Evaluating the Effect of Gum Arabic (*Acacia Senegal*) on Scopolamine-Induced Cognitive Impairment in Albino Mice: Assessment via the Forced Swim Test

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KEYWORDS

Gum Arabic, *Acacia Senegal*, Depression, cognitive impairment

ABSTRACT

Background
Gum Arabic (GA), a natural exudate from *Acacia Senegal*, is a dietary precursor of butyrate—a short-chain fatty acid with demonstrated neuroprotective and epigenetic regulatory effects. This study investigates GA's potential antidepressant properties in a murine model of scopolamine-induced cognitive impairment, addressing gaps in understanding its therapeutic role in depression.

Materials and Methods
Thirty albino mice (3–5 weeks old, 27 g average weight) were randomly allocated into six groups (n = 5/group). Groups received either Gum Arabic (GA, 10% *ad libitum*), piracetam (500 mg/kg/day orally), or tap water for 10 or 14 days. GA solutions were refreshed every 3 days, while piracetam was administered as a crushed tablet suspension. On the final day, mice were injected intraperitoneally with scopolamine hydrobromide (0.4 mg/kg) 45 minutes prior to the Forced Swim Test (FST). The FST was conducted in a glass cylinder (25–26°C water, 15 cm depth) over 6 minutes, with immobility time (seconds, minutes 2–6) recorded digitally and scored blindly.

Results
No significant differences in immobility time were observed between GA-treated and control groups at 10 or 14 days ($p > 0.05$). Piracetam exhibited a non-significant reduction in immobility with shorter treatment duration (10 days) compared to its 14-day regimen. Both GA and piracetam groups showed lower mean immobility times relative to controls, though statistical significance was not achieved.

Conclusions
GA treatment for 10 consecutive days showed no significant difference compared to the 14-day regimen. In contrast, piracetam's antidepressant-like effects were more pronounced with shorter treatment duration. Future studies should prioritize prolonged GA administration to evaluate its potential therapeutic benefits.

Background

Depression, a chronic neuropsychiatric disorder (1), affects approximately 5% of the global population, with a lifetime prevalence of 15–20%, and poses significant life-threatening risks (2,3). It disproportionately impacts women compared to men and disrupts physiological, emotional, and cognitive functioning (4). As a major risk factor for cardiovascular diseases, depression severely diminishes quality of life (5,6). In severe cases, it may lead to suicide, which ranks as the second leading cause of death among individuals aged 15–29 years (7). Consequently, depression is prioritized under the World Health Organization's (WHO) Mental Health Gap Action Program (mhGAP) (2).

Despite advancements in pharmacotherapy, fewer than half of global depression patients receive adequate treatment (8). Current medications, such as selective serotonin reuptake inhibitors (SSRIs) (9) and tricyclic antidepressants (TCAs) (10), exhibit limited efficacy and are associated with adverse side effects. These limitations underscore the urgent need for novel therapeutic agents.

Gum Arabic (GA), a water-soluble, edible exudate derived from the stems and branches of *Acacia senegal* and *A. seyal* trees, is widely utilized as a food additive, pharmaceutical excipient, and traditional remedy in Sudanese culture(11,12). Intestinal microbiota metabolizes GA into butyrate, a short-chain fatty acid (SCFA) with demonstrated neuroprotective properties (13,14). Butyrate exerts antioxidant, anti-inflammatory, and anti-apoptotic effects, mitigating cerebral ischemic/reperfusion injury (15). Moreover, it enhances brain-derived neurotrophic factor (BDNF) expression, promoting neuronal proliferation, migration, and differentiation (16,17). Preclinical studies indicate that sodium butyrate (NaB) alleviates depressive behaviors in maternal deprivation and chronic mild stress (CMS) models by upregulating neurotrophic factors (18,19). In chronic unpredictable mild stress (CUMS)-induced mice, NaB reversed depression-like phenotypes, restored blood-brain barrier (BBB) integrity, and elevated cerebral serotonin (5-HT) and BDNF levels(19).

