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Review paper

Dracocephalum moldovica: CULTIVATION, CHEMICAL COMPOSITION AND BIOLOGICAL ACTIVITY

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ABSTRACT: Moldavian balm or Moldavian dragonhead (*Dracocephalum moldavica* L.) is native to temperate climate of Asia, but it was naturalized in Eastern and central Europe, North Africa, China and north-eastern United States. This plant with its citrus like flavor is extensively used as a spice and for composition of teas, because of neral and geranial as major constituents of essential oil. *D. moldavica* is used in food aromatization, perfumery, alcoholic drinks industry, soaps and detergents. Apart from being used as medicinal and spice plant, it is grown as a honey-bearing plant and cultivated in gardens and parks as an ornamental plant. Seed is a good source of fatty oil with spicy taste and aromatic odor, rich in unsaturated fatty acids, principally the linolenic and linoleic acids. This categorizes *D. moldavica* seed into the group of raw materials suitable for nutraceuticals, food supplements, and functional food applications. Furthermore, numerous investigations show that this plant possesses good antioxidative, antimicrobial and insecticidal activity. It is also used as antinociceptive, sedative, neuroprotective, as well as cardiotonic agents, and for treating chronic mountain sickness.

Key words: *Moldavian balm, Moldavian dragonhead, essential oil, fatty oil, seed*

INTRODUCTION

Genus *Dracocephalum* belongs to the subtribe Nepetinae, tribe Menthae of Lamiaceae family. The genus contains 71 species, widespread in Northern Hemisphere regions (Naderifar et al., 2015; Amirnia et al., 2017). Moldavian balm or Moldavian dragonhead (*Dracocephalum moldavica* L.) is native to temperate climate of Asia. It presents native species in Iran, and because of that, a large number of studies were conducted in this country (Khoulenjani and Salamati, 2014). However, it is naturalized in Eastern and Central Europe. There are studies about the introduction of this plant in agriculture in Finland (Galambosi et al., 1989), Ukraine (Kotyuk, 2014), Germany (Horn et al., 2014), Romania (Dobrea et al., 2017; Nitu et al., 2017), Russia (Egorova, 2017), Czech Republic (Akter et al., 2017), Poland (Kocira et al., 2018), as well as in Turkey (Ehsan et al., 2014), Egypt (Hussein et al., 2006, El-Baky and El-Baroty, 2008) and China (Chu et al., 2011; Ding et al., 2015). It has also been introduced to north-eastern United States (Dziki et al., 2013; Ehsan et al., 2014; Janmohammadi et al., 2017). This plant species was introduced in Serbia too, in the collection garden of Institute of Field and Vegetable Crops, from Romania (Kišgeci et al., 1982). *D. moldavica* is a promising essential oil bearing plant, as well as an oilseed crop, same as *Salvia sclarea* (Aćimović et al., 2018).

This plant is very beautiful, with blue flowers and a citrus-like flavor, resembling that of lemon balm (*Melissa officinalis* L.) and catnip (*Nepeta cataria* L.) (Povilaityte et al., 2001). Because of this, it is cultivated in gardens as ornamental plant (Dmitruk et al., 2018). In some countries *D. moldavica* grows as a honey-bearing plant (Povilaityte et al., 2001). Experiments in Czech Republic showed that honey bees are the most abundant visitors and pollinators of *D. moldavica* (Akter et al., 2017). In Poland, it was concluded that during plant flowering, *D. moldavica* flowers reached 15.33-17.56 mg nectar per plant during 2.5 days, with 49.4-51.5% content of sugar (Dmitruk et al., 2018). Optimum duration of *D. moldavica* nectar secretion is from 12 to 14 hours. The honey value in pure culture is estimated at 129-650 kg/ha (Dmitruk et al., 2018).

