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ANTIDEPRESSANT-LIKE EFFECTS OF METHANOL LEAVES EXTRACT OF *Leptadenia hastata* (Asclepidiaceae) IN MICE

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ABSTRACT

Depression is a serious disorder that affects people in all communities across the world, a major cause of disability and morbidity worldwide. The drugs used in its management are associated with adverse effects and delayed response, hence it's important to look for antidepressant plants with proven advantages and favourable benefits. Leptadenia hastata (Pers.) Decne belongs to the family Asclepidiaceae and is widely used in Tropical Africa as a vegetable due to its low toxicity and therapeutic benefits, it is used in the treatment of evil spirit, psychiatric disorders and hallucination. The aim of this study was to evaluate the antidepressant-like effect of the methanol leaves extract of Leptadenia hastata (LHME) and its fractions. Phytochemical screening and acute toxicity (LD_{50}) study were done using standard procedures. Antidepressant-like effects of the LHME and its fractions was evaluated using the tail suspension test (TST) and forced swim test (FST). The intraperitoneal (i.p) median lethal dose was estimated to be > 5000 mg/kg. The LHME and Residual aqueous fraction (RAF) at dose 250-1000 mg/kg are significantly ($P<0.05$) and dose-dependently, while n-butanol fraction (NBF) at 400 mg/kg decreased the duration of immobility in the TST and FST respectively. There was no significant change in the number of squares crossed in the OFT. In conclusion, the L. hastata plant possesses antidepressant-like effects.

Keywords: Depression, Forced swim test, Leptadenia hastata, Medicinal plant and Tail suspension test

INTRODUCTION

Depression is a mental disorder that presents with depressed mood, loss of interest or pleasure (anhedonia), feelings of guilt or worthlessness, disturbed sleep (insomnia or hypersomnia), and anxiety (APA, 2013). Depression is a significant contributor to the global burden of diseases and a life-threatening disorder that affects hundreds of millions of people in all communities across the world (WHO, 2012). Almost 1 million lives are lost yearly due to suicide, which translates to 3000 suicide deaths every day (WHO, 2017). However, a number of synthetic drugs are being used as the standard treatment for depression, they have adverse effects that can compromise the therapeutic treatment, these common adverse effects include dry mouth, fatigue, gastrointestinal or respiratory problems, anxiety, agitation, drowsiness, and cardiac arrhythmias (Dhingra *et al*. 2005). Furthermore, medicinal plants continue to provide a vital role as remedies in the treatment of human diseases and disorders (Sani *et al*. 2018). Significant numbers of medicinal plants are in use in the traditional Ayurvedic and Unani system of medicine in India with the various part of the plants such as leaves, roots, bark, stems, seeds, flowers and fruits are used for medicinal purposes (Dhamijia *et al*. 2011).

Leptadenia hastata belongs to the family Asclepidiaceae widely used in Tropical Africa as food and medicinal plants (Burkil, 1985). The plant is medicinally important in the treatment of many ailments, used to ease labour, back pain and scorpion bite (Hussain and Karatela, 1989; Salamatu, 2009), scabies, sexual potency, hypertension and skin diseases (Dambatta and Aliyu, 2011). This plant appears to be benign with low toxicity and used in the treatment of evil spirit, Psychiatric disorders, loss of consciousness, hallucination and urinary ailments (Burkill, 1985; Hussain and Karatela, 1989; Kinda *et al.* 2017).

Despite these effects on the aspect of CNS, there has not been any report of its effect on depression which is also a pathological state of CNS. Therefore, the present study aimed to evaluate the antidepressant-like effects of LHME and its fractions using forced swim test (FST), tail suspension test (TST) models in mice.

MATERIALS AND METHODS

Drugs and Chemicals

The chemicals used for the experiment included: Imipramine (Tofranil® GSK, Britain), Methanol, n-Butanol, Ethylacetate, Chloroform (Sigma Aldrich, USA) and distilled water.

Collection of plant material

The leaves of *L. hastata* was collected from Kumbotso in Kano State, Nigeria in September 2017. It was authenticated by a botanist at the Department of Biological Sciences Herbarium; Bayero University, Kano with a voucher specimen number (BUKHAN 0248) deposited in the herbarium for future reference.

