Ez zoubi et al. Clinical Phytoscience (2020) 6:9
https://doi.org/10.1186/s40816-019-0142-y

Clinical Phytoscience

REVIEW Open Access

A Phytopharmacological review of a Mediterranean plant: *Lavandula stoechas* L

Yassine Ez zoubi[1,2*], Dalila Bousta[3] and Abdellah Farah[2]

Abstract

The Mediterranean region is characterized by a diverse vegetation cover, and the *Lavandula* genus is one of the most important medicinal and aromatic plants in this region. It has been used in traditional medicine as a treatment for anxiety and insomnia and to improve sleep quality for a long history. Lavender is commonly used in perfumes, soaps, bath powders, and scented sachets. It can flavor teas or food even at low concentrations. Several ethnopharmacological studies have demonstrated its use in treating several diseases; it has anti-inflammatory, antioxidant, antispasmodic, sedative, insecticidal, antimicrobial and antifungal activities. This paper reviews the geographical distribution, traditional uses, chemical composition, and pharmacological activities of the *Lavandula stoechas*.

Introduction

Six thousand years ago, several ancient civilizations in present-day Egypt, China and India began to use aromatic and medicinal plants to treat diseases and for spiritual purposes [21, 43]. Although the use of medicinal herbs for therapeutic purposes is a practice as old as the history of mankind, aromatherapy has undergone an important evolution during the twenty-first century, enabling the development of a science of aromatherapy [26]. This herbal remedy has shown considerable value in treating diseases using extracts from aromatic and medicinal plants, including essential oils, alcoholic and hydrolic extracts, fruit juices, and extracts distilled from resins [22, 81].

The flora of the Mediterranean area includes many aromatic and medicinal species that have long been an integral part of the local culture, covering an extensive area with different environmental conditions [4, 21, 24, 64]. The Mediterranean population has been a depository for endogenous knowledge that it has been acquired empirically through the generations.

Among the medicinal plants used in the Mediterranean basin, the species belonging to the *Lamiaceae*, *Asteraceae*, and *Apiaceae* families are the most common in this region [53]. Some of thes, including sage, rosemary [20, 38], thyme [36], oregano [44], lavender [45, 54] and other *Lamiaceae* species [50, 54, 58], have already been studied for their pharmacological activities.

The synonyms of *Lavandula* L., according to Upson (2002), are *Stoechas* Mill., *Fabricia* Adans., *Chaetostachys* Benth., *Sabaudia* Buscal. and Muschl. and *Isinia* Rech. f. The genus *Lavandula* is composed of approximately 39 species, many hybrids, and nearly 400 registered cultivars (Upson & Andrews 2004). The best-known and economically valued species are *L. angustifolia*, *L. stoechas*, *L. latifolia* and the L. x *intermedia* hybrid.

Plants in the *Lavandula* genus are sub-shrubs or sometimes perennial shrubs up to one meter in height. They are in full bloom between mid-June and mid-July and prefer acidic soils. Inflorescence is common to the *Lavandula* genus. The flowers, with pedicel, are arranged in whorls and held in clusters of cylindrical or quadrangular cymes. They often are purple, blue, violet (Fig. 1), pink or lilac. The *L. stoechas* was likely the first to be used for their essential oils. The Romans, Greeks, and Arabs all recognized their medicinal properties [58].

L. stoechas is a well-known plant species and **is** used throughout the Mediterranean region for its medicinal virtues, mainly attributed to its essential oil content. It is also used for the preparation of traditional meals and herbal teas, and for cosmetic purposes [60, 91].

