchone were found as the major compounds. In many studies, fenchone/camphor is the main compound in *L. stoechas* essential oil. In addition to these compounds, *L. stoechas* oil from Greece was found to contain α-cadinol. The main components of Moroccan *L. stoechas* essential oil were fenchone (30.5%), camphor (18.2%), 1,8-cineole (8.6%), and camphene (3.5%) (Zrira & Benjilali, 2003). In some reports, camphene, linalyl acetate, γ-terpinene, linalool, lavandulyl acetate, myrtenyl acetate, bornyl acetate, borneol, and caryophyllene were expressed as the main compounds (Ez zoubi *et al*., 2020).

In a study by Selmi et al. (2018), the bioactive compounds of the *L. stoechas* essential oil were investigated with GC-MS, and its main components were identified as d-fenchone (29.28%), α-pinene (23.18%), and camphor (15.97%). These cyclic compounds are in the group of oxygenated monoterpenes known for their antioxidant and free radical scavenging effects.

In a study by Gursoy *et al*. (2009), the presence of *p*-cymene, a rarely found compound, was detected in samples of Turkish essential oils. It has been reported that α-pinene and viridiflorol are commonly found in essential oil samples of plants grown in Italy, Turkey, and Algeria (Carrasco *et al*., 2015; Ez zoubi *et al*., 2020).

In a study by Tanker *et al*. (2007), the essential oil yield of *L. stoechas* was determined to be 0.86% in flowers and 0.57% in leaves. As a result of the gas chromatography analysis, the researchers determined that the monoterpenic hydrocarbons α-pinene, camphene, β-pinene, and limonene were found in the essential oil, while the oxygenated compounds included camphor, fenchone, cineol, borneol, linalool, and linalyl acetate. In addition, according to the results of planimetric measurements made in the chromatogram of *L. stoechas* essential oil, they determined that its composition consisted of 23.29% camphor, 10.87% fenchone, 4.07%

cineole, 1.5% linalool, and linalyl acetate. The essential oil obtained from the leaves and flowers of *L. stoechas* is widely used in pharmacy (Gülmen, 2018).

6.2. Phenolic Compounds

In phytochemical studies, it has been determined that the aerial parts of the plant contain components such as luteolin, acacetin, vitexin, and longipine (Oraloğlu, 2018).

The main components of flavonoids in leaves of *L. stoechas* are simple flavone glycosides (flavone di-*O*-glycosides and flavone 7-*O*-monoglycosides). Xaver & Andary (1988) revealed apigenin 7-glucoside, luteolin, luteolin 7-glucoside, and luteolin 7-glucuronide (Ez zoubi *et al*., 2020).

6.3. Other Compounds

L. stoechas extracts were detected to contain oleanolic, ursolic, and vergatic acids, β-sitosterol, α-amyrin, α-amyrin acetate, lupeol, erythrodiol, luteolin, acacetin, vitexin, two longipinen derivatives (longipin-2-en-7p,9a-diol-1-one and longipin-2-en-7p,9a-diol-1-one-9-monoacetate), 7-methoxy coumarin (smooth muscle relaxant) (Ez zoubi *et al*., 2020).

7. PHARMACOLOGICAL EFFECTS

Many of the traditional uses of *L. stoechas* have been explored in some recent studies. Ancient researchers such as İbn Sina and Aghili emphasized the psycho-neurological effects of *L. stoechas* such as antiepilepsy and anti-depression (Farsam *et al*., 2016).

7.1. Anti-inflammatory Effect

The anti-inflammatory effects of *L. stoechas* were evaluated by inducing inflammation through a lipopolysaccharide-macrophage model. This in vitro study showed that *L. stoechas* essential oil at concentrations of 0.16 µL/mL and 0.32 µL/mL significantly reduced nitrite production in cell cultures without causing cellular damage (Zuzarte *et al*., 2013; Ez zoubi *et al*., 2020).

