

Antidepressant-Like Effects of *Dracocephalum moldavica* L. in Mouse Models of Immobility Tests

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History

- Submission Date: 18-05-2019;
- Review completed: 10-05-2019;
- Accepted Date: 10-05-2019.

DOI : 10.5530/pj.2019.11.154

Article Available online

<http://www.phcogj.com/v11/15>

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ABSTRACT

The aim of this investigation was to evaluate the antidepressant activity of the ethanolic extracts of "toronjil azul" (*Dracocephalum moldavica* L.). **Methodology:** The forced swimming test (FST) and tail suspension test (TST) were performed on CD-1 mice to evaluate the antidepressant activity of the ethanolic extracts. The ethanolic extracts were administered orally at an 80 and 100 mg/kg. The animals were dosed 1, 6 and 24 h before initiating the FST assay and 40 minutes before for the TST assay. Imipramine and fluoxetine were dosed at 15 mg/kg, while the flavonoid quercetin was given at a lower concentration of 10 mg/kg as a positive controls. **Results:** The extracts of *Dracocephalum moldavica* L. and significantly decreased the immobility time in the FST and TST assays when compared with the negative control and reported similar values than those obtained with the positive controls. **Conclusion:** The results obtained indicate that extract of *Dracocephalum moldavica* L. have antidepressant effect similar to those obtained by.

Key words: Depression, *Dracocephalum moldavica* L., Forced swim test, Tail suspension test.

INTRODUCTION

Depression is a mental disorder which according with the World Health Organization is the second cause of disability worldwide, and it has been estimated that around 350 million people suffer from depression. Depression is characterized by a depressed mood and loss of interest or pleasure in almost all daily activities. Depressed individuals have feelings of worthlessness or guilt, difficulty in thinking, concentrating or making decisions. In the most severe cases situations recurrent thoughts of death or suicidal ideation are common; according to the World Health Organization about 800 000 people commit suicide worldwide. There are also physical alterations including decreased energy, loss of appetite, changes in body weight, altered sleep patterns and psychomotor activity. At least seven to eight of the after mentioned symptoms have to be presented during a period of two or more weeks to have a positive diagnostic according to the Diagnostic and Statistical Manual of Mental Disorders.^{1,2}

The physiopathology of the disease is explained by the monoamine hypothesis which states that a deterioration of the serotonergic and noradrenergic systems causes a decrease in the production of monoamines altering the chemical brain communication.³ Recently, it has been shown that an increase of stress affecting cortisol release is associated with brain cell damage and reduction of the hippocampal specifically the CA1-CA3 region.⁴

During centuries many plants and more recently hallucinogens mushrooms with the psicoactive compound spilocybin, have been associated with an efficient and safe antidepressive effect. Among the

several plants studies with an antidepressive action, *Dracocephalum moldavica* L. is a plant that belongs to the family *Lamiaceae*. The plant is a herbaceous type with a height of 80 cm, native to Central Asia, but they can be reproduced throughout the eastern and central part of Europe. According with to popular knowledge, the plant has been used vastly to combat heart disease, blood pressure, angina, atherosclerosis, neuralgia, migraine, headache and toothache. Additionally, it has been reported that some extracts of the plant have sedative and analgesic effects.^{5,6}

In Mexico *Dracocephalum moldavica* L. has been adapted in the central region of the country, growing during all year, even though the weather conditions are different from the ones in its found homeland. DmL has a characteristic smell of lemon giving the presence of the essential oils, geraniol and citral, which have been described with a relax and tranquilizing effect. In traditional Mexican medicine, *Dracocephalum moldavica* L. is known as "toronjil azul or toronjil chino" and it has been used as a tranquilizing and sedative remedy. Moreover, a synergic effect, on the sedative and tranquilizing effect of toronjil azul is seen when administered together with *Agastache mexicana* ssp. *xolocotziana* also known as "toronjil blanco".^{7,8}

In Mexico its main use is the combination of two plants known "toronjil morado", it has been reported that this infusion is known as "the three toronjiles" which is recommended for some nervous diseases.^{7,8} Some studies of *Agastache* species have been used in traditional medicine, recent studies reveal the frequent appearance of flavonoid glycosides and flavonoids compounds. Since it is well known that