MORPHOLOGICAL CHARACTERISTICS

D. moldavica is an annual plant with numerous stems (up to 6), 22-45 cm high, simple or branched, usually erect or ascending. Internodes are 3-4.7 cm long; sparsely covered by short minutely retrorse hairs, purplish. Leaves are basal, cauline leaves wither early, oblong to ovate-triangular, 1.7-2.4 cm long 0.8-1.2 cm wide, margin crenate to dentate; obtuse at apex, usually attenuate or rarely cordate at base, on both surfaces with a short eglandular indumentum, petiole as long as blade, 1.2-1.8 cm long, shorter upward (Jeong et al., 2016). Flowers are arranged in pseudo-whorls growing in leaf axils. The calyx and corolla are clearly bilabial. The corolla can be purple-blue or white. At the basal part, it forms a relatively long tube accessible to insects with sufficiently long tongues. However, the widened throat of the flower provides bees with access to nectar as well. A disc-shaped nectary is located at the ovary base (Dmitruk et al., 2018).

Essential oil accumulates in exogenous oil-containing cells at the dorsal sides of the dental leaves, and in the inflorescence. One can find six flowers in each sympodium of the inflorescence, and stem of the inflorescence holds 20-25 pseudo-verticils. The plants flower over a 30 day period. The plant produces nectar, which supports production of honey at the rate of 200 kg per hectare (Domokos, 1994; Rahimzadeh et al., 2017; Fallah et al., 2018).

D. moldavica seeds started to germinate after 44 h and gradually reached the highest germination after 126 h. The quick water uptake stage lasted 7 h, after which water content reached 223%. After 14 h, seeds became covered with mucilage (Zhao et al., 2018). *D. moldavica* is sown in spring, and flowering begins 90 days later (Domokos, 1994). It has a vegetation period of 190 days requiring 1877.9°C and 325.2mm of rainfall. Plants are harvested for seed (developed) after 137 days, the sum of accumulated temperatures being of 2492.1°C and of rainfall of 355mm (Dobrea et al., 2017).

CULTIVATION PRACTICES

The growing interest in the cultivation of *D. moldavica* can be explained by the fact that it is extensively used as a spice, and also because essential oil contains neral and geranial as the major constituents. Because of that, the smell of *D. moldavica* resembles that of *M. officinalis*, and because *D. moldavica* is more adapted to a colder climate than *M. officinalis*, it can be its substitute (Galambosi et al., 1989).

Factors that have been studied include fertilization, optimal harvesting time, weed control, the selection of more productive forms, the influence of altitude and the raising of seedlings against field sowing. However, the results are different for different agro ecological conditions.

For Finnish conditions it was established that moderate nitrogen fertilization (<30 kg/ha) significantly increased the herb yield, and higher doses had no further effect. (Galambosi et al., 1989). However, in Iranian conditions, it was established that the increased rates of NH_4NO_3 and microelements (Fe, Zn and Mn) resulted in high leaf yield and higher essential oil production per hectare (Nejatzadeh-Barandozi et al., 2015). Positive effects of microelements such as Fe are also recorded by other authors (Khalili and Amirnia, 2014; Yousefzadeh and Sabaghnia, 2016). Foliar application of iron in dose of 6 ml/L had a significant effect on branch number, fresh and dry weight, biomass and oil percentage (Khalili and Amirnia, 2014). The study indicated that application of 1 g/L iron nano-fertilizer increased *D. moldavica* dry mass yield and essential oil yield cultivated in semiarid region conditions of Iran (Yousefzadeh and Sabaghnia, 2016). However, boric acid application in different concentrations (0, 3, 6 and 9 kg/ha) by foliar spraying before the flowering stage did not influence the chemical composition of the essential oil (Ehsan et al., 2014).

Organic fertilizers may also increase the content and yield of essential oil, and can be suggested as a suitable alternative to chemical fertilizers (Hussein et al., 2006; Badawy et al., 2009; Janmohammadi et al., 2014; Rahbarian, 2014). The biggest positive effects on increasing biological yield, chlorophyll, carotenoid and free sugar content as well as on essential oil content was observed in 400 mg/L humic acid treatment. In addition, humic acid in combination with 10% ethanol significantly improved morphological characteristics, photosynthetic pigments and yield of essential oil of *D. moldavica* (Samadimatin and Hani, 2017). Furthermore, seed inoculation with sulfur oxidizing bacteria (*Thiobacillus* strains) improves nutrients availability in calcareous soils (Rahimzadeh et al., 2017). Priming with potassium nitrate can improve morphological characteristic and performance of the *D. moldavica* (Mosa and Fateh, 2015).