Butyrate's therapeutic mechanisms are largely attributed to its epigenetic regulatory effects, particularly histone deacetylase inhibition (HDACi), which modulates post-translational histone modifications (17). Emerging evidence links histone hypoacetylation to neurodegenerative disorders such as Parkinson's disease (PD) and Alzheimer's disease (AD) (20–23). Dietary interventions targeting histone acetylation, including butyrate-rich compounds like GA, may thus offer neuroprotective benefits (16,18,19,24,25).

Given this evidence, we hypothesize that GA exhibits neuroprotective potential. This study investigates its antidepressant-like effects in a scopolamine-induced murine model using the FST.

Materials and Methods

Animals

This study received ethical approval from the Sudan Veterinary Council (No. EA/0020/2018). Thirty albino mice (male and female), aged 3–5 weeks (average weight: 27 g), were used. Mice were housed in temperature-controlled (22 ± 4°C) and photoperiod-regulated (12-hour light/dark cycle) rooms at Al Neelain University's Faculty of Pharmacy animal facility. Animals were housed in separate metal cages, with cage numbers and tail markings used for identification. They had ad libitum access to standard laboratory diet and tap water. Behavioral tests were conducted during daylight hours (8:00 AM–5:00 PM).

Drugs and Chemicals

- GA: A 10% w/v solution was prepared by dissolving GA powder (SAFAST®; gift from Savanna Company) in tap water (100 g/L). Solutions were freshly prepared every 3 days, yielding an approximate daily intake of 20 g/kg body weight (26).
- Piracetam: Administered orally at 500 mg/kg/day as a suspension in tap water (NEUROCET® 400 mg tablets, crushed and suspended) (27).
- Scopolamine hydrobromide: Injected intraperitoneally (0.4 mg/kg) to induce cognitive impairment via muscarinic receptor blockade (28).

Nootropics Overview

Piracetam, a nootropic agent, enhances central nervous system functions such as memory and learning, likely via glutamate receptor modulation (27).

Experimental Protocol

Mice were randomly divided into six groups (n = 5/group):

1. Group 1 (Test drug-14): GA (10% w/v) *ad libitum* for 14 days.
2. Group 2 (Standard drug-14): Piracetam (500 mg/kg/day) for 14 days.
3. Group 3 (Control-14): Tap water for 14 days.
4. Group 4 (Test drug-10): GA (10% w/v) *ad libitum* for 10 days.
5. Group 5 (Standard drug-10): Piracetam (500 mg/kg/day) for 10 days.
6. Group 6 (Control-10): Tap water for 10 days.

On day 15 (Groups 1–3) or day 11 (Groups 4–6), mice received scopolamine hydrobromide (0.4 mg/kg, i.p.). Behavioral testing FST commenced 45 minutes post-injection.

FST

The FST, a validated preclinical depression model (29), was conducted in a glass cylinder (16 cm diameter × 28 cm height) filled with water (25–26°C; 15 cm depth). Mice were unable to touch the bottom or escape. Tests lasted 6 minutes, with immobility time (floating with minimal movement to stay afloat) recorded between minutes 1–6. Water was replaced between trials. Sessions were digitally recorded for blinded manual scoring using a stopwatch (30–32).

Statistical Analysis

Data are expressed as mean ± SD. One-way ANOVA followed by post hoc tests (SPSS v26) compared groups, with $p < 0.05$ deemed statistically significant.

Results

Effect on Depression-Like Levels in the Forced Swimming Test (FST) – Treatment for 14 Days:

The mean immobility time was lowest in the GA group, followed by piracetam, then control groups. No significant difference was observed between groups treated for 14 days ($p > 0.05$; Table 1).

Effect on Depression-Like Levels in the Forced Swimming Test (FST) – Treatment for 10 Days:

The mean immobility time was lowest in the piracetam group, followed by control, then GA groups. No significant difference was observed between groups treated for 10 days ($p > 0.05$; Table 1).

