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Role of Monoaminergic Neurotransmission on the Antidepressant Effect of Leaf and Root Extracts of *Rauwolfia vomitoria* on the Locomotion and Immobility of Sprague-Dawley Rats

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Authors' contributions

This work was carried out in collaboration among all authors. Author IIA performed the laboratory work, analyzed the data and wrote the manuscript. Author OATE designed the experiments critically reviewed and edited the manuscript. Author MNIE reviewed and edited the manuscript. All authors read and approved the final manuscript.

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ABSTRACT

Rauwolfia vomitoria is one of the medicinal plants which is used traditionally to manage hypertension, diabetes and mental disorder. The scientific evidence to suggest its medicinal use especially in mental health treatment is lacking. This study aimed to investigate the antidepressant-like effect of the leaf and root extracts of *R. vomitoria* in the rat model using neurobehavioural indices; open field test and forced swimming test. Subsequently, the effect of the extracts on monoamine neurotransmitters system was investigated. The neurobehavioral response of rats by open field test and forced swim test showed that there was a reduction in the explorative tendencies of the rats administered the aqueous and ethanol root extracts (125, 250, 500 mg/kg) compared to the control while forced swim test reduced the immobility time of rats across all treatment groups except 500 mg/kg group. Neurotransmitter levels (serotonin, dopamine and

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norepinephrine) in plasma and brain of rats administered the different concentration of root extracts exhibited significant ($p<0.05$) increase. Thus, the mode of action may be due in part to the increase in monoamine levels or by suppression of the reuptake of the monoamine neurotransmitters. This study established that *R. vomitoria* root extract has antidepressant-like effect in rats.

Keywords: Rauwolfia vomitoria; leaf; root extracts; antidepressants; neurotransmitters.

1. INTRODUCTION

Medicinal plants have been used over the years in complementary and alternative medicine for the management and treatment of variety of diseases and preservation of human health. One of the plants of medicinal value from the humid tropics is *Rauwolfia*, a tropical shrub with white or greenish flowers [1]. The plant *Rauwolfia vomitoria* belongs to the family *Apocynaceae* and it is called serpent wood, serpent snake root and swizzle stick, as well as, “asofeyeje” in Yoruba, “ira” in igbo,“wadda” in Hausa, “akata” in Bini and “Mmoneba” or “utoenyin” in Efik. It is mostly found in the forest of the southern part of Nigeria [2]. Research showed that herbal preparations of *R. vomitoria* have been used in traditional folk medicine in Africa as antioxidant, antipyretic, antiglycemic, anticonvulsant, analgesic, antipsychotic, anticancer, sedative properties and for mental disorder [3,4].

Depression is a mental disorder characterized by sadness, loss of interest or pleasure, feeling of guilt or low self-worth, disturbed sleep or appetite, feeling of tiredness and poor concentration [5,6,7]. It is a potentially life-threatening disorder that affects about 400 million people worldwide [8,9]. It can occur at any age from childhood to late life. There is no known single cause of depression. It could also be developed for different reasons and it has many triggers such as abuse, medications, conflicts or genetics [10,11]. The monoamine theory is one of the important theories describing the chemistry of depression. The monoamine theory of depression states that depression is associated with a decrease in monoamine neurotransmitter (serotonin, nor epinephrine and dopamine) levels in the synaptic cleft [12]. These neurotransmitters are chemicals produced at nerve endings which help in the transmission of nerve impulses.

Depression treatment protocols have involved drugs that increase the amount of monoamine neurotransmitters in the brain either by blocking a monoamine degrading enzyme (monoamine oxidase) or by blocking the reuptake of the neurotransmitters into the pre synaptic neuron. Antidepressants usually take 2-4 weeks for effectiveness [13]. However, the synthetic neurotransmitters currently in use are associated with a lot of side effects. This has led to the search of medicinal plants which may have lesser side effects with better efficacy as a result of the phytochemicals present in them. In addition, the neurobehavioural effects of medicinal plants could be potentiated using the open field test (OFT) and forced swimming test (FST) in animal models to screen medicinal plants that are suspected to possess antidepressant-like effect [14].

2. MATERIALS AND METHODS

2.1 Materials

All chemicals and reagents used were of analytical grade. HPLC grade solvents were used for HPLC determination. Nor epinephrine bitartate salt and 5-hydroxyl tryptamine (serotonin hydrochloride) were obtained from Sigma –Aldrich (USA). Dopamine was obtained from Biotech (India).

2.2 Plant Collection and Identification

The leaf and root of *R. vomitoria* were collected from Lambo Lasunwom village, Ikorodu, Lagos State, South West, Nigeria in April, 2015. The plant was identified and authenticated by Department of Botany, University of Lagos. A Voucher Specimen was deposited in the University herbarium with reference number LUH 6213.

2.3 Preparation of Leaf and Root Extracts of *R. vomitoria*

R. vomitoria leaves were washed with distilled water to free them of dust and sand. The cleaned leaves were air dried at room temperature (28 ± 2.0°C) until dry and ground to a powdery form. Roots were cleaned and cut into tiny pieces. The roots were left to dry and then ground to a coarse powdery form with Christy-Norris Laboratory Hammer Mill and kept in an air tight container

until needed for use. The leaf and root powders were extracted by Soxhlet extraction [15]. Ethanol and water (5 L) were used for extraction of 600 g dried ground plant material for 6-8h. Upon complete extraction, the solvents were completely evaporated using a rotary evaporator and extracts were stored at 4°C until needed.