Cite this article: Jiménez Zúñiga MI, Hurtado Mariles AJ, Castrejón Flores JL, Mondragón Herrera JA, Ramírez Sotelo MG, Cerón Montes GI, *et al.* Antidepressant-Like Effects of *Dracocephalum moldavica* L. in Mouse Models of Immobility Tests. *Pharmacogn J.* 2019;11(5):976-83.

some flavonoid compounds can act on the Central Nervous System (CNS).⁹⁻¹¹ The presence of this type of compounds in *Agastache* species could be related to their therapeutic effects.¹²

However, the use of these two plants has not been studied for their effectiveness in the treatment of different diseases, despite their use in traditional Mexican medicine, there is no data on the activity in the CNS. Bearing in mind the above, the main aim of this work was to evaluate the effects on the CNS of extract ethanolic of *Dracocephalum moldavica* L., using the models of the Forced Swimming Test and Tail Suspension Test. In addition, acute toxicity was evaluated and the identification and quantification of the extract components was carried out.

MATERIALS AND METHODS

Plants material

Aerial parts of *Dracocephalum moldavica* L. (DmL) were collected in "San José Tlacotitlán, Santiago Mamalhuazuca, Ozumba, Estado de Mexico". The botanical identification was carried out by M. en C. Abigail Aguilar Contreras, and a sample of this specie was deposited at the Medicinal Herbarium of the Centro Médico Nacional Siglo XXI, IMSS (Registry No. 16258).

Preparation of ethanolic extract of *Dracocephalum moldavica* L. (DmL-EtOH)

Aerial parts of DmL (50 g), were dried in an oven (FELISA FE-291A) at 45°C for 3 days and extracted using a sonicator (AS3120B ultrasonic cleaner) 3 successively rounds with 96% ethanol (EtOH) at room temperature. Next the extracts were concentrated under reduced pressure at 45°C. Pharmacological evaluation was using 80% Tween as the vehicle for the administration of the (DmL-EtOH) extracts and the doses were expressed in milligrams of DmL per kilogram of body weight per mouse.

Phytochemical screening and quantification of the secondary metabolites

The (DmL-EtOH) extracts were qualitatively tested for the presence of phytochemicals as it has been described before.¹³

The quantification of the secondary metabolites, including phenols, tannis and flavonoids concentrations was determinate by colorimetric methods using gallic acid, tannic acid and quercetin as standards.¹⁴⁻¹⁶

Chemical characterization of (DmL-EtOH)

5 g of the dry plant was weighed, added in 20 mL of methanol and extracted by solid-liquid extraction for 12 hours. Then, 1 mL of the extract was adsorbed in silica gel 60 with a particle size of 0.063-0.2 mm, eluted with 25 mL of methanol and filtered with a membrane of 0.22 µm.

A mobile phase was prepared with methanol and acid water (0.1% phosphoric acid) in a ratio of 77:23. All the components of the mobile phase were filtered on a 0.22 µm membrane. The temperature of the column (Corctecs® C-18 a particle size of 2.7 µm) was maintained at 25 °C, the volume of the injection loop was 10 µL and the flow of the mobile phase was 0.5 mL/min. Subsequently, the column was equilibrated for 30 min with the mobile phase. The standards and the extracts were read at different wavelengths in an UHPLC model Acquity Arc of the Waters brand.¹⁷

Animals

Adult male CD-1 mice (25–35 g) were housed five per cage in a temperature-controlled (22–23°C) room under inverted light/dark conditions (12 h light/dark cycle, lights turned on at 22:00 h) and were maintained on standard rodent feed and allowed to drink water. All animals were handled in agreement with the general principles of laboratory animal care (NIH publication # 85-23, revised in 1985;

directive 2010/63/EU of the European parliament and of the council) and the 'Norma Oficial Mexicana'.¹⁸ Declaration of Helsinki on the welfare of experimental animals. All behavioral evaluations were performed between 9:00 and 16:00 h and the complete experimental sessions were videotaped and analyzed by a blind observer who was unaware of the treatment conditions.

Drugs

All the drugs in this study were administered orally in a total volume of 10.0 mL/Kg of body weight. The DmL-EtOH extract were dissolved in 80% Tween. Imipramine (Psicofarma Mexico City, Mexico), fluoxetine (Psicofarma Mexico City, Mexico) and quercetin (Aldrich-Sigma, Mexico City, Mexico) were dissolved in an isotonic solution (0.9% NaCl). The control animals received the same vehicle volume (isotonic solution, 0.9% NaCl).