Due to excessive agricultural activities, saline lands are a rising issue worldwide, therefore to tackle this problem it is necessary to identify and select resistant species and cultivars (Arzhe et al., 2015). However, irrigation water for crop growth can also cause salt stress. *D. moldavica* plants can be grown in newly reclaimed soils under salt stress and the high alkalinity associated with arid soils can be countered by application of different sources of soil amendment i.e. agricultural sulfur, gypsum and pyrite (Aziz et al., 2013). Salicylic acid also can improve growth features of *D. moldavica* under saline conditions (Arzhe et al., 2015). The Increase of salinity and water stress levels caused significant reduction in germination percentage, germination rate, seed vigor index and radical and plumule length. The highest seed germination percentage was recorded in control, while the lowest was at 200 mm salinity treatment (Alaei et al., 2015).

Apart from saline stress, draught stress is also a big problem in agriculture. Water deficit stress is the most important environmental factor limiting plant growth and production.

Nano-titanium dioxide (nano anatase TiO_2) can have various profound effects on the crop physiological, biochemical and morphological characteristics. Results showed that under normal irrigation, foliar applications of 10 ppm TiO_2 nanoparticles increased plant shoot dry mass and essential oil content. Furthermore, water-deficit stress induced damage such as oxidative stress and membrane damage can be ameliorated by foliar application of TiO_2 nanoparticles at concentration of 10 ppm (Mohammadi et al., 2016). It is established that foliar application of melatonin in dose of 100 μM induces tolerance to draught stress through regulating the antioxidant system (Kabiri et al., 2018). Irrigation treatments had significant effects on growth, wield and water relations. As the amount of irrigation water decreased, the plant height, leaf area, leaf number, leaf chlorophyll, fresh and dry weight of shoot and root, and other morphologic parameters, as well as yield were affected (Alaei and Omibdaigi, 2014).
Application of biostimulants instigates many physiological processes that enhance nutrition efficiency, abiotic stress tolerance and quality traits of crops, regardless of their nutrient content. Foliar application of environmental-friendly preparation Atonik (preparation with nitrophenol, compound naturally occurring in plant cells) improve the efficiency of the photosynthetic apparatus and chlorophyll content in leaves of *D. moldavica* plants, and have positive impact on the metabolic processes of plants (Kocira et al., 2018). Additionally, biostimulant Fylloton (based on *Ascophyllum nodosum* free aminoacids of vegetable origin obtained in the enzymatic hydrolysis) helps improve the efficiency of photosyntethic apparatus, and it can be recommended for use in sustainable agriculture (Kocira et al., 2015).
Weeds are one of the most important problems in medicinal plant production and may cause a significant loss in both plant yield and their active ingredients. Evaluation of different weed control techniques such as hand weeding, herbicide control (Treflan pre emergence and Galant Super post emergence) and soil solarization (use of clear polyethylene) show that the maximum biological yield and essential oil content were obtained from weed free conditions (hand weeding at 10 days interval until harvest), followed by two hand weeding (at 20 and 40 days after sowing) and soil solarization. Overall findings of current experiment suggested that eco-friendly approach, manly soil solarization and regular manual weeding might be the best option to combat problems as well as to obtain satisfactory herbage yield and an acceptable quality of essential oil content in *D. moldavica*. This finding has important implications for developing non-chemical weed control in medicinal plants (Janmohammadi et al., 2017).

CHEMICAL COMPOSITION OF AERIAL PARTS

Yield of the aboveground parts of *D. moldavica* is between 5.7 and 8.3 t/ha (Domokos, 1994). The fresh plant contains 0.06-0.7% volatile oil. Accumulation of volatile oils increases in the generative period, and it is maximal in the time when blossoms fall (Ahl et al. 2015; Mosa and Fateh, 2015). The optimal time for harvesting for the purpose of obtaining the volatile oil is during full flowering, when ripening seeds are also present (Domokos, 1994; Rahimzadeh et al., 2017; Fallah et al., 2018). Essential oil from aerial parts is pale yellow (El-Baky and El-Baroty, 2008; Borghei et al., 2015).