Table 1: Effects of GA, piracetam, and tap water treatment on immobility time in the forced swimming test for different durations, using **one-way analysis of variance (ANOVA)** followed by LSD Post Hoc Test.

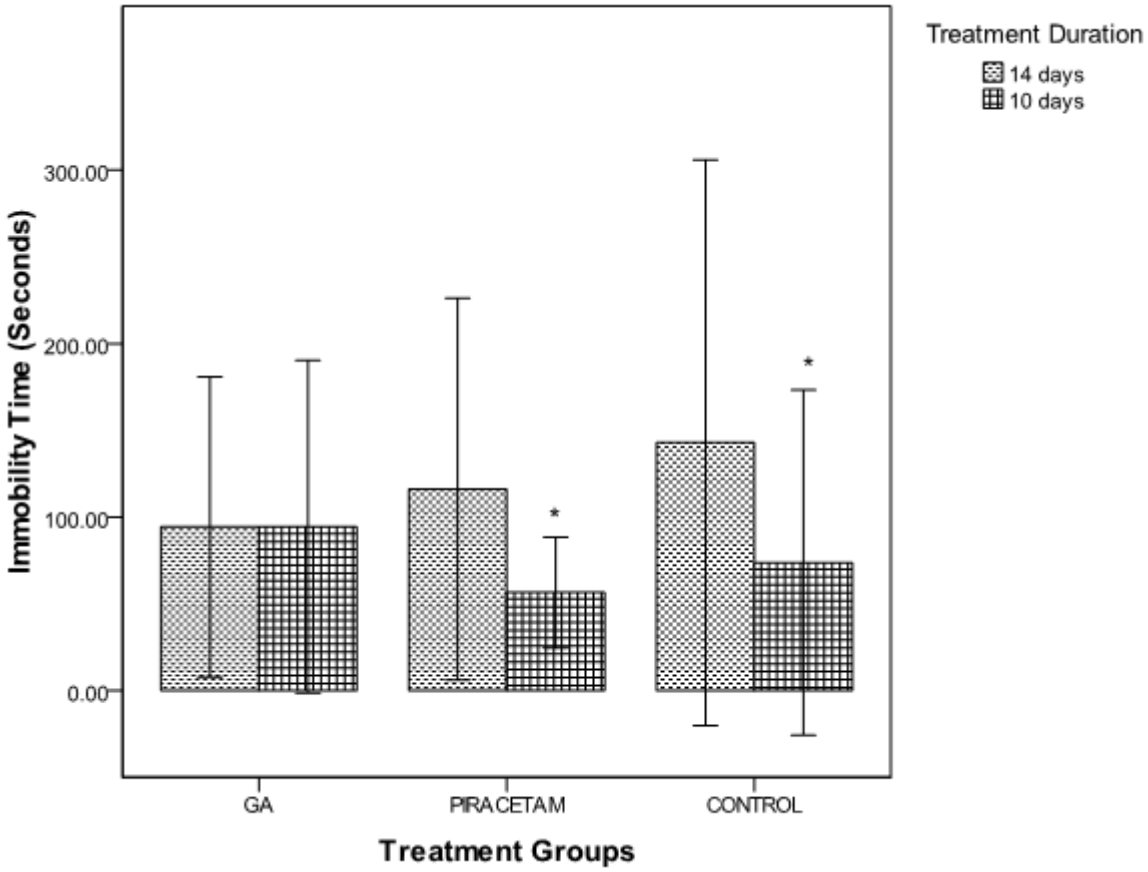
Treatment Group (n=5)	**Treatment Duration (Days)**	**Mean Immobility Time in FST ± Standard Deviation (Seconds)**	**Statistical Significance (p-value) for Separate Treatment Durations**
GA	14	94.4 ± 43.24	Piracetam (14): 0.589 Control (14): 0.239
Piracetam	14	116.2 ± 55.02	GA (14): 0.589 Control (14): 0.507
Control	14	143.0 ± 81.51	GA (14): 0.239 Piracetam (14): 0.507
GA	10	94.4 ± 47.96	Piracetam (10): 0.170 Control (10): 0.442
Piracetam	10	56.6 ± 15.94 *	GA (10): 0.170 Control (10): 0.519
Control	10	73.8 ± 49.77 *	GA (10): 0.442 Piracetam (10): 0.519
Total (n=30)		96.40 ± 55.59	

*Significantly lower than control (14 days) group. "Source: Authors".

