AJPR
Avicenna Journal of Pharmaceutical Research
Avicenna J Pharm Res, 2023; 4(1):x-x. doi:10.34172/ajpr.1088
http://ajpr.umsha.ac.ir

XX

The Aqueous Extract of *Mentha piperita* (Peppermint) Can Alter Depression Parameters: A Behavioral Study in Mice

Moghari F.[1], Esmaeili S.[2*], Sarahroodi S.[3*]

[1]Faculty of Pharmacy and Pharmaceutical Sciences, Tehran Medical Sciences, Islamic Azad University, Tehran, Iran
[2]Traditional Medicine and Materia Medica Research Center, Department of Traditional Pharmacy, School of Traditional Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[3]Department of Pharmacology and Toxicology, Faculty of Pharmacy and Pharmaceutical Sciences, Tehran Medical Sciences, Islamic Azad University, Tehran, Iran

Article history:
Received: x xx, 2022
Revised: xx 20, 2022
Accepted: x xx, 2022
ePublished: x xx, 2022

***Corresponding author:**
Shadi Sarahroodi
Email: sarahroodi@yahoo.com

Somayyeh Esmaeili
Email: soesmaeili@yahoo.com

Abstract

Background: This study aimed to investigate the potential antidepressive-like effect of the aqueous extract of *Mentha piperita* (peppermint) leaves using two predictive models of depression, namely, forced swimming test (FST) and tail suspension test (TST), in male Wistar albino mice. For this purpose, after weighting, coding, and classifying the mice, they were grouped (n = 6) as test (175 mg/kg, 350 mg/kg, and 700 mg/kg *M. piperita* aqueous extract; i.p.) and control (20 mg/kg fluoxetine and 30 mg/kg imipramine; i.p.) groups and the blank group (normal saline; i.p.) and received medication or extract for 28 days before the tests.

Results: All doses of the aqueous peppermint extract compared to the control group markedly reduced the immobility duration in both FST and TST when administered intraperitoneally for 28 days. In addition, our results demonstrated that 350 mg/kg and 700 mg/kg of the peppermint aqueous extract increased swimming time significantly ($P<0.001$) without any significant change in climbing (struggling) duration.

Conclusion: The results of this study suggest that the aqueous extract of *Mentha piperita* leaves has anti-depressant-like activity in the animal models of depression that might be a cause of increasing central serotonergic activity. However, more studies are required to determine the exact mechanisms of action.

Keywords: Antidepressant-like effect, *Mentha piperita*, Aqueous extract, Forced swimming test, tail suspension test, Serotonergic activity, Mice

Please cite this article as follows: Moghari F, Esmaeili S, Sarahroodi S. The aqueous extract of *Mentha piperita* (peppermint) can alter depression parameters: a behavioral study in mice. Avicenna J Pharm Res. 2023; 4(1):x-x. doi:10.34172/ajpr.1088

Introduction

Major depression (major depressive disorder), one of the most common and severe psychiatric medical conditions, affects about 300 million of the world's population (1). It is the second cause of disability in industrial countries after cardiovascular diseases (2). Depression may lead to suicidal ideation in some patients and negatively affect cognitive behavior (3). Available pharmacological options for this condition include monoamine oxidase inhibitors, tricyclic antidepressants, selective serotonin reuptake inhibitors, serotonin and norepinephrine reuptake inhibitors, serotonin modulators, and atypical antidepressants (4).

Nevertheless, all of our available medications for depression are associated with adverse drug reactions such as weight gain (5), sexual dysfunction (6), gastrointestinal complaints (7,8), and cardiovascular disease (9), as well as some life-threatening side effects (1).

Side effects may diminish patient admission and delay recovery (10). In addition, recent studies have revealed that less than half of patients have recovered by consuming antidepressants (11).

Thus, seeking new effective antidepressants with the least possible number of adverse effects seems to be necessary.

Many herbal-originated medications are discovered through their use in traditional medicine (12). Several herbal medicines, such as *Hypericum perforatum* L. (13), *Valeriana officinalis* L. (14), *Melissa officinalis* L., and *Verbena officinalis* L. (15), have successfully entered the market as complementary and alternative medicines for psychiatric conditions (16). Their most important advantages are the lower price of herbal drugs and their availability and safety (17). The mentioned items make them a suitable choice even for self-medication. It is evident that among various types of self-medication, which is considered a serious challenge to our health system worldwide (18-21), self-treatment with herbals is

safer, cheaper, and has a highly long history (17).