According to ethnobotanical and phytopharmacological studies, *L. stoechas* is used in Morocco to treat

* Correspondence: y.ezzoubi@uae.ac.ma; ezzoubiyassine@yahoo.fr
[1]Biotechnology, Environmental Technology and Valorization of Bio-resources team, Department of Biology, Faculty of Science and Technology Al-Hoceima, Abdelmalek Essaadi University, Ajdir 32003 Tetouan, Morocco
[2]Laboratory of Applied Organic Chemistry, Faculty of Sciences and Technology, Sidi Mohamed Ben Abdellah University, Po.Box 2202, – Route d'Imouzzer, Fez, Morocco
Full list of author information is available at the end of the article

Fig. 1 *L. stoechas* plants from Taounate city /Morocco

rheumatic diseases and nephrotic syndromes, as an antispasmodic agent, and to reduce pain and inflammatory problems [25, 27].

Several researchers are interested in the pharmacological effects of *L. stoechas* essential oils and extracts, and have evaluated their antibacterial [29], antifungal, insecticidal, anti-leishmanial [14], antioxidant [28, 57], and anti-inflammatory properties [12, 28]. However, other potentials pharmacological effects of this oil have not yet been evaluated.

The present review provides a comprehensive summary of the ethnobotanical and ethnophamacological uses, chemical composition and biological activities of *L. stoechas*.

Geographical distribution

L. stoechas is spread over three continents (Africa, Europe and Asia). It is growing around the Mediterranean basin, including in Morocco, Algeria, Tunisia, Spain, Greece, France, Italy, and Turkey. It is also found in Saudi Arabia and Iran (Fig. 2) [85]. In Morocco, this plant typically grows at high altitudes on calcareous soils, especially in the north of Morocco, in the middle and high Atlas and Rif mountains. In Tunisia, it is distributed in the north, north-east and Cap Bon regions at altitudes from 400 to 1000 m [39]. According to Mohd et al. [58], *L. stoechas* is also found in Bihar and Bengal in India. It has been introduced throughout Europe and to temperate/subtemperate areas in the Americas, Asia, and Australia [47].

Traditional uses

L. stoechas is a well-known species used throughout the Mediterranean region for its medicinal virtues such as its cephalic (tonic), and carminative properties. It is prescribe to treat pulmonary infections and inflammatory diseases (Table 1). The plant is also used in folk medicine as an antispasmodic in colic pain and for various diseases of the central nervous system, such as epilepsy and migraine.

L. stoechas also has positive effects on wounds, urinary tract infections, against eczema, and has analgesic, sedative and antiseptic properties. It is also, used as a culinary herb to prepare a particular type of couscous, to flavor certain traditional meals, and to prepare tea and soup [12, 60, 91]. In the Maghreb countries, such as Morocco, Algeria, and Tunisia, this plant is used in the traditional pharmacopeia to treat headaches, depression, diabetes, and inflammatory and rheumatic diseases [12, 25, 75].

In the Palestinian tradition, the decoction of the areal part of lavender is used to treat migraine and epilepsy [32]. The flower infusion is used in Turkish phytotherapy as an expectorant, antispasmodic, carminative, menstrual regulari, stimulant, deobstruent, resoluent and wound healing agent [82].

Phytochemical screening

Many phenolics have been identified in the *Lavandula* genus, including protocatechuic, caffeic, ferulic, chlorogenic and rosmarinic acids, pinobanksin, pinocembrin, quercetin and luteolin [46].

Among the numerous chemical compounds known in *L. stoechas*, Ez Zoubi et al. [27] revealed the presence of several chemical families in the hydroethanolic extract,

