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Evaluation of the antidepressant potential of bavachinin in male mice

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ABSTRACT

Background: Major depressive disorder (MDD) is a highly prevalent and disabling psychiatric condition, and current pharmacotherapies are often limited by delayed onset of action and adverse effects. Natural compounds with antidepressant potential, such as bavachinin, a flavanone derived from *Psoralea corylifolia*, may represent promising alternatives.

Objective: This study evaluated the antidepressant-like effects of bavachinin in a mouse model of depression.

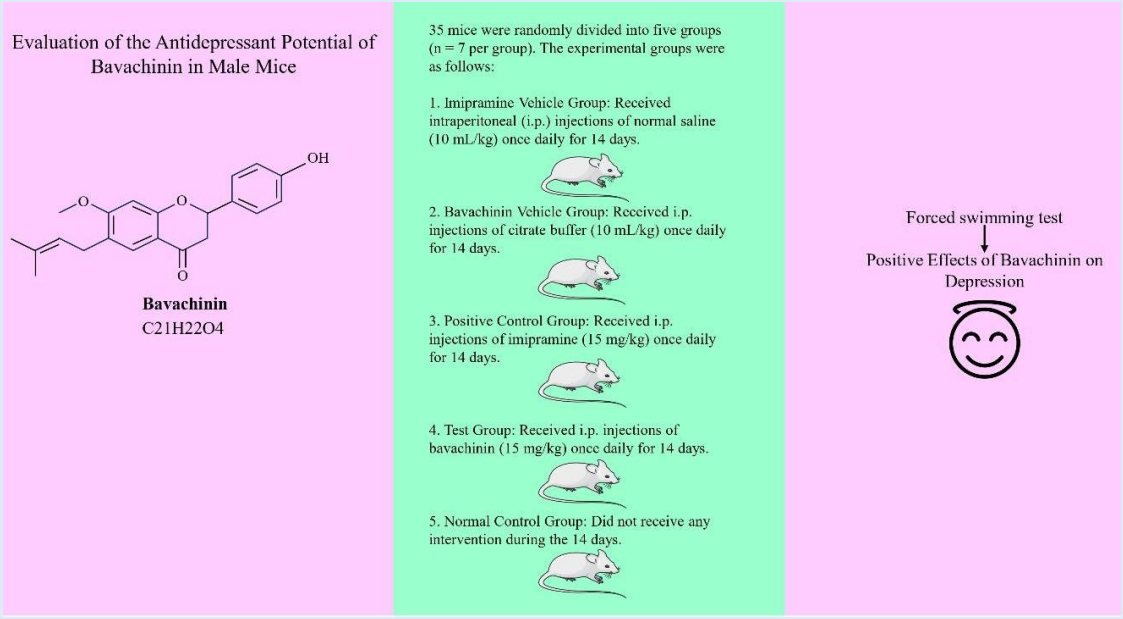
Methods: Thirty-five adult male mice were randomly assigned to five groups (n = 7): standard control, imipramine vehicle, bavachinin vehicle, imipramine (15 mg/kg), and bavachinin (15 mg/kg). Treatments were administered intraperitoneally for 14 days. Antidepressant activity was assessed using the forced swimming test (FST), and immobility time was compared across groups using one-way ANOVA followed by Tukey's post hoc test.

Results: Bavachinin (15 mg/kg) significantly reduced immobility time compared to the normal control group ($p = 0.0356$), indicating an antidepressant-like effect. The reduction in immobility was comparable to that observed with the standard antidepressant imipramine (15 mg/kg), with no significant difference between the two groups ($p = 0.6770$).

Novelty of study: This study is one of the first experimental investigations to evaluate the antidepressant-like effects of bavachinin, a bioactive compound from *Psoralea corylifolia*, in an animal model of depression. By directly comparing bavachinin with the standard antidepressant imipramine in the forced swimming test, it provides evidence that bavachinin exerts a comparable reduction in immobility time. This highlights bavachinin as a promising natural candidate for antidepressant therapy, addressing the gap in safe and effective alternatives to synthetic drugs.

Conclusion: Bavachinin demonstrated significant antidepressant-like activity in mice, comparable to imipramine. The potential mechanisms may involve monoamine oxidase (MAO) inhibition and/or peroxisome proliferator-activated receptor (PPAR) activation. These findings suggest that bavachinin may serve as a promising natural candidate for future antidepressant development. Further research with extended protocols and mechanistic evaluations is warranted.

Keywords: Bavachinin; Antidepressant-like effects; Forced swim test; Male mice; Monoamine oxidase inhibition; PPAR activation; Flavanone compound; Immobility time.



Graphical Abstract: Evaluation of the antidepressant potential of bavachinin in male mice

INTRODUCTION

Major Depressive Disorder (MDD) is a prevalent mental illness that impacts around 185 million individuals worldwide [1]. The World Health Organization (WHO) ranked it as the third leading cause of disease burden globally in 2008 and has predicted that it will rise to the top by 2030 [2].