Preparation of plant extract

Fresh leaves of *L. hastata* was dried under shade for three weeks after which they were blended using mortar and pestle, sieved until a fine powder that weighed 1000 g was produced. The powdered plant material was cold macerated with 5 L 70 % ^{v}/v methanol with constant shaking for 7 days and then filtered using Whatman filter paper No 1. The filtrate was then concentrated to dryness in an oven at 45°C, which was then kept in desiccators for use in the study. The percentage yield was then calculated.

Experimental Animals

Swiss albino mice of either sex weighing (18 to 22 g) were obtained from Animal House Facility of Department of Pharmacology and Therapeutics, Faculty of Pharmaceutical Sciences, Bayero University, Kano. Mice were housed in standard cages under natural day and light cycle. The animals were fed on standard laboratory animal diet and water *ad libitum.* All experimental protocols were as approved by the University Animal Ethics Committee with reference number BUK/CHS/REC/VII/53.

Phytochemical screening

Freshly prepared The *L. hastata* methanol leaves extract (LHME) and its fractions were subjected to phytochemical tests for the detection of various chemical constituents using standard protocols (Evans, 1996).

Acute toxicity studies

The median lethal dose (LD_{50}) of the extract and fractions was determined using the method described by Lorke, 1983. The method is biphasic in nature and a total of 13 mice of either sex were used. Three groups of three mice each were administered with the LHME (i.p) at doses of 10, 100 and 1000 mg/kg body weight and were observed for sign and symptoms of toxicity and death for 24 hrs. In the second phase which was determined by the first phase, three groups of one mouse each were treated with the extract at doses of 1600, 2900 and 5000 mg/kg. They were observed for sign and symptoms of toxicity 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.

Tail Suspension Test (TST)

The TST was performed according to the method described by Steru et al, (1985). Thirty mice were divided into five groups of six mice each. Group I was treated (i.p) with 10 ml/kg distilled water, group II with 10 mg/kg imipramine, while group III, IV and V were treated with 250, 500 and 1000 mg/kg of LHME (i.p) respectively. Thirty minutes later, mice were suspended on the edge of the shelf 58cm above a tabletop by adhesive tape placed approximately 1cm from the tip of the tail. The duration immobility was then recorded for a period of 6 minutes

Forced Swim Test (FST)

The FST was performed according to the method described by Porsolt et al, (1977). Thirty mice were divided into five groups of six mice each. Group I was treated (i.p) with 10 ml/kg distilled water, group ii with 10 mg/kg imipramine, while group iii, iv and v were treated with 250, 500 and 1000 mg/kg of LHME (i.p) respectively. Thirty minutes later, each mouse was placed in a Plexiglas cylinder tank of 40 cm height and 18 cm width filled with 15cm water at 25℃. The test consists of 6 minutes exposure, with the first 2 minutes serving as habituation period and the last 4 minutes consisting of the test itself, which yields the duration of immobility. 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.

Open field test (OFT)

The OFT was performed according to the method described by Prut & Belzung, (2003). Twenty five mice were divided into five groups of five mice each. The first, second and third groups were treated with 250, 500 and 1000 mg/kg of LHME (i.p). The fourth and fifth groups were treated with distilled water (10 ml/kg) and imipramine (10 mg/kg) respectively. After thirty minutes of administration, each mouse was placed in white wooden open field apparatus (70×70×35 cm, length × breadth × height).

The exploratory behaviour of each mouse in the apparatus was recorded for 5 minutes. The apparatus was cleaned with 10% ethanol between each mouse placement

Fractionation

The Fractionation was carried out to reduce the complexity of chemical compounds in natural products (plants) in order to obtained semi pure extract. The fractionation of LHME was carried out by suspending the extract in 300 mL of distilled water and partitioning with different organic solvents (chloroform, ethyl acetate and n-butanol) in order of increasing polarity by using separating funnel (Yaro *et al.* 2015). The fractions were evaporated in an oven at 40 °C. The yields were kept in a desiccator for use in the study.

The four (4) fractions obtained from LHME are as follows: Chloroform fraction (CHF), Ethylacetate fraction (EAF), n-butanol fraction (NBF) and Residual aqueous fraction (RAF) which were subjected to TST, FST and OFT as above.