Essential oil content in above ground parts depends on many factors, among which are population and growing technology (fertilization, harvesting time). Investigations in Iran with 7 landraces of *D. moldavica* show that oil content varied between 0.03 and 0.12% (Borghei et al., 2015). The increase of ploidy levels caused major changes in some morphological and physiological traits and active substances in *D. moldavica* (Omidbaigi et al., 2010). Apart from this, essential oil content significantly varied during phenological stages, i.e. harvesting time (Khalili and Amirnia, 2014). Fertilization also has significant effect on essential oil percentage (Hegazy et al., 2016; Samadimatin and Hani, 2017). Depending on the plant part, the amount of essential oil and composition can also vary (Kotyuk and Rakhmetov, 2017).

Chemical composition of essential oil from aerial parts of *D. moldavica*, also depends on many factors, among which origin, cropping system, fertilization, salt stress, weed management, etc. (Aziz et al., 2013; Fallah et al., 2018; Janmohammadi et al., 2017). A review of chemical composition of *D. moldavica* essential oil is shown in Table 1. However, the principal compounds in almost all essential oils are geranyl acetate and geraniol. Investigations show that the geranyl acetate, geranial and geraniol in essential oil reach their maximum levels during the flowering, while the content of neral, decreases during flowering. These observations indicate that the biosynthesis of geranyl acetate is dominant at the beginning of the vegetative period, but is superseded by biosynthesis of geranial and geraniol, from the early stage of flowering. It indicated that the optimal harvest time proved to be during the flowering stage, when the oil content is the highest and thus also the amount of the main terpenes is the highest (Holm et al., 1988). However, significantly different chemical composition of *D. moldavica* was reported in China, where the dominant compounds were: 1,8-cineol (31.25%) and 4-terpineol (22.82%), followed by cumin alcohol (4.29%) and α-terpineol (4.21%) (Chu et al., 2011).

Table 1. Chemical composition of different *D. moldavica* samples

COUNTRY	Source	linalool	neral (=cis-citral)	geraniol	geranial (=citral)	nerol	neryl acetate	geranyl acetate
Egypt	Hussein et al., 2006.	16.8-37.5	-	2.2-9.9	11.6-24.2	0.2-6.5	0.2-1.0	0.2-2.5
Egypt	El-Baky and El-Baroty, 2008.	1.38	11.99	14.96	23.67	3.16	5.0	24.93
Iran	Omidbaigi et al., 2010.	-	14.10-15.40	16.30-19.50	9.10-9.90	5.50-5.80	4.70-5.40	36.30-40.40
Iran	Maham et al., 2013.	1.54	31.05	17.08	31.14	-	4.03	0.48
Egypt	Aziz et al., 2013.	2.28-2.72	17.82-18.83	0.50-9.33	19.13-35.19	1.65-2.91	1.47-2.49	18.97-30.36
Turkey	Ehsan et al., 2014.	1.1-1.5	17.7-20.2	7.7-10.2	23.7-27.6	1.9-2.1	-	36.5-43.6
Egypt	Ahl et al., 2015.	1.93-2.74	17.85-18.36	12.66-16.68	19.37-20.42	1.49-3.31	2.79-5.39	27.02-28.81
Egypt	Hegazy et al., 2016.	1.97-2.03	19.93-20.56	15.69-17.91	22.57-24.56	1.49-2.31	-	28.85-29.60
Iran	Golparvar et al., 2016.	1.35	16.25	24.31	11.21	0.35	0.91	36.62
Ukraine	Kotyuk and Rakhmetov, 2017.	-	10.25-43.49	3.35-28.14	11.52-42.45	2.76-15.76	1.17-1.25	0.37-14.65
Iran	Ehsani et al., 2017.	0.82	21.21	19.60	28.52	1.86	1.76	16.72
Iran	Janmohammadi et al., 2017.	0.36-1.47	13.38-21.26	16.86-22.05	21.81-29.32	-	0.37-2.52	22.51-24.72
Iran	Fallah et al., 2018.	0.14-0.5	21.90-28.57	1.47-4.85	29.08-39.44	0.02-0.14	0.50-1.99	24.68-34.80