It is diagnosed when an individual has a persistently low or depressed mood, anhedonia or loss of interest in pleasurable activities, feelings of guilt or worthlessness, lack of energy, poor concentration, appetite changes, psychomotor retardation or agitation, sleep disturbances, or suicidal ideation. To be diagnosed with MDD, an individual must have five of the symptoms listed

above, one of which must be depressed mood or anhedonia, causing social or occupational impairment. Moreover, a history of manic or hypomanic episodes must be excluded. Children and adolescents with MDD may exhibit an irritable mood [3].

MDD can be addressed through multiple treatment approaches, such as medication, psychotherapy, interventions, and lifestyle changes. The first line of treatment for MDD typically involves medication, psychotherapy, or a combination of both therapies. Research has shown that combining medication with psychotherapy is often more effective than using either treatment alone [4,5]. Electroconvulsive therapy is more effective than any other treatment method for severe major depression [6]. Medications approved by the FDA for managing MDD include the following: all antidepressants have similar effectiveness but vary in their side effects. Selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), serotonin modulators, atypical antidepressants, tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), and additional medications, such as mood stabilizers and antipsychotics, can be included to boost the effects of antidepressants [3]. However, patients frequently do not follow synthetic antidepressant regimens because of adverse effects or notable delays in effectiveness. Serious side effects associated with synthetic antidepressants include headaches, erectile dysfunction, addiction, seizures, and suicidal thoughts [7].

Research is also being conducted on herbal medications, which are well-known for having fewer adverse effects and being more cost-effective. Consequently, owing to their broad spectrum of therapeutic benefits, medicinal plants have attracted considerable attention worldwide as adjuncts to existing medications or even as alternative treatments for depression [8]. Approximately 16–44% of individuals with mental diseases take complementary and alternative therapies, and the vast majority of them experience depression [9].

Bavachinin (BVC) is a natural small molecule found in the Chinese plant Fructus psoraleae. Its pharmacological actions are extensive and include anti-inflammatory, antioxidant, antibacterial, antiviral, immunomodulatory, and anticancer activities [10]. However, its effects and mechanisms in the treatment of MDD remain unclear. Previous studies have suggested that bavachinin may exert antidepressant effects through pathways involving competitive MAO-B inhibitory effects [11].

This study aimed to investigate the antidepressant effects of bavachinin in a male mouse model of depression. Depression in mice was assessed by measuring their immobility time in the forced swimming test (FST).

MATERIALS AND METHODS

Animals and Experimental Design: This experimental study was conducted on 35 adult male mice (weighing 20–30 grams). All animals were housed under standard laboratory conditions (12-hour light/dark cycle, temperature maintained at 23±1°C, and relative humidity of 45–55%). Mice were acclimated to laboratory conditions before the experiment began. Animals were housed in plastic cages with metal lids. Animals had ad libitum access to a standard pellet diet and tap water delivered via specialized drinking bottles. Bedding consisted of wood shavings, and cages were cleaned and disinfected with ethanol twice a week. Mice were euthanized humanely at the end of the study, and carcasses were disposed of in a dedicated animal waste burial site. The Qazvin University of Medical Sciences Research Ethics Committee gave its approval to this study

(Ethics Code: IR.QUMS.REC.1400.034), and it complies with EU Directive 2010/63/EU on animal experiments.

After an acclimatization period, 35 mice were randomly assigned to 5 groups (n = 7 per group). Bavachinin (15 mg/kg) and imipramine (15 mg/kg) were administered intraperitoneally (i.p.) once daily for 14 consecutive days. The dosages were selected based on previous literature [12-14]. The experimental groups were as follows:

1. Imipramine Vehicle Group: Received intraperitoneal (i.p.) injections of normal saline (10 mL/kg) once daily for 14 days.
2. Bavachinin Vehicle Group: Received i.p. injections of citrate buffer (10 mL/kg) once daily for 14 days.
3. Positive Control Group: Received i.p. injections of imipramine (15 mg/kg) once daily for 14 days.
4. Test Group: Received i.p. injections of bavachinin (15 mg/kg) once daily for 14 days.
5. Normal Control Group: Did not receive any intervention during the 14 days.

Forced Swimming Test (FST); On day 14, antidepressant-like activity was assessed using the Forced Swimming Test. Each mouse was placed individually into a transparent glass container (25 cm length × 12 cm width × 8 cm height) filled with water at 25°C. Mice were gently released into the water from a height of 20 cm. The test lasted 6 minutes: the first 2 minutes were for acclimatization, and immobility was recorded for the last 4 minutes using a stopwatch. Immobility was defined as the absence of limb movements except those necessary to keep the animal's head above water. The test was conducted one hour after the last drug or vehicle administration [15].

Statistical Analysis: Statistical analysis was performed using SPSS software version 25. One-way analysis of variance (ANOVA) was used to compare group means. When significant differences were observed, the Tukey-Kramer post hoc test was applied for pairwise comparisons. A p-value < 0.05 was considered statistically significant.

RESULTS

A total of 35 adult male mice were randomly assigned to five groups (n = 7 per group) and subjected to the FST on day 14. The mean immobility time for each group is presented below. There has been a significant difference between the bavachinin group and the normal group ($p < 0.05$) and the imipramine group and the normal group ($p < 0.01$).

