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Original Article

Acute Antidepressant-Like Effects and Biphasic Dose–Response Profiles of *Melissa officinalis* and *Nepeta menthoides* in Mice

Fatemeh Abbaszadeh[1], Masoumeh Jorjani[1,2], Mohsen Naseri[3,4], Sedighe Talebi[4*]

[1]Neurobiology Research Center, Institute of Neuroscience and Cognition, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[2]Department of Pharmacology, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[3]Traditional Medicine Clinical Trial Research Center, Shahed University, Tehran, Iran
[4]Department of Traditional Medicine, School of Persian Medicine, Shahed University, Tehran, Iran

*Corresponding Author: Sedighe Talebi, Email: s.talebi@shahed.ac.ir

Summary

Introduction: Depression remains a major global health challenge, with many patients poorly responding to standard monoaminergic antidepressants. This has prompted exploration of alternative treatments possessing antioxidant and neuroprotective effects. *Melissa officinalis* (MO) and *Nepeta menthoides* (NM), medicinal plants rich in rosmarinic acid and flavonoids, are traditionally used in Persian medicine for mood disorders and have demonstrated antidepressant potential in preclinical models. However, their acute dose–response effects have not been thoroughly studied. This study aimed to assess the acute antidepressant actions and define the therapeutic windows of MO and NM aqueous extracts in mice.

Methods: Sixty-six male N-MRI mice were randomly assigned to 11 groups receiving single oral doses of NM (100–1200 mg/kg) or MO (350–950 mg/kg), fluoxetine (20 mg/kg), imipramine (10 mg/kg), or saline. Behavioral assessments included the Open Field Test (OFT), Tail Suspension Test (TST), and Forced Swim Test (FST).

Results: Both extracts demonstrated dose-dependent biphasic behavioral effects, with antidepressant-like activity observed at lower doses. NM (100 mg/kg) and MO (550 mg/kg) produced the greatest reductions in immobility time, comparable to fluoxetine and imipramine. In contrast, higher doses showed diminished or reversed efficacy. Locomotor activity findings indicated that the reduced immobility observed at effective doses was not attributable to hyperactivity.

Conclusion: These findings establish the optimal acute effective doses for NM and MO and emphasize the critical importance of dose selection in herbal antidepressant therapy. Future studies should assess chronic effects and elucidate underlying biochemical mechanisms.

Keywords: Depression, *Nepeta menthoides*, Dose-response, *Melissa officinalis*, Persian medicine, Aqueous extract

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Introduction

Depression is a multifactorial and globally prevalent mental disorder that significantly impacts emotional well-being, cognitive performance, and quality of life. Despite the availability of numerous antidepressant drugs, such as selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs), their clinical utility is often limited by delayed onset of action, incomplete response,[1,2] and are sometimes associated with tolerability concerns, including sedation, gastrointestinal disturbances, and sexual dysfunction.[3,4] Consequently, there is an increasing interest in developing novel, safe, and effective therapeutic alternatives derived from natural products. Herbal medicines, which contain a wide range of bioactive compounds, have gained considerable attention due to their potential to modulate neurochemical and oxidative pathways implicated in mood regulation.[5] Among these, *Melissa officinalis* (MO: lemon balm) and *Nepeta menthoides* (NM: Persian lavender) are two medicinal plants widely recognized in traditional Persian medicine for their calming, mood-enhancing, and anxiolytic properties.[6,7]

Melissa officinalis, a member of the Lamiaceae family, is rich in rosmarinic acid, flavonoids, and terpenoids that exhibit neuroprotective, antioxidant, and serotonergic-modulating effects. Previous studies have demonstrated that its aqueous and ethanolic extracts can reduce anxiety, improve sleep quality, and alleviate depressive-like symptoms.[8,9] Similarly, *Nepeta menthoides*, another Lamiaceae species, contains nepetalactones, iridoid glycosides, and phenolic compounds known for their sedative, anti-inflammatory, and antidepressant properties.[10,11] However, while several studies have examined their pharmacological activities, there remains a lack of systematic evaluation regarding their dose-dependent behavioral effects.