Apart from essential oil, *D. moldavica* aerial parts contain flavonoids, iridoids, tannins, and hydroxycinnamic and carboxylic acids (Popova et al., 2008). The total phenolic content from estimated by the Folin-Ciocalteu assay was 289.55 mg of GAE/g of dry extract, and rosmarinic acid was the major polyphenol of extract (107.11 mg/g of dry extract) (Aprotosoaie et al., 2016). Also, a new caffeic acid tetramer compounds, named

(+) methyl rabdosiin, together with seven known caffeic acid multimers and one caffeic acid monomer, were isolated from the aerial parts of *D.* moldavica. These compounds exhibited potent protective activities at 12.5 μg/mL against hydrogen peroxide-induced apoptosis (Zhang et al., 2017). Eight compounds were identified as apigenin, luteolin, kaempferol, isorhamnetin, tilianin, agastachoside, acacetin-7-O-(6-O-Malonyl-beta-D-glucopyranoside) and syringaresinol (Gu et al., 2004).

CHEMICAL COMPOSITION OF SEED

D. moldavica seed is brown, tree-edged with characteristic white outlines around the caruncle. Weight per 1000 seed is between 2.0 and 2.5 g, with 2.5-3.0 mm in length and 1.0-1.2 mm in diameter (Domokos, 1994). *D. moldavica* seed yield ranged between 1.5 and 3.4 t/ha (Domokos, 1994; Rahimzadeh et al., 2017; Fallah et al., 2018). For seed production, harvesting can be done when the seeds in the middle of the inflorescence and are in the state of waxen ripeness. Chemical composition of *D. moldavica* seed is: moisture around 6.0%, content of crude oil between 18-29%, crude protein between 17-21.4%, crude fiber around 30.2%, starch 25.6% and mucilage content is between 10 and 16% (Domokos, 1994; Dziki et al., 2013; Zhao et al., 2018).

As mentioned above, *D. moldavica* seed is a good source of fatty oil. Seed oil is yellow, spicy and has an aromatic odor. Refractive index (at 25°C) is 1.480, while density (at 25°C) is 0.932. However, it is rich in unsaturated fatty acids (about 90%), primarily the linolenic and linoleic acids (about 60 and 20%, respectively) which belong to essential fatty acids (Domokos, 1994; Dziki et al., 2013). Apart from this, *D. moldavica* seed mucilage also possesses high biological potential as a novel antioxidant edible film with interesting specifications it can be used to package several food products (Beigomi et al., 2018). Furthermore, total phenolics content ranged from 4.97 to 5.32 mg GAE/g, while antioxidant capacity of *D. moldavica* seed averaged about 40% which corresponded to EC_{50} values of 0.12 and 0.13 mg/ml. These interesting properties categorise *D. moldavica* seed into the group of raw materials suitable for nutraceuticals, food supplements, and functional food applications (Dziki et al., 2013).

Having in mind the application of seed as a component in nutrition, the microbiological quality is very important. Investigations show that most dominant fungi occurring on *D. moldavica* seed are *Alternaria alternata* and *Fusarium sporotrichioides* (Frac et al., 2015). For sterilization of seed surface, sodium hypochlorite solution is commonly used. However, the best germination percent is obtained at 4% of sodium hypochlorite solution concentration in 8 min exposure time (Varasteh et al., 2015).

BIOLOGICAL ACTIVITY

D. moldavica is used in food aromatization (canned fish, gems, candies and syrups), perfumery, alcoholic drinks industry, soaps and detergents, park decorations. It is also used in medicine in the form of tea blends/infusions (Naie et al., 2016). Dried leaves of the *D. moldavica* seem to be a prospective functional additive for extruded crisps with high nutritional value, especially because of the dietary fiber and rosmarinic acid content, a strong antioxidant potential and acceptable sensory properties (Wojtowicz et al., 2017). Moreover, the application of *D. moldavica* residues as bagasse waste (oilcake) collected after pressing and added to corn crisps could be an effective way of limiting the oil waste after pressing and increasing the sustainability of waste management. A new range of nutritionally valuable snacks could be introduced to the market (Oniszczuk et al., 2017).