- Normal Control Group: 172.9
- Imipramine Vehicle Group: 170.0
- Bavachinin Vehicle Group: 166.6
- Imipramine (15 mg/kg) Group: 98.4
- Bavachinin (15 mg/kg) Group: 121.0

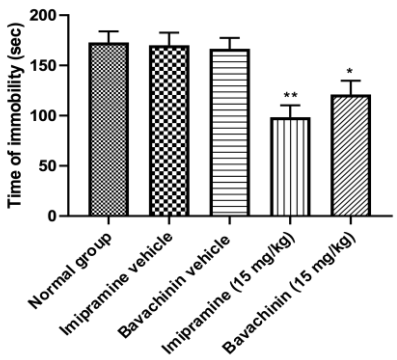


Figure 1. A bar graph comparing the average immobility time of the groups.

Table 2 compares the average immobility time (in seconds) between every pair of groups. Both imipramine (15 mg/kg) and bavachinin (15 mg/kg) show much lower immobility time than controls and vehicles.

Table 2. Comparison of the average immobility time of mice in different groups.

Test Details	Mean(1)	Mean(2)	Mean Diff.	Q
Normal group vs. Imipramine vehicle	172.9	170	2.857	0.2357
Normal group vs. Bavachinin vehicle	172.9	166.6	6.286	0.5226
Normal group vs. Imipramine (15 mg/kg)	172.9	98.43	74.43	6.188
Normal group vs. Bavachinin (15 mg/kg)	172.9	121	51.86	4.311
Imipramine vehicle vs. Bavachinin vehicle	170	166.6	3.429	0.2850
Imipramine vehicle vs. Imipramine (15 mg/kg)	170	98.43	71.57	5.950
Imipramine vehicle vs. Bavachinin (15 mg/kg)	170	121	49.00	4.074
Bavachinin vehicle vs. Imipramine (15 mg/kg)	166.6	98.43	68.14	5.665
Bavachinin vehicle vs. Bavachinin (15 mg/kg)	166.6	121	45.57	3.789
Imipramine (15 mg/kg) vs. Bavachinin (15mg/kg)	98.43	121	-22.57	1.877

Table 3 presents the results of Tukey's multiple-comparison test, which assesses the statistical significance of differences in immobility time across experimental groups. The analysis shows that both imipramine (15 mg/kg) and bavachinin (15 mg/kg) produced a significant reduction in immobility time compared with the normal control group ($p = 0.0012$ and $p = 0.0356$, respectively), confirming their antidepressant-like effects in the Forced Swimming Test. Moreover, the difference between bavachinin and imipramine was not statistically significant ($p = 0.6770$), suggesting that bavachinin exerts an antidepressant effect comparable to the standard drug.

Table 3. Comparison of the mean immobility time of mice using Tukey's multiple comparison test.

Tukey's multiple comparisons test	95.00% CI of Diff.	Adjusted P value	Below Threshold?
Normal group Vs. Imipramine vehicle	-46.48 to 52.20	0.9998	No
Normal group vs. Bavachinin vehicle	-43.05 to 55.63	0.9958	No
Normal group vs. Imipramine (15 mg/kg)	25.09 to 123.8	0.0012	Yes
Normal group vs. Bavachinin (15 mg/kg)	2.517 to 101.2	0.0356	Yes
Imipramine vehicle vs. Bavachinin vehicle	-45.91 to 52.77	0.9996	No
Imipramine vehicle vs. Imipramine (15 mg/kg)	22.23 to 120.9	0.0019	Yes
Imipramine vehicle vs. Bavachinin (15 mg/kg)	-0.3406 to 98.34	0.0523	No
Bavachinin vehicle vs. Imipramine (15 mg/kg)	18.80 to 117.5	0.0032	Yes
Bavachinin vehicle vs. Bavachinin (15 mg/kg)	-3.769 to 94.91	0.0812	No
Imipramine (15 mg/kg) vs. Bavachinin (15 mg/kg)	-71.91 to 26.77	0.6770	No

DISCUSSION

According to the Global Burden of Disease (GBD) 2019 report, depressive disorders came in at number 13 among the top 25 causes of disability-adjusted life years (DALYs) [16]. Both the pathogenic causes of MDD and the mechanisms underlying the effects of pharmaceutical therapies for MDD are intricate and poorly understood [17]. Depression is a complex disorder influenced by both genetic and environmental factors [18]. Antidepressant drugs primarily enhance monoamine neurotransmission by targeting serotonin, norepinephrine, and dopamine. They achieve this through multiple mechanisms: inhibiting the reuptake of these neurotransmitters (as with TCAs, SSRIs, and SNRIs), preventing their breakdown in presynaptic neurons (as with MAOIs), increasing their release (e.g., mirtazapine), or acting directly on their receptors (e.g., agomelatine). These actions increase postsynaptic receptor stimulation, compensating for the neurophysiological deficits associated with depression, thereby improving synaptic signaling and alleviating depressive symptoms [19]. Despite the availability of pharmacological therapies, only 60% of patients with depression respond well to them; the remaining patients endure adverse effects that force them to stop taking their medication [20].