Statistical Analysis

All values are expressed as mean ± SEM. Data were analyzed using One-way analysis of variance (ANOVA) followed by Bonferroni *post hoc* test. In all the tests, the criterion for statistical significance was $p<0.05$.

RESULTS

Acute toxicity studies

The intraperitoneal median lethal dose of LHME in mice was estimated to be >5000 mg/kg body weight.

Effect of LHME on the Tail Suspension Test

Treatment with LHME significantly ($p < 0.01$ and $p < 0.001$) decreased the duration of immobility time at doses dependent manner. Imipramine (10mg/kg) also significantly ($p<0.001$) decreases the duration of immobility time as compared to the control group (Table 1).

Table 1: **Effect of LHME on immobility time (Sec.) in mice Tail Suspension Test.**

Treatment mg/kg	Immobility time (sec) TST
Control	203.00±7.43
IMP 10	68.50±3.94**
LHME 250	158.00±16.86*
LHME 500	110.33±7.31**
LHME 1000	101.00±3.74**

Values presented as Means ± SEM. * = $P<0.01$, ** = $P<0.001$ compared to control group using One-way ANOVA followed by Bonferroni test as the *post hoc:* n = 6, Control = Distilled water 10ml/kg. LHME = *Leptadenia hastata* methanol leaves extract.

Effect of TMME on the Forced Swim Test

Treatment with LHME significantly ($p<0.001$) decreased the duration of immobility time and increased swimming time at doses dependent manner. Imipramine (10mg/kg) also significantly ($p<0.001$) decreases the duration of immobility time as compared to the control group (Table 2).

Table 2: Effect of LHME on immobility time (Sec.) in mice Forced Swim Test.

Treatment mg/kg	Immobility time (sec) FST
Control	169.33±2.73
IMP 10	21.67±2.16**
LHME 250	89.83±3.49**
LHME 500	61.00±2.37**
LHME 1000	31.17±2.86**

Values presented as Means ± SEM. ** = $P<0.001$ compared to control group using One-way ANOVA followed by Bonferroni test as the *post hoc:* n = 6, Control = Distilled water 10 ml/kg. LHME = *Leptadenia hastata* methanol leaves extract.

Effect of LHME on the locomotor activity in the OFT

The locomotor activity of mice was assessed in the open field arena. To avoid the possibility of false-positive results of LHME from FST and TST, as shown in (Table 3), treatment with LHME at doses of 250, 500 and 1000 mg/kg and imipramine at 10 mg/kg had no significant effect on the number of squares crossed in mice.

Table 3: Effect of LHME on locomotor activity in mice open field test.

Treatment mg/kg	Mean number of squares crossed
Control	45.00 ±6.25
IMP 10	44.20±6.64
LHME 250	43.00±7.18
LHME 500	42.80±6.14
LHME 1000	40.20±6.84

Values presented as Means ± SEM. No significant different $P > 0.05$ with the experimental groups compared to control group using One-way ANOVA followed by Bonferroni test as the *post hoc*: n= 6, Control = Distilled water, with the test duration of 5 min. LHME = *Leptadenia hastata* methanol leaves extract.

Preliminary phytochemical constituents of *L. hastata* fractions

Table 4: Preliminary phytochemical constituents of *L. hastata* fractions

Constituents	Inferences			
	CHF	EAF	NBF	RAF
Alkaloids	-	+	+	+
Glycosides	+	+	+	+
Flavonoids	-	+	+	+
Tannins	-	+	+	+
Saponins	-	+	+	+
Steroids	+	+	+	+
Anthraquinones	-	-	-	-

Key: + = presence, **-** = absence, CHF = Chloroform fraction, EAF = Ethylacetate fraction, NBF = n-Butanol fraction and RAF = Residual aqueous fraction

Table 5: The Percentage yield (%) and Median lethal dose (*i.p* LD_{50}) of the different fractions of *L. hastata* in mice

Fractions	Yield (%)	LD_{50} (mg/kg)
CHF	2.26	2154
EAF	9.58	3800
NBF	9.54	3800
RAF	40.34	>5000

Key: CHF = Chloroform fraction, EAF = Ethylacetate fraction, NBF = n-Butanol fraction and RAF = Residual aqueous fraction

Effects of *L. hastata* fractions on the Tail Suspension Test

Treatment with the NBF and RAF significantly ($p<0.01$ and $p<0.001$) decreased the duration of immobility time. Similarly, the standard drug, imipramine (10mg/kg) also significantly ($p<0.001$) decreased the duration of immobility time as compared to the control group. However, no significant response obtained at all tested doses of CHF and EAF compared to control (Table 6).