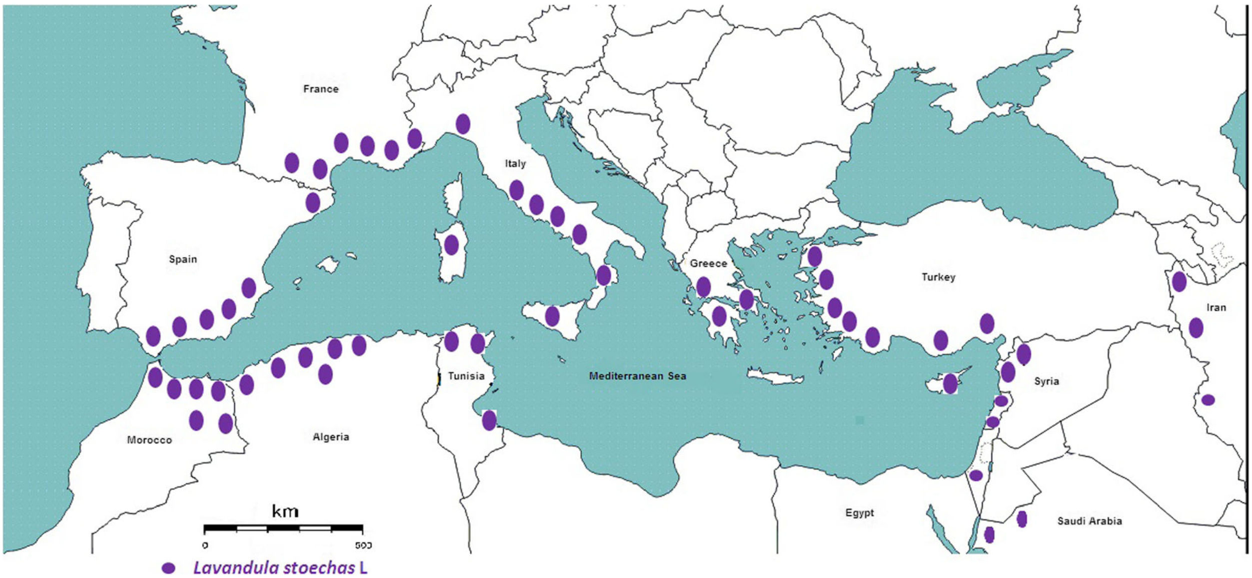

Fig. 2 Geographic Distribution from *L. stoechas*

such as flavonoids, catechic tannins, sterols, coumarins, leucoanthocyans and mucilages. *Lavandula antineae* Maire was found to produce flavonoids and tannins [80] and *Lavandula officinalis* L. was found to contain coumarins [5]. Xavier et al. [88] revealed the presence of apigenin 7-glucoside, luteolin, luteolin 7-glucoside, and luteolin 7-glucuronide. The main constituents of flavonoids in the leaves of the species *L. stoechas* are simple flavone glycosides (flavone di-O-glycosides and flavone 7-O-monoglycosides). The following compounds have been detected in the areal parts of *L. stoechas* extracts: oleanolic, ursolic and vergatic acids; β-sitosterol; α-amyrin; α-amyrin acetate; lupeol; erythrodiol; luteolin; acacetin; vitexin; two longipinane derivatives (longipin-2-ene-7β,9α-diol-1-one and longipin-2-ene-7β,9α-diol-1-one-9-monoacetate); 7-methoxy coumarin; and lavanol ([87]; Manzoor et al. 1969).

Chemical constituents of *L. stoechas* essential oils

The terpenic compound of the species *L. stoechas* have been determined in different Mediterranean countries (Algeria, Greece, Spain, Corsica, Turkey, Morocco, Tunisia, etc), with variable results (Table 2). Fenchone, camphor, and 1,8-cineole compounds are the most commonly identified major compounds. Several studies have shown that the fenchone/camphor chemotype are the major compounds in *L. stoechas* essential oils ([12]; Angioni et al. 2006). Carrasco et al. (2015) distinguished

Table 1 Ethnomedicinal uses of *L. stoechas* in some Mediterranean countries

Countries	Local names (ethnic)	Plant parts used	Traditional uses	Preparation form	References
Algeria	Halhal	Aerial part	Analgesic Teeth	Infusion	[73]
Greece	NI*	Leaves	Anti-diabetes, menstrual pains, kidney stones, carbuncles, otitis and hyper-tension.	Infusion and essential oils	[78].
Iran	Ossoghodus	Leaves	Anticonvulsant, Sedative Antispasmodic	Infusion	[62]
Morocco	Halhal	Aerial part	Rheumatism, system digestive, cystitis and nephritis	Decoction	[25]
Pakistan	Ustu khuddoos	Aerial part	Epilepsy and migraine	Decoction	[32]
Portugal	Rosmaninho	Aerial part	For heart-burn, for sea-sickness, blood circulation andsedative	Infusion	[16, 63]
Spain	Cantueso, cap díase, bofarull	Flowered aerial part	As herbal tea and for making liqueur	Infusion	[84].
Turkish	Karabaş	Flowering branches	Expectorant, menstrual regulari, antispasmodic and carminative	Infusion	[67, 84]