Total flavonoids extract from *D. moldavica*, which is poorly water-soluble and has low oral bioavailability, was successfully encapsulated in the composite phospholipid liposome formulations. They encapsulate Total flavonoids extract from *D. moldavica* constituents with high EE values. According to the physicochemical properties and drug in-vitro release of Total flavonoids extract from *D. moldavica* composite phospholipid liposome, which with high entrapment efficiency, small size, well suited polymey disperse index and the final composite phospholipid liposome was able to potentially promote releasing of Total flavonoids extract from *D. moldavica*. According to the Permeability Studies, the permeation enhancer effect observed for the composite phospholipid liposome makes them attractive candidates that could be effective in improving bioavailability of Total flavonoids extract from *D. moldavica* after oral administration. They were also stable after 6 months of storage at 4°C (Zeng et al., 2016).

ANTIOXIDANT ACTIVITY

Determination of total phenolic and flavonoid content in methanol, ethanol and methanol/ethanol extracts of leaf in Iranian *D. moldavica* was studied as well as the antioxidant activity. Methanol extract had the highest phenolic and flavonoid content, anthocyanin, DPPH and H_2O_2 radical scavenging activity. Ethanol extract showed the least amount of all. Methanol/ethanol extract showed the highest amount in two oxides including nitric and superoxide radical scavenging activities; it also showed the highest Ferric Reducing Ability Power. The obtained chromatograms of the plant using High Performance Liquid Chromatography showed that the highest and the lowest found phenolic compounds were caffeic acid and vanilic acid, respectively. The results show that this plant is a suitable natural antioxidant to reduce the oxidative stress in humans. However, the high scavenging property of *D. moldavica* L. may be due to hydroxyl groups existing in the phenolic compounds that can scavenge the free radicals. These extracts can be used as easily accessible source of natural antioxidants and a possible food supplement or in pharmaceutical applications. It can also be used in stabilizing food against oxidative deterioration (Aslanipour et al., 2017).

The results showed that methanol was a considerably more effective solvent to extract antioxidative substances from dragonhead than acetone. *D. moldavica* methanol extract was efficient both in retarding corn oil peroxidation and in scavenging DPPH free radicals. The effectiveness of dragonhead acetone oleoresin isolated from the whole herb and deodorized acetone extract isolated from deodorized herb was significantly lower. Their activities were similar in DPPH radical scavenging, whereas deodorized acetone extract was more efficient in stripped corn oil than acetone oleoresin. Rosmarinic acid, found in dragonhead for the first time, was the major antioxidant constituent. The presence of apigenin, which can contribute to the antioxidant activity of dragonhead, was also reported (Povilaityte et al., 2001).

In vitro antioxidant assays with *D. moldavica* methanol extract reveled remarkable scavenging effects against DPPH (EC_{50}=23.10 µg/ml), ABTS (EC_{50}=8.0 µg/ml) and superoxide anion radicals (EC_{50}=445.5 µg/mL). The extract showed a high ferrous ion chelating activity (EC_{50}=35.70 µg/mL), a considerable reducing capacity, and good dydroxil radical scavenging properties. *D. moldavica* extract reduced, in a concentration dependent manner, DNA damage induced by bleomycin in normal human dermal fibroblasts as measured by comet assay and micronucleus test. Exposure of dermal fibroblasts to D. moldavica extract (100 μg/mL) after preincubation with bleomycin (10 μg/mL) resulted in the most significant antigentoxic activity. The protective effect may be due to the free radical scavenging activity, iron-chelating properties and the possible intervention on DNA repair processes (Aprotosoaie et al., 2016).

Methanolic extracts of the culture were assayed for total phenolic content using the Folin-Ciocalteau method, and antioxidant activities using three *in vitro* tests: ABTS radical scavenging, ferric ion reduction (FRAP) and lipid peroxidation (LPO). Rosmarinic acid content and antioxidant potential were found to be higher in cell suspension culture than in root-derived callus. The cell suspension culture also exhibited higher concentrations of RA and ABTS radical scavenging activity than those of the aerial parts of six-month-old field-grown plants of *D. moldavica* (Weremczuk-Jeżyna et al., 2017).