Table 6: Effects of *L. hastata* fractions on immobility time (Sec.) in mice Tail Suspension Test.

Treatment ml/kg	Immobility time (sec) TST
Control	207.50±5.46
IMP10	103.83±7.16**
CHF 150	212.67±5.99
CHF 300	198.83±7.19
CHF 600	194.67±5.25
EAF 200	204.67±4.39
EAF 400	194.67±6.97
EAF 800	192.00±7.92
NBF 200	146.17±7.00*
NBF 400	131.83±14.46**
NBF 800	188.50±5.21
RAF 250	160.17-3.75*
RAF 500	157.50±3.02*
RAF 1000	118.83±9.46**

Values presented as Means ± SEM. * = $P<0.01$, ** = $P<0.001$ compared to control group using One-way ANOVA followed by Bonferroni test as the *post hoc:* n = 6, Control = Distilled water 10ml/kg. CHF = Chloroform fraction, EAF=Ethylacetate fraction, NBF=n-Butanol fraction and RAF=Residual aqueous fraction.

Effects of *L. hastata* fractions on the Forced Swim Test

Treatment with the NBF and RAF significantly (p<0.01 and p<0.001) decreased the duration of immobility time and increased swimming time. Similarly, the standard drug, imipramine (10mg/kg) also significantly (p<0.001) decreased the duration of immobility time as compared to the control group. However, no significant response obtained at all tested doses of CHF and EAF compared to control (Table 7).

Table 7: Effect of *L. hastata* fractions on immobility time (Sec.) in mice Forced Swim Test.

Treatment ml/kg	Immobility time FST
Control	75.83±3.76
IMP 10	25.83±4.81**
CHF 150	77.67±5.73
CHF 300	84.33±5.52
CHF 600	81.00±5.96
EAF 200	84.00±6.14
EAF 400	92.17±8.87
EAF 800	92.17±5.38
NBF 200	86.33±7.54
NBF 400	37.50±3.39**
NBF 800	40.50±4.80*
RAF 250	46.17-3.78*
RAF 500	41.00±2.42*
RAF 1000	34.00±5.03**

Values presented as Means ± SEM. * = P<0.01, ** = P<0.001 compared to control group using One-way ANOVA followed by Bonferroni test as the *post hoc:* n = 6, Control = Distilled water 10ml/kg. CHF = Chloroform fraction, EAF=Ethylacetate fraction, NBF=n-Butanol fraction and RAF=Residual aqueous fraction.

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Effects of *L. hastata* fractions on the locomotor activity in the OFT

The locomotor activity of mice was assessed in the open field arena. To avoid the possibility of false-positive results of the *L. hastata* fractions in FST and TST, as shown in (Table 8), treatment with *L. hastata* fractions at all tested doses and imipramine at (10 mg/kg) had no significant effect on the number of squares crossed in mice.

Table 8: Effects of *L. hastata* fractions on locomotor activity in mice open field test

Treatment mg/kg	Mean number of squares crossed
Control	42.80±7.71
IMP 10	37.40±6.35
CHF 150	49.60±8.48
CHF 300	55.20±2.78
CHF 600	48.80±7.06
EAF 200	27.20±3.25
EAF 400	31.80±5.12
EAF 800	31.20±5.16
NBF 200	38.00±7.04
NBF 400	40.60±7.99
NBF 800	23.40±7.41
RAF 250	40.80±7.22
RAF 500	34.80±6.85
RAF 1000	40.20±4.32

Values presented as Means ± SEM. P >0.05 compared to the control group using One-way ANOVA followed by Bonferroni test as the *post hoc*: n= 6, Control = Distilled water 10 ml/kg, with the test duration of 5 min. CHF = Chloroform fraction, EAF=Ethylacetate fraction, NBF=n-Butanol fraction and RAF=Residual aqueous fraction.

