Nigerian Journal of Pharmaceutical Sciences
Vol. 24, No1, 2025, ISSN: 0189-823X

ANTIDEPRESSANT ACTIVITY OF METHANOL LEAF EXTRACT OF *ZIZIPHUS MAURITIANA* LAM IN SWISS ALBINO MICE

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ABSTRACT

The leaves of *Ziziphus mauritiana* have been reported to be used in the management of depressive illnesses in traditional medicine. The present study aimed at investigating the antidepressant activity of the methanol leaf extract of *Ziziphus mauritiana* (25, 50,100 and 200 mg/kg) using tail suspension (TST) and forced swim tests (FST) while the effect of the extract on recognition memory, motor coordination, and exploration activity was also evaluated using novel object recognition (NORT), beam walking assay (BWAT) and open field tests (OFT) respectively in mice. The LD_{50} of the extract was found to be above 5000 and phytochemical constituents such as flavonoids, cardiac glycoside, and alkaloids were present. The extract significantly decreased the duration of immobility in the TST and FST and produced insignificant change in exploratory activity and motor coordination in OFT and BWAT when compared with the control group. The methanol leaf extract of *Ziziphus mauritiana* possesses antidepressant property.

Keywords: *Ziziphus mauritiana;* Depression; antidepressant; tail suspension test

INTRODUCTION

Depression is a neuropsychiatric disorder affecting a huge percentage of the active population especially in developed country and significant contributor to the global burden of disease that affect people in all communities across the world (WHO, 2023) with steadily increasing incidence and major socio-economic consequences and has become an important public health problem projected to be the leading cause of mental illness by 2030 (Gbadamosi *et al*., 2022). These problems can become chronic or recurrent and lead to substantial impairments in an individual ability to take care of his or her everyday responsibilities, and at worst it can lead to suicide (WHO, 2012). The total estimated incidence of people living with depression increased worldwide by 49.86%, from 172 million in 1990 to 258 million in 2017, with a notable increase in Western sub-Saharan Africa of 124.42% (Suraj *et al.,* 2021). More than 700 000 people die due to suicide every year and thus considered the fourth leading cause of death in 15–29-year-olds (Global Health Data Exchange (GHDx), 2023, White House Conference on Mental Health, 1999). The complexity and heterogeneity of depression make it difficult to identify a single underlying abnormality, and suggest that there are multiple causes of depression (Bun Hee and Yong, 2010), such as unemployment and poverty, old age, illness, medical conditions, Hormonal factors, malnutrition, neurotransmitter malfunction, responsibilities at work and home, single parenthood, mental abuse, and unequal parental treatment of sibling, physical or

sexual abuse, catastrophic injury and social rejection (Lindert *et al.,* 2014).

The prevalence of depression is about 322 million people globally (Liu *et al*., 2020), 2% in Oyo State, Nigeria, more among women than men and adolescents, more in the rural areas than in the urban areas of Ibadan, Nigeria (Amoran *et al.,* 2007), more in resident doctors than non-resident doctors 3 South-East state of Nigeria (Aguocha *et al*., 2015), more among Nigerian college students with alcohol dependence (Abiodun, 2006). Depression is projected to reach second place as leading contributor to the global burden of disease following cardiac disease by the year 2030 (Li *et al*., 2017). The high lifetime prevalence of this disabling condition, coupled with limitations in existing medications, make it necessary for the development of improved therapeutics (Nollet *et a*l., 2013). Additionally, many of these patients who show remission with antidepressant therapy present a relapse of depression upon treatment cessation (Neto *et al*., 2011). However, these modern treatments are expensive, complex and inaccessible for African populations in rural area and medicinal plants have been used as main sources of therapeutic agents for mankind (Samina *et al.,* 2017). A number of medicinal plants have been reported to be used in management of psychiatric illnesses including depressive illness in Northern Nigeria one of such plant is *Ziziphus mauritiana* or Jujubes which is a called ziziphon in Arabic, jujube, Indian plum, Chinese apple in English, or magarya in Hausa.