Both psychological and pharmaceutical therapies are evidence-based treatments for depression. SSRIs are typically used as the first line of treatment because they are safer and better tolerated than other antidepressants. If SSRIs do not work, the treatment plan may need to try another SSRI or move to a different class of antidepressants, such as MAOI, TCA, or SNRI [21]. Considering the widespread nature and significant impact of depression, many researchers have undertaken various studies to enhance our understanding of the onset, persistence, and management of depressive episodes.

The benefits of treating depression with Traditional Chinese Medicine (TCM) include high feasibility, good tolerance, precise results, and minimal side effects. Additionally, TCM's broad therapeutic expertise and overall concept of the unification of nature and man make it a promising treatment for depression [22]. Chinese herbal therapy offers more benefits than Western medication in the prevention and treatment of depression. These include multitargeting, high efficacy, low toxicity, few adverse effects, low drug resistance, and sustained efficacy. According to a systematic review, Chinese herbal medication was linked to fewer side effects than antidepressants [23].

Additionally, numerous studies have demonstrated that Chinese herbal therapy may prevent depression in its early stages [24]. Consequently, Chinese herbal medicine may be considered an alternative to antidepressants [25]. Recent reviews highlight the growing therapeutic potential of bioactive compounds such as polyphenols and flavonoids, which offer multifunctional benefits. This highlights their promise in the context of depression management [26].

Psoralea corylifolia L. (Leguminosae) has been used as a traditional medicinal plant to treat various illnesses since ancient times. It is extensively available and frequently used in Chinese and Ayurvedic medicine [27]. Psoralea corylifolia seeds contain flavanone bavachinin [11]. In this study, we specifically examined the antidepressant effects of this compound.

Available safety data suggest that bavachinin appears to be largely safe at low doses. For example, a study by Nepal et al. showed that intraperitoneal injection of bavachinin up to 5 mg/kg (three times a week for four weeks) did not cause any noticeable side effects and did not change the body weight of mice [14]. However, more recent evidence has shown that

bavachinin can cause hepatotoxicity under pre-inflammatory conditions (e.g., in combination with LPS). Shi et al. showed that bavachinin can activate the inflammasome, and its combination with LPS challenge in mice caused liver injury, whereas LPS or bavachinin alone had no effect [28].

The antidepressant properties of extracts of *Psoralea corylifolia* have been reported in several studies. For instance, Marzieh Sarbandi Farahani and colleagues described the mechanisms underlying its antidepressant effects and the active phytochemicals responsible. They highlighted psoralidin, a compound isolated from the seeds of *P. corylifolia*, which exerts its effects partly by modulating the hypothalamic–pituitary–adrenal (HPA) axis [29]. Furthermore, Psoralidin has demonstrated a favorable impact in the forced swim test in a mouse model of depression. Psoralidin administration resulted in changes in dopamine levels and a significant increase in 5-hydroxyindole acetic acid and 5-hydroxytryptamine levels in the brain. Psoralidin decreased the levels of three hormones involved in stress regulation in mice: serum corticosterone, adrenal corticotropin-releasing hormone, and corticotropin-releasing factor [30]. Furocoumarins have been shown to possess antidepressant properties in another investigation using mouse models. In this study, the seed extract of P. corylifolia was compared with well-known antidepressants. In contrast to amitriptyline (10 and 20 mg/kg) and fluoxetine (13 mg/kg), the dose range utilized was 7.5–100 mg/kg [31]. In the present study, we used imipramine, which has a proven antidepressant effect, as a positive control.

Bavachinin was reported to have pan-PPAR agonist activity. Peroxisome proliferator-activated receptor (PPARs) agonists have become important targets for the treatment of metabolic syndrome because they help regulate the metabolism of glucose, lipids, and cholesterol. In another study, five scaffold-hopping analogs of bavachinin, three isoflavanones, and five isoflavones were created, synthesized, and assessed for pan-PPAR agonist activity using reporter gene assays. The pan-PPAR agonist 2-(4-hydroxyphenyl)-6-isopentenyl-7-methoxy-2,3-dihydroquinolin-4(1H)-one (21) was shown to have equal PPAR-γ agonist activity and significantly more vigorous PPAR α/β agonist activity than bavachinin [32]. Bavachinin has been reported to exhibit peroxisome proliferator-activated receptor-γ (PPAR-γ) agonist activity [33]. Bavachinin has been shown to activate PPARγ, leading to the death of non-small cell lung cancer cells. This action is mediated by elevated ROS level [34].

As previously mentioned, several studies have suggested that stimulation of PPARs can have antidepressant effects; therefore, PPAR agonists can be used to treat depression. This study also highlighted that the PPAR agonist action of bavachinin could be the mechanism underlying its antidepressant effects. For instance, a study by R. Colle et al. highlighted the potential value of PPAR gamma agonists in treating major depressive episodes [35]. Another study tested whether pioglitazone, an insulin-sensitizing PPAR-γ agonist, could reduce depressive symptoms in 34 patients with bipolar depression and insulin resistance who did not respond adequately to mood stabilizers. Over 8 weeks of adjunctive treatment, patients showed significant improvements in depressive and anxiety symptoms, daily functioning, and insulin sensitivity. Higher baseline inflammation (IL-6 levels) predicted greater symptom improvement, and reductions in IL-6 correlated with mood improvement, suggesting that pioglitazone may alleviate depression, partly by improving metabolic health and reducing inflammation [36]. Another study reviewed eight clinical trials (four open-label and four randomized controlled) involving 448 patients with major depression to evaluate the antidepressant effects of PPAR-γ agonists (pioglitazone or rosiglitazone). Patients received these agents for 6–12 weeks, either alone or as