*NI: Not Indicated

Table 2 Major constituents of volatile oils from *L. stoechas*

Countries	Parts of plants	Majors compounds	Total compounds	References
Algeria	Flowers	- Linalyl Acetate (15.26%) - Camphor (11.25%) - γ-Terpinene (11.2%) - Linalool (10.68%) - 1,8-Cineole (10.25%)	49	[11]
Greece	Leafs	- Fenchone (44.8%) - 1,8-Cineole (16.7%) -α-Cardinol (7.2%) -Camphor (6.2%)	62	[56]
Italy	Aerial parts	-Fenchone (37.0%) -Camphor (27.3%) -Bornyl acetate (6.2%) - 1,8 Cineole (6%)	22	[91]
Morocco	Aerial parts	-Fenchone (30.5%) -Camphor (18.2%) −1,8-Cineole (8.6%) -Camphene (3.5%)	27	[90]
Pakistan	Aerial parts	- Camphor (46.24%) -Borneol (6.71%) - Caryophyllene (4.72%) - 1,8-Cineole (3.69%)	13	[89]
Portugal	Aerial parts	-Fenchone (41.9%) - Camphor (34.6%) - linalool (2.7)	42	[30]
Spain	Aerial parts	- Fenchone (37%) −1,8-Cineole (17.8%) -Camphor (15.6%) - Linalool (7.5%)	50	[2]
Tunisia	Aerial parts	-Fenchone (34.3%) - Comphor (27.4%) - Lavandulyl acetate (5.6%) −1,8-Cineole (3.4%)	33	[57]
Turkey	Flowers	- Fenchone (32.03%) - Camphor (14.71%) -Myrtenyl acetate (11.7%) - 1,8-Cineole (7.67%)	34	[82]

fenchone (37%), camphor (15.6%), and 1,8-cineole (17.8%). In addition to fenchone, camphor, and 1,8-cineole compounds, the oils of *L. stoechas* from Greece were found to contain α-cardinol (7.2%) [56]. The main components of Moroccan *L. stoechas* oils were found to be fenchone (30.5%), camphor (18.2%), 1,8-cineole (8.6%), and camphene (3.5%) [90]. Camphene, linalyl acetate, γ-terpinene, linalool, lavandulyl acetate, myrtenyl acetate, bornyl acetate, borneol and caryophyllene were found as the major compounds in some reports (Fig. 3).

However, the absence of some of the compounds mentioned above led to the identification of different biochemotypes of *L. stoechas*. The chemotype found by Topal et al. [86] was characterized by the absence of volatile compounds such as α-pinene, limonene, myrtenyl acetate, and viridiflorol. Gursoy et al. [35] detected the presence of p-cymene, a compound rarely found in the samples of Turkish essential oils. Alpha-pinene and viridiflorol are the compounds commonly found in samples of essential oils grown in Italy, Turkey and Algeria; in addition, caryophyllene oxide is a characteristic compound of essential oils of Turkish and Algerian origins [2].

The aroma profile of *L. stoechas* growing in Corsica revealed a significant variation of the major compounds, including fenchone (14.9% to 75.5%), camphor (2.5% to 56.2%),and 1,8-cineole (0.17% to 8%) [69]; this differentiation was explained by the longitudinal variation of the varieties studied ([69]; Nicolas et al. 1998). Finally, these variations in chemical profile could be explained by different environmental conditions, geographical origins, parts of the plant that were extracted, and extraction methods [52, 61, 68].