Mentha piperita L. (peppermint), belonging to the Lamiaceae family, is native to the Mediterranean region and has been spread around the globe due to its medicinal properties, taste, and aroma (22). This *Mentha* species is famous for its medicinal and flavoring properties and has been used in medications, food, and cosmetics (23). Peppermint has several biological activities, such as antifungal (24), antibacterial (25), antimutagenic (26), chemo-preventive (27), carminative (28), anti-inflammatory (29), antispasmodic (30), analgesic (31) and antiallergic activities (32).

Based on the mentioned evidence of the beneficial effects of *M. piperita* on the nervous system, the present study was conducted to evaluate the antidepressant effects of its aqueous extract in mice.

Materials and Methods

Animals

In this experimental study, 72 male albino NMRI mice weighing 22-32 g were randomly divided into 12 groups of 6. The animals were obtained from Pasteur Institute (Iran) and housed in a 12-hour light/12-hour dark cycle, controlled temperature (24–26 ˚C), and relative humidity of 45-55%. They were housed in groups of 6 in Plexiglas animal cages with free access to tap water and standard rodent chow. All experiments were performed between 8:00 AM and 2:00 PM from May to August 2021 at Tehran Medical Sciences Islamic Azad University, School of Pharmacy, and each animal was used only once. The rules of the National Institute of Health carried out the experimental protoco l.

Plant Material and Preparation of Extracts

Mentha piperita leaves were purchased from a grocery in Tehran, Iran, and identified by Mr. Alireza Dolatyari at the Traditional Medicine and Materia Medica Research Center Herbarium, Shahid Beheshti University of Medical Sciences, Tehran, Iran (No. HMS-4618). Plant leaves were dried in the shadow until desiccated. Then, all were crushed into powder and stored at room temperature in appropriate containers. About 150 g of dried powder was infused for 30 minutes in 1500 mL of boiled distilled water by filtration and concentrated by vacuum evaporation. Next, it was dried at a low temperature.

Drugs

The aqueous extract of *M. piperita* leaves, fluoxetine hydrochloride (Arya Pharmaceutical Company, Iran), and imipramine hydrochloride (Medicine Pars Company, Iran), all in powder form, were used for this study. The doses were selected based on extract dry weight. All extracts and drugs were dissolved in normal saline and administered at a constant volume of 10 mL/kg intraperitoneally (i.p.).

The positive control groups received fluoxetine (20 mg/kg, i.p.) and imipramine (30 mg/kg, i.p.). Negative control groups were treated with normal saline (10 mL/kg, i.p.), and the test groups were administered 175 mg/kg, 300 mg/kg, and 700 mg/kg of *Mentha* aqueous extract, respectively.

Behavioral Tests

Tail Suspension Test

In this animal model, mice were individually suspended by their tail at a height of 50 cm above the floor of the table edge with the aid of adhesive tape at about 1 cm from the tip of the tail. The animals were separated both visually and acoustically from each other during the whole test. The total duration of immobility induced by tail suspension was manually calculated with a stopwatch for 6 minutes. The first 2 minutes were allocated to matching the animals to the environment, and the last 4 minutes were recorded in seconds by chronometer as immobility duration. The animals who did not exhibit any body movements and hung inertly were considered immobile (33).

Forced Swimming Test

In this behavioral model, the mice were separately drooped in the tank of the glass cylinder (40 cm in height and 25 cm in diameter). The water level (25 ˚C) was 15 cm from the bottom and was marked on the tank to ensure that the volume of water was consistent across mice. During the swim test, the tank's dimensions were selected so that the mice could not touch the bottom of the tank, either with their feet or their tails. The height of the tank was high enough to prevent the mice from escaping from the tank. Each mouse was judged immobile when it ceased the struggle and remained motionless, floating on the water, making only necessary movements to keep its head above it. Each animal's immobility, swimming, and climbing duration were registered during the 4-minute test after 2 minutes of adaptation. The reduction of immobility time reflects the antidepressive-like effect (34).