Antidepressant-like effect in the forced swimming test (FST)

Mice were individually placed in glass cylinders (height: 40 cm, diameter: 19.5 cm) containing 35 cm of water at 25 ± 1°C. All animals were forced to swim for a 15 min period (pre-test), followed by a 5-min session (test) at 24 h later.¹⁹⁻²³

Six independent groups of mice (n = 5 per group) were used in this experiment. Two groups were administered orally with (DmL-EtOH) 80 and 100 mg/Kg. Additionally, one group was administered quercetin (QUE) while two independent groups were used as positive controls receiving imipramine (IMI) and fluoxetine (FLU) 15 mg/Kg. All test sessions were videotaped, and afterward, the immobility time accumulated during the test was registered by an observer that was unaware of the pharmacological treatments.

Tail suspension test (TST)

The total duration of immobility of the different groups induced by tail suspension was measured according to the method Steru *et al.* and Can *et al.*^{24,25} The mice were suspended from the edge of a table at 50 cm above the floor with adhesive tape placed approximately 1 cm from the tip of the tail. Immobility time was recorded during a 6 min period.

Acute toxicity study (LD₅₀)

The LD₅₀ of the extracts was determined by administration through orally by modifying Lorke's method.²⁶ Briefly, in the first stage, the ethanolic extracts was administered orally at increasing doses of 250, 500, 750 and 1000 mg/Kg to the four groups of three mice each. The animals were observed for 1 h for signs and symptoms of toxicity. Later observations were made every 24 h for week. In the second phase, higher doses of 2500, and 5000 mg/Kg were administered to the groups consisting of three animals. These mice were carefully observed until their total recovery or death. The surviving animals were observed for 14 days to determinate mortality.

Statistics

The results are expressed as mean ± S.E.M. Statistical analysis of the data was performed using one-way analysis of variance ANOVA followed by Dunnet's multiple comparison tests. A level of significance (P < 0.05) was considered for each test, using the software GraphPad Prism 5.

RESULTS

Phytochemical studies and quantification of the secondary metabolites. The phytochemical screening examination and the quantification on the interest compounds of the ethanolic extract are shown in (Table 1).

The content of total phenols was determined by the Folin-Ciocalteu method of the ethanolic extract amounted to 0.933 ± 0.105 (DmL-

EtOH) mg equivalents of gallic acid (GAE)/g plant. The total flavonoids in the total extract were $0.110 \pm 1 \times 10^{-5}$ (DmL-EtOH) mg equivalents to quercetin (QE)/g of plant. Quantification of tannins was determined by the Folin-Ciocalteu method. The ethanolic extract is the one that contains the highest amount of total tannins $0.204 \pm 4 \times 10^{-4}$ (DmL-EtOH) mg tannic acid equivalents (TAE)/g plant.

Effect of extracts in the FST

The results of (DmL-EtOH) are shown in Figure 1. The results showed that the drugs, IMI (15 mg/Kg) and FLU (15 mg/kg) and the natural compound QUE (10 mg/Kg) significantly reduced the immobility time, the mice showed more activity, compared to the control group only administered with the vehicle. Importantly a similar effect to that seen with the drugs is seen with the (DmL-EtOH) total extract at 100 mg/Kg and 80 mg/Kg. Additionally, we determined the swimming time in all the groups under the different treatments (Figure 2).

Effect of extracts in the TST

To confirm the FST results, we determined the anti-depressant effect using the tail suspension test (TST). Figure 3 shows the result of the test under the different treatments. These results corroborate that the (DmL-EtOH) total extract at a dose of 100 mg/Kg and 80 mg/Kg significantly reduced the immobility time compared to the control group (vehicle).

Acute toxicity tests

Toxicity performed on the ethanolic extracts of (DmL-EtOH) did not show any toxicity in terms of LD_{50} indices according to the Lorke classification; however, some mild adverse effects including sleep and decrease of locomotor activity were seen when the ethanolic extract (DmL-EtOH) was administered at a dose of 750 mg/Kg.