Pharmacological activities

Anti-inflammatory effects

The anti-inflammatory effects of *L. stoechas* were evaluated by inducing inflammation via a lipopolysaccharide-macrophage model. The results of this in vitro study showed that *L. stoechas* essential oil in concentrations of 0.16 μL/mL and 0.32 μL/mL significantly reduced nitrite production in cell cultures without causing cellular damage [91].

In another experimental model, Algieri et al. [3] found an anti-inflammatory effect of *L. stoechas* extraction, with values similar to those recorded by a steroidal anti-inflammatory drug (glucocorticoid dexamethasone). Rats treated with the *L. stoechas* extract in doses of 10 mg/kg and 25 mg/kg exhibited reduced inflammation of the tissues by 1 cm to 2 cm; the anti-inflammatory effect was explained by the regulation of inflammatory precursors, including matrix metalloproteinase 9, inducible nitric oxide synthase, cyclooxygenase 2, and pro-inflammatory cytokines.

L. stoechas extract was also shown to exhibit inhibitory activity in paw edema induced by carrageenan; however, it had no effect on 12-O-tetradecanoylphorbol 13-acetate (TPA) induced ear edema [6]. A concentration of 200 μg/mL was shown to decrease pro-inflammatory cell viability by 63% after 3 h of incubation. Neutrophil elimination through apoptosis could be implicated in the resolution of acute inflammation, whereas the reduction of reactive oxygen species produced by neutrophils, such as the superoxide anion and the hydroxyl radical, could be implicated in the overall reduction of inflammation. Ez Zoubi et al. [27] demonstrated that treatment with the hydroethanolic extract of the aerial part of *L. stoechas* (10%) induces a significant decrease in paw volume of rats, with a reduction in paw volume of 74 ± 7%, compared with diclofenac used as a control anti-inflammatory (69 ± 10.3%). Flavonoid and mucilage extracts significantly reduced edema by 85.1 ± 6.2% and 61.71 ± 7.3%, respectively, indicating that

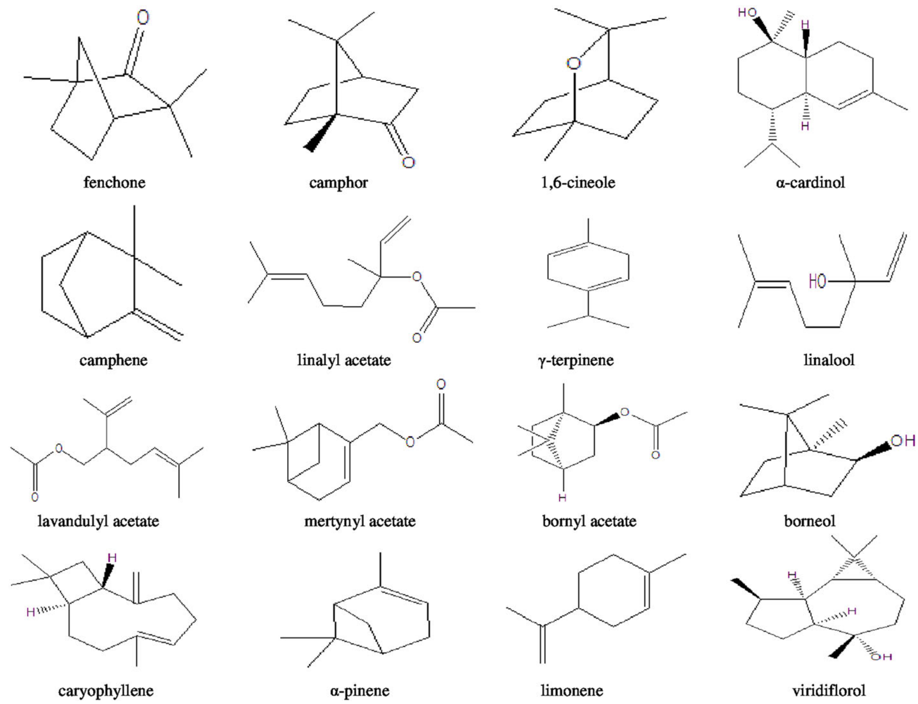

Fig. 3 Chemical structures of major compounds in *L.stoechas* essential oil

flavonoids and mucilages in *L. stoechas* extract may be responsible for the observed anti-inflammatory effects.

