

Evaluation of Antidepressant-like Effect of *Olax Subscorpioidea* Oliv. (Olacaceae) Extract in Mice

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Key words

- antidepressant
- mental illness
- immobility
- *Olax subscorpioidea*
- yohimbine

Abstract

Olax subscorpioidea is a shrub or tree found in Nigeria, and other parts of Africa. It is indicated in the management of inflammatory disorder, mental illness, convulsion, pain, and cancer. Based on the folkloric use in the management of mental illness, antidepressant activity of *Olax subscorpioidea* (6.25–50 mg/kg, i.p.) was investigated using forced swimming, tail suspension, yohimbine induced lethality and reserpine induced depression tests. The results showed that, *Olax subscorpioidea* produced significant dose dependent reduction in

immobility time in forced swimming [F (5, 24)=17.22, p<0.0001] and tail suspension [F (5, 24)=14.94, p<0.0001] tests without causing changes in locomotor activity in open field test. It was also found that *Olax subscorpioidea* significantly reduced diarrhea in reserpine model of depression [F (5, 24)=10, p<0.0001]. None of the doses potentiated yohimbine induced lethality in mice. In conclusion *Olax subscorpioidea* possessed antidepressant action, thus justifying its use in the management of mental illness.

Introduction

Depression is an affective disorder characterized by change in mood, loss of interest or pleasure, feelings of guilt or low self-worth, disturbed sleep or appetite, low energy, psychomotor retardation and melancholia. It is a major health condition with life time prevalence in the range of 10–15% [1]. World Health Organization [2] and Richelson et al., [3] estimated that 5.8% of men and 9.5% of women undergoing a depressive episode in their life time mostly end up committing suicide. Its negative social impact and impairing effect on daily activities and wellbeing has led to incapability and loss of productivity [4]. Most current therapeutic interventions employed in the management of depressive disorder are marred by their bizarre and undesirable side effects which tend to limit their clinical usefulness. Another drawback is that available treatments remain sub-optimal, with a delay of 3–6 weeks before their clinical effects can be achieved and lack of efficacy is also observed in many cases [5,6].

In the light of the fact that plants present a large untapped source of structurally novel com-

pounds that might serve as lead for the development of novel drugs, the exploration of traditional source of medicine for more promising antidepressant drugs is justified. Studies have shown that herbs have been used as alternative therapy for depression [7]. *Olax subscorpioidea* (OS) locally called 'ifon' is a shrub or tree that is widely distributed in Nigeria and some parts of Africa. In Congo Republic folk medicine, stem with leaves of *Olax subscorpioidea* decoction, and steam bath have been used to treat rheumatism and articular pains [8]. Ethno-botanical survey showed that OS has been indicated in the management of asthma in South West Nigeria and as recipe for the management of cancer [9,10]. Its use in combination with another plant in the treatment of anxiety and mental illness disorders has been reported. [11]. Studies have shown that stem of OS contains alkaloids, steroids, and flavonoids together with other active ingredients in the ethanoic extract with the exception of saponins which is present in the aqueous extract alone and demonstrates antimicrobial activity [12]. Based on the ethnomedicinal use in mental illness and some other CNS disorders and lack of scientific report supporting its use in these conditions, the study

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is therefore, designed to evaluate antidepressant activity of Ethanol Extract of *Olox subscorpioidea* Leaves (EEOSL) in animal models.

Materials and Methods

Plant materials

The leaves of *Olox subscorpioidea* were collected in February 2012 at the Gambari Forest Reserve, Ibadan, the Oyo state capital, Nigeria. The taxonomical identification and authentication of the plant was done at the herbarium section of the Forestry Research Institute of Nigeria (FRIN), Ibadan, Nigeria. A voucher specimen with identification number 109924 was deposited and compared with the reference specimen.

Preparation of plant material and drugs

Air-dried leaves (150 g) were pulverized and soaked in 50% ethanol (1.5 L) for 48 h. The filtrate was concentrated with a rotary evaporator to give a semisolid residue and evaporated to dryness to form solid residue (8.7 g). It was kept in the desiccator for further use. The dried extract was then subsequently reconstituted in distilled water at appropriate concentrations for the various experiments. All drugs and the extract were dissolved in distilled water and administered by intraperitoneal (i.p.) route.

