ASIAN JOURNAL OF PHARMACEUTICAL AND CLINICAL RESEARCH

INNOVARE ACADEMIC SCIENCES
Knowledge to Innovation

Vol 19, Issue 2, 2026

Online - 2455-3891
Print - 0974-2441

Research Article

PRE-CLINICAL NEUROPHARMACOLOGY EFFICACY AND TOXICITY OF AVENIA SATIVAUM IN RATS

MANASI KHADANGA[1]*, NITYANANDA SAHOO[2], NIHAR RANJAN KAR[1]

[1]Department of Pharmacy, School of Pharmacy and Life Sciences, Centurion University of Technology and Management, Bhubaneswar,
[2]Department of Pharmacy, Nityananda College of Pharmacy, Balasore, Odisha, India.
*Corresponding author: Manasi Khadanga; Email: mmanasikhadanga@gmail.com

Received: 30 August 2025, Revised and Accepted: 03 January 2026

ABSTRACT

Objective: The present study investigates the neuropharmacological potential of methanolic and ethanolic leaf extracts of *Avena sativa* L. in experimental models of depression.

Methods: Acute toxicity evaluation revealed no mortality, morbidity, or behavioral abnormalities following a single oral dose of 2000 mg/kg, confirming the safety of both extracts. Based on this, 100 and 200 mg/kg doses were selected for behavioral assessment. Antidepressant-like activity was evaluated using the forced swimming test (FST) and tail suspension test (TST).

Result: Rats treated with methanolic extract at 100 mg/kg (arteriovenous methanolic [AVM]-100) exhibited significantly reduced immobility times in both FST (46.2 s) and TST (50.7 s), closely approximating the standard drug (39.6 s and 43.0 s, respectively,**p<0.001). Higher doses (AVM-200) and ethanolic extracts (arteriovenous ethanolic [AVE]-100 and AVE-200) showed moderate reductions, suggesting a non-linear dose-response relationship. Locomotor activity analysis further supported the antidepressant profile of AVM-100, which showed the highest count (680) without signs of hyperactivity, indicating reversal of psychomotor retardation. The observed effects are likely mediated by neuroactive phytochemicals, such as avenanthramides and flavonoids, known to modulate neurotransmitter systems and stress-response pathways.

Conclusion: Overall, the findings highlight the therapeutic promise of *A. sativa* methanolic extract, particularly at 100 mg/kg, as a safe and effective plant-based candidate for managing depressive disorders.

Keywords: *Avena sativa* L, Antidepressant, Forced swimming test, Tail suspension test.

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INTRODUCTION

Depression is a multifactorial and recurrent mental health disorder that significantly impairs cognitive, emotional, and social functioning across diverse populations. Depression affects people of almost all ages and socioeconomic backgrounds and is the second most common cause of disability globally, according to the World Health Organization [1]. Its etiology is complicated and results from the interaction of biological, psychological, and social elements [2], including as environmental impacts, neurotransmitter disorders, hereditary predisposition, and long-term stress. Persistent low mood, anhedonia, psychomotor irregularities, disturbed sleep and appetite, cognitive impairment, and, in extreme situations, suicidal ideation are clinical manifestations of depressive disorders [3]. Beyond its psychological effects, depression is becoming more well acknowledged as a systemic disorder linked to increased risks of diabetes, cancer, stroke, cardiovascular disease, and sensory impairments [4,5]. Dysregulation of monoamine neurotransmitters, such as serotonin, dopamine, and noradrenaline, as well as disruptions in the hypothalamic-pituitary-adrenal (HPA) axis, including abnormal levels of cortisol and adrenocorticotropic hormone, are also implicated by neurobiological research [6,7].

While tricyclic antidepressants, monoamine oxidase inhibitors, and selective serotonin reuptake inhibitors continue to be the mainstay of treatment, they are frequently linked to side effects, such as weight gain, insomnia, cardiovascular problems, and delayed therapeutic onset [8,9]. These restrictions have increased interest in phytochemicals produced from plants that have neuroprotective, antioxidant, and psychotropic qualities as safer substitutes or supplements for the treatment of depression [10].

Polyphenolic compounds, particularly flavonoids, have gained attention for their ability to modulate mitochondrial function, stabilize neuronal membranes, and regulate apoptotic pathways – mechanisms crucial for neuronal survival during chronic stress and depressive states [11]. Oats, or *Avena sativa* L., have long been known to provide therapeutic benefits for neurological and mental conditions, such as sadness and anxiety [12]. Triterpene saponins (avenacins), phenolic acids, flavonoids, and the special avenanthramides, which have strong anti-inflammatory, neuromodulatory, and antioxidant properties, are abundant in oat grains [13-15]. These phytochemicals have been shown to affect monoaminergic transmission, modify intracellular signaling pathways, such as cyclic AMP, Mitogen-activated protein kinase, and Phosphoinositide 3-kinase/Akt, and reduce hyperactivity of the HPA axis – mechanisms linked to behavioral despair and mood regulation [16].