DISCUSSION

The *L. hastata* plant is medicinally important in the treatment of many ailments, used to ease labour, back pain and scorpion bite, scabies, sexual potency, hypertension and skin diseases. This plant appears to be benign with low toxicity and used in the treatment of evil spirit, Psychiatric disorders, loss of consciousness, hallucination and urinary ailments (Burkill, 1985; Hussain and Karatela, 1989; Kinda *et al*. 2017). The therapeutic benefits of Traditional remedies depend upon one or a combination of the phytochemical constituents of medicinal plants. However, the phytochemical constituents of the methanol leaves extract of *L. hastata* have shown to contain secondary metabolites that include: alkaloids, flavonoids, tannins, glycosides, saponins and steroid (Sani *et al.* 2019). The present study investigated the antidepressant-like effects of LHME and its fractions through acute animal models of behavioural despair, the TST and FST which are well-established animal models for screening of antidepressant drugs. The LHME and its fractions (NBF and RAF) reversed the anhedonia state by significant decreases the duration of immobility time in TST and FST. Our findings have shown that the LHME and RAF at dose 250-1000 mg/kg are significantly and dose-dependently, while n-butanol fraction (NBF) at 400 mg/kg decreased the duration of immobility in the TST and FST respectively. These effects were comparable with that of the reference antidepressant imipramine. In these animal models, Immobility exhibited by rodents when subject to unavoidable stress such as forced swimming and tail suspension reflects a state of despair or lowered mood, which is thought to reflect depressive episodes in humans (Cryan *et al*. 2005). Therefore, the duration of immobility is considered as the core indicator of FST and TST to evaluate the antidepressant effects. These tests are the most widely utilized models for screening potential antidepressant drugs. The time spend immobile by the animal during the 6 minutes period is a measure of escape related behaviour (Helena *et al.* 2013). These tests are quite sensitive to major antidepressant drugs, such as selective serotonin reuptake inhibitors (SSRIs), tricyclics and monoamine oxidase inhibitors (MAOIs), can effectively reduce the immobility time and increase the activity (Porsolt *et al.* 1977; Steru *et al*. 1985). Thus, the ability of *L. hastata* and fractions (NBF and RAF) at the tested dose that significantly reduced the duration of immobility is an indication of its antidepressant properties. Thus, the predictive validity of TST and FST in an animal model of depression has been confirmed in many studies but with some defects of false positive (Porsolt *et al.* 1977; Steru *et al.* 1985; Bourin *et al.* 2001). In both tests, antidepressants can be distinguished from psychostimulants drugs such as caffeine, amphetamine and methylphenidate that act to stimulate the CNS, caused marked motor stimulation in an open field arena, in contrast to antidepressants, which do not (Steru *et al.* 1985). Hence, to avoid the possibility of false-positive result, the effect of the LHME and its fractions on locomotor activity was assessed in the OFT. The findings have shown that the LHME and its fractions did not evoke any significant changes in the number of squares crossed, which suggested that the reduced immobility time observed in both TST and FST induced by LHME and its fractions (NBF and RAF) has nothing to do with the central psychostimulant effect.

The Pharmacological research to ascertain the safety and efficacy of the medicinal plant are of great concern when seeking for a novel drug (Shehu *et al*. 2017). The LD_{50} of the LHME and RAF were estimated to be >5000 mg/kg body weight, whereas that of CHF, EAF and NBF as 2154, 3800 and 3800 mg/kg body weight respectively as described by Lorke, (1983). Furthermore, the pharmacological actions of medicinal plants depend upon one or a combination of the presence of specific phytochemical constituents. Studies have been shown that some phytochemical constituents like alkaloids, flavonoids, steroids, Tannins and saponins have been reported to have antidepressant activities (Youdim and Joseph, 2001; Mroczek *et al.* 2007; Yadav *et al.* 2016). Thus, the antidepressant-like effect exhibited by *L. hastata* plant may be due to these phytochemical constituents found present in the plant.

CONCLUSION

The *L. hastata* plant possesses potential antidepressant-like effects and may have potential therapeutic value in the management of depressive disorders. Our findings have been shown that the LHME and RAF at dose 250-1000 mg/kg are significantly and dose-dependently, while NBF at 400 mg/kg decreased the duration of immobility time in the TST and FST respectively.

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