Herbal compounds often display non-linear dose–response relationships, where moderate doses exert therapeutic benefits but higher concentrations may produce paradoxical or adverse effects. This biphasic phenomenon has been reported in several botanical extracts and may be attributed to receptor saturation, feedback inhibition, or activation of counter-regulatory pathways.[12] Understanding the precise therapeutic window is therefore essential for optimizing efficacy and safety in both experimental and clinical contexts. Addressing this gap, the present study was designed to systematically evaluate a wide range of MO and NM doses in mice, thereby defining their optimal effective range and clarifying their acute antidepressant potential.

Methods

Aqueous Extraction Procedure for M. officinalis and N. menthoides

The preparation of the aqueous extracts of NM and MO was carried out as previously described by Talebi et al..[13] In brief, the dried aerial parts were soaked in hot water, filtered, and concentrated using a rotary evaporator. The study was conducted in accordance with the ARRIVE (Animal Research: Reporting of in Vivo Experiments) guidelines.

Animals

A total of 66 male N-MRI mice, weighing between 20 and 25 grams, were obtained from the Razi Research Institute in IRAN. The animals were acclimatized for one week prior to experimentation under standard laboratory conditions, including a temperature-controlled environment (21–25°C), and a 12-hour light/dark cycle. Food and water were provided ad libitum throughout the acclimation period. All procedures involving animals were conducted in accordance with the guidelines established by the NIH Animal Care and Use Committee[14]. The experimental protocol received prior approval from the Animal Ethics Committee of Shahed University (code No. IR.SHAHED.REC.1397.036, 2018).

Experimental Protocol

A total of 66 male N-MRI mice were randomly assigned into 11 experimental groups (n = 6 per group). The groups consisted of four NM-treated groups (100, 300, 600, and 1200 mg/kg), four MO-treated groups (350, 550, 750, and 950 mg/kg), two positive control groups receiving fluoxetine (20 mg/kg) or imipramine (10 mg/kg), and one saline-treated control group. Random allocation was performed prior to treatment administration. The selected dose ranges were designed to span a broad pharmacological window in order to identify the optimal effective dose and determine whether the extracts exhibited a biphasic dose–response pattern. Dose selection was based on previously published studies as well as preliminary LD50 measurements performed prior to the behavioral experiments.[13,15,16] Behavioral evaluations commenced one-hour post-treatment, during which each animal underwent three distinct tests. A control group (NS) was included to provide a baseline for comparison, enabling the assessment of the independent effects of the experimental treatments. A 0.3 mL dosing solution was individually prepared for each animal by dissolving the appropriate amount of extract powder or standard antidepressant- fluoxetine or imipramine - in 0.9% normal saline, in accordance with the specified dosage requirements. All behavioral scoring and outcome assessments were conducted by independent observers blinded to treatment allocation in order to minimize observer bias.

Open Field Test

The open field test (OFT) was performed using a square box (measuring 40 cm on each side and 40 cm in height, subdivided into 16 equal compartments). Each animal was placed in a corner and allowed to explore for five minutes. Between tests, the box was cleaned with 70% alcohol. Two observers manually recorded the total number of squares crossed by the animals as a measure of locomotor activity.[17] This test was used on drug-treated mice to separate the effects of locomotor ability from immobility time observed in the (FST) and tail suspension test (TST). Accordingly, OFT was performed first and considered as a confirmatory outcome, while immobility in the TST and FST represented the primary outcomes of the study.

Tail Suspension Test

The TST was performed post-treatment. Groups of six mice were suspended 40 cm above the floor, secured by adhesive tape positioned approximately 2.5 cm from the distal end of their tails, for a period of six minutes. The immobility time was measured during the final five minutes of the test. Prolonged immobility in the TST is indicative of depressive-like behavior. Each mouse participated in the test only once.[18,19]

Forced Swim Test

At following treatment, each mouse was individually placed into a cylindrical glass tank measuring 30 cm in height and 16 cm in diameter, containing 25 cm of water maintained at a temperature of 25 ± 2°C. Animals were subjected to a six-minute swim test, during which immobility time was recorded throughout the last five minutes as an indicator of depressive-like behavior. After testing, mice were gently dried with a towel, and the water was changed before the subsequent trial. Prior to the experiment, the animals were acclimated by being exposed to water for 15 minutes.[20,21] Each mouse was tested only once.