However, there is relatively little research on the bioactive components of *A. sativa* leaves, with the majority of the literature currently in publication concentrating on the phytochemical makeup and neuroactive characteristics of *A. sativa* grains. Chlorophylls, flavonoids, tricin derivatives, phenolic acids, and antioxidant substances with possible neuroprotective properties have been found in oat leaves, according to preliminary research. For instance, flavones like tricin and luteolin derivatives, which are known to alter neurotransmitter pathways and lessen oxidative stress, have been found in considerable amounts in leaf extracts. However, there is currently no agreement on the antidepressant effectiveness or underlying mechanisms of *A. sativa* leaf extracts, and thorough characterization of their phytochemical profile and neuropharmacological activity is still lacking.

This lack of clarity represents an important knowledge gap, as phytochemical profiles can vary substantially between plant parts, and the presence of grain-specific compounds, such as avenanthramides cannot be assumed in leaves without direct analytical evidence. Therefore, to appropriately determine the therapeutic value of oat leaves, investigations assessing their neuropharmacological potential are crucial.

When considered together, *A. sativa's* phytochemical diversity indicates the possibility of an antidepressant effect; yet, the paucity of data regarding leaf-specific components highlights the need for targeted research. The current work attempts to close this gap by assessing *A. sativa* L.'s methanolic leaf extract's antidepressant capability. Employing the forced swimming test (FST) in albino rats and to investigate potential neuromodulatory pathways based on the types of bioactive compounds found in oat leaves.

METHODS

Plant material collection and authentication

Young leaves of *A. sativa* Linn. were collected from Odisha, India, and authenticated by Dr. M. Venkaiah, Professor (Retd.), Department of Botany, Utkal University, Bhubaneswar, Odisha.

Processing of plant material

Fresh leaves were washed thoroughly under running tap water to remove dust and debris, followed by rinsing with distilled water. The cleaned leaves were shade-dried for 7 days, pulverized using a mechanical grinder, and sieved to obtain a uniform coarse powder.

Preparation of extracts

Using a Soxhlet extractor, the powdered leaf material (100 g) was first defatted with petroleum ether at 60–80°C for 6–8 h. Using a Soxhlet device, the defatted marc was air-dried and then extracted separately using 90% ethanol and 90% methanol. Following extraction, a rotary evaporator (Evator, Media Instrument Mfg. Co., Mumbai, India) was used to filter and concentrate each solvent extract under low pressure to produce semisolid residues. After that, they were dried to a consistent weight.

Extraction yield

Extraction yield was calculated using:

Yield (% w/w)=(Weight of dried extract/Weight of initial dried plant powder)×100

The yields obtained were: Ethanolic extract: 8.72 g (8.72% w/w), Methanolic extract:10.14 g (10.14% w/w)

Both ethanolic and methanolic extracts were subjected to standard preliminary phytochemical tests (Table 1) to detect the presence of major secondary metabolites, including:

Quantitative phytochemical analysis

To justify any differences in biological activity between the two extracts, the following quantitative assays were carried out:

- Total phenolic content: Determined using the Folin–Ciocalteu method and expressed as mg gallic acid equivalents extract.
- Total flavonoid content: Estimated using the aluminum chloride colorimetric method and expressed as mg quercetin equivalents extract.

These analyses provided essential preliminary chemical characterization beyond simple physical appearance and strengthened the scientific validity of comparing extract efficacy.

Acute toxicity analysis

Acute oral toxicity of the methanolic and ethanolic extracts of *A. sativa* was evaluated according to the Organisation for Economic Co-operation and Development guideline 423 (Acute Toxic Class Method). Healthy adult female Wistar albino rats (8–16 weeks old, 150–210 g) were fasted overnight before dosing, with free access to water. A single oral dose of 2000 mg/kg body weight of the extract was administered using an oral gavage. The toxicity of the methanol extract was performed in albino rats weighing from 125 to 130 g. All experiments were performed according to the Institutional Animal Ethical Committee guidelines. The experimental animals were divided into three groups (n=6) and *A. sativa* extract was supplemented at a single dose (2000 mg/kg) to the experimental animal. Body weights were recorded on day 0, day 7, and day 14. Then the behavioral changes and mortality were continuously monitored for every 24 h up to 96 h. No behavioral changes and mortality were observed during this period and the selected doses were safe to the experimental animal.