Antioxidant effect

The antiradical potency of the *L. stoechas* extract grown in Morocco was tested using the 2,2-diphenyl-1-picryl-hydrazyl (DPPH) scavenging assay [28]. At concentrations of 4 mg/mL, 2 mg/mL, and 1 mg/mL, the hydroethanolic extract decreased the DPPH signal by 85.5%, 57.8%, and 44%, while butylated hydroxytoluene (synthetic antioxidant) decreased the signal by 78.3%, 73.0%, and 65%. The half maximal inhibitory concentration (IC50) of the extract in this study was 1400 μg/mL higher than BHT (IC50 = 200 μg/mL).

Ceylana et al. [18] evaluated the anti-radical activity of the methanolic extract of *L. stoechas* and recorded an IC50 of 300 μg/mL, compared with BHT and BHA with IC50 values of 200 μg/mL and 100 μg/mL, respectively. In a comparative study by Sariri et al. [72], the water extracts of four lavender species from the north of Iran were studied to investigate theirpotency as tyrosinase inhibitors. The study showed a variable antioxidant power of the four *Lavandula* species, with antiradical values of 9.2 μg/mL, 12.5 μg/mL, 38.7 μg/mL, and 65.1 μg/mLfor *L. angustifolia*, *L. stoechas*, *L. dentate,* and *L. latifolia*, respectively. Sebai et al. [75] evaluated the antioxidant activity using the radical-scavenging activity and DPPH methods, which revealed that the volatile compounds of *L. stoechas* were characterized by a high antioxidant capacity (IC50 = 221.43 μg/mL), although this was lower than that of the control antioxidant (ascorbic acid, IC50 = 87.57 μg/mL).

Messaoud et al. [57] reported an IC50 value of 2321.7 μg/mL in Tunisian *L. stoechas* essential oils. Moreover, Barkat and Laib [11] found an IC50 of 584 ± 0.58 μg/mL in Algerian *L. stoechas* essential oils from dry flowers. A large number of studies carried out on the antiradical activity of plant extracts have shown that phenolic compounds, particularly flavonoids, are potentially antioxidant substances with the capacity to trap free radicals ([7, 9, 66]).

Carrasco et al. (2015) demonstrated that linalool and thymol compounds are responsible for the antioxidant activity of *L. stoechas* essential oils. Phenolic acids and flavonoids in *L. stoechas* such as rutin and caffeic acid also have antioxidant activity [7].

The antioxidant characteristics of the phenolic compounds in *L. stoechas* are mainly attributed to their ability to eliminate free radicals; for example, they reduce oxidative stress induced in diabetic rats [74] and have hepatoprotective and renoprotective effects against malathion-induced oxidative stress in young male mice [76].

Antispasmodic and sedative effects

The anti-spasmodic effect of *L. stoechas* extract was evaluated on rabbit jejunum [32]. The authors recorded an anti-spasmodic effect of doses between 0.1 mg/mL and 1.0 mg/mL of *L. stoechas* hydromethanolic extracts without recording a negative effect on the jejunum tissues. This spasmolytic activity may be due to the presence of 7-methoxycoumarin, which has been reported to be a smooth muscle relaxant [51]. In the same study, Gilani et al. [32] demonstrated that the extract of *L. stoechas* has sedative properties at a dose of 600 mg/kg; pentobarbital sleeping time was prolonged from 39.4 ± 5.74 min to 65.4 ± 5.72 min, similar to diazepam, a standard sedative drug [40]. The tested rats were calm, dull, and relaxed. This study provides evidence for the traditional usage of this plant as a sedative.