The preliminary phytochemical screening of the plant methanol extract identified the presence of saponin, tannins, flavonoids and alkaloids which may be responsible for neuroprotective, hemo-preventive (Samina *et al.,* 2017), anti-nephritic (David *et al*., 2017), antidiabetic (Najafi *et a*l., 2013), anxiolytic (Liu et al., 2003), antipyretic (AbdulRauf *et al*., 2016), learning and memory enhancement (Une *et al*., 2012), Cognition effects (Sadiq *et al.*, 2011), and many part of the plant has been reported to be useful in treatment of CNS disorders such as seizures and convulsion.

However, there is paucity of information on the antidepressant effect of *Ziziphus Mauritania* lam as it is always included as part of ingredient used for exorcism in psychological disorder therapy locally in Northern Nigeria and this work will attempt to bridge this gap of knowledge. The present study therefore aimed at investigating the antidepressant properties of methanol leaf extract of *Ziziphus mauritiana.*

MATERIALS AND METHODS

Reagents and Chemicals

Imipramine (Tofranil GSK brand USA, Batch Number: 0624), Normal saline (Dana Pharmaceuticals Ltd), Distilled water.

Instruments and Equipment

Stainless Steel Cages, Saw Dust, Feeds, Weighing Balance, Beaker, Cotton Wool, Methylated spirit tissue, Heater, Bucket, Feeder, 2ml syringes, oral cannula, mortar and pestle, top Watch, Masking Tape Marker, Sucrose, Digital Cameras (JVC Micro HDD, Hard disc Cam recorder (Everio 30GB,35xOptical zoom/AF,Hybrie:LY36228-001A, F=2.2,Company Name: Victor Company of Japan, Ltd. and Samsung (ES95) N363 F2.5 bright lens 5x optical zoom,6.2 Mega Pixels DC=5.0V,S/N AZZQCNNOD-00EKJ).

Plant Collection, Identification and Extract Preparation

The leaves of *Ziziphus mauritiana* plant attached to the stalk were collected from Tudun wada, Zaria, Kaduna state in March, 2015. The sample was identified by Dr Sunusi Namadi at Herbarium section of the Department of Botany, Ahmadu Bello University, Zaria, by comparing with existing specimen (VSN:90123).

Fresh *Ziziphus mauritiana*, were air dried under shade and subsequently size-reduced into coarse powder. The dried powder material was extracted with 500 ml of methanol (95%) using maceration method. The filtrate was allowed to evaporate to dryness and the extract was then stored in a desiccator until needed for use. Solution of the extract was freshly prepared for each experiment.

Experimental Animals

One hundred and forty-four (144) apparently healthy Swiss Albino mice weighing between 19 –22 g were used for this study. The animals were obtained from the Animal House of the Department of Pharmacology and Therapeutics, Ahmadu Bello University Zaria. The mice were kept in a well-ventilated cage with normal photoperiod and were allowed to acclimatize to the housing and experimental conditions for two weeks. They were given access to standard animal feeds and tap water *ad libitum*. Ethical Approval for the study was sought and obtained from the Ahmadu Bello University Committee on Animal Use and Care (ABUCAUC) with approval number ABUCAUC/2023/015.

Phytochemical Analysis

Phytochemical screening was conducted according to the standard protocol (Evans, 1996).

Acute toxicity study (LD_{50})

The acute toxicity study was carried out based on the method described by Lorke (1983). Briefly, the method was done in two phases, in the first phase, three groups of three mice each were treated orally with dose of 10, 100 and 1000 mg/kg body weight and observed for signs and symptoms of toxicity and death for 24 hours. In the second phase, three groups each containing one mouse was treated with three more specific doses of the extract (2900 and 5000 mg/kg). After oral administration of extract, animals were also observed individually for signs of toxicity such as behavioral changes including convulsion, difficulty in movement, tremor, salivation, writhing and death for 24 hours. The LD_{50} was determined by calculating the geometric mean of the lowest dose that caused death and the highest dose for which the animal survived (0/1 and 1/1) (Lork, 1983).