Experimental animals and housing conditions

Adult Wistar albino rats (150–210 g) of either sex were used for evaluation of anti-depressant activity, whereas for examination of sub-acute toxicity, only male Wistar albino rats of 8–16 weeks old were taken. The animals were housed for at least 1 week in the laboratory animal room before testing in standard polypropylene cages at room temperature of 34±2°C and at 60–65% relative humidity. Food and water were given ad libitum unless otherwise specified. For the antidepressant activity study, six groups of rats (n=6 per group) were employed. Group I served as the control and received a vehicle (saline/CMC). Group II received the standard drug fluoxetine at the specified dose. Groups III and IV were treated with the ethanolic extract of *A. sativa* at 100 mg/kg and 200 mg/kg, respectively, administered orally. Groups V and VI were treated with the methanolic extract of *A. sativa* at 100 mg/kg and 200 mg/kg, respectively, administered orally. The experimental protocols were approved by the institutional Animal Ethics Committee (AIEC) of Centurion University of Technology and Management , India (Regd.No. CUTM/IAEC-16).

Experimental design

Group I: Normal Control (saline/CMC)
Group II: Fluoxetine
Group III: Ethanolic extract of *A. sativa* (100 mg/kg)
Group IV: Ethanolic extract of *A. sativa* (200 mg/kg)
Group V: Methanolic extract of *A. sativa* (100 mg/kg)
Group VI: Methanolic extract of *A. sativa* (200 mg/kg).

Experimental animals and housing conditions

Adult Wistar albino rats (150–210 g) of either sex were used for evaluation of acute toxicity, muscle relaxant activity, and anti-depressant activity, whereas for examination of sub-acute toxicity, only male Wistar albino rats of 8–16 weeks old were taken. The animals were housed for at least 1 week in the laboratory animal room before testing in standard polypropylene cages at room temperature of 34±2°C and at 60–65% relative humidity. Food and water were given ad libitum unless otherwise specified.

Antidepressant activity

FST

The FST, a widely accepted behavioral paradigm for evaluating antidepressant-like activity in rodents, was employed to assess the efficacy of plant extracts in experimental albino rats. This test models behavioral despair by subjecting animals to an inescapable stressor, with minimal physical risk, requiring only that they maintain their heads above water. Experimental animals were randomly assigned to three groups: Control, standard, and treatment. Each group consisted of six albino rats (n=6). Methanolic and ethanolic extracts were administered to the treatment groups at two distinct dose levels. Before the test session, animals underwent a pre-swim habituation session lasting 15 min, conducted 24 h earlier in transparent plastic cylinders (height: 18.5 cm; diameter: 12.5 cm) filled with 13.5 cm of water maintained at room temperature. On the test day, each rat was individually placed into the same water-filled cylinder, and behavioral observations were recorded during the final 4 min of a 6-min test period. Immobility was operationally defined as the absence of active escape-directed

behaviors, with the animal remaining motionless except for minimal movements required to keep its head above the water surface. The FST was carried out as described previously (Yousuf *et al*., 2020) [17].

Tail suspension test (TST)

In TST, the rat is suspended by its tail, which induces hemodynamic stress of being hung in an uncontrollable position. After an initial period of struggle, the rat becomes immobile. Administration of antidepressant drugs decreases the duration of immobility, and the rat remains actively engaged in escape-directed behavior for a longer period of time. The animal was suspended by its tail on a rod 80 cm above the floor with the help of an adhesive tape applied 1 cm from the tip of its tail. Initial escape-orientated behavior ceases after some time, and the animal undergoes spells of immobility. The duration of immobility was measured for a period of 6 min. An animal was considered immobile only when it was completely motionless. The experimental Albino rats were monitored for 7 min and the result was observed (Suryawanshi *et al*., 2022) [18].

Locomotor activity analysis

Locomotor activity was performed to analyze the mobility of the albino rat. A total of 30 albino rat was divided into five different groups (n=6). To the experimental animal, methanol extract (25 mg/kg, 50 mg/kg, and 100 mg/kg) was supplemented, imipramine hydrochloride was used as the standard, and physiological saline was administered to the control rats. Plant extract and standard were administered to the experimental and positive control animals before 30 min of the experimental trials. The experimental Albino rats were maintained in an open field apparatus composed of a 45 cm arena (diameter) divided into 16 equal areas. After 15 h of final treatment, the experimental rat was placed in the center of the arena. The behavioral parameters, such as rearing frequencies, locomotion, and defecations, were observed within 5 min (Alsalem *et al*., 2022) [19].