Laboratory animal

Male Swiss Albino mice (20–25 g) used in this study were obtained from the Laboratory Animal Centre of the College of Medicine, University of Ibadan, Nigeria. The animals were kept in well-ventilated and hygienic compartments, maintained under standard environmental conditions and fed with standard rodent pellet (Livestock Feed PLC, Lagos, Nigeria) and water ad libitum. The experimental procedures adopted in this study were in accordance with the United States National Institutes of Health Guidelines for Care and Use of Laboratory Animals in Biomedical Research (NIH, 1985).

Drugs and chemicals

Yohimbine (Sigma-Aldrich (St. Louis, MO, USA), reserpine (Pfizer Inc., New York, NY, USA), imipramine (Shanghai Zhongxi Pharmaceutical Co., Ltd. Shanghai, China).

Acute toxicity test

The method described by Lorke [13] was used to determine the LD₅₀, which is the index of acute toxicity. Swiss Albino mice (20–25 g) of either sex were used. This method involved an initial dose finding procedure, in which the animals were divided into 3 groups of 3 animals. Doses of 10, 100 and 1000 mg/kg were administered intraperitoneally (i.p.). One dose for each group. The treated animals were monitored for 24 h mortality and general behavior. From the results of the above step, 4 different doses of (500, 800, 2000 and 3000 mg/kg) were chosen and administered i.p. respectively to 4 groups of one mouse per group. The treated animals were monitored for 24 h. The LD₅₀ was then calculated as the geometric mean of the lowest dose showing death and the highest dose showing no death.

Antidepressant activity

Forced swimming test (FST)

Male mice (20–24 g) were used in the forced swimming test [14]. Mice were assigned to 6 different groups (n=5 for each group).

Group (1) received distilled water (10 mL/kg), group (2–5) received OS (6.25, 12.5, 25, 50 mg/kg) respectively while group (6) received Imipramine (25 mg/kg). 30 min later, mice were dropped one at a time into a Plexiglas cylinder (25 cm height, diameter 10 cm containing water to a height of 10 cm at 23–25 °C) and observed for 6 min. After the first 2 min of the initial vigorous struggling, the animals were immobile. A mouse was judged immobile if it floated in the water in an upright position and made only slight movements to prevent sinking. The total duration of immobility was recorded during the last 4 min of the 6 min test.

Tail suspension test

The total duration of immobility following tail suspension was measured according to the method described for evaluating potential antidepressants [15]. Mice were assigned to 6 different groups (n=5 for each group). Group (1) received distilled water (10 mL/kg), group (2–5) received OS (6.25, 12.5, 25, 50 mg/kg) respectively while group (6) received Imipramine (25 mg/kg). 30 min later mice were suspended on the edge of a table, 50 cm above the floor with the help of an adhesive tape placed approximately 1 cm from the tip of the tail. Immobility time was recorded during 6 min period in different groups. The animal was considered to be immobile when it did not show any movement of the body and hanged passively.

Open field Test (OFT)

In order to rule out any unspecific locomotor effect of *olax subscorpioidea* on antidepressant-like effect of these compounds, mice were administered with the same regimen as in FST or TST. Their locomotor activities (crossing activity) were evaluated in the open field paradigm. Before each test, animals were kept in the test room at least 1 h before open-field test (OFT) for habituation. The ambulatory behaviour was assessed in open-field described by Rodrigues et al. [16]. The main apparatus consisted of square arena (50 cm × 50 cm × 40 cm) high with grey surface covering every wall. The floor of the arena was divided equally into 25 squares (10 cm × 10 cm) marked by black lines. All animals were used only once in this test. These animals were different from those used in the FST and TST. Group (1) received distilled water (10 mL/kg), group (2–5) received OS (6.25, 12.5, 25, 50 mg/kg) respectively while group (6) received Imipramine (25 mg/kg). 30 min after, each mouse was placed individually at the center of the arena and allowed to explore freely. The number of squares crossed with all paws (crossing) were observed and counted in 5 min. The square arena was cleaned with a solution of 70% alcohol between tests and dried after occupancy by each mouse in order to hide animal clues and to prevent each mouse from being influenced by the odors present in the urine and feces of the previous mouse.