Statistical Analysis

Statistical analyses were performed using GraphPad Prism 7.0. Data are presented as mean ± SEM for each group. Normality of data distribution and homogeneity

of variances were assessed before conducting parametric analyses. Group differences were analyzed using one-way ANOVA followed by Tukey's post hoc test for multiple pairwise comparisons within each behavioral endpoint. Statistical significance was considered at $P<0.05$. In addition to p-values, effect sizes were calculated and reported using partial eta squared (ηp^2) and omega squared (ω^2) to estimate the magnitude of treatment effects.

Results

Behavioral Assessments

Effects of NM and MO on Locomotor Activity in the OFT

In the OFT, locomotor activity in the NS, fluoxetine, imipramine, NM 100 mg/kg, and MO 550 mg/kg groups did not differ significantly, indicating that these treatments did not alter spontaneous motor behavior. NM treatment produced a significant dose-dependent reduction in locomotor activity (Figure 1A), with higher doses (300, 600, and 1200 mg/kg) significantly decreasing the number of crossed squares compared with NS, fluoxetine, imipramine, and NM 100 mg/kg groups ($P<0.001$, $F_{(6, 35)}=10.63$, partial $\eta^2=0.65$, $\omega^2=0.58$). In contrast, MO treatment produced a milder effect on locomotion (Figure 1B). Although higher doses (750 and 950 mg/kg) tended to reduce the number of crossed squares relative to NS and lower-dose groups, these changes were less pronounced ($P=0.0243$, $F_{(6, 35)}=2.814$, partial $\eta^2=0.33$, $\omega^2=0.21$). These findings suggest that higher doses, particularly of NM, may exert locomotor-suppressive or sedative-like effects.

Effects of NM and MO on Immobility Time in the TST

Treatment with different doses of NM (100–1200 mg/kg) and MO (350–950 mg/kg) produced significant biphasic dose-dependent alterations in immobility time during the TST in mice. The NM 100 mg/kg dose ($P<0.001$, $F_{(6, 35)}=10.94$, partial $\eta^2=0.65$, $\omega^2=0.59$; Figure 2A) and the MO 550 mg/kg dose ($P<0.001$, $F_{(6, 35)}=5.26$, partial $\eta^2=0.47$, $\omega^2=0.38$; Figure 2B) significantly reduced immobility time compared with the NS control group and other treatment groups, indicating antidepressant-like effects. Fluoxetine and imipramine also markedly reduced immobility time, confirming the validity of the model. In contrast, higher doses of NM and, to a lesser extent, MO attenuated these effects and increased immobility time, supporting a biphasic dose–response profile ($P<0.01$).

Effects of NM and MO on Immobility Time in the FST

Administration of NM (100–1200 mg/kg) significantly altered immobility time in the FST in a dose-dependent manner ($F_{(6, 35)}=9.294$, $P<0.001$, partial $\eta^2=0.61$, $\omega^2=0.54$). The lowest dose of NM (100 mg/kg) significantly reduced immobility time compared with the NS group, suggesting an antidepressant-like effect. In contrast, higher doses (300–1200 mg/kg) progressively increased immobility time, with the 1200 mg/kg dose producing the greatest increase, suggesting possible sedative-like or motor-suppressive effects. (Figure 3A).

Similarly, MO treatment (350–950 mg/kg) significantly affected immobility time ($F_{(6, 35)}=12.20$, $P<0.001$, partial $\eta^2=0.68$, $\omega^2=0.62$). Notably, the 350 mg/kg induced a marked increase in immobility. The most pronounced reduction in immobility was observed at 550 mg/kg, while higher doses gradually attenuated this effect, and the highest dose (950 mg/kg) increased immobility relative to lower doses. (Figure 3B).

Reference antidepressants (imipramine and fluoxetine) significantly reduced immobility time, validating the FST paradigm. Overall, both NM and MO exhibited dose-dependent biphasic effects, with antidepressant-like activity at lower doses and reduced efficacy or opposite behavioral effects at higher doses.