an add-on therapy. The results showed that PPAR-γ agonists produced antidepressant effects in all open-label trials and in 3 of 4 randomized controlled trials, with no significant adverse events reported. Improvements in depressive symptoms are linked to better insulin resistance markers and reduced inflammation (notably lower IL-6 levels), suggesting that PPAR-γ agonists may help treat depression by targeting metabolic dysfunction and inflammation [35]. Another study indicated that pioglitazone, as a PPARγ agonist, exerted antidepressant-like and neuroprotective effects in rats. In the LPS-induced model, which mimics inflammation-related depression and cognitive impairment, pioglitazone (20–30 mg) improved learning and memory performance, reduced pro-inflammatory cytokine levels (IL-6 and TNF-α), lowered oxidative stress markers, and increased antioxidant defenses, IL-10, and BDNF levels in the hippocampus. These findings suggest that pioglitazone may alleviate depression-related symptoms by reducing inflammation and oxidative stress while enhancing neurotrophic support [37].

It has been shown that total furocoumarins of *Psoralea corylifolia* (TFPC) exert antidepressant-like effects in a chronic mild stress mouse model. TFPC treatment reversed behavioral deficits, such as reduced sucrose intake, and normalized stress-induced biochemical changes, including increased MAO-A and MAO-B activities, elevated cortisol levels, and oxidative stress markers (SOD and MDA). These findings suggest that the antidepressant activity of TFPC may be mediated through the regulation of the MAO system, HPA axis, and oxidative pathways, supporting its potential as a therapeutic option for depression [38]. Moreover, in another study, bavachinin, a selective and competitive human MAO-B inhibitor, showed much more potent inhibition of hMAO-B than hMAO-A, analog, bavachin, had activating effects. Bavachinin effectively reduced hMAO-B activity with an IC50 of ~8.82 µM, competitively inhibited hMAO-B with a Ki much lower than that of hMAO-A, and exhibited an inhibition efficiency comparable to that of the standard drug selegiline. Molecular docking studies suggested that the C7-methoxy group of bavachinin contributes to its high affinity, selectivity, and reversible inhibition. These results indicate that BNN could serve as a potent and selective MAO-B inhibitor [11]. Inhibition of MAO-A and MAO-B has long been known as a mechanism of antidepressant action, and MAO inhibitor drugs are currently used to treat depression. Bavachinin also exerts inhibitory effects on MAO-A and MAO-B, as demonstrated in the studies above. Considering the results obtained from the present study showing the antidepressant effect of bavachinin and previous studies conducted on this subject, the antidepressant effect of bavachinin on mice may be caused by the mechanism of MAO inhibition.

Bavachinin can be viewed as one of many dietary bioactives studied for mood regulation. For example, saffron's bioactive constituents (crocin, precrocin, safranal, etc.) have been shown to positively modulate central nervous system pathways involved in anxiety and depression [39]. Likewise, daily intake of Hibiscus sabdariffa (roselle) juice for one week significantly improved mood in a controlled trial [40]. Even common foods rich in antioxidants and polyphenols – such as peanuts and other nuts – are being evaluated for cognitive and emotional benefits [41]. More complex nutritional interventions have also shown promise: one study found that a combined regimen of probiotics, prebiotics, and plant phytonutrients markedly reshaped the gut–brain axis and reduced depressive symptoms (negative mood scores fell by ~38%) in healthy adults [42]. In a similar vein, dietary micronutrients like zinc are under investigation as adjunctive treatments to enhance antidepressant efficacy [43]. Together, these examples illustrate how functional food and supplement strategies

can influence mood and depression. Overall, according to the results of our study, bavachinin may have antidepressant effects and could be used as a first-line or complementary treatment for depression in the future. Based on existing studies, the mechanism of the antidepressant effect of this substance could be via agonism of PPAR, especially PPAR gamma, or via inhibition of MAO.

Limitations of our study include the use of only the FST as a single behavioral paradigm without incorporating additional complementary behavioral or cognitive assessments. For example, the chronic unpredictable stress model (CUMS), tail suspension test, and sucrose preference test have been used in the literature to assess depressive symptoms. The short treatment duration (14 days), which limits understanding of long-term efficacy and safety, the high cost of preparing bavachinin and its limited access, and the small sample size are other limitations. Moreover, only one dose (15 mg/kg) was tested, and the response at different doses in the FST is necessary to determine the dose-response relationship. Finally, although we hypothesized in the discussion that the possible antidepressant effects of bavachinin may be mediated by MAO inhibition or PPAR-γ activation, no biochemical assays (in vitro or in vivo) were performed to measure MAO activity or PPAR-γ signaling in this study directly. Therefore, these mechanisms are currently hypothetical and require further studies.