Statistical Analysis

The data were analyzed using GraphPad Prism version 9.00 for Windows (GraphPad Software, Inc., San Diego, CA, USA). One-way analysis of variance (ANOVA), followed by Tukey's post hoc test, was used to identify statistical differences between means. All data were presented as means ± standard error of means, and statistical differences were considered significant at a P value of less than 0.05.

Results

Figure 1 depicts the effects of *M. piperita* aqueous extract (175 mg/kg, 350 mg/kg, and 700 mg/kg i.p.) on swimming duration. The one-way ANOVA indicated a significant increase in swimming duration [$F(5, 26) = 7.841$, $P < 0.001$] in mice treated with *Mentha* extract (175 mg/kg, 350 mg/kg, and 700 mg/kg i.p.) compared to the vehicle group. Based on the results of the one-way ANOVA, no significant differences were found in the swimming duration yielded with *Mentha* extract (175 mg/

kg, 350 mg/kg, and 700 mg/kg i.p.) in comparison to that produced with imipramine and fluoxetine.

Figure 2 shows the effect of the *Mentha piperita* aqueous extract (175 mg/kg, 350 mg/kg, and 700 mg/kg i.p.) on immobility duration in a forced swimming test (FST). The one-way ANOVA demonstrated a significant decrease in immobility duration [F (5, 21) = 34.36, $P < 0.001$) in the mice treated with *Mentha* extract (175 mg/kg, 350 mg/kg, and 700 mg/kg i.p.) compared to the control group. Nonetheless, immobility time had no significant decrease ($P > 0.05$) when compared with the imipramine and fluoxetine groups. The results revealed that *Mentha* extract (350 mg/kg and 700 mg/kg i.p.) significantly decreased ($P < 0.05$) the immobility duration of mice in comparison to the *Mentha* extract (175 mg/kg i.p.) group.

Figure 3 displays the effect of the *Mentha* extract in different doses, fluoxetine, and imipramine, on mice's climbing' (struggling) duration in the FST. According to our analysis, only imipramine significantly ($P < 0.001$) increased climbing time in comparison with the control (saline) group. Nonetheless, this behavior did not improve markedly in different doses of *Mentha* extract and fluoxetine-treated groups ($P > 0.05$).

The effect of fluoxetine, imipramine, and *Mentha* extracts (175 mg/kg, 350 mg/kg, and 700 mg/kg) on mice's duration of immobility in the tail suspension test (TST) is depicted in Figure 4. In this test, fluoxetine ($P < 0.05$), imipramine ($P < 0.05$), as well as 700 mg/kg of *Mentha* extract ($P < 0.05$), could significantly reduce the immobility time in comparison with the control group. Nevertheless, there was no significant reduction in the duration of immobility with 175 mg/kg and 350 mg/kg of *Mentha* extract compared to the control group ($P > 0.05$).

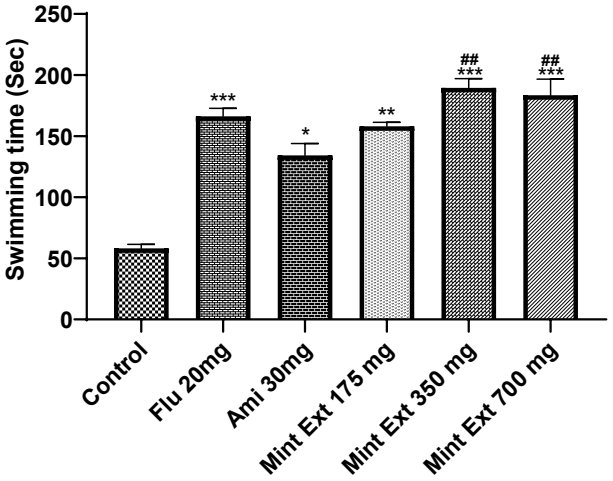

Figure 1. Effects of *Mentha piperita* Aqueous Extract (175 mg/kg, 350 mg/kg, and 700 mg/kg), Fluoxetine (Flu 20 mg/kg), and Amitriptyline (Ami 30 mg/kg) on the Duration of Swimming Time in FST. *Note*. FST: Forced swimming test; SD: Standard deviation. Data are presented as means ± SD (n = 6). * $P < 0.05$, ** $P < 0.01$, and *** $P < 0.001$ compared with the control group. ## $P < 0.01$ compared with the amitriptyline-treated group