Animal groupings and Treatment

Thirty-six mice were divided into six groups of six mice each. Group 1 were treated with 10 mL/kg normal saline orally, groups 2, 3, 4 and 5 were treated with the respective doses of 25, 50,100 and 200 mg/kg of methanol leaf extract of *Ziziphus mauritiana* orally. Group 6 were orally treated with imipramine 20 mg/kg orally. All the behavioural tests were carried out on daily basis separately on different animals. The mice were subjected to the behavioural tests 1 hour after the administration of the extract.

Tail Suspension Test (TST)

One hour post treatment, mice were suspended on the edge of the shelf 58 cm above a table top by adhesive tape placed approximately 1 cm from the tip of their tail. The duration of immobility was then recorded for a period of 6 minutes (Steru *et al*., 1985). Typically, Mice consider

immobile only when they hung passively and completely motionless (Cryan *et al.*, 2005). The animals were used only once in this test. The apparatus was cleaned with 70% ethanol in between the test. All tail suspension tests were performed between 10:00 am and 14:00pm

Forced Swim Test (FST)

One hour post treatment, each mouse was placed in a plexiglass cylinder tank of 40 cm height and 18 cm width filled with 15 cm water at 25℃. The total duration of immobility was measured over 5 minutes. The experiment was recorded with the aid of a camera suspended at the top of the apparatus. A mouse was considered immobile whenever it remained floating passively in the water in a slightly hunched but upright position with its nose just above the surface (Porsolt, 2000). Following swimming sessions, they were then towel dried and returned to their housing condition. The animals were used only once in this test. All the forced swim tests were performed between 10:00 am and 14:00

Open Field Test (OFT)

One hour after treatment, mice were individually handled by the base of their tails at all times and placed into the center or one of the four corners of the apparatus (white Plexiglas box (70 x 70 x 35cm, length, breath and height of which the floor was divided into 16 visible squares (15 x 15cm) with a central square), and allowed to explore for 5 minutes. The behaviour of each rodent was recorded with the aid of a camera. The apparatus was cleaned with 70 % ethyl alcohol and permitted to dry between the tests to remove any olfactory cue (Careau *et al.*, 2012).

Beam walking assay

Fine motor coordination and balance were assessed using narrow beam measures 1-3 cm wide and is elevated between a pole (Luong *et al*., 2011).The mice were previously trained for 2 days to recognize a goal box by allowing them to walk on ruler of length 80cm, width 3cm placed 30cm above the table by a wooden support to a targeted goal box thrice to be aware that there was a goal box that could be reached, and mice that passed the trials were recruited in this test. One hour after the treatment, each mouse was placed at one end of the beam which was 60 cm long, 8 mm in diameter and elevated 30 cm above a table and allowed to walk to the targeted goal box. Fallen mice were returned to the point of fall, a maximum of one minute was allowed on beam. The number of foot slips (one or both hind limbs slipped from the beam) was counted (Stanley *et al.,* 2012).

Novel Object Recognition Test (NORT)

An hour post treatment each mouse was introduced in to 3 sessions of tests, habituation day, training day, and testing day. During the Habituation Day or orientation day, the mouse was allowed to explore the empty arena for 2 minutes. On the Training day or exploration day, the mouse was allowed to explore 2 identical objects placed at the same length for 10 minutes while on the Test day or experimental day, one of the two objects was replaced with a novel object and mouse was allowed to explored for 5 minutes and time taken for novel and familiar object exploration were recorded with the aid of a camera suspended at the top of the apparatus (Huang *et al*., 2014).The apparatus was cleaned with 70% ethanol solution between the test. Exploration time for the objects by each mouse was hand-scored using stopwatches. Mice with exploration time

less than 3 seconds were not used for the test. Exploration of object is taken as the animal moving its nose close to the object at a distance of about 2 cm. In addition, if animal placed the fore paws on the objects but not climbing it is considered exploration. Data from this test were expressed as (1) exploration time (in seconds) of each object which was calculated as time spent exploring familiar or novel object by total exploration time of both objects and (2) a discrimination index (DI) between objects, calculated as the exploration time difference between the novel object (N) and the familiar object (F) divided by the total exploration time of both objects (DI = [N–F)/(N+F)], a high significant discrimination index reflects good recognition memory (Lueptow, 2017).