Statistical analysis

The data obtained in the studies were subjected to one-way analysis of variance for determining the significant difference. The intergroup significance was analyzed using Dunnett's t-test. A $p<0.05$ was considered statistically significant [20]

RESULTS AND DISCUSSION

Acute toxicity studies

No mortality or morbidity was observed in animals through the 14-day period following single oral administration. Morphological characteristics (fur, skin, eyes, and nose) appeared normal. No salivation, diarrhea, lethargy, or unusual behaviors, such as self-mutilation and walking backward, were observed. Gait and posture, reactivity to handling or sensory stimuli, and grip strength was all normal. Food and water intake showed daily fluctuations within the range of control animals. Individual body weights are given in Table 2. None of the animals lost body weight and all rats showed expected gains in body weight over the study period. This indicates that the Methanolic and ethanolic extract from *A. sativa* L leaves were safe to a single dose of 2000 mg/kg, body weight. Hence 100 and 200 mg/kg oral doses of *A. sativa* L were selected to evaluate neuropharmacological activities [21,22].

FST

The FST revealed that rats treated with the methanolic extract of *A. sativa* at 100 mg/kg (arteriovenous methanolic [AVM]-100) exhibited a significantly reduced immobility time (46.2 s) compared to the control group (105.8 s), indicating strong antidepressant-like activity. This effect was comparable to the standard drug (39.6 s), suggesting that AVM-100 may possess potent mood-enhancing properties. In contrast, higher doses of methanolic extract (AVM-200) and both doses of ethanolic extract (AVE-100 and AVE-200) showed moderate reductions in immobility (62.4s and 65.2 s), implying a less pronounced antidepressant effect and a possible non-linear dose-response relationship (Fig. 1).

Table 1: Preliminary phytochemical screening

Serial No	Phytochemical test	Ethanolic extract	Methanolic extract
1	Alkaloids	+	+
2	Flavonoids	+	+
3	Phenolics	+	+
4	Saponins	+	+
5	Tannins	+	+
6	Terpenoids	+	+
7	Glycosides	+	+

Table 2: Body weight data of rats

Time point	Sex	Dose (mg/kg bw)	F1	F2	F3
Before treatment	Female	2000	157.5	135.1	119.1
2nd day	Female	2000	162.5	141.5	135.5
4th day	Female	2000	168	146.3	147.8
6th day	Female	2000	171.7	152.2	162.8
8th day	Female	2000	175.7	165	169.3
10th day	Female	2000	185.2	170.6	177.7
12th day	Female	2000	192.5	181.7	185.7
14th day	Female	2000	196.8	184.8	190.4

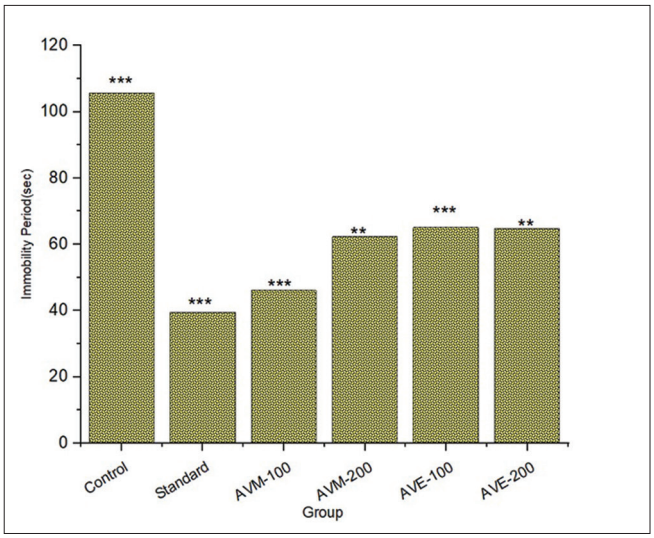

Fig. 1: Effect of arteriovenous methanolic and arteriovenous ethanolic (AVE) extract of *Avena sativa* (100 and 200 mg/kg), standard fluoxetine (25 mg/kg) and control on duration of immobility time in forced swimming test. Results are presented as mean (n=6). ***p<0.0001 when compared with controlexperiments, **p<0.001 when compared with control experiments

TST

The TST results demonstrated a clear reduction in immobility time among rats treated with *A. sativa* L. extracts, indicating antidepressant-like activity. The control group exhibited the highest immobility duration (93.54 s), reflecting baseline behavioral despair. In contrast, the standard drug group showed the lowest immobility (43.00 s), confirming the sensitivity of the model and the efficacy of conventional antidepressant treatment.