In the study of Algieri *et al*. (2016), it was determined that *L. stoechas* extract showed anti-inflammatory effects with values similar to those recorded by a steroidal anti-inflammatory drug (glucocorticoid dexamethasone) (Ez zoubi *et al*., 2020).

L. stoechas extract has been shown to exhibit inhibitory activity in paw edema induced by carrageenan (Amira *et al*., 2012). A 200 µg/mL concentration has been shown to reduce pro-inflammatory cell viability by 63% after 3 hours of incubation. Ez zoubi *et al*. (2020) compared treatment with an aqueous-alcoholic extract (10%) of the aerial part of *L. stoechas* with diclofenac (69%) used as a control anti-inflammatory and found that rats caused a significant reduction in the volume of paw edema. They showed that flavonoid and mucilage extracts reduced edema by 85.1% and 61.71%, respectively, and as a result, flavonoids and mucilages in *L. stoechas* extract may be responsible for the observed anti-inflammatory effects.

In another study, the anti-inflammatory property of *L. stoechas* extract was tested in two inflammatory experimental models, and an anti-inflammatory effect in the intestine was observed as a result of the study. According to the results obtained, their potential use as herbal medicine in gastrointestinal disorders has been confirmed (Miraj, 2016).

The essential oil from the flowers of *L. stoechas* has proven promising as an anti-inflammatory agent. The study determined that it helps to facilitate the decrease in the production of nitric oxide molecule, which is involved in the inflammatory response and stimulated by some of the pro-inflammatory cytokines in the body. In addition, it has been proven that massage therapy with *L. stoechas* essential oil is effective in the postpartum healing process by helping episiotomy wound healing and reducing pain and inflammation (Wells *et al*., 2018).

7.2. Antioxidant Activity

L. stoechas shows a powerful antioxidant capacity because it contains 1,8-cineole and camphor in high amounts (Wells *et al*., 2018). In a study by Carrasco *et al*. (2015), linalool and thymol were shown to be responsible for the antioxidant effect of *L. stoechas* essential oil. It has been stated that phenolic acids and flavonoids such as rutin and caffeic acid also have antioxidant effects.

The antioxidant properties of the phenolic compounds of *L. stoechas* are mainly based on their free radical scavenging effects; for example, it has been found to have hepatoprotective and renoprotective effects against oxidative stress-induced in diabetic rats and malathion-induced oxidative stress in young male mice (Ez zoubi *et al*., 2020).

In a study by Ceylan *et al*. (2015), the antiradical effect of the methanolic extract of *L. stoechas* was evaluated, and an IC_{50} of 300 µg/mL was recorded compared to BHT and BHA with IC_{50} values of 200 µg/mL and 100 µg/mL, respectively.

Sariri *et al*. (2009) investigated the tyrosinase inhibitory capacities of aqueous extracts of four lavender species collected from northern Iran. As a result of the study, they found that the antiradical value of *L. stoechas* was 12.5 µg/mL (Ez zoubi *et al*., 2020).

Sebai *et al*. (2015) used ascorbic acid (IC_{50} = 87.57 µg/mL) as a control group in their study using radical scavenging activity and DPPH methods to determine the antioxidant effect. As a result, it was revealed that the compounds in the essential oil of *L. stoechas* exhibited a high antioxidant capacity (IC_{50} = 221.43 µg/mL).

In a study by Messaoud *et al*. (2012), an IC_{50} value of 2.32 mg/mL was reported in Tunisian *L. stoechas* essential oil. In addition, in their study, Barkat & Laib (2012) obtained an IC_{50} value of 584 µg/mL in the essential oil obtained from dried flowers of Algerian *L. stoechas*. Numerous studies on the antiradical effect of plant extracts have shown that phenolic compounds, especially flavonoids, are potential antioxidant compounds capable of scavenging free radicals (Barazandeh, 2002; Ez zoubi *et al*., 2020).