Scientific Innovation and Practical Implications: Our findings advance current understanding of natural antidepressant agents by showing that bavachinin exhibits significant antidepressant-like effects, potentially mediated by MAO inhibition and/or PPAR activation. This positions bavachinin as both a mechanistically interesting compound for future pharmacological research and a potential candidate for the development of safer, plant-derived antidepressants. In practical terms, bavachinin may serve as a complementary or alternative therapy for patients intolerant to conventional drugs, while also opening new avenues for translational research into novel molecular targets for depression treatment.

CONCLUSIONS

In summary, this study demonstrates that bavachinin produces antidepressant-like effects in male mice, with efficacy comparable to that of imipramine. These findings suggest that bavachinin could serve as a promising natural compound for the treatment of depression, likely through mechanisms involving PPAR activation or MAO inhibition. Further studies with larger sample sizes, extended treatment durations, and molecular analyses are warranted to confirm its mechanisms and therapeutic potential.

Abbreviations: MDD: Major depressive disorder; MAO: Monoamine oxidase; PPAR: Peroxisome proliferator-activated receptor; WHO: World Health Organization; SSRIs: Selective serotonin reuptake inhibitors; SNRIs: Serotonin–norepinephrine reuptake inhibitors; TCA: Tricyclic antidepressants; MAOIs: Monoamine oxidase inhibitors; BVC: Bavachinin; I.P.: Intraperitoneal; ANOVA: Analysis of variance; GBD: Global Burden of Disease; TCM: Traditional Chinese Medicine; TFPC: total furocoumarins of Psoralea corylifolia; DALY: Disability-adjusted life yea; CUMS: chronic unpredictable stress model

Conflict of Interest: The authors have no relevant financial or non-financial interests to disclose.

Ethics approval*:* The EU Directive 2010/63/EU for animal experimentation has been followed, and the procedures used were approved by the Ethics Committee on the application of animals in medical studies at Qazvin

University of Medical Sciences, Qazvin, Iran (IR.QUMS.REC.1400.034).

Authors' Contributions: S.G.: Writing – original draft, Investigation, Formal Analysis. F.A.: Writing – original draft, Writing – review & editing, Investigation. E.B: Writing – original draft, Writing – review & editing, Data curation. AN.M.: Writing – review & editing. Y.N.: Writing – review & editing, Supervision, Project administration, Conceptualization, Resources. All the authors commented on the previous manuscript versions. All authors have read and approved the final manuscript.

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REFERENCES

1. Marx W., Penninx B. W. J. H., Solmi M., Furukawa T. A., Firth J., Carvalho A. F., et al. Major depressive disorder. *Nat Rev Dis Primers*. 2023; 9(1): 44. DOI: https://doi.org/10.1038/s41572-023-00454-1
2. Malhi G. S., Mann J. J. Depression. *Lancet.* 2018; 392(10161): 2299–2312. DOI: https://doi.org/10.1016/S0140-6736(18)31948-2
3. Bains N., Abdijadid S. Major Depressive Disorder. https://www.ncbi.nlm.nih.gov/books/NBK559078/. Last Update: April 10, 2023
4. Cuijpers P., Dekker J., Hollon S. D., Andersson G. Adding psychotherapy to pharmacotherapy in the treatment of depressive disorders in adults: a meta-analysis. *J Clin Psychiatry.* 2009; 70(9):1219-1229. DOI: https://doi.org/10.4088/JCP.09r05021
5. Cuijpers P., van Straten A., Warmerdam L., Andersson G. Psychotherapy versus the combination of psychotherapy and pharmacotherapy in the treatment of depression: a meta-analysis. *Depress Anxiety.* 2009; 26(3):279-288. DOI: https://doi.org/10.1002/da.20519
6. Pagnin D., de Queiroz V., Pini S., Cassano G. B. Efficacy of ECT in depression: a meta-analytic review. *J ECT.* 2004; 20(1):13-20. DOI: https://doi.org/10.1097/00124509-200403000-00004
7. Bremner J. D. Isotretinoin and neuropsychiatric side effects: Continued vigilance is needed. *J Affect Disord Rep.* 2021; 6:100230. DOI: https://doi.org/10.1016/j.jadr.2021.100230
8. Khadanga M., Kar N. R., Sahoo N., Tripathy B. Recent advancements in digital and traditional treatment strategies for major depressive disorder using medicinal herbs. *Digital Chinese Medicine*. 2024; 7(4): 365-387. DOI: https://doi.org/10.1016/j.dcmed.2025.01.002
9. Kang D., Dong H., Shen Y., Ou J., Zhao, J. The clinical application of Chinese herbal medication to depression: A narrative review. *Front Public Health.* 2023; 11:1120683. DOI: https://doi.org/10.3389/fpubh.2023.1120683
10. Deng H., Jiang J., Shu J., Huang M., Zhang Q. L., Wu L. J., et al. Bavachinin Ameliorates Rheumatoid Arthritis Inflammation via PPARG/PI3K/AKT Signaling Pathway. *Inflammation.* 2023; 46(5):1981-1996. DOI: https://doi.org/10.1007/s10753-023-01855-w
11. Zarmouh N. O., Mazzio E. A., Elshami F. M., Messeha S. S., Eyunni S. V., Soliman K. F. Evaluation of the Inhibitory Effects of Bavachinin and Bavachin on Human Monoamine Oxidases A and B. *Evid Based Complement Alternat Med*. 2015; 2015:852194. DOI: https://doi.org/10.1155/2015/852194
12. Ferreira F. R., Oliveira A. M., Dinarte A. R., Pinheiro D. G., Greene L. J., Silva W. A., et al. Changes in hippocampal gene expression by 7-nitroindazole in rats submitted to forced swimming stress. *Genes Brain Behav*. 2012; 11(3):303-313. DOI: https://doi.org/10.1111/j.1601-183X.2011.00757.x
13. Campos-Cardoso R., Silva C. P. B., Carolino R. O. G., Anselmo-Franci J. A., Tirapelli C. R., Padovan C. M. Imipramine attenuates anxiety- and depressive-like effects of acute and prolonged ethanol-abstinence in male rats by modulating SERT and GR expression in the dorsal hippocampus. *Behav Brain Res*. 2021; 408:113295. DOI: https://doi.org/10.1016/j.bbr.2021.113295
14. Nepal M., Choi H. J., Choi B. Y., Kim S. L., Ryu J. H., Kim D. H., et al. Anti-angiogenic and anti-tumor activity of Bavachinin by targeting hypoxia-inducible factor-1α. *Eur J Pharmacol*. 2012; 691(1-3):28-37.