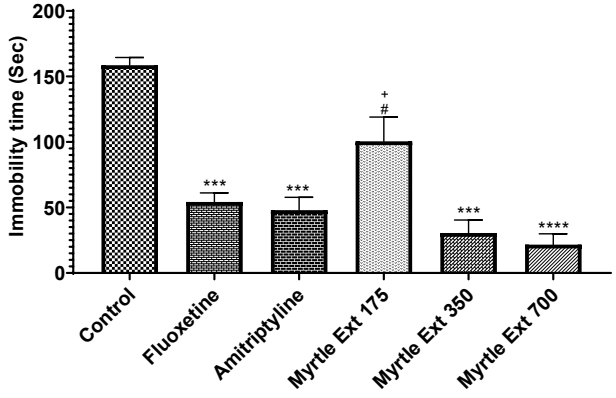

Figure 2. Effects of *Mentha piperita* Aqueous Extract (175 mg/kg, 350 mg/kg, and 700 mg/kg), Fluoxetine (Flu, 20 mg/kg), and Amitriptyline (Ami, 30 mg/kg) on the Duration of Immobility Time in FST. *Note*. FST: Forced swimming test; SD: Standard deviation. Data are indicated as means ± SD (n = 6). *** $P < 0.001$, **** $P < 0.0001$ compared with the control group. # $P < 0.05$ compared with the fluoxetine-treated group. + $P < 0.05$ compared with the imipramine-treated group

Discussion

In the present study, we used the TST as well as the FST to compare the effects of *Mentha piperita* aqueous extract

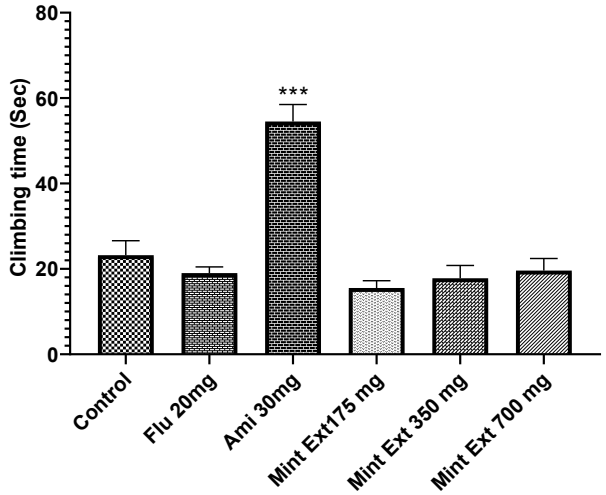

Figure 3. Effects of *Mentha piperita* Aqueous Extract (175 mg/kg, 350 mg/kg, and 700 mg/kg), Fluoxetine (Flu, 20 mg/kg), and Amitriptyline (Ami, 30 mg/kg) on the Duration of Climbing Time in FST. *Note*. FST: Forced swimming test; SD: Standard deviation. Data are expressed as means ± SD (n = 6). *** $P < 0.001$ compared with the control group

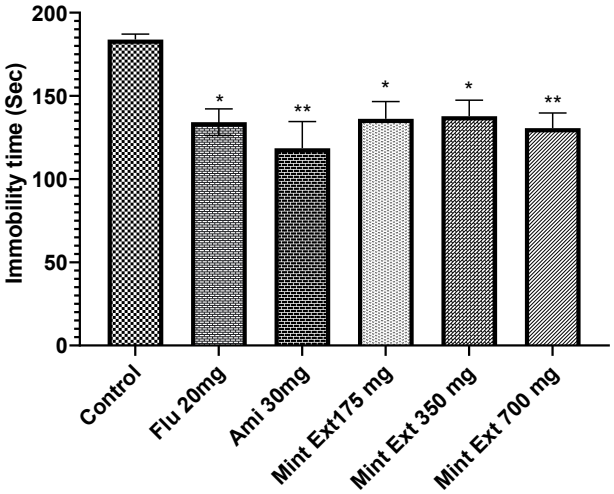

Figure 4. Effects of *Mentha piperita* Aqueous Extract (175 mg/kg, 350 mg/kg, and 700 mg/kg), Fluoxetine (Flu, 20 mg/kg), and Amitriptyline (Ami, 30 mg/kg) on the Duration of Immobility Time in TST. *Note*. TST: Tail suspension test; SD: Standard deviation. Data are presented as means ± SD (n = 6). * $P < 0.05$ and ** $P < 0.01$ compared with the control group

with imipramine (a standard tricyclic antidepressant) and fluoxetine (a selective serotonin reuptake inhibitor as a common antidepressant) on antidepressant-like behaviors such as immobility and swimming in mice.