Different studies on the antioxidant effects of extracts of *L. stoechas* extracted with water and ethanol at different concentrations determined that it inhibited lipid peroxidation at significant rates. It has been determined that the total phenol content in the plant's ethanol extract is higher than that in the water extract (Öztekin Kahraman & Özoğul, 2018).

7.3. Antimicrobial Activity

In a study conducted by Sarac & Ugur (2009), the antimicrobial effect of *L. stoechas* essential oil grown in Turkey was determined against gram-positive and gram-negative bacteria. Antibiotic-resistant *Staphylococcus aureus*, *S. epidermidis*, *Streptococcus mutans*, *Escherichia coli*, *Pseudomonas stutzeri*, *Stenotrophomonas maltophilia*, *Micrococcus luteus*, and *Bacillus subtilis* were found to be the most sensitive bacteria to essential oil. Cherrat *et al*. (2014) reported that Moroccan-derived *L. stoechas* essential oil showed superior antimicrobial activity against gram-positive bacteria than gram-negative ones. It was determined that it exhibited the highest antimicrobial effect against *E. coli*, *Listeria monocytogenes*, and *S. aureus* with inhibition diameters of 16.2, 32.0, and 28.0 mm, respectively (Ez zoubi *et al*., 2020).

A comprehensive assessment of the essential oil composition and biological activities extracted from the aerial flowering parts of wild-growing *L. stoechas* collected from eleven different locations in northern Algeria was conducted. As a result, the essential oil showed resistance to most of the 16 tested strains of bacteria, fiber fungus, and yeast. It has been observed that it exhibited a significant antimicrobial effect, and its minimum inhibitory concentrations (MIC) varied between 0.16 - 11.90 mg/ml (Miraj, 2016).

The essential oil of *L. stoechas* collected from Turkey (Gören *et al*., 2002) and Tunisia (Bouzouita *et al*., 2005) showed a strong antimicrobial effect similar to other essential oils rich in sesquiterpenes. A recent study tested its antimicrobial activity against eight pathogenic bacterial strains, including *E. coli*, *L. monocytogenes*, *S. aureus*, *Proteus mirabilis*, *P. aeruginosa*, and *B. subtilis*, a microtitration assay. As a result of the study, it was stated that the highest inhibition was obtained against *L. monocytogenes* and *S. aureus* (Bouyahya *et al*., 2017). It has been observed in different studies that camphor and 1,8-cineole have antimicrobial effects among the main compounds in *L. stoechas* oil, especially against *S. aureus*, *E. coli*, and *L. monocytogenes* (Hendry *et al*., 2009; Mahboubi & Kazempour, 2009). Many studies have shown that minor components in *L. stoechas* essential oil have synergistic antimicrobial effects (Gill *et al*., 2002; Mourey & Canillac, 2002). It has been stated that gram-positive bacteria are more sensitive to essential oil than gram-negative ones due to their outer membrane differences (Ozcelik *et al*., 2003; Kaplan *et al*., 2007; Ez zoubi *et al*., 2020).

The essential oil of *L. stoechas* showed significant antimicrobial effects against gram-negative bacteria *S. typhimurium* and *P. vulgaris*. The essential oil of *L. stoechas* showed antimicrobial activity against *E. coli*, *P. aeruginosa*, *Enterobacter aerogenes*, *S. epidermidis*, and *S. aureus*. It has been stated that the rate of penetration and degradation of the essential oil into the cell wall and cell membrane proteins varies according to the bacterial species and their concentrations (Wells *et al*., 2018). In a study conducted in 2005, *L. stoechas* subsp. *stoechas* essential oil was obtained by distillation from the aerial parts, and it was found to contain 1.1% essential oil. Of the 26 compounds determined in the GC-MS analysis, 8 of them, corresponding to 91.63% of the essential oil, were identified as camphor with 43.47%. The essential oil's total antioxidant capacity (TAC) was determined by the spectrophotometric phosphomolybdenum method at 13.316 mmol. It was found to be equivalent to α-tocopherol acetate. Antimicrobial effect studies of essential oil were carried out by the disk diffusion method. It was observed that it showed a more substantial antimicrobial effect than standard antibiotics against *P. vulgaris* and an antifungal effect close to nystatin against *Candida albicans* (Miraj, 2016).