Antibacterial activity

Many essential oils exhibit antibacterial and antiviral activities and have been shown to be potent therapeutic agents. These oils are used against both pathogenic and non-pathogenic organisms [77]. Cherrat et al. [19] reported that Moroccan *L. stoechas* essential oils showed superior antibacterial activity against Gram-positive bacteria compared with Gram-negative bacteria; for example, they exhibited the highest antimicrobial activities against *Escherichia coli* O157, *Listeria monocytogenes* and *Staphylococcus aureus* with inhibition diameters of 16.2 ± 0.60 mm, 32.0 ± 2.00 mm and 28.0 ± 0.70 mm, respectively. Sarac and Ugur [71] recorded the antibacterial activity of *L. stoechas* essential oil cultivated in Turkey against both Gram-positive and Gram-negative bacteria. *S. aureus*, *S. epidermidis*, *S. mutans, E. coli*, *P. stutzeri*, *S. maltophilia*, *M. luteus*, *C. luteola,* and *B. subtilis* were the most sensitive bacteria to the essential oil and are antibiotic-resistant bacteria.

L. stoechas essential oils from Turkey (Goren et al. [34]) and Tunisia [15] both showed strong antimicrobial activity, similar to other sesquiterpene rich essential oils. A recent study tested antimicrobial activity against eight pathogenic bacterial strains, including *E. coli*, *S. aureus*, *L. monocytogenes*, *Proteus mirabilis*, *Pseudomonas aeruginosa* and *B. subtilis* using amicrotitration assay [14]. The study indicated that the highest inhibition was obtained against *L. monocytogenes* and *S. aureus* with inhibition diameters of 23 ± 0.85 mm and 21 ± 0.25 mm, respectively.

Camphor and 1,8-cineole, among the major compounds in *L. stoechas* oils, have an antibacterial effect, especially against *S. aureus*, *E. coli* and *L. monocytogenes* [37, 48, 79].

Several studies showed that minor components in the *L. stoechas* essential oils have synergistic antimicrobial activity [33, 59]. Gram-positive bacteria were more susceptible to the essential oils than Gram-negative bacteria, likely due to outer membrane differences [15, 42, 65].

Antifungal activity

Several studies have evaluated the antifungal activity of *L. stoechas* essential. Benabdelkader et al. [12] evaluated the antifungal activity of 11 *L. stoechas* essential oils and confirmed the presence of antifungal activity against filamentous fungi (*Aspergillus niger* and *Fusarium oxysporum*) and yeasts (*Candida albicans*). Similarly, *L. stoechas* essential oils tested on filamentous fungi and molds had antifungal activity on various strains of clinical origin (*Candida albicans, Candida krusei*, and *Candida guilliermondii*) and on clinical dermatophytes (*Epidermophyton floccosum* and *Trichophyton mentagrophytes*), with inhibition zones between 0.32 μl/ml and 5 μl/ml [91].*L. stoechas* essential oils also demonstrated antifungal activity against *Rhizoctonia solani* and *Fusarium oxysporum*, but had less effect on *Aspergillus flavus* (Angioni et al. 2006). The antifungal activity of *L. stoechas* essential oils has been reported to be specifically related to the presence of antifungal compounds such as camphor, 1,6-cineole, and fenchone, and the synergistic effect of the major and minor constituents of this oil [12, 91].

Insecticidal and larvicidal activities

The use of insecticides and chemical larvicides is currently the most popular technique for controlling insects. However, the intensive use of these insecticides has caused contamination of the food chain and the appearance of resistant insects. The use of molecules and extracts of botanical origin appear to be the best alternative to fight against insects and larvae (Isman 2000). El Ouali Lalami et al. [23] found that *L. stoechas* essential oil has a positive effect against *Anopheles labranchiae*, a vector for malaria transmission, with a lethal dose of 500 mg/ml (LC50 = 112.51 mg/L; LC90 = 294.51 mg/L).