Among the experimental groups, the methanolic extract at 100 mg/kg (AVM-100) produced a significant reduction in immobility time (50.70 s), closely approaching the standard drug's effect. This suggests that AVM-100 possesses potent antidepressant-like properties, likely attributable to its rich content of neuroactive

polyphenols, such as avenanthramides and flavonoids, which are known to modulate neurotransmitter systems and stress-response pathways. The higher dose of methanolic extract (AVM-200) showed a moderate effect (54.60 s), indicating a less pronounced response than AVM-100. This may reflect a non-linear dose-response relationship, where increased concentration does not proportionally enhance efficacy – possibly due to receptor saturation or metabolic feedback mechanisms. Ethanolic extracts (arteriovenous ethanolic [AVE]-100 and AVE-200) resulted in higher immobility times (62.60 and 65.80 s, respectively), suggesting milder antidepressant effects. The lack of significant dose-dependent improvement implies that ethanol may be less efficient than methanol in extracting key bioactive compounds responsible for mood regulation. Overall, the TST findings align with the FST results, reinforcing the conclusion that the methanolic extract of *A. sativa* at 100 mg/kg is the most effective formulation in reducing behavioral despair. These results support the therapeutic potential of *A. sativa* as a natural antidepressant and highlight the importance of the extraction method and dose optimization in maximizing its efficacy (Fig. 2).

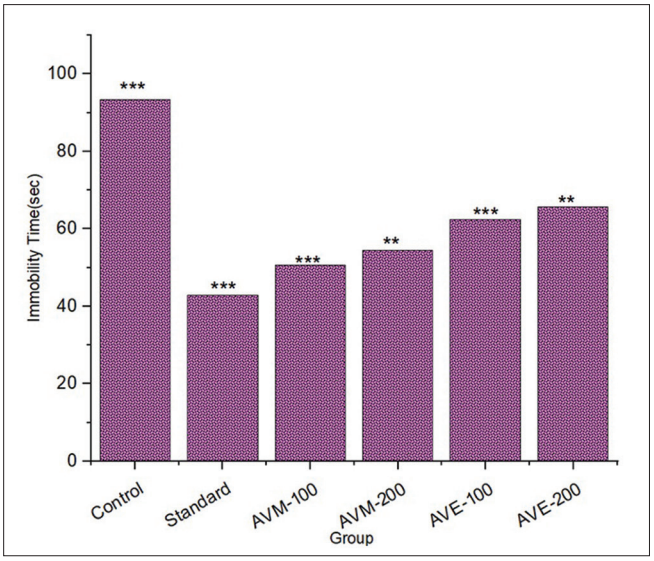

Fig. 2: Effect of arteriovenous methanolic and ethanolic extract of *Avena sativa* (100 and 200 mg/kg), standard fluoxetine (25 mg/kg) and control on duration of immobility time in tail suspension test. Results are presented as mean (n=6). ***p<0.0001 when compared with control experiments, **p<0.001 when compared with control experiments

Locomotor activity study

The analysis of locomotor activity revealed differential behavioral responses across treatment groups, providing insight into the central nervous system effects of *A. sativa* L. extracts. The control group exhibited a baseline locomotor count of 587, while the standard antidepressant group showed a moderate increase to 650, consistent with expected psychomotor activation associated with antidepressant efficacy. Among the experimental groups, the methanolic extract at 100 mg/kg (AVM-100) produced the highest locomotor count (680), suggesting a pronounced central stimulatory effect without signs of hyperactivity. This enhancement in locomotor behavior may reflect the reversal of psychomotor retardation – a core symptom of depression – and supports the antidepressant-like profile of AVM-100. The increase is likely attributable to the presence of neuroactive polyphenols, such as avenanthramides and flavonoids, which are known to modulate neurotransmitter systems and improve mitochondrial function**.** In contrast, AVM-200 (610 counts) showed a milder increase, indicating a possible dose-dependent plateau or reduced efficacy at higher concentrations. Ethanolic extracts (AVE-100 and AVE-200) demonstrated minimal changes (586 and 600 counts, respectively), suggesting limited central activation and weaker antidepressant-like potential. These findings align with the FST and TST results, reinforcing the conclusion that AVM-100 is the most effective formulation in promoting behavioral activation and alleviating depressive-like symptoms. Overall, the locomotor activity data support the therapeutic relevance of *A. sativa* methanolic extract, particularly at lower doses, and highlight the importance of extraction method and dose optimization in maximizing antidepressant efficacy (Fig. 3).