The FST is the most widely used paradigm of antidepressant screening in mice and rats. A significant relationship has been demonstrated between the effectiveness and efficacy of an agent and a FST (34). FST is sensitive to a broad range of antidepressant agents and can differentiate between antidepressants and medications not aimed at managing depression (e.g., benzodiazepines), primarily antianxiety or neuroleptic agents (35-37). The TST is another animal model for estimating the anti-depression effects of chemical and herbal agents in rodents (37). TST has higher pharmacological sensitivity and is less stressful than FST (38). Several studies have proven that climbing is sensitive to drugs with selective effects on noradrenergic transmissions such as imipramine (39) and other TCAs . At the same time, swimming is sensitive to serotonergic agents such as fluoxetine and other selective serotonin reuptake inhibitors (40). The results of our study revealed that fluoxetine reduced the immobility time and increased the swimming time but did not affect the climbing time. Nonetheless, imipramine increased the climbing time without significantly changing the swimming time (41). In the present study, all doses of the aqueous extract of *M. piperita* compared with the control group significantly reduced immobility time (a posture thought to reflect a state of "behavior despair" in which animals have given up the hope to escape) of mice exposed to TST. However, only 350 mg/kg and 700 mg/kg of the *Mentha* extract could insignificantly reduce immobility time in FST compared to the control group.

On the other hand, all doses of the *Mentha* extract increased swimming time in comparison to the control group, but 350 mg/kg and 700 mg/kg of the extract increased swimming time more pronouncedly than the imipramine group. The other part of our study demonstrated that the climbing behavior did not significantly enhance compared to our control group. Therefore, according to the results of our research, the behavior pattern that is induced by the aqueous extract of *M. piperita* is similar to serotonergic medications such as fluoxetine (immobility time reduction and swimming time enhancement) while different from noradrenergic agents, similar to amitriptyline (an increase in climbing time but no change in swimming duration). Although the exact mechanism of the antidepressant effect of *M. piperita* has not been established, consistent with the results of other studies and our findings, serotonergic neurotransmission has a vital role in the antidepressant-like activity of Mentha.

Several studies reported that *M. piperita* aqueous extract consists of several active compounds, which may be responsible for antidepressant effects.

The phytochemistry of *M. piperita* has shown several ingredients such as terpenoids, steroids, phenols, flavonoids, and alkaloids (42). Menthol is the most crucial compound in peppermint (the essential oil) (43), and many biological and pharmacological properties of peppermint are assumed to be related to menthol (44), which is a monoterpene, and previous studies have confirmed its anti-inflammatory and analgesic effects (45). Menthol is also an antioxidant; one study revealed that antioxidants have antidepressant effects (41). On the other hand, the other demonstrated that antioxidants could inhibit 5-HT reuptake (46), which could increase 5-HT in synaptic clefts and desensitize the 5-HT receptors involved in depression. The other significant components of peppermint are menthone (a monoterpene), 1,8-cineole (a terpene), and linolenic acid, which, based on their antioxidant properties, may demonstrate antidepressant effects (47).

Conclusion

In general, the results of our study showed that *M. piperita* might have potential therapeutic applications in depressive disorders, and its effect is comparable with fluoxetine. However, further studies are required to determine the exact antidepressant mechanism of *M. piperita* and to find and extract the active ingredient responsible for this pharmacological property of *M. piperita*.

Acknowledgments

This study is extracted from a Doctor of Pharmacy thesis (IR.IAU.PS.REC.1400,291) submitted to the Pharmacy Faculty, Tehran Medical Sciences Islamic Azad University, Tehran, Iran. The authors are grateful to Tehran Chemie Pharmaceutical Company and Dr. Nima Naderi for providing fluoxetine and amitriptyline pure powders, respectively.