In addition to the essential oil, according to literature data, it was determined that the ethanol extract obtained from *L. stoechas* also exhibited antimicrobial activity. According to Canli et al. (2019), it was reported that ethanol extract was effective on all test microorganisms except *E. coli* and *K. pneumoniae*.

The antifungal effect of the essential oil of *L. stoechas* was evaluated in the study by Benabdelkader *et al*. (2011), and its antifungal effect against filamentous fungi (*Aspergillus niger* and *Fusarium oxysporum*), yeasts (*C. albicans*) was confirmed. *L. stoechas* essential oil also showed antifungal activity against *Rhizoctonia solani* and *F. oxysporum*, but less on *A. flavus*. Among the tested compounds, fenchone, limonene, and myrtenal were more effective in inhibiting the growth of *R. solani* (Angioni *et al*., 2006). It has been reported that the antifungal effect of *L. stoechas* essential oil is related to the presence of antifungal compounds such as camphor, 1,8-cineole, and fenchone and the synergistic effect of the major and minor components of this oil (Benabdelkader *et al*., 2011; Zuzarte *et al*., 2013; Ez zoubi *et al*., 2020).

A different study determined that *L. stoechas* also acted as a bio fungicide against *Verticillium dahliae* isolated from organic tomatoes. In addition, *L. stoechas* essential oil showed a significant antifungal effect against *Botrytis cinerea*, which causes gray mold disease in tomatoes (Wells *et al*., 2018).

In a study on the antifungal effect of *L. stoechas* against pathogenic *Candida* species, *C. albicans*, *C. krusei*, *C. tropicalis*, *C. guilliermondii*, and *C. glabrata* isolated from the Duzce University Faculty of Medicine hospital were used as the test microorganisms. Ethanol, chloroform, and ethyl acetate extracts of the plant were prepared with the Soxhlet, and 25 µl, 50 µl, and 75 µl of these extracts were adsorbed onto sterile discs, and their antifungal effect spectra were determined on the test microorganisms using the disk diffusion method. Standard antifungal antibiotics (Griseofulvin, Fluconazole, Amphotericin B, Miconazole, Nystatin, Flucytosine, Clotrimazole, Ketoconazole, Itraconazole) were used as the control group and the results were compared. As a result, extracts obtained from *L. stoechas* showed much higher antifungal efficacy than standard antifungal antibiotics. The results supported the ethnobotanical use of *L. stoechas*. It is thought that the potential extracts of the plant can also be used for the treatment of Candidemia in the future (Gedik, 2015).

In a study, according to the results of the qualitative bacteriological examination, it was understood that the essential oil obtained from the branches and leaves was quite active against *B. subtilis*, *S. aureus*, *P. mirabilis*, *E. coli*, and *P. aeruginosa*. The chloroform extract of the plant was only moderately active against *C. albicans* and did not show activity against the others. The methanol extract of the plant showed moderate activity against *S. aureus* and potent activity against *P. mirabilis* and *E. feacalis*. While β-sitosterol was only intensely active against *S. aureus*, it was found to show feeble activity against *S. epidermidis* and *P. mirabilis*. β-sitosterol acetate showed remarkable activity against *Klebsiella pneumonia*, *P. aeruginosa*, *E. feacalis*, and *C. albians* (Ayral, 1997).