Statistical Analysis

All values were evaluated using SPSS version 22.0 software. Results were presented as means ± SEM and analyzed using One-way ANOVA followed by the Bonferroni post *hoc* test for multiple comparisons. Significant level was set when *p* less than 0.05 when compared with control group.

RESULTS

The Phytochemical Screening of the *Ziziphus mauritiana* Leaf

The phytochemical analysis of *Ziziphus mauritiana* leaf revealed the presence of alkaloids, carbohydrates, cardiac glycosides, flavanoids, saponins, steroid, triterpenes and tannins. However, anthraquinones were absent (Table 1).

Acute Toxicity Study of Methanol Leaf Extract of *Ziziphus mauritiana*

The median lethal dose (LD_{50}) of Methanol leaf extract of *Ziziphus mauritiana* was estimated to be above 5000 mg/Kg body weight.

Effect of Methanol Leaf Extract of *Zizipus mauritiana* on Immobility of Mice in Tail Suspension Test

The methanol leaf extract of *Ziziphus mauritiana* at 25 mg/kg and 200 mg/kg significantly decreased duration of immobility when compared with the distilled water [F (5, 30) =29.401, $p<0.001$] (Table 2). However, significant decrease in duration of immobility in the Imipramine 20 mg/kg treated group was also observed.

Table 1. Phytochemical Constituents of the Analysis of Methanol Leaf Extract of *Ziziphus mauritiana* Lam

S/NO	Constituents	Test Inferences	Inferences
1	Carbohydrates	Molisch test	+
2	Anthraquinones	Bontrager's test	-
3	Glucosides	Fehling test	+
4	Cardiac glycosides	Kelle Killiani test	+
5	Saponins	Frothing test	+
6	Steroid and interpenes	Lieberman Burchard test	+
7	Flavonoids	Shinoda test	+
8	Alkaloids	Dragendorff test	+
9	Tannins	Ferric Chloride test	+

KEY: + = Presence - = Absence

Table 2. Effect of the Methanol Leaf Extract of *Ziziphus mauritiana* on Immobility Time (TST) in Mice

Treatment Group	Immobility time (sec)
DW 10 ml/kg	309.50 ±10.93
ZZM 25 mg/kg	183.50 ±17.64*
ZZM 50 mg/kg	275.83 ±7.15
ZZM 100 mg/kg	270.12 ±6.97
ZZM 200 mg/kg	198.00 ±8.74*
Imipramine 20 mg/kg	137.00±16.90*

Animals were treated once with Methanol Leaf Extract of *Ziziphus mauritiana* (25, 50,100, 200 mg/kg *po*), Distilled water (10ml/kg), or Imipramine (20mg/kg *po*). The table represent the mean ±SEM of 6 animals. Data was analyzed using one way ANOVA followed by Bonferroni post hoc test, *$p \leq 0.001$ significantly different from Distilled water treated animals. ZZM= Methanol Leaf Extract of *Ziziphus mauritiana,* DW= Distilled water.

Effect of Methanol Leaf Extract of *Zizipus mauritiana* on Immobility of Mice in Forced Swim Test (FST)

The Methanol leaf extract of *Ziziphus mauritiana* at 100 mg/kg significantly decrease the duration of immobility, when compared with the distilled water [F (5, 30) =7.072*, p=0.07*]. However, significant decrease in duration of immobility in the Imipramine 20mg/kg treated group was also observed (Table 3).