Phytochemical study of extracts of (DmL-EtOH)

The determination of chemical compounds of the extract (DmL-EtOH), was achieved by the conditions established in the experimental section. The results showed the presence of quercetin and catequin, according to the retention time of 1 minutes, the presence of these compounds could be observed in comparison with the reference standards (Figure 4).

DISCUSSION

According to the literature consulted *Dracocephalum moldavica* L., have been used as an ingredient in the preparation of some foods, tea and as remedy in traditional medicine for the treatment of different stomach disorders, headaches, in the treatment of nerves and congestion. Moreover, some studies have reported an antioxidant effect of these plants as well as their cardioprotective and vasodilatory effect.^{5,6,27,28} However, there are not pharmacological studies on the antidepressant, sedative and anxiolytic effects of these plants until now. Therefore, the aim of the present study was to evaluate the antidepressant effect produced by the aerial parts of *Dracocephalum moldavica* L. using a despair model.

In the first part of our results we performed a phytochemical screening of ethanolic DmL extract that showed the presence of flavonoids, primarily auronas, chalconas, xanthonas, flavones, catechol type tannins and catechol type phenols. Some studies of Agastache species have been demonstrated the presence of flavonoids and flavonoid glucoside compounds. Other reports have shown the presence of oils in DmL plant but this is not the case in our analysis. This difference is attributed to the solvents use in the extraction. In our case we focus on the use of polar solvents, because they favour the accumulation on flavonoids which as it has been well establish have a therapeutic effect on the Central Nervous System (CNS).⁹⁻¹² Thus, the abundance of the

Table 1: Preliminary phytochemical screening of ethanolic extract.

Class of compound	Ethanolic DmL
Alkaloids	+
Flavonois	+
Phenolic compounds	+
Tanins	+
Coumarins	-
Sesquiterpenlactones	-
Reducing sugars	+
Cardiac glycosides	+
Saponins	+
Steroids	+
Cyanogenic glycosides	+

+: Present; -: Absent.