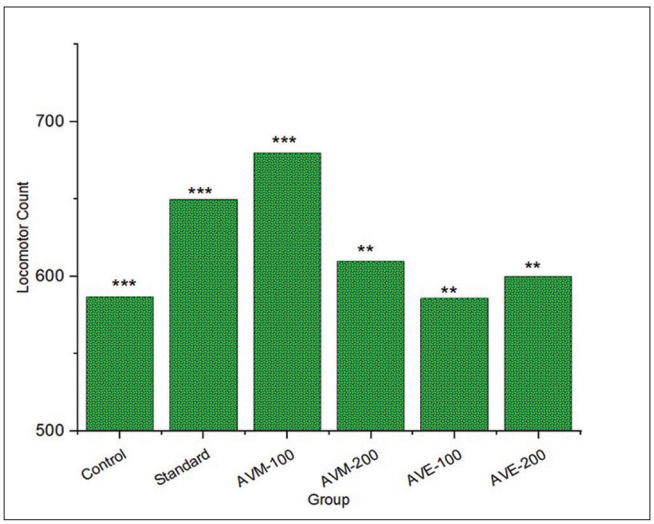

Fig. 3: Effect of arteriovenous methanolic and arteriovenous ethanolic extract of *Avena sativa* (100 and 200 mg/kg), standard fluoxetine (25 mg/kg) and control on locomotor activity. Results are presented as mean (n=6). ***p<0.0001 when compared with control experiments, **p<0.001 when compared with control experiments

The AVM-100 group exhibited the highest rearing frequency (Fig. 4a) among all experimental groups, followed by the Standard and AVM-200 groups, indicating enhanced exploratory behavior; in contrast, the AVE-100 and AVE-200 groups showed markedly reduced rearing activity, suggesting potential sedative or anxiogenic effects. Defecation levels (Fig. 4b) were highest in the Control and AVE-100 groups, while the Standard and AVM-100 groups showed markedly reduced defecation, suggesting a potential anxiolytic effect of the treatments; intermediate values were observed in the AVM-200 and AVE-200 groups

Limitations

One significant weakness of the current investigation is that the chemical makeup of the methanolic and ethanolic leaf extracts was not determined. Without phytochemical profiling, such as high-performance liquid chromatography (HPLC) or liquid chromatography-mass spectrometry (LC-MS) analysis, we cannot definitively determine which chemicals are responsible for the antidepressant properties. As a result, any mechanistic interpretations of avenanthramides, flavonoids, or other phytochemicals should be regarded as speculative.

Future scope

Future research should concentrate on the detailed phytochemical characterization of *A. sativa* leaf extracts using analytical techniques, such as HPLC, LC-MS, or Gas chromatography-mass spectrometry to determine the active ingredients responsible for the neuropharmacological effects. Individual compounds will be isolated and evaluated to further understand their distinct roles and mechanisms of action. In addition, investigating dose-response interactions and molecular pathways may improve *A. sativa*'s medicinal potential in depression management.

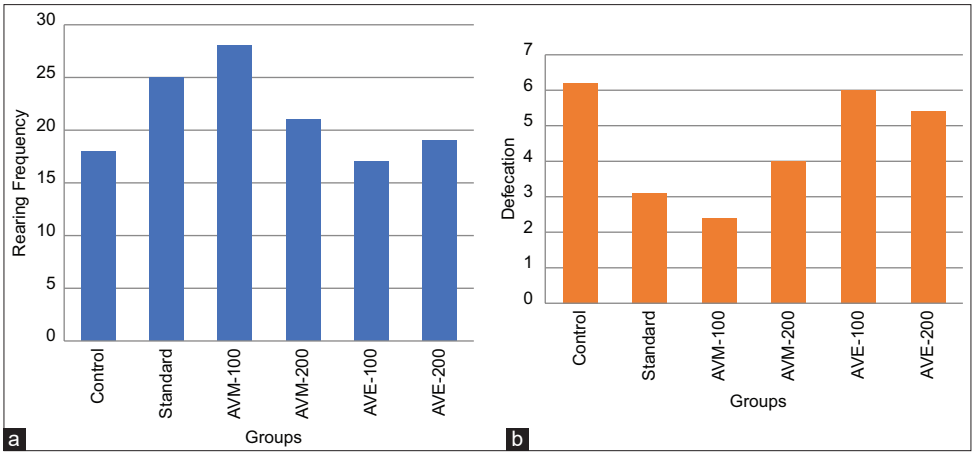

Fig. 4: Effect of arteriovenous methanolic and arteriovenous ethanolic extract of *Avena sativa* (100 and 200 mg/kg), standard fluoxetine (25 mg/kg) and Control on (a) rearing frequency, (b) Defecation