Compared Effect of Different Treatment Durations on Depression-Like Levels in the Forced Swimming Test (FST):

- No significant difference was observed between GA groups (14 and 10 days) ($p > 0.05$).
- GA groups (14 and 10 days) showed lower immobility times compared to the control group (14 days), but this was statistically insignificant ($p > 0.05$).
- The piracetam group (10 days) exhibited a lower immobility time than the piracetam group (14 days), though this reduction was insignificant ($p > 0.05$). However, this value was significantly lower than the control group (10 days).
- The control group (10 days) showed a significantly lower immobility time than the control group (14 days) ($p < 0.05$).
- Mean ± SD for each group is shown in Table 1. A comparison between treatment groups across durations is illustrated in Figure 1.

Figure 1: Comparison between treatment groups across durations regarding immobility time in the forced swimming test (FST). Error bars: ±2 SD, using one-way ANOVA followed by LSD post hoc test (n = 5). *** = Significantly lower than control (14 days) group** (piracetam (10): p = 0.016; control (10): p = 0.048).



Discussion

The Porsolt FST, a validated preclinical model for assessing potential antidepressant agents (31–33), was utilized in this investigation. In the 14-day treatment cohort, mice administered GA exhibited a shorter mean immobility duration compared to piracetam-treated and control groups. These observations are consistent with earlier findings (34), where control rats displayed prolonged immobility. For the 10-day regimen, GA treatment did not significantly alter immobility time. However, both piracetam and control groups demonstrated reduced immobility durations. A statistically significant difference emerged between the 10-day and 14-day control groups, implying that extended experimental timelines exacerbate immobility behavior in the FST. While the 10-day piracetam group showed a numerically lower immobility time than its 14-day counterpart, this difference lacked statistical significance. Notably, 10-day piracetam administration significantly reduced immobility relative to the 14-day control group.

Piracetam's dose-dependent attenuation of immobility in rodents (34) aligns with its documented ability to enhance cortical hypoxia resistance and restore bioelectrical activity in depression models. It also mitigates neuronal suppression induced by KCl, AMP, and pentobarbital (35,36).

GA's 10-day versus 14-day administration showed no significant difference in immobility. Previous research indicates that 8-week SUPERGUM™ supplementation (25 g/day) elevates serum butyrate levels twofold (14). The marginally reduced immobility in GA groups (vs. 14-day

control) may reflect enhanced active coping behaviors, suggesting subtle therapeutic effects. Similarly, the 14-day piracetam group displayed higher immobility than GA-treated mice, underscoring GA's comparative efficacy. In adenine-induced chronic renal failure models, GA counteracted motor deficits and FST immobility, corroborating its antidepressant-like potential (37). Elevated immobility in GA groups (vs. 10-day control) may represent an energy-conservation strategy, a recognized adaptive response to chronic stress (38).

Butyrate's biphasic effects, which vary depending on treatment duration, complicate the interpretation of its mechanisms of action (39). Our findings align with studies that reported NaB's antidepressant-like effects in mice (18,19) and those that linked histone deacetylase inhibitors to antidepressant efficacy (39). They also correspond to reports demonstrating synergistic antidepressant effects of butyrate and estradiol benzoate in ovariectomized rats, mediated through 5-HT1A receptor modulation (40) and altered hypothalamic gene expression (41). NaB elevates BDNF levels, which enhances neurogenesis and synaptic plasticity—key pathways disrupted in depression (41,42).

Critics posit that FST immobility reflects adaptive survival strategies rather than despair (38). While NaB modulates hippocampal histone acetylation (43), chronic administration fails to replicate acute antidepressant effects, suggesting chromatin remodeling alone may not suffice to drive behavioral responses (43).