Yohimbine induced lethality test

To reveal whether noradrenergic system is involved in the antidepressant-like effect of the extract, yohimbine induced lethality test was performed [17]. Mice were assigned to 6 different groups (n=5 for each group). Group (1) received distilled water (10 mL/kg), group (2–5) received OS (6.25, 12.5, 25, 50 mg/kg) respectively while group (6) received Imipramine (25 mg/kg) 30 min prior to yohimbine administration (35 mg/kg, intraperitoneal injection). The number of dead mice was calculated during a 24 h period after injection of yohimbine.

Reserpine induced depression

6 groups of animal (Group 1–6) were reserpinised by administration of reserpine (2.5 mg/kg, i.p.) 1 h after the respective drug administration. Group (1) received distilled water (10 mL/kg), group (2–5) received OS (6.25, 12.5, 25, 50 mg/kg) respectively while group (6) received Imipramine (25 mg/kg). The acute effects of *Olox subscorpioidea* and Imipramine on reserpine induced diarrhea were observed. Mice were observed for the presence of diarrhea at 1, 2, 3 & 4 h after reserpine injection.

Statistical analysis

All data are presented as mean \pm SEM. The results were analyzed by One way analysis of variance (ANOVA) and post hoc tests (Student's-Newman-Keuls) were carried out to determine the source of significant main effect using GraphPad InStat® Biostatistics software. The level of significance for all tests was set at $p < 0.05$.

Results

Acute toxicity test

The LD₅₀ of *Olox subscorpioidea* crude extract in mice was found to be 300 mg/kg i.p. body weight.

Effect of *olax subscorpioidea* on immobility time of forced swimming test (FST)

OS at 6.25 mg/kg and 12.5 mg/kg significantly reduced ($P < 0.05$) immobility time of mice in FST as compared to the control (vehicle) while doses at 25 mg/kg and 50 mg/kg did not reduce immobility time in mice. Clinically effective antidepressant imipramine at 25 mg/kg produced a marked significant reduction ($P < 0.05$) in the duration of immobility as compared with control (○ Fig. 1).

Effect of *olax subscorpioidea* on immobility time of tail suspension test (TST)

OS at 6.25 mg/kg and 12.5 mg/kg significantly reduced ($P < 0.05$) immobility time of mice in TST as compared to the control while

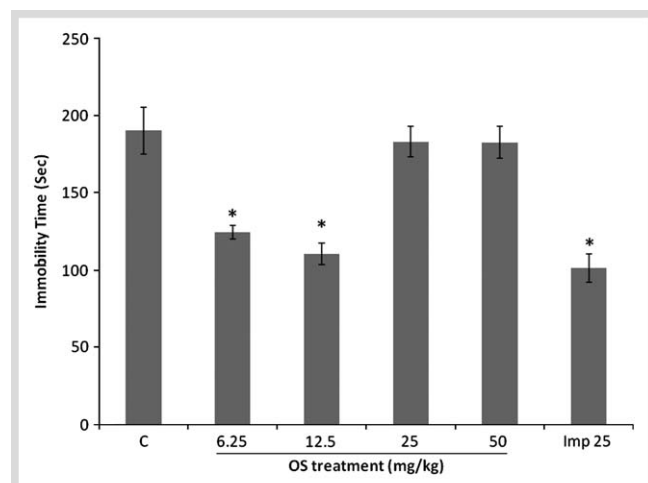


Fig. 1 Effect of OS on immobility time of Forced Swimming Test (FST). The results are expressed as Mean \pm SEM (n = 5). One way ANOVA revealed that there is significant [F (5, 24) = 17.22, $p < 0.0001$] difference between various treatment groups. * indicates significant difference from the control $P < 0.05$. Imp = imipramine (25 mg/kg); C = control; OS = *olax subscorpioidea*

doses at 25 mg/kg and 50 mg/kg did not reduce immobility time in mice. The clinically effective antidepressant imipramine at 25 mg/kg produced a marked significant reduction ($P < 0.05$) in the duration of immobility as compared with control (○ Fig. 2).