CONCLUSION

The present study demonstrates that methanolic and ethanolic extracts of *A. sativa* L. leaves are safe at a single oral dose of 2000 mg/kg, with no observable toxicity or behavioral abnormalities over a 14-day period. Behavioral evaluations using the FST and TST revealed that the methanolic extract at 100 mg/kg (AVM-100) produced the most significant reduction in immobility time, closely approximating the effect of the standard antidepressant. This suggests potent antidepressant-like activity, likely mediated by neuroactive phytochemicals, such as avenanthramides and flavonoids, which are known to modulate neurotransmitter systems and stress-response pathways. Locomotor activity analysis further supported these findings, with AVM-100 showing the highest count (680), indicating enhanced psychomotor function without signs of hyperactivity. This behavioral activation may reflect the reversal of psychomotor retardation, a core symptom of depression, and reinforces the therapeutic relevance of AVM-100. In contrast, higher doses of methanolic extract (AVM-200) and both doses of ethanolic extract (AVE-100 and AVE-200) exhibited moderate or minimal effects across all behavioral parameters, suggesting a non-linear dose-response relationship and highlighting the importance of extraction method and dose optimization.

Overall, the study supports the antidepressant potential of *A. sativa* L., particularly its methanolic extract at 100 mg/kg, and provides a scientific basis for its further development as a plant-based therapeutic agent for mood disorders.

ACKNOWLEDGMENTS

I would like to express my heartfelt gratitude to my supervisor, Dr. Nihar Ranjan Kar of Centurion University of Technology and Management, for his unwavering support, insightful guidance, and encouragement throughout the course of my research. I am also sincerely thankful to Dr. Nityananda Sahoo for his valuable assistance and contributions that enriched the quality of my work. My deep appreciation extends to Research Terminal, Hyderabad, for their technical support in conducting the animal activity studies, which played a vital role in the successful execution and progress of this project.

AUTHORS CONTRIBUTION

Manasi Khadanga: Conceptualization, literature search, writing – original draft. Nityananda Sahoo: Methodology, writing – review and editing, supervision. Nihar Ranjan Kar: Data curation, visualization, proofreading.

CONFLICT OF INTEREST

Nil.

FUNDING

Nil.

REFERENCES

1. Marx W, Penninx BW, Solmi M, Furukawa TA, Firth J, Carvalho AF, *et al*. Major depressive disorder. Nat Rev Dis Primers. 2023 Aug 24;9(1):44. doi: 10.1038/s41572-023-00454-1, PMID 37620370
2. Remes O, Mendes JF, Templeton P. Biological, psychological, and social determinants of depression: A review of recent literature. Brain Sci. 2021 Dec 10;11(12):1633. doi: 10.3390/brainsci11121633, PMID 34942936
3. Alberti A, Araujo Coelho DR, Vieira WF, Moehlecke Iser B, Lampert RM, Traebert E, *et al.* Factors associated with the development of depression and the influence of obesity on depressive disorders: A narrative review. Biomedicines. 2024;12(9):1994. doi: 10.3390/biomedicines12091994, PMID 39335507
4. Berk M, Köhler-Forsberg O, Turner M, Penninx BW, Wrobel A, Firth J, *et al*. Comorbidity between major depressive disorder and physical diseases: A comprehensive review of epidemiology, mechanisms and management. World Psychiatry. 2023 Oct;22(3):366-87. doi: 10.1002/wps.21110, PMID 37713568
5. Ţ7713568NK ŞT, Dinescu VC, Gheorman V, Dragne IG, Gheorman V, Forţofoiu MC, *et al*. Exploring multidisciplinary approaches to comorbid psychiatric and medical disorders: A scoping review. Life (Basel). 2025 Feb 6;15(2):251. doi: 10.3390/life15020251, PMID 40003660
6. Milic J, Jovic S, Sapic R. Advancing depression management through biomarker discovery with a focus on genetic and epigenetic aspects: A comprehensive study on neurobiological, neuroendocrine, metabolic, and inflammatory pathways. Genes. 2025 Apr 25;16(5):487. doi: 10.3390/genes16050487, PMID 40428308
7. Jentsch MC, Van Buel EM, Bosker FJ, Gladkevich AV, Klein HC, Oude Voshaar RC, *et al*. Biomarker approaches in major depressive disorder evaluated in the context of current hypotheses. Biomark Med. 2015 Mar 1;9(3):277-97. doi: 10.2217/bmm.14.114, PMID 25731213
8. Correia AS, Cardoso A, Vale N. Highlighting immune system and stress in major depressive disorder, Parkinson's, and Alzheimer's diseases, with a connection with serotonin. Int J Mol Sci. 2021 Aug 7;22(16):8525. doi: 10.3390/ijms22168525, PMID 34445231
9. Perkovic MN, Erjavec GN, Strac DS, Pivac N. Biomarkers of depression: Potential diagnostic tools. In: Kim YK, editor. Understanding Depression. Vol. 2. Clinical Manifestations, Diagnosis and Treatment. Singapore: Springer; 2017 Oct 25. p. 35-51. doi: 10.1007/978-981-10-6577-4_3
10. Balakrishnan R, Azam S, Cho DY, Su-Kim I, Choi DK. Natural phytochemicals as novel therapeutic strategies to prevent and treat Parkinson's disease: Current knowledge and future perspectives. Oxid Med Cell Longev. 2021;2021(1):6680935. doi: 10.1155/2021/6680935, PMID 34122727
11. Kabra A, Garg R, Brimson J, Živković J, Almawash S, Ayaz M, *et al.* Mechanistic insights into the role of plant polyphenols and their nano-