Discussion

This study provides an evaluation of the acute antidepressant-like effects of *Nepeta menthoides* and *Melissa officinalis* aqueous extracts in mice, systematically

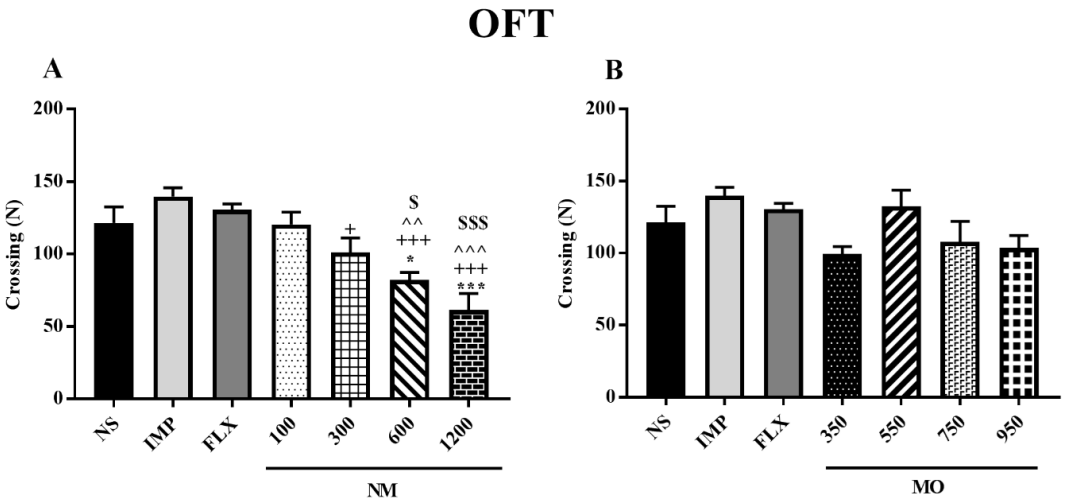

Figure 1. Dose-response effect of *NM* (mg/kg) (A) and *MO* (mg/kg) (B) on the number of squares crossed in the open-field test during the acute phase. Data are expressed as mean ± SEM (n = 6) and were analyzed using one-way ANOVA followed by Tukey's post hoc test. $^{*}P<0.05$, $^{***}P<0.001$ vs. NS, $^{\wedge\wedge}P<0.01$ vs. FLX, $^{+}P<0.05$, $^{+++}P<0.001$ vs. IMP, $^{\$}P<0.05$, $^{\$\$\$}P<0.001$ vs. NM 100 mg/kg. NM: aqueous extract of *Nepeta menthoides* (Mashhadi lavender), MO: aqueous extract of *Melissa officinalis*, N: number of crossed squares, NS: normal saline (10 mL/kg), FLX: fluoxetine 20 mg/kg, IMP: imipramine 10 mg/kg