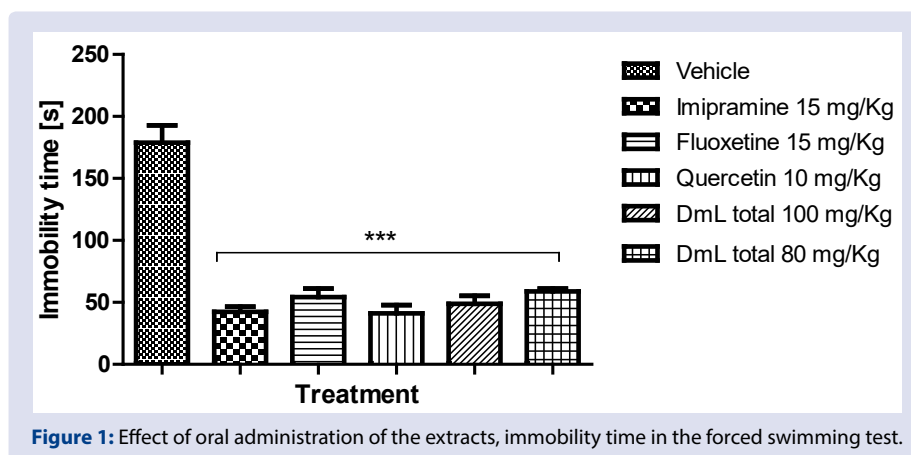
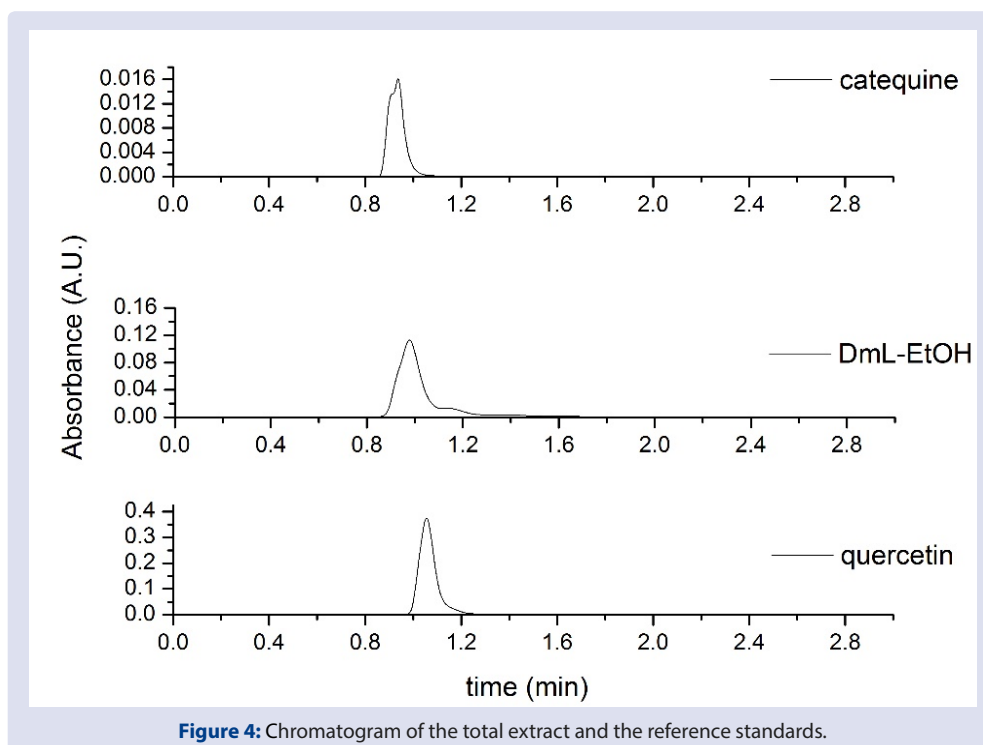
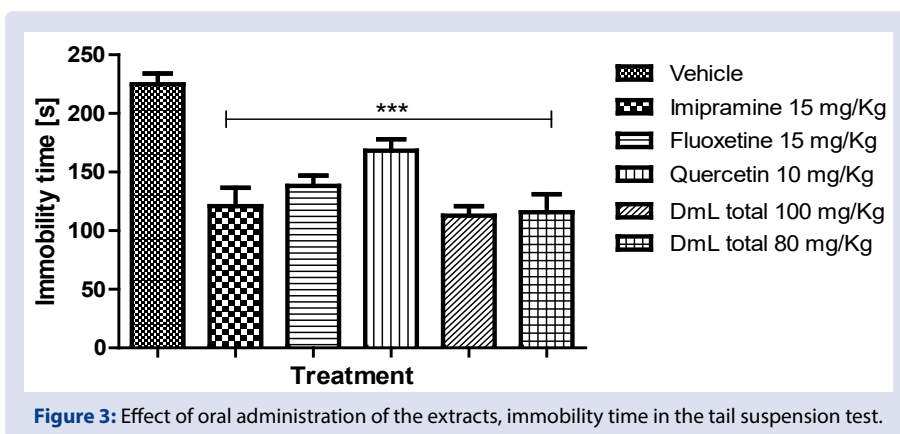
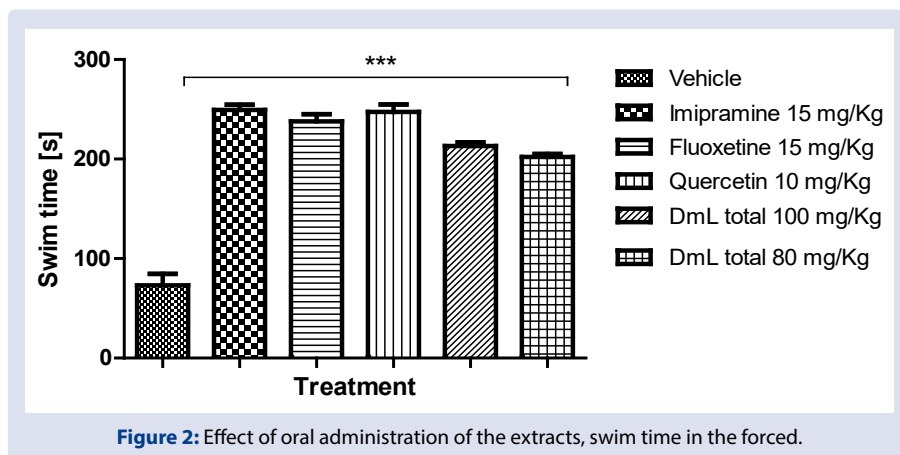