formulations in the management of depression. Front Pharmacol. 2022 Nov 7;13:1046599. doi: 10.3389/fphar.2022.1046599, PMID 36419621

12. Kennedy DO, Bonnländer B, Lang SC, Pischel I, Forster J, Khan J, *et al*. Acute and chronic effects of green oat (*Avena sativa*) extract on cognitive function and mood during a laboratory stressor in healthy adults: A randomised, double-blind, placebo-controlled study in healthy humans. Nutrients. 2020 May 29;12(6):1598. doi: 10.3390/nu12061598, PMID 32485993
13. Hassamal S. Chronic stress, neuroinflammation, and depression: An overview of pathophysiological mechanisms and emerging anti-inflammatories. Front Psychiatry. 2023 May 11;14:1130989. doi: 10.3389/fpsyt.2023.1130989, PMID 37252156
14. Perrelli A, Goitre L, Salzano AM, Moglia A, Scaloni A, Retta SF. Biological activities, health benefits, and therapeutic properties of avenanthramides: From skin protection to prevention and treatment of cerebrovascular diseases. Oxid Med Cell Longev. 2018;2018(1):6015351. doi: 10.1155/2018/6015351, PMID 30245775
15. Tripathi V, Singh AS, Ashraf MT. Avenanthramides of oats: Medicinal importance and future perspectives. Pharmacogn Rev. 2018 Jan 1;12(23):66. doi: 10.4103/phrev.phrev_34_17
16. Liu J, Meng T, Wang C, Cheng W, Zhang Q, Cheng G. Natural products for the treatment of depression: Insights into signal pathways influencing the hypothalamic-pituitary-adrenal axis. Medicine (Baltimore). 2023 Nov 3;102(44):e35862. doi: 10.1097/MD.0000000000035862, PMID 37932977
17. Yousuf S, Marifatul Haq SM, Rasool A, Zulfajri M, Hanafiah MM, Nafees H, *et al*. Evaluation of antidepressant activity of methanolic and hydroalcoholic extracts of *Acorus calamus* L. rhizome through tail suspension test and forced swimming test of mice. J Tradit Chin Med Sci. 2020 Sep 1;7(3):301-7. doi: 10.1016/j.jtcms.2020.07.002
18. Suryawanshi MR, Kanhed AM, Kulkarni VM, Bhosale SH, Yadav MR. Design, synthesis, and computational studies of phenylacetamides as antidepressant agents. Mol Divers. 2022 Dec;26(6):3157-72. doi: 10.1007/s11030-021-10374-5, PMID 35128584
19. Alsalem M, Haddad M, Altarifi A, Aldossary SA, Kalbouneh H, Abojaradeh AM, *et al.* Impairment in locomotor activity as an objective measure of pain and analgesia in a rat model of osteoarthritis. Exp Ther Med. 2020 Dec;20(6):165. doi: 10.3892/etm.2020.9294, PMID 33093903
20. Stephy PP, Mohan PK, Ajeesh Krishna TP, Ajeesh Krishna TP, Selva Kumar S, Walter Christhuraj C, *et al*. Pharmacognostical studies of the leaf and stem of *Tetrastigma leucostaphylum* (Dennst.) Alston ex Mabb. with special reference to soil chemistry. Vegetos. 2025 Sep 3;38:1-3.
21. Ifora I, Hamidi D, Susanti M, Wahyuni FS. Enhanced combined effects of *Garcinia cowa* bark extract and doxorubicin on cell cycle regulation and P53 expression in T47d breast cancer cells. Int J App Pharm. 2025 Nov 7;17(6):471-7.
22. Rajendra PP, Kumar M. Synthesis and optimization of magnesium Aluminometasilicate-templated mesoporous nanoparticles for cannabidiol delivery: A novel approach. Int J Appl Pharm. 2025 Nov 7;17(6):451-63.