Table 3. Effect of the Methanol Leaf Extract of *Ziziphus Mauritiana* Lam on Duration of Immobility of Mice in FST (Forced Swim Test)

Treatment Group	Immobility time (sec)
DW 10 ml/kg	117.00±7.84
ZZM 25 mg/kg	152.33±16.83
ZZM 50 mg/kg	160.33±14.93
ZZM 100 mg/kg	165.00±10.30*
ZZM 200 mg/kg	158.33±9.28
Imipramine 20 mg/kg	85.50±9.61*

Animals were treated once with Methanol Leaf Extract of *Ziziphus mauritiana* (25, 50,100, 200 mg/kg po), Distilled water (10ml/kg), or Imipramine (20mg/kg po). The Table represent the mean ±SEM of 6 animals. Data was analyzed using one way ANOVA. *p < 0.05 significantly different from Distilled water treated animals. ZZM= Methanol Leaf Extract of *Ziziphus mauritiana*, DW= Distilled water.

Effect of Methanol Leaf Extract of *Zizipus mauritiana* on behaviour of Mice in Open Field Test (OFT)

There was no statistically significant difference in the numbers of line crossing among the animals treated with the methanol leaf extract of *Ziziphus mauritiana* at all the tested doses [F (5,30) =2.407, *p=0.060].* (Table 4).

Table 4. Effect of the Methanol Leaf Extract of *Ziziphus mauritiana* on Gross Locomotion in Open Field Test (OFT) by Mice

Treatment Group	Frequency of Line crossing
DW 10 ml/kg	109.17±11.91
ZZM 25 mg/kg	84.33±14.78
ZZM 50 mg/kg	111.33±12.91
ZZM 100 mg/kg	78.33±11.06
ZZM 200 mg/kg	113.00±8.09
Imipramine 20 mg/kg	76.50±10.04*

Animals were treated once with Methanol Leaf Extract Methanol of *Ziziphus mauritiana* (25, 50,100, 200 mg/kg *po*), Distilled water (10ml/kg), or Imipramine (20mg/kg *po*). The Table represent the mean ±SEM of 6 animals. Data was analyzed using one way ANOVA followed by Dunnet post hoc test; **p< 0.05* insignificantly different from Distilled water treated animals. ZZM= Methanol Leaf Extract of *Ziziphus mauritiana,* DW= Distilled water

Effect of Methanol Leaf Extract of *Zizipus mauritiana* on behaviour of Mice in Beam Walking Assay Test (BWAT)

The Methanol leaf extract of *Ziziphus mauritiana* increased the number of foot slips but was not statistically significant difference when compared with the control at all the tested doses [F (5, 29) =0.969, *p>0.05*] (Figure 1).

Effect of Methanol Leaf Extract of *Zizipus mauritiana* on behaviour of Mice in Novel Object Recognition Test

There was no statistically significant difference in novel object exploration and familial object exploration among the animals treated with methanol leaf extract of *Ziziphus mauritiana,* at all the tested doses and Imipramine F (5,30) =0.536, *p<0.747*], F (5,30) =2.572, *p=0.48*] respectively (Table 6 and 7). However, there were also no statistically significant difference in percentage preference in novel object exploration among the animals treated with methanol leaf extract of *Ziziphus mauritiana* at all the tested doses and Imipramine when compared with distilled water [F (5,30) =1.786, *p=0.147*] (Figure 2).