Figure 1: Effect of oral administration of the extracts, immobility time in the forced swimming test.



flavonoids compounds in our extract might have the therapeutical effect proposed.¹²

According to Estrada-Reyes *et al.*,²⁹ the biological action of flavonoids has been attributed to their antioxidant properties; mainly due to the chelating potential that gives them their chemical structure, in such a way that the antioxidant activity can be due to their reducing capacities per se or to influence the oxidation-reduction (redox) intracellular state.³⁰ Additionally, they exert neuroprotective effects in cells and animal models through different biological processes such as the attenuation of oxidative stress.³¹ As it has been well established the antioxidant activity of flavonols and flavones is associated with their structural characteristics composed by the presence of hydroxyl groups in the 3' and 4'; positions of the ring B, the hydroxyl group in C-3 and an unsaturation of ring C giving an effective capacity to capture free radicals, a requirement for a maximum antioxidant capacity.³¹ Phytotherapy studies have confirmed that flavonoids are able to influence the mood and activity of the CNS.

To evaluate the antidepressant effect of our extracts we used the forced swim and tail suspension tests which are vastly used for the determination of antidepressant effect of chemical synthesized compounds and plants extracts. During the experimental development, in the test prior to the study, acute stress is induced in the mice, which is easy to observe with a behavior of immobility, this behavior is improved by some antidepressants such as IMI and FLU in the period of the test.^{20, 32,33} The results show that the repeated orally administration of *DmL* at a dose of 100 mg/kg of the total extract induced a statistically significant reduction in the immobility time similar to the effect obtained by commercially used drugs, imipramine and fluoxetine, and quercetin an isolated flavonoid with antidepressant effect.³⁴ It has been shown that swimming has an effect in the levels of serotonin. Previous studies have shown that the administration of fluoxetine at concentrations of 5, 10 and 20 mg/kg and, a single dose of 10 mg/kg of quercetin both selective inhibitor of serotonin reuptake and a non selective inhibitor of noradrenaline and serotonin used as a positive control in our experiments respectively, increases the mobility of previously stressed mice. Thus, it is possible that our extract has a pharmacological effect over the levels of both neurotransmitters. However, more studies are needed to determine the exact antidepressant mechanism and the compound(s) associated with the effect.³⁵⁻⁴⁰

Another aim of the present study was to evaluate the toxicity of the ethanolic extracts administered orally from the aerial parts of *DmL*. As mentioned in the results section, the compound showed a low level of toxicity according to the classification proposed by Abou-Donia, giving that rising doses up to 5000 mg/kg were not associated with death, although moderate adverse effect were seen. Thus our extract not only was efficient for the treatment of depression but also resulted safer when compared with other authors.^{27,41}

According to Martínez *et al.*⁴² the extracts of *Dracocephalum moldavica* L. demonstrated the presence of apigenin 7-O-β-D-(6''-O-malonyl)-glucoside, according to Estrada *et al.*¹² in studies conducted with *Agastache*, the presence of compounds such as flavonoids (C-glycosides of apigenin and luteolin) was found, compounds to which the anxiolytic property is attributed.

According to Zielinka *et al.*⁴³ the presence of various flavonoids such as apigenin and catechin were detected in *Agastache*. According to the reports, the content of various flavonoids such as apigenin and quercetin was observed, this was detected when the period of flowering began in the spices of *Agastache*.

CONCLUSIONS

The results obtained indicate that extract of *DmL*, have antidepressant effect similar to those obtained by commercially available drugs. Moreover, the extract resulted less toxic and with minor adverse effect

when compared with other methods of extraction. Nonetheless, more studies are needed to determine and isolate the active compound and elucidate the mechanism of action.

ACKNOWLEDGEMENTS

The authors thank the Medicinal Herbarium of Centro Médico Nacional Siglo XXI for the characterization of the study plants.