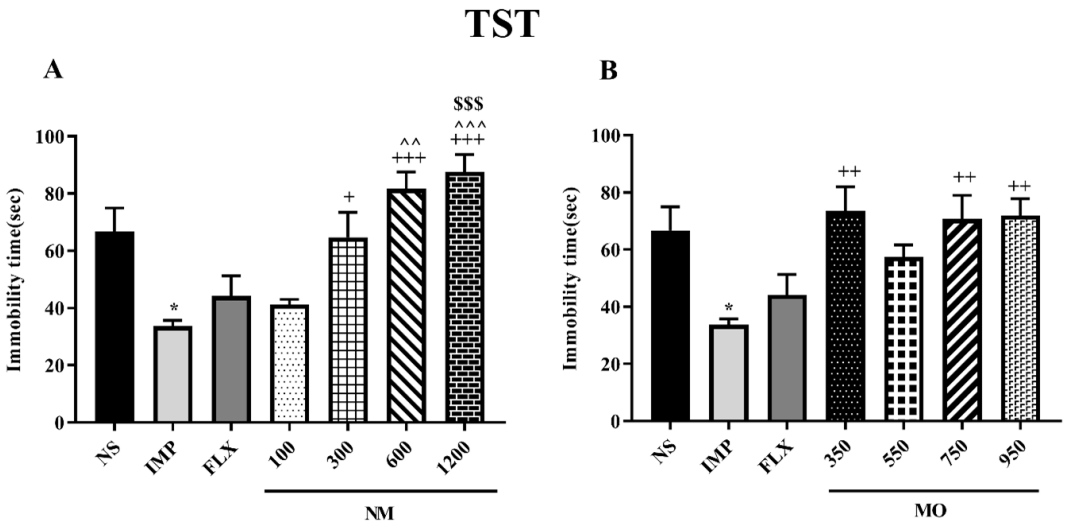

Figure 2. Dose-response effect of *NM* (mg/kg) (A) and *MO* (mg/kg) (B) on immobility time in the tail suspension test during the acute phase. Data are expressed as mean ± SEM (n = 6) and were analyzed using one-way ANOVA followed by Tukey's post hoc test. $^{*}P<0.05$ vs. NS; $^{\wedge\wedge}P<0.01$, $^{\wedge\wedge\wedge}P<0.001$ vs. FLX; $^{+}P<0.05$, $^{++}P<0.01$, $^{+++}P<0.001$ vs. IMP; $^{\$\$\$}P<0.001$ vs. NM 100 mg/kg. NM: aqueous extract of *Nepeta menthoides* (Mashhadi lavender), MO: aqueous extract of *Melissa officinalis*, NS: normal saline (10 mL/kg), FLX: fluoxetine 20 mg/kg, IMP: imipramine 10 mg/kg

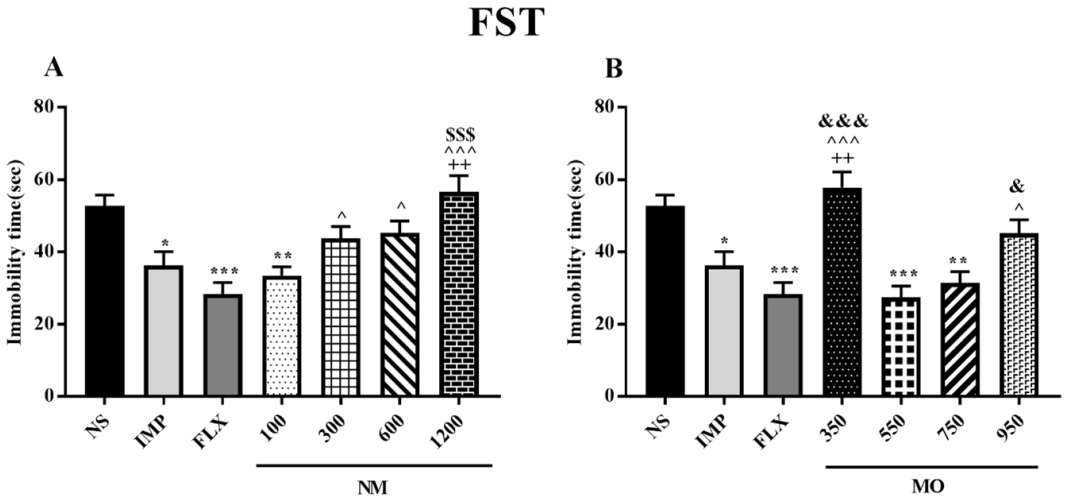

Figure 3. Dose-response effect of *NM* (mg/kg) (A) and *MO* (mg/kg) (B) on immobility time in the forced swim test during the acute phase. Data are expressed as mean ± SEM (n = 6) and were analyzed using one-way ANOVA followed by Tukey's post hoc test. $^{*}P<0.05$, $^{**}P<0.01$, $^{***}P<0.001$ vs. NS; $^{\wedge}P<0.05$, $^{\wedge\wedge\wedge}P<0.001$ vs. FLX; $^{++}P<0.01$ vs. IMP; $^{\$\$\$}P<0.001$ vs. NM 100 mg/kg; $^{\&}P<0.05$, $^{\&\&\&}P<0.001$ vs. MO 550 mg/kg. NM: aqueous extract of *Nepeta menthoides* (Mashhadi lavender), MO: aqueous extract of *Melissa officinalis*, NS: normal saline (10 mL/kg), FLX: fluoxetine 20 mg/kg, IMP: imipramine 10 mg/kg

examining a range of doses and identifying their optimal therapeutic windows. Both botanicals demonstrated robust, dose-dependent reductions in immobility in the TST and FST, with NM at 100 mg/kg and MO at 550 mg/kg eliciting the strongest effects, comparable to the standard antidepressants fluoxetine (20 mg/kg) and imipramine (10 mg/kg). Crucially, the observed responses were biphasic: higher doses of each extract produced attenuated or reversed efficacy, highlighting the importance of precise dose selection when employing herbal interventions in depression models.