Using DPPH, ABST and BCBT assays for evaluating antioxidant activity of the *D. moldavica* essential oil it can be concluded that they possess remarkable potential for being used as natural preservatives in food industries (Ehsani et al., 2017). The antioxidant capacity of *D. moldavica* essential oil is significantly affected by cropping pattern and fertilization source. The IC50 values were found to range from 1.45 to 5.28 μg/ml (Fallah et al., 2018).

ANTIMICROBIAL ACTIVITY

According to the disc diffusion agar assay and microdilution method, it can be concluded that *D. moldavica* essential oil revealed a significant antimicrobial effects against *Escherichia coli*, *Salmonella typhimurium*, *Staphylococcus aureus* and *Listeria monocytogenes* (Ehsani et al., 2017). *D. moldavica* essential oil exhibits significantly high antibacterial and antifungal activities in comparison to a positive reference standard (chloramphenicol). The MIC values are about 0.07 mg/ml for the tested bacteria (*Bacillus cereus*, *B. subtilis*, *Klebsiella pneumoniae*, *Staphylococcus aureus*, *Micrococcus luteus* and *Serratia marcescens*) and 0.08 mg/ml for the tested fungi (*Aspergillus niger*, *Rhizopus stolonifer*, *Fusarium oxysporum* and *Mucor hiemalis*). There was agreement between MICs and clear zones of inhibition against tested bacterial strains. Inhibition zones of bacterial growth in the bioautograms had R*f*s=0.1, 0.3, 0.42, 0.54 and 0.73. These active components are identified by GC-MS after separation with preparative TLC as geraniol and nerol; geranyl-acetate; geranial; neral; neryl acetate and methyl nerolate, respectively. The use of *D. moldavica* essential oil could thus provide a powerful tool in controlling pathogenic microorganisms in food and pharmaceutical industry (El-Baky and El-Baroty, 2008; Keikhaie et al., 2018).

A novel green approach for the synthesis of silver nanoparticles (AgNPs) using aqueous seed extract of *D. moldavica* under ambient conditions has also been reported. Resulting in considerably improved AgNPs production due to its ability to control nanostructures, the suggested plant-mediated synthesis method is an inexpensive approach capable of producing AgNPs at room temperature. Through a process of characterizing nanoparticles, the present study demonstrated that AgNPs are capable of rendering high antibacterial results, and therefore show great potential for the preparation of antibacterial drugs. Results confirmed that the *D. moldavica* is a higher quality eco-friendly and a safer source for AgNPs synthesis than the conventional chemical or physical methods and its utility invites further investigation. The synthesized AgNPs showed excellent antimicrobial activities against *Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Serratia marcescens*, *Staphylococcus epidermidis* and *Bacillus subtilis* (Pak et al., 2016).

ANTINOCICEPTIVE ACTIVITY

The intraperitoneal LD_{50} of the *D. moldavica* essential oil in mice was calculated to be 600 mg/kg. *D. moldavica* essential oil administration at 5-20 mg/kg produced a significant antinociceptive effect in the formalin test and at 20 mg/kg in the acetic acid induced writhing test. The essential oil failed to demonstrate any significant influence on hot-plate reaction latency. The results suggest that the *D. moldavica* essential oil possess analgetic properties that support the folk medicinal use of this plant (Maham et al., 2013).

SEDATIVE ACTIVITY

D. moldavica is used as a tranquilizer and as a remedy for nervous conditions relief in the Mexican traditional medicine. Therefore, the sedative, anxiolytic-like and antidepressant-like effects of the aqueous extract of aerial parts of *D. moldavica* were evaluated in behavioral models in mice. The general toxic effects of *D. moldavica* were evaluated as well as their chemical analysis was performed. *D. moldavica* prolonged the pentobarbital-induced sleeping time, induced sedation in the hole-board test, decreased spontaneous activity and produced motor coordination impairment in mice. However, *D. moldavica* did not show anxiolytic effects in the avoidance exploratory behavior test or hole-board test and it was not effective in forced swimming test. The *D. moldavica* treatment produced mortalities with LD_{50} = 470 mg/kg body weight. *D. moldavica* induced sedative actions and a general inhibition of CNS activity observed by the decrease of animals' general activity, motor coordination and exploration (Martínez-Vázquez et al., 2012).