DOI: https://doi.org/10.1016/j.ejphar.2012.06.028

15. Can A., Dao D. T., Arad M., Terrillion C. E., Piantadosi S. C., Gould T. D. The mouse forced swim test. *J Vis Exp*. 2012; (59):e3638. DOI: https://doi.org/10.3791/3638
16. GBD 2019 Mental Disorders Collaborators. Global, regional, and national burden of 12 mental disorders in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet Psychiatry.* 2022; 9(2):137-150. DOI: https://doi.org/10.1016/S2215-0366(21)00395-3
17. Cui L., Li S., Wang S., Wu X., Liu Y., Yu W., et al. Major depressive disorder: hypothesis, mechanism, prevention and treatment. *Signal Transduct Target Ther.* 2024; 9(1):30. DOI: https://doi.org/10.1038/s41392-024-01738-y
18. Uher R. The implications of gene-environment interactions in depression: will cause inform cure?. *Mol Psychiatry.* 2008; 13(12):1070-1078. DOI: https://doi.org/10.1038/mp.2008.92
19. Andrade C., Rao N. S. How antidepressant drugs act: A primer on neuroplasticity as the eventual mediator of antidepressant efficacy. *Indian J Psychiatry.* 2010;52(4):378-386. DOI: https://doi.org/10.4103/0019-5545.74318
20. Remali J., Aizat W. M. Medicinal plants and plant-based traditional medicine: Alternative treatments for depression and their potential mechanisms of action. *Heliyon.* 2024; 10(20):e38986. DOI: https://doi.org/10.1016/j.heliyon.2024.e38986
21. Rivero-Santana A., Perestelo-Perez L., Alvarez-Perez Y., Ramos-Garcia V., Duarte-Diaz A., Linertova R., et al. Stepped care for the treatment of depression: a systematic review and meta-analysis. *J Affect Disord.* 2021; 294:391-409. DOI: https://doi.org/10.1016/j.jad.2021.07.008
22. Gao J., Zhang W. J., Yang F. A Review of Traditional Chinese Medicine for the Treatment of Depression. *Psychosom Med Res*. 2022; 4(1): 6. DOI: https://doi.org/10.53388/202206
23. Yeung W. F., Chung K. F., Ng K. Y., Yu Y. M., Ziea E. T., Ng B. F. A systematic review on the efficacy, safety and types of Chinese herbal medicine for depression. *J Psychiatr Res.* 2014; 57:165-175. DOI: https://doi.org/10.1016/j.jpsychires.2014.05.016
24. Zhang Y. W., Cheng Y. C. Challenge and Prospect of Traditional Chinese Medicine in Depression Treatment. *Front Neurosci.* 2019; 13:190. DOI: https://doi.org/10.3389/fnins.2019.00190
25. Da X. L., Yue L. F., Li X. J., Chen J. B., Yuan N. J., Chen J. X. Potential therapeutic effect and methods of traditional Chinese medicine on COVID-19-induced depression: A review. *Anat Rec (Hoboken).* 2021; 304(11):2566-2578. DOI: https://doi.org/10.1002/ar.24758
26. Martirosyan D. Functional Food Science and Bioactive Compounds. *Bioactive Compounds in Health and Disease.* 2025; 8(6): 218 - 229. DOI: https://doi.org/10.31989/bchd.v8i6.1667
27. Alam F., Khan G. N., Asad M. H. H. B. Psoralea corylifolia L: Ethnobotanical, biological, and chemical aspects: A review. *Phytother Res.* 2018; 32(4):597-615. DOI: https://doi.org/10.1002/ptr.6006
28. Shi W., Gao Y., Yang H., et al. Bavachinin, a main compound of Psoraleae Fructus, facilitates GSDMD-mediated pyroptosis and causes hepatotoxicity in mice. *Chem Biol Interact*. 2024; 400:111133. DOI: https://doi.org/10.1016/j.cbi.2024.111133
29. Farahani M. S., Bahramsoltani R., Farzaei M. H., Abdollahi M., Rahimi R. Plant-derived natural medicines for the management of depression: an overview of mechanisms of action. *Rev Neurosci.* 2015;26(3):305-321. DOI: https://doi.org/10.1515/revneuro-2014-0058
30. Yi L. T., Li Y. C., Pan Y., Li J. M., Xu Q., Mo S. F., et al. Antidepressant-like effects of psoralidin isolated from the seeds of Psoralea Corylifolia in the forced swimming test in mice. *Prog Neuropsychopharmacol Biol Psychiatry.* 2008;32(2):510-519. DOI: https://doi.org/10.1016/j.pnpbp.2007.10.005
31. Chopra B., Dhingra A. K., Dhar, K. L. Psoralea corylifolia L. (Buguchi) - folklore to modern evidence: review. *Fitoterapia.* 2013; 90:44-56. DOI: https://doi.org/10.1016/j.fitote.2013.06.016
32. Yi J., Du G., Zhao Y., Zhang L., Li B., Zhu W., et al. Bavachinin analogues as agonists of pan-peroxisome proliferator-activated receptors. *Med Chem Res*. 2018; *27*(7): 1851-1862. DOI: https://doi.org/10.1007/s00044-018-2197-6
33. Du G., Feng L., Yang Z., Shi J., Huang C., Guo F., et al. Separation and peroxisome proliferator-activated receptor-γ agonist activity evaluation of synthetic racemic bavachinin enantiomers. *Bioorg Med Chem Lett.* 2015;25(12):2579-2583. DOI: https://doi.org/10.1016/j.bmcl.2015.04.029