Authors' Contribution

xxx

Conceptualization:
Data curation:
Formal analysis:
Funding acquisition:
Investigation:
Methodology:
Project administration:
Resources:
Software:
Supervision:
Validation:
Visualization:
Writing–original draft:
Writing–review & editing:

Competing Interests

None.

Ethical Approval

This study was approved by the Research Ethics Board at Islamic Azad Tehran Medical Sciences University (IR.IAU.PS.REC.1400.291).

Funding

xxx

References

1. Salehi A, Rabiei Z, Setorki M. Antidepressant effects of

hydroalcoholic extract of *Alpinia officinarum* rhizome on chronic unpredictable stress induced depression in BALB/c mice. J Med Plants. 2020;19(73):170-9. doi: 10.29252/jmp.1.73.170.
2. Namjou A, Yazdani N, Abbasi E, Rafieian-Kopaei M. The antidepressant activity of *Matricaria chamomilla* and *Melissa officinalis* ethanolic extracts in non-reserpinized and reserpinized BALB/c mice. Jundishapur J Nat Pharm Prod. 2018;13(4):e65549. doi: 10.5812/jjnpp.65549.
3. Khalid L, Rizwani GH, Sultana V, Zahid H, Khursheed R, Shareef H. Antidepressant activity of ethanolic extract of *Hibiscus rosa sinenesis* Linn. Pak J Pharm Sci. 2014;27(5):1327-31.
4. Sheffler ZM, Patel P, Abdijadid S. Antidepressants. In: StatPearls. Treasure Island, FL: StatPearls Publishing; 2022.
5. Citrome L, McEvoy JP, Saklad SR. Guide to the management of clozapine-related tolerability and safety concerns. Clin Schizophr Relat Psychoses. 2016;10(3):163-77. doi: 10.3371/1935-1232.10.3.163.
6. Clayton A, Keller A, McGarvey EL. Burden of phase-specific sexual dysfunction with SSRIs. J Affect Disord. 2006;91(1):27-32. doi: 10.1016/j.jad.2005.12.007.
7. Oehrberg S, Christiansen PE, Behnke K, Borup AL, Severin B, Soegaard J, et al. Paroxetine in the treatment of panic disorder. A randomised, double-blind, placebo-controlled study. Br J Psychiatry. 1995;167(3):374-9. doi: 10.1192/bjp.167.3.374.
8. Bet PM, Hugtenburg JG, Penninx BW, Hoogendijk WJ. Side effects of antidepressants during long-term use in a naturalistic setting. Eur Neuropsychopharmacol. 2013;23(11):1443-51. doi: 10.1016/j.euroneuro.2013.05.001.
9. Arroll B, Macgillivray S, Ogston S, Reid I, Sullivan F, Williams B, et al. Efficacy and tolerability of tricyclic antidepressants and SSRIs compared with placebo for treatment of depression in primary care: a meta-analysis. Ann Fam Med. 2005;3(5):449-56. doi: 10.1370/afm.349.
10. Li JM, Zhao Y, Sun Y, Kong LD. Potential effect of herbal antidepressants on cognitive deficit: pharmacological activity and possible molecular mechanism. J Ethnopharmacol. 2020;257:112830. doi: 10.1016/j.jep.2020.112830.
11. Osanloo N, Najafi-Abedi A, Jafari F, Javid F, Pirpiran M, Memar Jafari MR, et al. *Papaver rhoeas* L. hydroalcoholic extract exacerbates forced swimming test-induced depression in mice. Basic Clin Neurosci. 2016;7(3):195-202. doi: 10.15412/j.bcn.03070304.
12. Murlanova K, Cohen N, Pinkus A, Vinnikova L, Pletnikov M, Kirby M, et al. Antidepressant-like effects of a chlorogenic acid- and cynarine-enriched fraction from *Dittrichia viscosa* root extract. Sci Rep. 2022;12(1):3647. doi: 10.1038/s41598-022-04840-9.
13. Ng QX, Venkatanarayanan N, Ho CY. Clinical use of *Hypericum perforatum* (St John's wort) in depression: a meta-analysis. J Affect Disord. 2017;210:211-21. doi: 10.1016/j.jad.2016.12.048.
14. Bent S, Padula A, Moore D, Patterson M, Mehling W. Valerian for sleep: a systematic review and meta-analysis. Am J Med. 2006;119(12):1005-12. doi: 10.1016/j.amjmed.2006.02.026.
15. Yuan H, Ma Q, Ye L, Piao G. The traditional medicine and modern medicine from natural products. Molecules. 2016;21(5):559. doi: 10.3390/molecules21050559.
16. Srivastava JK, Gupta S. Antiproliferative and apoptotic effects of chamomile extract in various human cancer cells. J Agric Food Chem. 2007;55(23):9470-8. doi: 10.1021/jf071953k.
17. Singh V, Amdekar S, Verma O. *Ocimum sanctum* (Tulsi): bio-pharmacological activities. Webmed Central Pharmacol. 2010;1(10):WMC001046.