Future studies should explore GA's optimal dosing, treatment duration, and mechanistic role in murine depression models.

Recommendations and Strategic Directions for Future Research

To advance understanding of GA therapeutic potential, future studies should prioritize several key steps. Expanding sample sizes would improve statistical robustness and enable subgroup analyses, such as sex-specific responses. Incorporating complementary behavioral tests—including the tail suspension test or sucrose preference test—could provide a multidimensional assessment of antidepressant-like effects. Standardizing GA administration via controlled oral gavage, rather than *ad libitum* intake, would ensure consistent dosing and clarify dose-response relationships. Direct measurement of serum or brain butyrate levels is essential to confirm GA metabolism and correlate its bioavailability with behavioral outcomes. Extending treatment durations beyond 14 days may reveal cumulative or delayed therapeutic effects, while mechanistic investigations into molecular targets—such as BDNF expression, histone acetylation, or 5-HT1A receptor modulation—are critical to elucidate GA's mode of action. Additionally, dose-response studies with varying GA concentrations could identify optimal therapeutic thresholds.

Conclusion

This study found no statistically significant reduction in immobility time with GA administration over 10–14 days in the FST, though a modest trend toward improvement was noted. Piracetam, conversely, demonstrated clearer antidepressant-like effects with shorter treatment duration. While GA's neuroprotective properties—potentially mediated through butyrate—remain intriguing, definitive conclusions require further validation. Prioritizing larger cohorts, extended treatment timelines, and mechanistic analyses in future research will be pivotal to confirm GA's efficacy and unravel its underlying pathways. Such efforts are vital for bridging preclinical insights into tangible clinical applications for depression and related neuropsychiatric disorders.

Abbreviations

BDNF brain derived neurotrophic factor; CMS chronic mild stress; FST Forced Swim Test; G Group; GA Gum Arabic; HDACi histone deacetylase inhibitors; NaB; SSRIs selective serotonin reuptake inhibitors; TCAs tricyclic antidepressants.

Declarations

Ethics approval and consent to participate

The current study was approved by Sudan Veterinary council, No EA/0020/2018.

Consent for publication

Not applicable

Availability of data and material

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

SMIA and AMS designed the study. SMIA and MMIA carried out experimental protocols. SMIA and MFL analyzed the data. SMIA prepared the first manuscript draft. MFL and AMS revised the final draft. All authors read and approved the final manuscript.

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References

1. Dhingra D, Valecha R. Evidence for involvement of the monoaminergic system in antidepressant-like activity of an ethanol extract of Boerhaavia diffusa and its isolated constituent, punarnavine, in mice. Pharm Biol [Internet]. 2014 [cited 2025 Mar 6];52(6):767–74. Available from: https://pubmed.ncbi.nlm.nih.gov/24559436/
2. World Health Organization. Depression module – evidence profile DEP3: Brief, structured psychological treatment for adults with depressive episode/disorder. 2023;
3. Guilbert JJ. The world health report 2002 - reducing risks, promoting healthy life. Educ Health (Abingdon) [Internet]. 2003 Jul [cited 2025 Mar 6];16(2):230. Available from: https://pubmed.ncbi.nlm.nih.gov/14741909/
4. Li M, Lu S, Wang G, Zhong N. The Effects of Gender Differences in Patients with Depression on Their Emotional Working Memory and Emotional Experience. Behav Neurol [Internet]. 2015 [cited 2025 Mar 6];2015:807343. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC4633552/
5. You Y, Shou X, Zhang X, Fan S, Chai R, Xue W, et al. Psycho-Cardiological Disease: A Bibliometric Review From 2001 to 2021. Front Cardiovasc Med. 2022 Apr 29;9.
6. Li X, Zhou J, Wang M, Yang C, Sun G. Cardiovascular disease and depression: a narrative review. Front Cardiovasc Med [Internet]. 2023 [cited 2025 Mar 6];10:1274595. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC10710900/
7. Harmer B, Lee S, Rizvi A, Saadabadi A. Suicidal Ideation. Acute Med A Symptom-Based Approach [Internet]. 2024 Apr 20 [cited 2025 Mar 6];415–20. Available from: https://www.ncbi.nlm.nih.gov/books/NBK565877/
8. Mekonen T, Chan GCK, Connor JP, Hides L, Leung J. Estimating the global treatment rates for depression: A systematic review and meta-analysis. J Affect Disord [Internet]. 2021 Dec 1 [cited 2025 Mar 6];295:1234–42. Available from: https://pubmed.ncbi.nlm.nih.gov/34665135/