34. Ge L. N., Yan L., Li C., Cheng K. Bavachinin exhibits antitumor activity against nonsmall cell lung cancer by targeting PPARγ. *Mol Med Rep.* 2019;20(3):2805-2811. DOI: https://doi.org/10.3892/mmr.2019.10485
35. Colle R., de Larminat D., Rotenberg S., Hozer F., Hardy P., Verstuyft C., et al. PPAR-γ Agonists for the Treatment of Major Depression: A Review. *Pharmacopsychiatry.* 2017; 50(2):49-55. DOI: https://doi.org/10.1055/s-0042-120120
36. Kemp D. E., Schinagle M., Gao K., Conroy C., Ganocy S. J., Ismail-Beigi F., et al. PPAR-γ agonism as a modulator of mood: proof-of-concept for pioglitazone in bipolar depression. *CNS Drugs.* 2014; 28(6):571-581. DOI: https://doi.org/10.1007/s40263-014-0158-2
37. Beheshti F., Hosseini M., Hashemzehi M., Soukhtanloo M., Khazaei M., Shafei, M. N. The effects of PPAR-γ agonist pioglitazone on hippocampal cytokines, brain-derived neurotrophic factor, memory impairment, and oxidative stress status in lipopolysaccharide-treated rats. *Iran J Basic Med Sci.* 2019; 22(8):940-948. DOI: https://doi.org/10.22038/ijbms.2019.36165.8616
38. Chen Y., Wang H. D., Xia X., Kung H. F., Pan Y., Kong L. D. Behavioral and biochemical studies of total furocoumarins from seeds of Psoralea corylifolia in the chronic mild stress model of depression in mice. *Phytomedicine.* 2007; 14(7-8):523-529. DOI: https://doi.org/10.1016/j.phymed.2006.09.007
39. Asgary S., Yazdiniapour Z. Saffron and depression. *Bioactive Compounds in Health and Disease*. 2021. 4(5): 90-92. DOI: https://doi.org/10.31989/bchd.v4i5.808
40. Almoraie N.M., Aljefree N.M., Althaiban M.A., Hanbazaza M.A., Wazzan H.A., Shatwan I.M. The Effect of Roselle (Hibiscus) Juice on Mood Improvement in Healthy Adults. *Functional Foods in Health and Disease*. 2022; 12(9): 601-613. DOI: https://doi.org/10.31989/ffhd.v12i10.985
41. Reeder N., Tolar-Peterson T., Adegoye G. A., Dickinson E., McFatter E. The effect of daily peanut consumption on cognitive function and indicators of mental health among healthy young women. *Functional Foods in Health and Disease*. 2022; 12(12): 734-747. DOI: https://doi.org/10.31989/ffhd.v12i12.1010
42. Talbott S.M., Talbott J.A, Stephens B.J., Oddou M.P. Modulation of Gut-Brain Axis Improves Microbiome, Metabolism, and Mood. *Functional Foods in Health and Disease.* 2020; 10(1): 37-54. DOI: https://doi.org/10.31989/ffhd.v10i1.685
43. Chandagari J., Santrosyan G., McCarthy J, Martirosyan D. Zinc in the management of Major Depressive Disorder: Evidence for supplementation and dietary strategies. *Agriculture and Food Bioactive Compounds.* 2025; 8(6): 121-140. DOI: https://doi.org/10.31989/afbc.v2i6.1660