Effect of OS on locomotor activity of OFT

Treatment with OS at 6.25 mg/kg and 12.5 mg/kg which significantly reduced duration of immobility in FST and TST produced no significant difference in number of crossing activity of mice in OFT. Antidepressant Imipramine at 25 mg/kg which reduced duration of immobility of mice in FST and TST produced no significant difference in number of crossing activity as compared to control (○ Fig. 3).

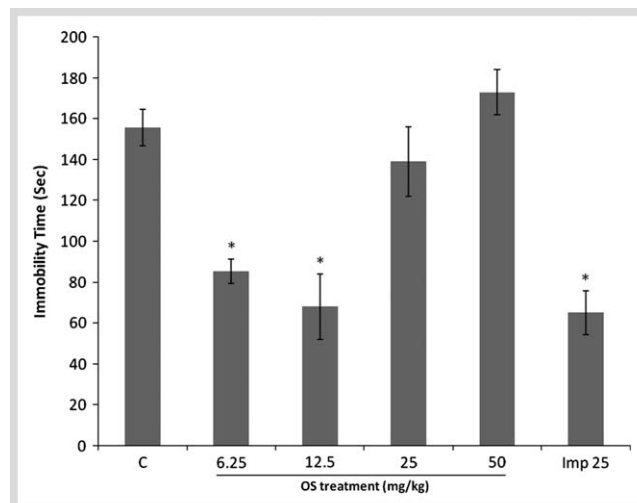


Fig. 2 Effect of OS on immobility time of Tail Suspension Test (TST). The results are expressed as mean \pm SEM (n = 5). One way ANOVA revealed that there is significant [F (5, 24) = 14.94, $p < 0.0001$] difference between various treatment groups. * indicates significant difference from the control $P < 0.05$. Imp = imipramine (25 mg/kg); C = control; OS = *olax subscorpioidea*

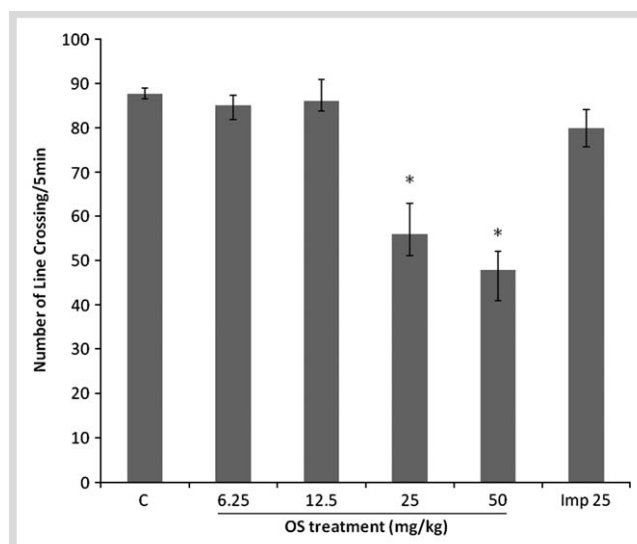


Fig. 3 Effect of OS on the locomotor activity of mice in OFT. The results are expressed as mean \pm SEM (n = 5). One way ANOVA revealed that there is significant [F (5, 24) = 35.98, $p < 0.0001$] difference between various treatment groups. * indicates significant difference from the control $P < 0.05$. Imp = imipramine (25 mg/kg); C = control; OS = *olax subscorpioidea*

Effect of *olax subscorpioidea* on yohimbine induced lethality test

Comparing with control OS (6.25–50 mg/kg) did not significantly potentiate yohimbine toxicity in mice. Antidepressant imipramine at 25 mg/kg produced a marked significant increase in the number of death ($P < 0.05$) as compared with control (Table 1).