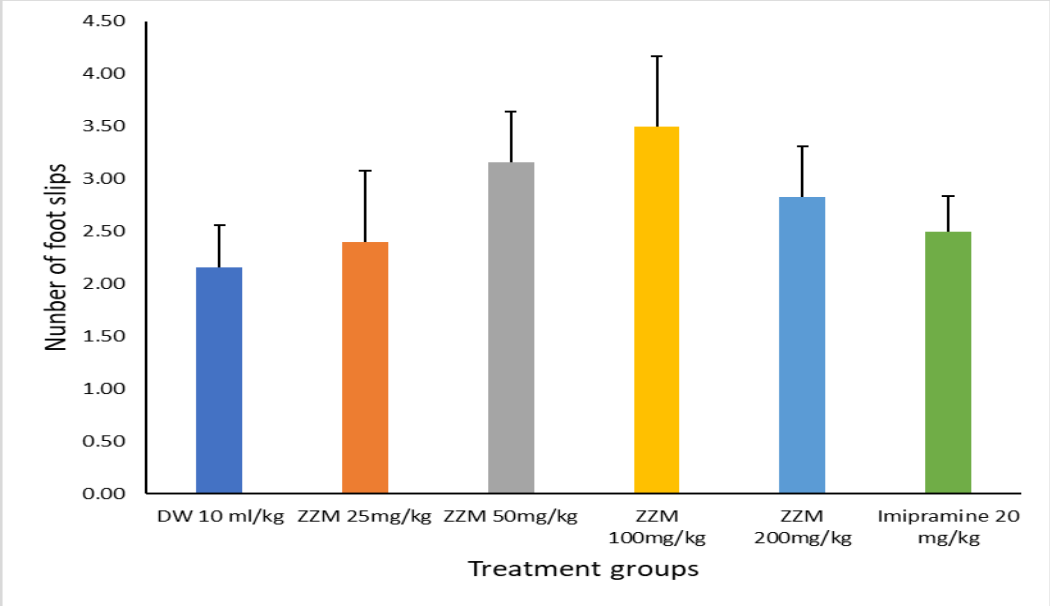

Figure 1. Effect of the Methanol Leaf Extract of *Ziziphus mauritiana* on Motor Coordination in Mice

Animals were treated once with Methanol Leaf Extract of *Ziziphus mauritiana* (25, 50,100,200mg/kg *po*), Distilled water (10ml/kg), or Imipramine (20mg/kg *po*). Each column represents the mean ±SEM of 6 animals. Data was analyzed using one way ANOVA. *p>0.05* insignificant different with distilled water treated animal. ZZM= Methanol Leaf Extract of *Ziziphus mauritiana,* DW= Distilled water.

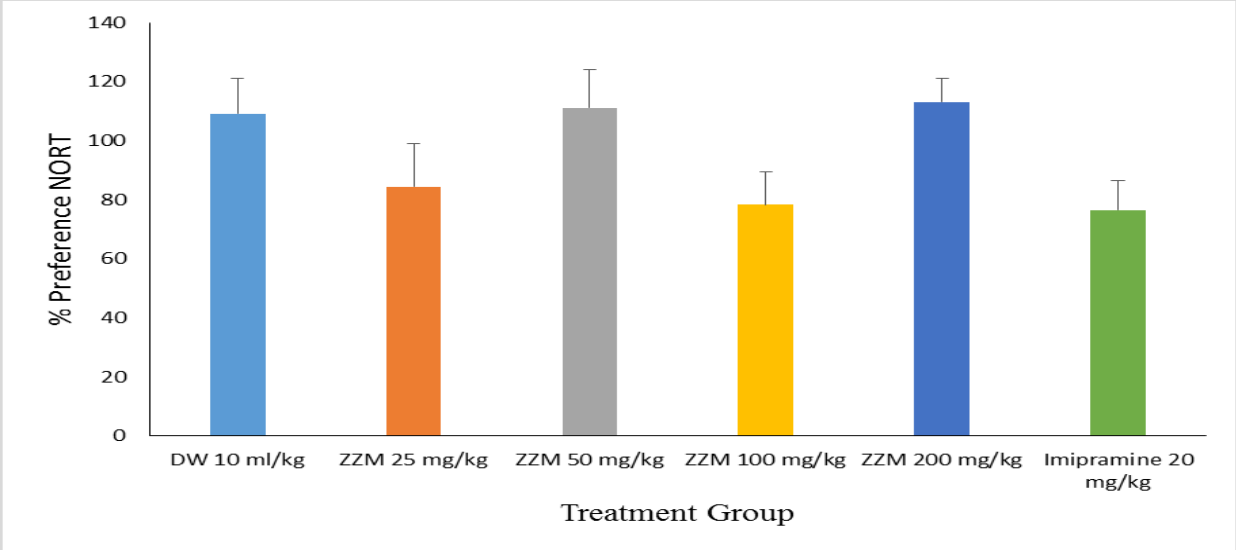

Figure 2. Effect of the Methanol leaf extract of *Ziziphus Mauritiana* on percentage preference in Mice