9. Edinoff AN, Akuly HA, Hanna TA, Ochoa CO, Patti SJ, Ghaffar YA, et al. Selective Serotonin Reuptake Inhibitors and Adverse Effects: A Narrative Review. Neurol Int [Internet]. 2021 Sep 1 [cited 2025 Mar 6];13(3):387. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC8395812/
10. Kamp CB, Petersen JJ, Faltermeier P, Juul S, Siddiqui F, Barbateskovic M, et al. Beneficial and harmful effects of tricyclic antidepressants for adults with major depressive disorder: a systematic review with meta-analysis and trial sequential analysis. BMJ Ment Heal [Internet]. 2024 Jan 18 [cited 2025 Mar 6];27(1):e300730. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC10806869/
11. Jarrar AH, Stojanovska L, Apostolopoulos V, Feehan J, Bataineh MF, Ismail LC, et al. The Effect of Gum Arabic (Acacia senegal) on Cardiovascular Risk Factors and Gastrointestinal Symptoms in Adults at Risk of Metabolic Syndrome: A Randomized Clinical Trial. Nutrients [Internet]. 2021 Jan 1 [cited 2025 Mar 6];13(1):194. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC7826716/
12. Babiker R, Merghani TH, Elmusharaf K, Badi RM, Lang F, Saeed AM. Effects of gum Arabic ingestion on body mass index and body fat percentage in healthy adult females: Two-arm randomized, placebo controlled, double-blind trial. Nutr J. 2012;11(1).
13. Smith JG, Yokoyama WH, German JB. Butyric acid from the diet: actions at the level of gene expression. Crit Rev Food Sci Nutr [Internet]. 1998 [cited 2025 Mar 6];38(4):259–97. Available from: https://pubmed.ncbi.nlm.nih.gov/9626487/
14. Matsumoto N, Riley S, Fraser D, Al-Assaf S, Ishimura E, Wolever T, et al. Butyrate modulates TGF-β1 generation and function: Potential renal benefit for Acacia(sen) SUPERGUM™ (gum arabic)? Kidney Int [Internet]. 2006 Jan 2 [cited 2025 Mar 6];69(2):257–65. Available from: https://www.kidney-international.org/action/showFullText?pii=S0085253815514609
15. Sun J, Wang F, Li H, Zhang H, Jin J, Chen W, et al. Neuroprotective Effect of Sodium Butyrate against Cerebral Ischemia/Reperfusion Injury in Mice. Biomed Res Int [Internet]. 2015 Jan 1 [cited 2025 Mar 6];2015(1):395895. Available from: https://onlinelibrary.wiley.com/doi/full/10.1155/2015/395895
16. Kim HJ, Leeds P, Chuang DM. The HDAC inhibitor, sodium butyrate, stimulates neurogenesis in the ischemic brain. J Neurochem [Internet]. 2009 Aug [cited 2025 Mar 6];110(4):1226–40. Available from: https://pubmed.ncbi.nlm.nih.gov/19549282/
17. Konsoula Z, Barile FA. Epigenetic histone acetylation and deacetylation mechanisms in experimental models of neurodegenerative disorders. J Pharmacol Toxicol Methods. 2012 Nov 1;66(3):215–20.
18. Valvassori S, Varela R, Arent C, Dal-Pont G, Bobsin T, Budni J, et al. Sodium butyrate functions as an antidepressant and improves cognition with enhanced neurotrophic expression in models of maternal deprivation and chronic mild stress. Curr Neurovasc Res [Internet]. 2014 Oct 18 [cited 2025 Mar 6];11(4):359–66. Available from: https://pubmed.ncbi.nlm.nih.gov/25233278/
19. Sun J, Wang F, Hong G, Pang M, Xu H, Li H, et al. Antidepressant-like effects of sodium butyrate and its possible mechanisms of action in mice exposed to chronic unpredictable mild stress. Neurosci Lett. 2016 Apr 8;618:159–66.
20. Sadri-Vakili G, Cha JHJ. Mechanisms of disease: Histone modifications in Huntington's disease. Nat Clin Pract Neurol. 2006 Jun;2(6):330–8.
21. Sadri-Vakili G, Bouzou B, Benn CL, Kim MO, Chawla P, Overland RP, et al. Histones