18. Sarahroodi S. Self-medication: risks and benefits. Int J Pharmacol. 2012;8(1):58-9. doi: 10.3923/ijp.2012.58.59.
19. Sarahroodi S, Arzi A. Self-medication with antibiotics, is it a problem among Iranian college students in Tehran. J Biol Sci. 2009;9(8):829-32.
20. Sarahroodi S, Arzi A, Sawalha AF, Ashtarinezhad A. Antibiotics self-medication among Southern Iranian university students. Int J Pharmacol. 2010;6(1):48-52.
21. Sarahroodi S, Maleki-Jamshid A, Sawalha AF, Mikaili P, Safaeian L. Pattern of self-medication with analgesics among Iranian university students in central Iran. J Fam Community Med. 2012;19(2):125-9. doi: 10.4103/2230-8229.98302.
22. Arruda MO, Mendes SJ, Teixeira SA, de Mesquita LS, de Sousa Ribeiro MN, de Sousa Lima Galvão S, et al. The hydroalcoholic extract obtained from *Mentha piperita* L. leaves attenuates oxidative stress and improves survival in lipopolysaccharide-treated macrophages. J Immunol Res. 2017;2017:2078794. doi: 10.1155/2017/2078794.
23. Ghorbani M, Movahedi Z, Kheiri A, Rostami M. Effect of salinity stress on some morpho-physiological traits and quantity and quality of essential oils in peppermint (*Mentha piperita* L.). Environmental Stresses in Crop Sciences. 2018;11(2):413-20. doi: 10.22077/escs.2018.953.1188.
24. Aqil F, Beg AZ, Ahmad I. In vitro toxicity of plant essential oils against soil fungi. J Med Aromat Plant Sci. 2000;22-23:177-81.
25. Lirio LG, Hermano ML, Fontanilla MQ. Note antibacterial activity of medicinal plants from the Philippines. Pharm Biol. 1998;36(5):357-9. doi: 10.1076/phbi.36.5.357.4656.
26. Vuković-Gačić B, Simić D. Identification of natural antimutagens with modulating effects on DNA repair. In: Bronzetti G, Hayatsu H, De Flora S, Waters MD, Shankel DM, eds. Antimutagenesis and Anticarcinogenesis Mechanisms III. Boston, MA: Springer; 1993. p. 269-77. doi: 10.1007/978-1-4615-2984-2_25.
27. Samman MA, Bowen ID, Taiba K, Antonius J, Hannan MA. Mint prevents shamma-induced carcinogenesis in hamster cheek pouch. Carcinogenesis. 1998;19(10):1795-801. doi: 10.1093/carcin/19.10.1795.
28. Bellassoued K, Ben Hsouna A, Athmouni K, van Pelt J, Makni Ayadi F, Rebai T, et al. Protective effects of *Mentha piperita* L. leaf essential oil against CCl4 induced hepatic oxidative damage and renal failure in rats. Lipids Health Dis. 2018;17(1):9. doi: 10.1186/s12944-017-0645-9.
29. Sun Z, Wang H, Wang J, Zhou L, Yang P. Chemical composition and anti-inflammatory, cytotoxic and antioxidant activities of essential oil from leaves of *Mentha piperita* grown in China. PLoS One. 2014;9(12):e114767. doi: 10.1371/journal.pone.0114767.
30. de Sousa AA, Soares PM, de Almeida AN, Maia AR, de Souza EP, Assreuy AM. Antispasmodic effect of *Mentha piperita* essential oil on tracheal smooth muscle of rats. J Ethnopharmacol. 2010;130(2):433-6. doi: 10.1016/j.jep.2010.05.012.
31. McKay DL, Blumberg JB. A review of the bioactivity and potential health benefits of peppermint tea (*Mentha piperita* L.). Phytother Res. 2006;20(8):619-33. doi: 10.1002/ptr.1936.
32. Inoue T, Sugimoto Y, Masuda H, Kamei C. Antiallergic effect of flavonoid glycosides obtained from *Mentha piperita* L. Biol Pharm Bull. 2002;25(2):256-9. doi: 10.1248/bpb.25.256.
33. da Silva GD, Matteussi AS, dos Santos AR, Calixto JB, Rodrigues AL. Evidence for dual effects of nitric oxide in the forced swimming test and in the tail suspension test in mice. Neuroreport. 2000;11(17):3699-702. doi: 10.1097/00001756-200011270-00022.
34. Porsolt RD, Le Pichon M, Jalfre M. Depression: a new animal model sensitive to antidepressant treatments. Nature. 1977;266(5604):730-2. doi: 10.1038/266730a0.
35. Reinhold JA, Mandos LA, Rickels K, Lohoff FW. Pharmacological treatment of generalized anxiety disorder. Expert Opin Pharmacother. 2011;12(16):2457-67. doi: 10.1517/14656566.2011.618496.
36. Borsini F, Meli A. Is the forced swimming test a suitable model