Animals were treated once with Methanol Leaf Extract of *Ziziphus mauritiana* (25, 50,100, 200 mg/kg *po*), Distilled water (10ml/kg), or Imipramine (20mg/kg *po*). Each column represents the mean ±SEM of 6 animals. Data was analyzed using one way ANOVA. ZZM= Methanol Leaf Extract of *Ziziphus mauritiana,* DW= Distilled water.

DISCUSSION

Several challenges plague current treatments that limit the extent of the use of current antidepressants, from the onset of medication to effective therapeutic benefits, can result in exacerbation of depressive symptoms (Ismail *et al*., 2022). *Ziziphus mauritiana* is one of the medicinal plants that have been used as a source of important therapeutic agent in treatment of neuropsychiatric disorder. The leaves are ubiquitous, accessible and easy to use and well tolerated. Therefore, this study was designed to study the antidepressant activity of the Methanol leaf extract of the *Ziziphus mauritiana*. The biological or pharmacological actions of different part of these plants are due to the presence of specific phytochemical constituents (Beg *et al*., 2017). The LD_{50} of the extract was found be greater than 5000 mg/kg orally and is therefore safe for used as an indicated for been nontoxic as described by Lorke (1983). The mice pretreated with the methanol leaf extract of *Ziziphus mauritiana* significantly showed a decrease in immobility time when compared with the distilled water, and the result was quite comparable to imipramine that is the tricyclic antidepressant agent used as standard drug for the test. This may indicate that the extract possessed antidepressant activity on the central nervous system probably have been linked to the presence of saponins, flavonoids and alkaloids present in the extract. Therefore, the research of Liu *et al.* (2012) was in line with the present study who reported the antidepressant like effect of the ethanolic extract of *Ziziphus* specie in rat and Sharma *et al*. (2009) also reported the anti-depressant Activity of *Zizyphus xylopyrus*.

Forced swimming test was also conducted to screened the antidepressant activity of the extract, in contrast to the TST, FST has a risk of hypothermia due to submersion in water (Porsolt *et al.*, 1987), and has not been viewed as a consistent model for observing selective serotonin reuptake inhibitory action (Cryan *et al*., 2005). Therefore, deccrease in duration of immobility was observed also in forced swim test in the extract treated group.

This work also established that the methanol leaf extract of *Ziziphus mauritiana* has no any motor coordination effect (CNS inhibitions), since it did not produce a significant change in number of foot slips of mice in the beam walking assay. Additionally, Open field test was conducted to further eliminated the probability of false positive results in FST and TST as it was observed that there was an insignificant change in locomotion activity (number of line crossing), and exploratory behaviour (frequency of rearing) in methanol leaf extract of *Ziziphus mauritiana* in comparison with the distilled water and this suggested that the extract does not possess psychostimulatory effect (CNS stimulation). In the NORT, the Methanol leaf extract of *Ziziphus mauritiana* showed insignificant increase in novel object exploration, familial object exploration, and percentage preference for novel object when compared with the control and this suggested that the extract neither impair nor improve cognitive function (learning and memory capacities) following acute administration at the tested doses in mice. However, the work of Sadiq *et al*. (2009) stated that *Ziziphus mauritiana* seed extract has not improve spatial recognition memory on rats as measured by the Y –Maze which was greatly produced by the portion extracted by ethyl acetate and Une *et al*. (2012) also stated that the n-butanolic fraction of methanol extract of leaves of *Ziziphus mauritiana* antagonized the amnesic effect of scopolamine, improved learning, memory and cognition on the NORT in mice.

CONCLUSION

The methanol leaf extract of *Ziziphus mauritiana* lam possesses antidepressant activity. Further study to confirm and biochemically assay the exact antidepressant mechanism of the methanol leaf extract of *Ziziphus mauritiana* is essential.

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