7.4. Insecticidal and Larvicidal Effects

The effects of plant-derived molecules and extracts against insects and larvae are considered the best alternatives to chemical larvicides. It was reported that the essential oil of *L. stoechas* at a concentration of 500 mg/ml (LC_{50} = 112.51 mg/L; LC_{90} = 294.51 mg/L) was lethal against *Anopheles labranchiae*, a vector for malaria transmission (Lalami *et al*., 2016).

Bouyahya *et al*. (2017) tested the effects of *L. stoechas* essential oil on three *Leishmania* species and found LC_{50} values against *L. major*, *L. infantum*, and *L. tropic* as 0.9, 7.0, and 10.0 µg/mL, respectively (Ez zoubi *et al*., 2020).

In a study on the insecticidal activity of camphor, one of the main components detected in *L. stoechas* essential oil, camphor, showed significant anti-leishmanial activity against *L. major* (IC_{50} = 5.55 µg/mL) and *L. infantum* (IC_{50} = 7.90 µg/mL) (Mazyad & Soliman, 2001; Maia & Moore, 2011). The main components of *L. stoechas* essential oil, camphene, and 1,8-cineole, have been reported to be toxic to several insect species (Mazyad & Soliman, 2001; Yeh *et al*., 2009). In addition, 1,8-cineole showed excellent larvicidal activity against *Aedes aegypti* (Cavalcanti *et al*., 2004; Ez zoubi *et al*., 2020). In a study conducted, the essential oil obtained from the *L. stoechas* was found to have an insecticidal effect against adult *Tetranychus cinnabarinus* in crops (Wells *et al*., 2018).

7.5. Anticonvulsant, Antispasmodic and Sedative Activities

The antispasmodic effect of *L. stoechas* extract was evaluated in rabbit jejunum. The researchers determined that doses between 0.1 mg/mL and 1.0 mg/mL of *L. stoechas* aqueous methanolic extract had antispasmodic effects without noting any adverse effects on jejunum tissues. This spasmolytic activity is thought to be due to the presence of 7-methoxy coumarin, which is reported to be a smooth muscle relaxant (Gilani *et al*., 2000). In the same study, it was shown that *L. stoechas* extract had sedative properties at a dose of 600 mg/kg; Pentobarbital sleep time was extended from 39.4 minutes to 65.4 minutes, similar to diazepam, a standard sedative. This study provides evidence for the traditional use of this herb as a sedative (Gilani *et al*., 2000).

A study observed that the essential oil of *L. stoechas* has sedative and anticonvulsive effects in mice and antispasmodic activity in rabbit jejunum tissue. In addition, the anxiolytic effects of inhaled lavender, which is thought to be effectively similar to that of chlordiazepoxide, were tested in rat models using the "Elevated Plus Maze Test" and "Open Field Test", and as a result, an increase in serotonin production in the anterior cortex and sedative effects were observed at high doses (Wells *et al*., 2018).

7.6. Hepatoprotective and Nephroprotective Effects

In a study, the hepatoprotective and nephroprotective effects of *L. stoechas* essential oil against malathion-induced oxidative stress in young male mice, and the possible mechanisms involved in such protection were investigated. With essential oil treatment, malathion-induced total body loss, liver and kidney relative weight gain, hemodynamic and metabolic disorders, and hepatic and renal oxidative stress were abolished. The essential oil showed potential hepatoprotective and nephroprotective effects against malathion-induced oxidative stress in mice. It is thought that the beneficial effect of essential oil may be partially related to its antioxidant properties (Kültür *et al*., 2018).

To test the *in vivo* effect of essential oil on malathion-induced liver damage in a different study, mice were treated with various doses of essential oil and malathion for 30 days. Malathion-induced hepatotoxicity has been demonstrated by a decrease in plasma albumin content, as well as a significant increase in plasma bilirubin, AST, ALT, ALP, ACP, LDH, and p-GT levels. Interestingly, the levels of these parameters decreased in a dose-dependent manner when co-administered with the essential oil to animals. As a result, it was determined that essential oil showed protective effects against malathion-induced injury in rat liver and kidney, partly due to its antioxidant properties (Selmi *et al*., 2015).