associated with downregulated genes are hypo-acetylated in Huntington's disease models. Hum Mol Genet [Internet]. 2007 Jun [cited 2025 Mar 6];16(11):1293–306. Available from: https://pubmed.ncbi.nlm.nih.gov/17409194/

22. Rouaux C, Jokic N, Mbebi C, Boutillier S, Loeffler JP, Boutillier AL. Critical loss of CBP/p300 histone acetylase activity by caspase-6 during neurodegeneration. EMBO J [Internet]. 2003 Dec 15 [cited 2025 Mar 6];22(24):6537–49. Available from: https://pubmed.ncbi.nlm.nih.gov/14657026/
23. Sharma S, Taliyan R. Targeting Histone Deacetylases: A Novel Approach in Parkinson's Disease. Parkinsons Dis [Internet]. 2015 [cited 2025 Mar 6];2015:303294. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC4324954/
24. Cavaliere G, Catapano A, Trinchese G, Cimmino F, Penna E, Pizzella A, et al. Butyrate Improves Neuroinflammation and Mitochondrial Impairment in Cerebral Cortex and Synaptic Fraction in an Animal Model of Diet-Induced Obesity. Antioxidants (Basel, Switzerland) [Internet]. 2022 Dec 20 [cited 2025 Mar 6];12(1). Available from: http://www.ncbi.nlm.nih.gov/pubmed/36670866
25. Berni Canani R, Di Costanzo M, Leone L. The epigenetic effects of butyrate: Potential therapeutic implications for clinical practice. Clin Epigenetics [Internet]. 2012 Feb 27 [cited 2025 Mar 6];4(1):1–7. Available from: https://clinicalepigeneticsjournal.biomedcentral.com/articles/10.1186/1868-7083-4-4
26. Nasir O, Artunc F, Saeed A, Kambal MA, Kalbacher H, Sandulache D, et al. Effects of gum arabic (Acacia senegal) on water and electrolyte balance in healthy mice. J Ren Nutr. 2008 Mar;18(2):230–8.
27. [Relationship between facilitatory effect of piracetam on memory and glutamate receptors] - PubMed [Internet]. [cited 2025 Mar 6]. Available from: https://pubmed.ncbi.nlm.nih.gov/1685614/
28. Raut S, Parekar R, Jadhav K, Marathe P, Rege N. Effect of Jyotiṣmatī seed oil on spatial and fear memory using scopolamine induced amnesia in mice. Anc Sci Life [Internet]. 2015 [cited 2025 Mar 6];34(3):130. Available from: https://pubmed.ncbi.nlm.nih.gov/26120226/
29. Petit-Demouliere B, Chenu F, Bourin M. Forced swimming test in mice: a review of antidepressant activity. Psychopharmacology (Berl) [Internet]. 2005 Jan [cited 2025 Mar 6];177(3):245–55. Available from: https://pubmed.ncbi.nlm.nih.gov/15609067/
30. El zahaf NA, Elhwuegi AS. The effect of GABAmimetics on the duration of immobility in the forced swim test in albino mice. Libyan J Med [Internet]. 2014 Feb 18 [cited 2025 Mar 6];9(1). Available from: https://pubmed.ncbi.nlm.nih.gov/24560379/
31. Can A, Dao DT, Arad M, Terrillion CE, Piantadosi SC, Gould TD. The mouse forced swim test. J Vis Exp [Internet]. 2012 [cited 2025 Mar 6];(59). Available from: https://pubmed.ncbi.nlm.nih.gov/22314943/
32. Porsolt RD, Le Pichon M, Jalfre M. Depression: a new animal model sensitive to antidepressant treatments. Nature [Internet]. 1977 [cited 2025 Mar 6];266(5604):730–2. Available from: https://pubmed.ncbi.nlm.nih.gov/559941/
33. Porsolt RD, Bertin A, Jalfre M. "Behavioural despair" in rats and mice: strain differences and the effects of imipramine. Eur J Pharmacol [Internet]. 1978 Oct 1 [cited 2025 Mar 7];51(3):291–4. Available from: https://pubmed.ncbi.nlm.nih.gov/568552/
34. Gokhale V. EVALUATION OF EFFECT OF PIRACETAM IN EXPERIMENTAL MODELS OF DEPRESSION [Internet]. [cited 2025 Mar 7]. Available from: https://www.academia.edu/15539091/EVALUATION_OF_EFFECT_OF_PIRACETAM_