NEUROPROTECTIVE ACTIVITY

The findings suggested that *D. moldavica* total flavonoids have neuroprotective effects on cerebral ischemia/reperfusion injury which might be related to its antioxidant and anti-apoptosis activity. Results show that transient cerebral ischemia led to significant depress in GSH/GSSG ratio, depletion in antioxidant enzyme activities, rise in MDA, protein carbonyl, 8-OHdG contents, neuron apoptosis and neurological deficit scores. Pre-treatment with *D. moldavica* total flavonoids obviously attenuated the brain oxidative stress and damage, apoptosis and neurological deficits (Sun et al., 2014).

CARDIOTONIC ACTIVITY

D. moldavica has been traditionally used as a cardiotonic agent in folk medicine of some regions of Iran. The results of the study demonstrated that total extract of *D. moldavica* caused a significant reduction in the number of ventricular tachycardia, total ventricular ectopic beats and ventricular tachycardia duration in ischemic and reperfusion periods. In addition, the extract remarkably lowered the volume of infarcted tissue compared to the control group. Findings showed cardioprotective effects of total extract of *D. moldavica* against ischemia/reperfusion injuries in the isolated rat heart (NAJAFI et al. 2009). Furthermore, the study assessed the presence and mechanism of total flavonoid extracted from *D. moldavica* -related cardio-protection on myocardial ischemia reperfusion injury induced apoptosis *in vivo*. Taken together, these results provide convincing evidence of the benefit of total flavonoid extracted from *D. moldavica* pretreatment due to inhibited myocardial apoptosis as mediated by the PI3K/Akt/GSK-3β and ERK1/2 signaling pathways (Zeng et al., 2018).

CHRONIC MOUNTAIN SICKNESS

D. moldavica, a traditional Uygur medicine, possesses some key cardiac activities. A study designed to explore the treatment efficacy against chronic mountain sickness established that interleukin-6, C-reactive protein and malondialdehyde, were found to be significantly higher in chronic mountain sickness model group than the control group; while the concentrations of SOD and GSH-Px decreased. The study results show that *D. moldavica* could improve these levels, decrease pulmonary artery pressure, and improve the cardiac pathological state (Maimaitiyiming et al., 2014).

INSECTICIDAL ACTIVITY

The essential oil of *D. moldavica* exhibited strong fumigant toxicity against *Sitophilus zeamais* and *Tribolium castaneum* adults with LC50 values of 2.65 and 0.88 mg/L, respectively. The essential oil also showed contact toxicity against *S. zeamais* and *T. castaneum* adults with LC50 values of 22.10 and 18.28 μg/adult, respectively. The essential oil of *D. moldavica* may have the potential to be developed as a new natural fumigant for the control stored product insects (Chu et al., 2011; Ding et al., 2015).

CONCLUSIONS

This plant with its citrus like flavor is extensively used as a spice and for the composition of teas, because of neral and geranial as major constituents of the essential oil. *D. moldavica* is used in food aromatization, perfumery, alcoholic drinks industry, soaps and detergents. Apart from being used as a medicinal or spice plant, it is grown as a honey-bearing plant. It is also cultivated in gardens and parks as ornamental plant. Seed is a good source of fatty oil with spicy taste and aromatic odor rich in unsaturated fatty acids, primarily the linolenic and linoleic acids. This categorises *D. moldavica* seed into the group of raw materials suitable for nutraceuticals, food supplements, and functional food applications. Furthermore, numerous investigations show that this plant possesses good antioxidative, antimicrobial and insecticidal activity. Additionally, it is used as antinociceptive, sedative, neuroprotective, as well as cardiotonic agent, and for treating chronic mountain sickness.

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