for revealing antidepressant activity? Psychopharmacology (Berl). 1988;94(2):147-60. doi: 10.1007/bf00176837.
37. Cryan JF, Holmes A. The ascent of mouse: advances in modelling human depression and anxiety. Nat Rev Drug Discov. 2005;4(9):775-90. doi: 10.1038/nrd1825.
38. Thierry B, Stéru L, Simon P, Porsolt RD. The tail suspension test: ethical considerations. Psychopharmacology (Berl). 1986;90(2):284-5. doi: 10.1007/bf00181261.
39. Detke MJ, Rickels M, Lucki I. Active behaviors in the rat forced swimming test differentially produced by serotonergic and noradrenergic antidepressants. Psychopharmacology (Berl). 1995;121(1):66-72. doi: 10.1007/bf02245592.
40. Page ME, Detke MJ, Dalvi A, Kirby LG, Lucki I. Serotonergic mediation of the effects of fluoxetine, but not desipramine, in the rat forced swimming test. Psychopharmacology (Berl). 1999;147(2):162-7. doi: 10.1007/s002130051156.
41. Shahamat Z, Abbasi-Maleki S, Mohammadi Motamed S. Evaluation of antidepressant-like effects of aqueous and ethanolic extracts of *Pimpinella anisum* fruit in mice. Avicenna J Phytomed. 2016;6(3):322-8.
42. Singh R, Shushni MA, Belkheir A. Antibacterial and antioxidant activities of *Mentha piperita* L. Arab J Chem. 2015;8(3):322-8. doi: 10.1016/j.arabjc.2011.01.019.
43. Skalicka-Woźniak K, Walasek M. Preparative separation of menthol and pulegone from peppermint oil (*Mentha piperita* L.) by high-performance counter-current chromatography. Phytochem Lett. 2014;10:xciv-xcviii. doi: 10.1016/j.phytol.2014.06.007.
44. Spirling LI, Daniels IR. Botanical perspectives on health peppermint: more than just an after-dinner mint. J R Soc Promot Health. 2001;121(1):62-3. doi: 10.1177/146642400112100113.
45. Kamatou GP, Vermaak I, Viljoen AM, Lawrence BM. Menthol: a simple monoterpene with remarkable biological properties. Phytochemistry. 2013;96:15-25. doi: 10.1016/j.phytochem.2013.08.005.
46. Weinstock M, Poltyrev T, Bejar C, Youdim MB. Effect of TV3326, a novel monoamine-oxidase cholinesterase inhibitor, in rat models of anxiety and depression. Psychopharmacology (Berl). 2002;160(3):318-24. doi: 10.1007/s00213-001-0978-x.
47. Abbasi Maleki S, Bakhtiarian A, Nikoui V. The antidepressant-like effect of the ethanolic extract of *Mentha piperita* in forced swimming test and tail suspension test in male mice. J Ilam Univ Med Sci. 2018;26(4):34-42. doi: 10.29252/sjimu.26.4.34. [Persian].