Bouyahya et al. [14] tested the effects of *L. stoechas* essential oil on three species of *Leishmania* using the MTT (3-(4.5-dimethylthiazol-2yl)-2,5-diphenyltetrazolium bromide) assay. This study revealed LC50 of 0.9 ± 0.45 μg/mL, 7 ± 0.54 μg/mL and ˃10 μg/mL against *Leishmania major*, *Leishmania infantum* and *Leishmania tropic,* respectively.

Camphor, which is one of the majors components detected in *L. stoechas* essential oil, is known to have insecticidal activities [49, 55]. Indeed, camphor showed interesting antileishmanial activity against *L. major* (IC50 = 5.55 ± 1.27 μg/mL) and *L. infantum* (IC50 = 7.90 ± 0.42 μg/mL). Camphene and 1,8-cineol, which are major constituents of *L. stoechas*essential oils, were reported to be toxic for several insect species [8, 55, 70]. Moreover, 1,8-cineol showed a good larvicidal activity against *Aedes aegypti* [17].

Cytotoxic activity

Gören et al. [34] evaluated the cytotoxicity of *L. stoechas* essential oils against cancer cell lines including KB (human epidermoid carcinoma), LNCaP (hormone-dependent human prostate cancer), BC1 (human breast cancer), P388 (mouse leukemia), LU1 (human lung cancer), COL-2 (human colon cancer), and KV-B (+VLB) (drug-resistant KB). The essential oils were active against COL-2 and weakly active against LNCaP; P388 cells were very sensitive to the chloroform extract of *L. stoechas*.

Other pharmacological activities

Several ethnobotanical studies have reported the use of *L. stoechas* to treat diabetes or to reduce the level of hyperglycemia [10, 13, 41, 83]. However, few studies evaluated the anti-glycemic effect of the *L. stoechas* extract and essential oil [31, 75]. An in vivo study conducted by Sebai et al. [75] on the antidiabetic activity of *L. stoechas* essential oil revealed a protective effect against hyperglycemia and oxidative stress.

Conclusion

The biological activities of *L. stoechas* essential oils and extracts described in this review are mainly due to the plant's richness in bioactive molecules belonging to several chemical families, such as phenolics, flavonoids and monoterpenoids. These compounds possess pharmacological properties, including antispasmodic, sedative, anti-inflammatory, antioxidant, antimicrobial, antifungal, insecticidal, and larvicidal activities. Compounds from *L. stoechas* with a wide array of bioactivities can serve as lead compounds for drug development. In-depth phytopharmacological and phytochemical studies are needed to highlight the relationship between secondary metabolites and observed biological effects. Additional experimental studies that could substantiate and describe the correlation of the isolated phytochemicals from *L. stoechas* with their corresponding pharmacological effects are also needed.

Based on the different pharmacological effects illustrated in this review, we can conclude that this plant, abundant in the Mediterranean basin and not exploited, could attract the intention of the scientific community to conduct more in-depth analyses, especially clinical studies, in order to identify the molecule or molecules that have phytopharmacological power.

Acknowledgements
Not applicable.

Authors' contributions
Dalila bousta, selection, arrangement and compilation of suitable material. Farah Abdellah, relevant literature search. Yassine z zoubi, supervising the whole work.
All authors read and approved the final manuscript.

Funding
No funding.

Availability of data and materials
The datasets supporting the conclusions of this article are included with in the article.

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
There authors declare that they have no competing interest.

Author details
[1]Biotechnology, Environmental Technology and Valorization of Bio-resources team, Department of Biology, Faculty of Science and Technology Al-Hoceima, Abdelmalek Essaadi University, Ajdir 32003 Tetouan, Morocco. [2]Laboratory of Applied Organic Chemistry, Faculty of Sciences and Technology, Sidi Mohamed Ben Abdellah University, Po.Box 2202, – Route d'Imouzzer, Fez, Morocco. [3]Laboratory of Neuroendocrinology and Nutritional and Climatic Environment, Faculty of Sciences Dhar El Mehraz, University of Sidi Mohamed Ben Abdellah, Fez, Morocco.

Received: 30 May 2019 Accepted: 11 December 2019
Published online: 11 February 2020

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