7.7. Antihyperglycemic Effect

A few ethnobotanical studies have reported using *L. stoechas* in the treatment of diabetes or to reduce the level of hyperglycemia (Ez zoubi *et al*., 2020). It was found that linalool increased the peripheral utilization of glucose in the diaphragm of rats with streptozotocin in which they had diabetes. In addition, in studies on non-obese female diabetic mice, researchers have reported that camphor suppresses the development of autoimmune diabetes (Gülmen, 2018).

A study conducted by Sebai *et al*. (2013) found a decrease in CAT and SOD enzyme activities in liver and kidney tissues in rats with diabetes by administering alloxan (220 mg/kg). They found an increase in these enzyme activities and a significant decrease in blood glucose levels after *L. stoechas* subsp. *stoechas* essential oil was given. It was reported in another study that *L. stoechas* subsp. *stoechas* and *Rosmarinus officinalis* essential oil were administered separately to rats with diabetes mellitus with alloxan (160 mg/kg) for 15 days (intraperitoneal). SOD, CAT, and GPX antioxidant enzyme activity were found in testis, epididymis, and sperm tissues. MDA levels and blood glucose levels decreased. Researchers have reported that *L. stoechas* subsp. *stoechas* essential oil has a protective effect against oxidative stress caused by diabetes (Sebai *et al*., 2015).

In another study, the phytochemical profile of *L. stoechas* essential oil collected from the Ain-Draham (North-West of Tunisia) region and its protective effects against alloxan-induced diabetes and oxidative stress in the rat were described. Findings indicate that *L. stoechas* has a protective effect against diabetes and oxidative stress caused by alloxan treatment, and these effects are partly due to its potent antioxidant properties (Selmi *et al*., 2015; Miraj, 2016).

7.8. Anticancer Effect

According to the research results on cytotoxic activity, essential oil, 18 hydroxynorolean 12-14-diene-30-al-28-oic acid, and 11-oxo-β-amyrin were effective against carcinogenic cells. Similarly, chloroform root extracts were also found to be highly effective against mouse epidermoid cancer cells. An overall evaluation of the fractions and essential oil showed that 11-oxo-β-amyrin was active against one type of epidermoid cancer of the cognate. Fractions and essential oil are effective at different rates against cancer cell types other than epidermoid cancer (Ayral, 1997).

The cytotoxic activity of the essential oil obtained from *L. stoechas* in human pancreatic adenocarcinoma was investigated. According to the research results, it was shown that it causes cancer cell death, especially at a 1.0 µg/ml concentration. To demonstrate this efficacy of essential oil, the expression of genes responsible for the pathogenesis of pancreatic adenocarcinoma was also investigated. According to the data obtained, it was determined that the essential oil downregulated the expressions of KRAS and EGFR genes. According to all literature information and the results of these studies, it has been concluded that essential oil may be a potential alternative in the treatment of pancreatic cancer (Kalhan, 2019).

7.9. Other Pharmacological Effects

A different study stated that linalool has a protective effect against the damage caused by ultraviolet light on the skin (Gülmen, 2018). In *in vivo* and *in vitro* studies, cineol exhibited antioxidant, anti-inflammatory, and antiatherosclerotic activity effects and its effect on lipoprotein metabolism. Another substance in the composition of the essential oil of the plant is camphor. In the study of Garg & Jain (2017), it was stated that camphor has positive effects on the heart and circulatory system. Terpineol, a relatively non-toxic, volatile monoterpene alcohol, is an essential component of the essential oils of many plants. In the studies carried out, terpineol has been reported to have antimicrobial, antispasmodic, and immuno-stimulating properties. In a study by Tuzlacı (2002), it was observed that the infusion prepared from the flowering parts of *L. stoechas* has a cholesterol-lowering effect (Gülmen, 2018).