Identifying the optimal therapeutic window is crucial in both preclinical research and clinical application. It involves defining a dose range that maximizes therapeutic efficacy while minimizing adverse effects—a balance especially critical when working with phytochemicals. These natural compounds often demonstrate non-linear, biphasic dose-response behaviors, a phenomenon termed hormesis. In hormesis, low doses typically induce adaptive, beneficial effects by triggering modest overcompensation that promotes cellular homeostasis and function. Conversely, high doses produce inhibitory or toxic effects by overwhelming biological systems and causing damage that cannot be effectively repaired. This dual response is commonly represented as a U- or J-shaped curve, reflecting stimulation at low doses and inhibition at high doses. Understanding and establishing this therapeutic window is therefore essential for harnessing the full potential of phytochemicals while avoiding detrimental outcomes.[22,23] For example, natural compounds such as resveratrol and curcumin have been reported to exert neuroprotective and antidepressant-like effects at moderate doses, but lose efficacy or even become toxic when administered at excessively high levels.[24,25] In the present study, both NM and MO showed antidepressant-like effects at low and moderate doses, evidenced by

reductions in immobility time in the TST and FST. These effects were comparable to those produced by fluoxetine and imipramine, well-established antidepressants that modulate monoaminergic neurotransmission.[26,27] However, higher doses of NM and MO led to increased immobility and decreased locomotor activity in the OFT, suggesting possible sedative or motor-impairing effects. Therefore, part of the increased immobility observed in the TST and FST at higher doses may reflect reduced motor activity rather than purely depressive-like behavior. Hosseini et al. likewise demonstrated in a spinal cord injury model that higher doses of MO led to a reduction in motor function.[28]

Mechanistically, the antidepressant-like effects observed at moderate doses may involve modulation of monoaminergic neurotransmission - serotonin, norepinephrine, and dopamine, which are central targets of clinically used antidepressant drugs.[29] Both NM and MO contain phytoconstituents such as flavonoids, terpenoids, and phenolic acids,[15,30] reported to inhibit monoamine oxidase enzymes and increase synaptic monoamine availability.[31] In particular, they are rich in rosmarinic acid, shown to exert antidepressant effects partly through monoaminergic modulation and GABAergic system interactions.[13,32-34] Furthermore, these botanical extracts possess potent antioxidant and anti-inflammatory properties that may contribute to their antidepressant-like actions.[35,36] Chronic inflammation and oxidative stress are increasingly recognized as key factors in depression pathophysiology, promoting neurodegeneration and dysregulation of neuroplasticity.[37,38]

Conclusion

The present study provides a systematic acute dose–response evaluation of Nepeta menthoides and Melissa officinalis aqueous extracts in well-validated behavioral models of depression. Both botanicals exerted significant antidepressant-like effects in mice, with magnitudes comparable to fluoxetine and imipramine at their optimal doses. Importantly, the responses appeared to follow a dose-dependent, biphasic pattern, with efficacy tending to attenuate or reverse at higher doses despite identical experimental conditions. This finding underscores the necessity of rational dose selection in the translational use of herbal antidepressants, as optimal dosing ensures maximal therapeutic benefit while minimizing adverse effects. While the behavioral data are robust and consistent with prior investigations, the precise molecular targets and pathways underlying the antidepressant effects of NM and MO warrant further exploration. Future studies using biochemical assays to quantify neurotransmitter levels, receptor binding studies, and evaluation of inflammatory markers would provide direct mechanistic evidence. Additionally, future studies could investigate potential synergistic effects with standard antidepressants, which may offer opportunities for dose reduction and minimization of side effects, potentially enhancing clinical applicability. Together, these approaches will deepen understanding of NM and MO's pharmacodynamics and support their development as effective, evidence-based herbal therapies for depression.

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Authors' Contribution

Conceptualization: Fatemeh Abbaszadeh, Sedighe Talebi.
Data Curation: Masoumeh Jorjani.
Formal Analysis: Fatemeh Abbaszadeh, Mohsen Naseri.
Supervision: Sedighe Talebi.
Writing–Original Draft: Fatemeh Abbaszadeh, Sedighe Talebi.
Writing–Review & Editing: Sedighe Talebi.

Competing Interests

The authors declare no conflict of interest.

Ethical Approval

This article is a part of Ph.D. thesis by S. T. entitled "Dose-dependent effects of *Melissa officinalis* and *Nepeta menthoides* in the treatment of depression in an animal model" that was approved by the Ethics Committee of Shahed University, Tehran, Iran, with code No. IR.SHAHED.REC.1397.036, 2018.

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