CONFLICTS OF INTEREST

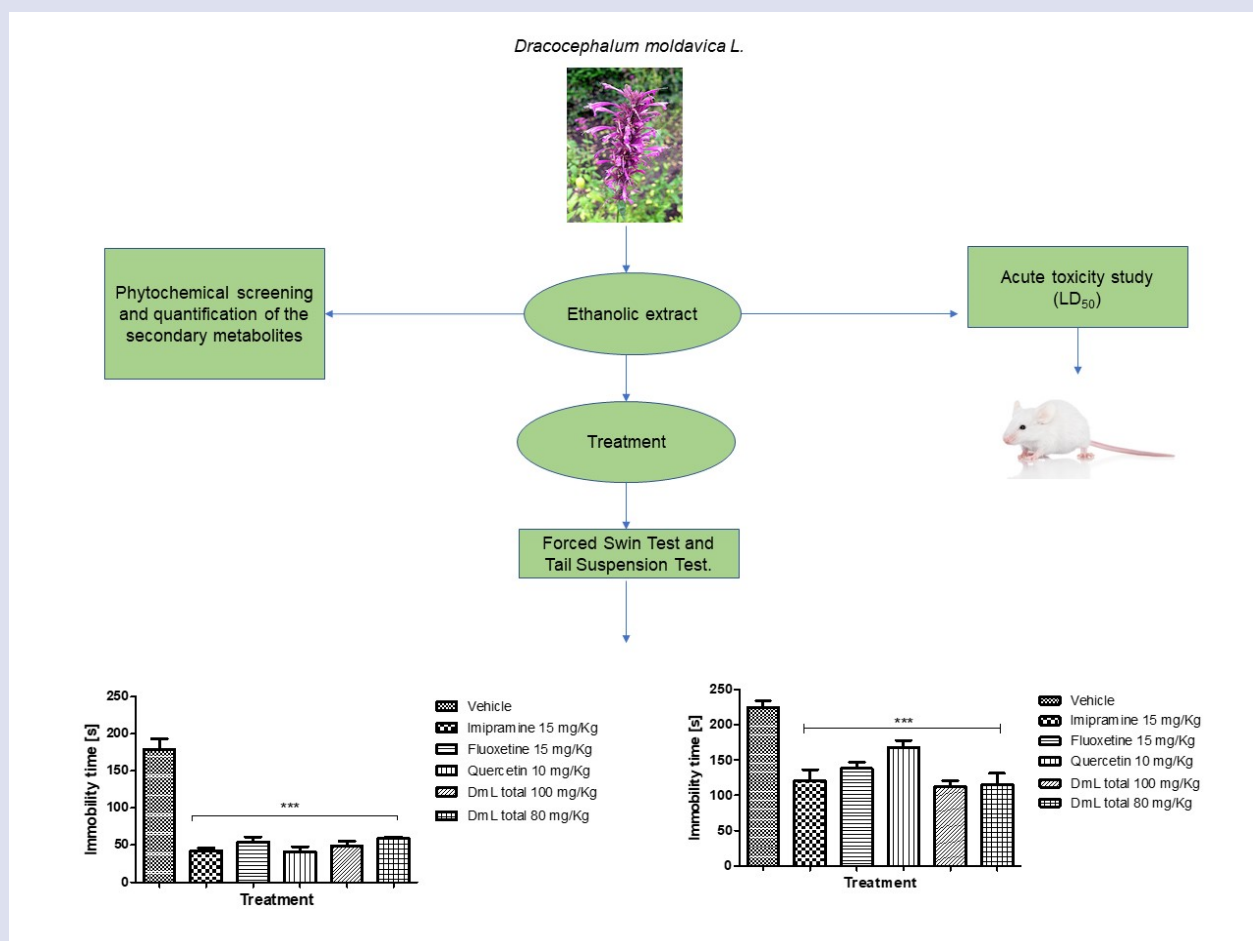
All authors declare that there are no conflicts of interest.

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GRAPHICAL ABSTRACT



ABOUT AUTHORS



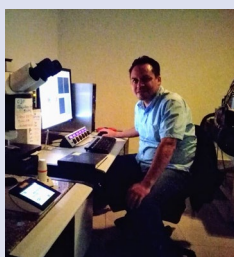
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Cite this article: Jiménez Zúñiga MI, Hurtado Mariles AJ, Castrejón Flores JL, Mondragón Herrera JA, Ramírez Sotelo MG, Cerón Montes GI, *et al.* Antidepressant-Like Effects of *Dracocephalum moldavica* L. in Mouse Models of Immobility Tests. *Pharmacog J.* 2019;11(5):976-83.