Effect of crude extract of *olax subscorpioidea* in reserpine induced depression

In reserpine induced depression test, OS (6.25, 12.5, 25, 50 mg/kg) produced significant ($p < 0.05$) decrease in the mean faecal droppings in all the groups compared to control. Anti-diarrhoea effect of *Olax subscorpioidea* was comparable to that of imipramine (Table 2).

Discussion

Behavioural studies have been shown to play an important part in the evaluation and development of antidepressant drugs [18]. Forced swimming test (FST) and tail suspension test (TST) are 2 important behavioural models widely and routinely used for screening new antidepressant compounds [19]. According to Porsolt [20] and Steru et al., [21] existence of significant correlation between clinical potency and potency of antidepressants has been established. The immobility displayed by animals subjected to an unavoidable and inescapable stress that characterizes these models has been hypothesized to reflect behavioural despair which in turn may reflect depressive disorder in humans. This immobile position is reduced by variety of therapeutically active antidepressants e.g. tricyclics, monoamine oxidase-inhibitors, and newer antidepressants [22,23].

Forced swimming test is based on the assumption that animals forced to swim in a restricted space will ultimately cease to appear attempts to escape and become immobile making only small movements necessary to keep their heads above the sur-

face of water [24]. In this present study however, OS (6.25 and 12.5 mg/kg) produced a statistically significant reduction in immobility time in forced swimming test, while OS (25 and 50 mg/kg) produced no effect on immobility time. Positive control antidepressant drug imipramine produced significant reduction in immobility time. Therefore the ability of OS to reduce immobility time in animals subjected to this stressful situation indicates its antidepressant like activity.

Similar results were obtained in TST with OS (6.25 and 12.5 mg/kg) and imipramine (25 mg/kg) producing significant reduction in immobility time while OS (25 and 50 mg/kg) did not affect immobility in these animals. The test having got an advantage of being able to detect broad spectrum of antidepressants irrespective of their mechanism of action, is however based on the observation that rodents mostly mice after initial escape behaviour, develop an immobile position when subjected to an inescapable stressful situation [25]. Animals are considered as immobile when they hang passively and completely motionless. The development of immobile posture by the animals which disengages them from active form of coping with stressful stimuli [26] represents behavioural despair which in turn may reflect depressive disorders in humans. Clinically effective antidepressants decrease immobility time in TST. The ability of the extract (OS) to reduce immobility time suggests that it may possess antidepressant activity.

While interpreting antidepressant-like effect of any test substance based on swimming performance and exploratory behaviour of rodents in either FST or TST, it is noteworthy that false positive results can be obtained for agents that stimulate locomotor activity [27]. Therefore the influence of the test substance in baseline locomotion in animal is of prime concern [28]. Agents like amphetamine, convulsants and anticholinergic which enhance locomotor activity or cause hyperkinesias in open field test (OFT) produce false positive results in FST and TST [27,29,30]. Hence the need of OFT as a paradigm to eliminate the bias that anti-immobility effect could be associated with hyperkinesia [31]. As psycho-stimulant will always give false positive result in FST and TST, one way to discern or discriminate between antidepressants and psycho-stimulants is that antidepressants would not cause general increase in motor activity [32]. Potential antidepressant activities of selective serotonin1A agonists based on anti-immobility activity in the forced swimming test in rats without effect on open-field activity have been suggested [33]. The observation that OS (6.25 and 12.5 mg/kg) did not increase the number of line crossed in open field eliminates exertion of psycho-stimulant-like action and confirms the assumption that antidepressant-like effect of the extract in TST and FST is specific [34]. Conversely, OS (25 and 50 mg/kg) statistically produced a significant reduction in the number of line crossed indicating gross sedation at these doses which masks its

Table 1 Effect of *Olax subscorpioidea* on Yohimbine-induced lethality Test.