A study investigating the effects of alcohol and water extracts of *L. stoechas* on the fibrinolytic system observed that the extracts activate the fibrinolytic system (dissolving the fibrin in the blood clot) in vitro. Thus, it was stated that the idea that *L. stoechas* contributed to the coronary system, vascular system, and circulatory system was supported (Öztekin Kahraman & Özoğul, 2018). According to the results of a different study conducted in the same year, it was determined that essential oil supplementation protected rats against the deterioration of lipid metabolic parameters caused by insecticide poisoning (Selmi *et al*., 2018).

The oil has also been reported to be beneficial as a nighttime sedative in the form of an air freshener in elderly patients, and its beneficial effects on stress have been proven (Gilani *et al*., 2000).

8. TOXICITY

L. stoechas is widely used in insecticides and non-cosmetic products due to the higher camphor content than other lavender species (Cavanagh & Wilkinson, 2002). It has been reported that *Lavandula* species with high camphor content, such as *L. stoechas*, can induce convulsions at high doses (Topçu, 2008). There are cases of poisoning, which is thought to be caused by camphor as the cause of toxicity. Convulsions have been observed as a result of inhaling the oil mixture containing camphor (Emery & Corban, 1999). Especially in children, convulsions have been reported after the use of these preparations. It is thought that these convulsions may be caused by camphor (Love *et al*., 2004).

Linalool and linalyl acetate, which are found in essential oils obtained from many lavender species, are found in the content of massage oils. It has been reported that linalyl acetate is narcotic and linalool is sedative (Cavanagh & Wilkinson, 2002). It has been shown that linalool and linalyl acetate in *Lavandula* species reduce the release of acetylcholine and change ion channel functions at the neuromuscular junction (Re *et al*., 2000). It is thought that the local anesthetic effect of linalyl acetate and linalool may be related to its antimuscarinic activity and/or ion (Na^{+} or Ca^{2+}) blockade (Ghelardini *et al*., 1999).

The LD_{50} dose of *L. stoechas* essential oil was determined as 1.88 mg/kg in a study. This result tells us that the plant may have a toxic effect at high doses, contrary to what is known. *L. stoechas* essential oil was also found to be pro-convulsant. This effect has been associated with camphor and camphene found in the essential oil. In studies with *L. stoechas* oil and antiepileptic drugs, diazepam and phenobarbital appeared to significantly inhibit the convulsions and lethality seen in *L. stoechas* toxicity at lethal doses in mice. It is thought that these two drugs are the most effective antidotal treatment in poisoning caused by *L. stoechas* oil and in preventing these poisonings (Topçu, 2008).

9. CONCLUSIONS

L. stoechas is an herb traditionally used for many ailments. Scientific studies based on these uses have documented the anti-inflammatory, antioxidant, antimicrobial, insecticide, larvicide, anticonvulsant, antispasmodic, sedative, hepatoprotective, nephroprotective, antidiabetic, and anticancer effects of the plant. Because of the data obtained as a result of its traditional use and scientific studies, it has been concluded that some regulations should be made on the cultivation of *L. stoechas* and the acquisition, formulation, and marketing of the essential oil. There are intensive studies and clinical data on its anti-inflammatory, antimicrobial, antioxidant, and anticonvulsant effects. In the light of these data, the plant needs to be cultivated, and its cultivation should be encouraged, and because of these effects, phyto-preparations should be prepared and introduced into the treatment area.

Declaration of Conflicting Interests and Ethics

The authors declare no conflict of interest. This research study complies with research and publishing ethics. The scientific and legal responsibility for manuscripts published in IJSM belongs to the authors.

Authorship Contribution Statement

Saliha Seyma Sahinler: Investigation, Resources, Writing - original draft. **Betul Sever Yilmaz:** Methodology, Supervision. **Cengiz Sarikurkcu:** Investigation, Supervision. **Bektas Tepe:** Investigation, Writing - original draft.

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