IN_EXPERIMENTAL_MODELS_OF_DEPRESSION

35. Vernon MW, Sorkin EM. Piracetam: An Overview of its Pharmacological Properties and a Review of its Therapeutic Use in Senile Cognitive Disorders. Drugs Aging. 1991;1(1):17–35.
36. Grau M, Montero JL, Balasch J. Effect of piracetam on electrocorticogram and local cerebral glucose utilization in the rat. Gen Pharmacol. 1987;18(2):205–11.
37. Ali BH, Ziada A, Al Husseni I, Beegam S, Nemmar A. Motor and behavioral changes in rats with adenine-induced chronic renal failure: influence of acacia gum treatment. Exp Biol Med (Maywood) [Internet]. 2011 Jan [cited 2025 Mar 7];236(1):107–12. Available from: https://pubmed.ncbi.nlm.nih.gov/21239740/
38. Church DM, Goodstadt L, Hillier LW, Zody MC, Goldstein S, She X, et al. Are Animal Models Relevant in Modern Psychiatry? PLoS Biol [Internet]. 2012 May 1 [cited 2025 Mar 7];29(5). Available from: https://www.psychiatrictimes.com/view/are-animal-models-relevant-modern-psychiatry
39. Raybuck JD, McCleery EJ, Cunningham CL, Wood MA, Lattal KM. The histone deacetylase inhibitor sodium butyrate modulates acquisition and extinction of cocaine-induced conditioned place preference. Pharmacol Biochem Behav. 2013 May 1;106:109–16.
40. Covington HE, Maze I, Vialou V, Nestler EJ. Antidepressant Action of HDAC Inhibition in the Prefrontal Cortex. Neuroscience [Internet]. 2015 Jul 9 [cited 2025 Mar 7];298:329. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC4441835/
41. Schroeder FA, Lin CL, Crusio WE, Akbarian S. Antidepressant-like effects of the histone deacetylase inhibitor, sodium butyrate, in the mouse. Biol Psychiatry [Internet]. 2007 Jul 1 [cited 2025 Mar 7];62(1):55–64. Available from: https://pubmed.ncbi.nlm.nih.gov/16945350/
42. Angelucci F, Brenè S, Mathé AA. BDNF in schizophrenia, depression and corresponding animal models. Mol Psychiatry [Internet]. 2005 Apr [cited 2025 Mar 7];10(4):345–52. Available from: https://pubmed.ncbi.nlm.nih.gov/15655562/
43. Gundersen BB, Blendy JA. Effects of the histone deacetylase inhibitor sodium butyrate in models of depression and anxiety. Neuropharmacology [Internet]. 2009 Jul [cited 2025 Mar 6];57(1):67–74. Available from: https://pubmed.ncbi.nlm.nih.gov/19393671/