Group	Dose (mg/kg)	No of death	% mortality
Distilled water	10 mL/kg	2/10	20
<i>Olax subscorpioidea</i>	6.25	2/10	20
	12.5	0/10	0
	25	0/10	0
	50	2/10	20
Imipramine	25	7/10	70*

The results are expressed as mean \pm SEM (n=5). One way ANOVA revealed that there is significant [$F(5, 24) = 21.73, p < 0.0001$] difference between imipramine and the control

*indicates significant difference from the control $P < 0.05$

Group	Dose mg/kg	60 min	120 min	180 min	240 min
Control	10 mL/kg	4.80 \pm 0.80	7.60 \pm 0.92	8.20 \pm 0.86	6.51 \pm 0.73
<i>Olax subscorpioidea</i>	6.25	1.60 \pm 0.50*	1.80 \pm 0.66*	2.40 \pm 0.92*	2.63 \pm 1.12*
	12.5	1.20 \pm 0.58*	1.20 \pm 0.58*	1.20 \pm 0.58*	2.01 \pm 0.35*
	25	0.40 \pm 0.24*	0.60 \pm 0.40*	1.20 \pm 0.37*	1.78 \pm 1.09*
	50	1.00 \pm 0.44*	1.20 \pm 0.37*	2.80 \pm 0.58*	1.58 \pm 0.55*
Imipramine	25	0.71 \pm 0.24*	0.82 \pm 0.28*	1.56 \pm 0.34*	0.92 \pm 0.35*

The results are expressed as mean \pm SEM (n=5). One way ANOVA revealed that there is significant [$F(5, 24) = 10, p < 0.0001$;

$F(5, 24) = 21.58, p < 0.0001$; $F(5, 24) = 17.45, p < 0.0001$; $F(5, 24) = 19.98, p < 0.0001$] difference between various treatment groups

*indicates significant difference from the control $P < 0.05$

Table 2 Effect of crude extract of *Olax subscorpioidea* in Reserpine Induced Diarrhoea.

antidepressant effect. This probably explains why the extract at higher doses could not exhibit anti-immobility effect seen at lower doses.

Yohimbine induced lethality test is another animal model used to further screen antidepressant potential of *olax subscorpioidea*. This model has been developed not only to detect potential antidepressant properties of new substances, but also to identify neurotransmitter systems that may be involved in the mechanism of actions of antidepressant drugs [35]. Yohimbine, an alpha 2 adrenergic antagonist, causes increased sympathetic discharge both in the peripheral and central nervous system. The antagonism of alpha 2 receptors also causes an increase in the level of serotonin [36]. Antidepressant drugs by enabling more amines to reach the receptors potentiate yohimbine induced lethality. This occurs either by their reuptake inhibition or reduced inactivation by monoamine oxidase inhibitors. Yohimbine induced lethality test reveals an adrenergic component of pharmacological activity of antidepressants and is sensitive to detect MAO inhibitors, tricyclic antidepressants, noradrenaline (NA), and selective serotonin reuptake inhibitors [37]. The present study showed that OS did not potentiate yohimbine induced lethality at all doses thus precluding involvement of the central adrenergic mechanism in its antidepressant action.

Studies have shown that reserpine can deplete amine stores and irreversibly inhibit the vesicular uptake of monoamines. This reduced level of monoamines in the brain has been implicated to be an underlining factor in the pathophysiology of depression. In this paradigm, physiological effects such as diarrhoea, ptosis and hypothermia are observed and these have been associated with the effect of reserpine as signs of depression [38]. These syndromes have been inhibited or reversed by major classes of antidepressant drugs. In this study, like imipramine significant reversal of diarrhoea by OS at all 4 dose levels used was noticed and thus indicating its antidepressant property.

In conclusion, it is obvious that administration of OS produced antidepressant-like effect in FST and TST, which is not due to the effect of psycho-stimulant or hyperkinesia. However, giving the fact that Forced swimming, Tail suspension, yohimbine induced lethality and reserpine induced depression tests are not the only models of depression by which the results obtained can be considered, interpreted and validated due to individual differences among experimental animals and clinical studies in human, there is therefore the need to advance the course of the study by evaluating the effect of the extract (OS) in other animal's behavioural model including relevant antidepressant doses of OS on its safety and efficacy level.

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Conflict of Interest

The authors stated that there is no conflict of interest regarding the publication of this article.

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