2.4 Neurobehavioural and Neuro-biochemical Studies

This study was done using the root extracts of *R. vomitoria.* Ninety Wistar rats (170.50 ± 6.50 g) fed commercial rat chow and water *ad libitum* were acclimatized for 14 days and maintained under standard condition (27 ± 2.0°C) and 12 h dark and light cycle). The rats were randomly divided into 9 groups consisting of 10 rats each.

Groups 1 and 2 (positive control) were orally administered citalopram 20 mg/kg and imipramine 15 mg/kg body weight respectively.

Groups 3-5 were administered aqueous root extracts of *R. vomitoria* (125 mg/kg, 250 mg/kg and 500 mg/kg body weight respectively).

Groups 6-8 were administered ethanol root extract of *R. vomitoria* (125 mg/kg, 250 mg/kg and 500 mg/kg body weight respectively).

Group 9 (negative control) received saline only.

Administration of drugs and extracts were carried out between 9.00 am and 10.00 am daily. Treatments ended on the 14th and 28th day respectively.

2.4.1 Neurobehavioural study

On the last day of administration, 1 h after the last dosage administration, neurobehavioural studies (open field test (OFT) and forced swim test (FST) were carried out.

2.4.1.1 Open Field Test (OFT)

The effect of the plant extracts on the locomotor activity of the animals was determined using the Open field test assay. OFT was carried out according to the method of [16]. A wooden box 40 x 30 x 20 cm with the floor divided into 16 equal squares was used. Each rat was placed at the corner of the apparatus. Behaviour was observed during a 5 min session. Locomotion of the rat was expressed in terms of total number of boxes crossed by the rat during a 5 min test. A count was considered when the rat totally crossed from one square to the next.

2.4.1.2 Forced Swim Test (FST)

The antidepressant-like effect of the root extract of *R. vomitoria* was evaluated using the forced swim test (FST) according to the method of [17] as modified by [18]. The rats were made to swim individually in a cylindrical transparent glass vessel (50 cm high and 21 cm diameter) filled with water (27 ± 2.0°C) to a height of 26 cm in such a way that their legs cannot touch the bottom of the cylinder. A time of 2 min was given for adaptation while the duration of immobility (non-movement) was manually recorded during the next 4 min of the total 6 min testing period [19]. Rats were considered to be immobile when they seized struggling and remained floating and motionless in water making only those movements necessary to keep their head above water. The water was changed after each experiment to avoid the influence of water temperature and substances left from previous session.

2.4.2 Neurobiochemical Study

After the OFT and FST studies, blood sample were collected by ocular puncture from the animals into lithium heparin bottles and stored in biofreezers at -80°C until used for neurobiochemical quantification (monoamines and monoamine oxidase). The animals were then sacrificed by cervical dislocation, the brain was excised, washed free of blood with normal saline (0.9% NaCl) and kept in 0.1 M phosphate buffer (pH7.2) and stored at -80°C until needed for further analysis.

2.4.2.1 Monoamines determination

The monoamine neurotransmitters which include serotonin, dopamine and norepinephrene concentrations in plasma and brain were carried out using HPLC by the method of [20].

2.5 Statistical Analysis

Data were presented as mean ± standard deviation. Results were subjected to analysis of variance (ANOVA) using Graph pad prism for windows, version 6.01 (Graph pad Software Inc), followed by Dunnet and Turkey's post hoc test where necessary. Where appropriate, $P \leq 0.05$ is considered statistically significant.

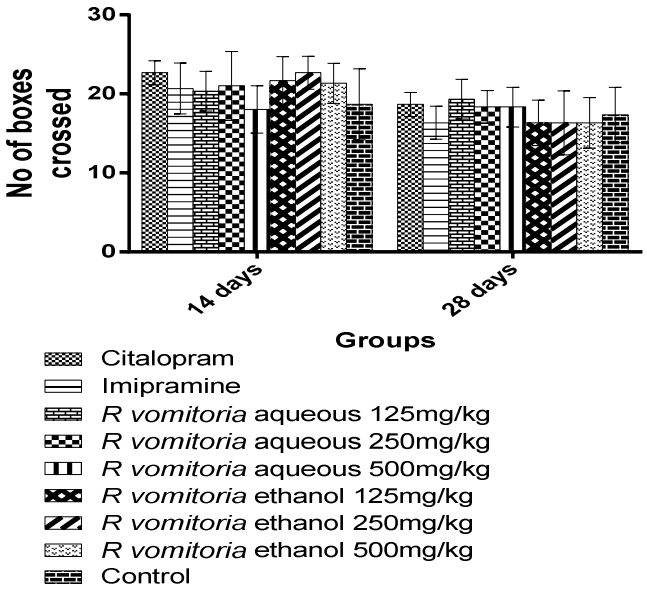

Fig. 1. Locomotory activity in open field test of rats administered plant extracts, antidepressants and normal saline for 14 and 28 days

Values are significant at P<0.05 compared to the control

3. RESULTS

3.1 Neurobehavioural Study

R. vomitoria administration across the various groups, showed no significant ($p<0.05$) difference in the locomotory activity of the open field test (Fig. 1). Meanwhile, in the forced swim test after 14 days of administration, *RVRa* 125 mg and *RVRe* 125 mg treated groups showed a significant ($p<0.05$) decrease in immobility time as compared to the control while in *RVRe* 500 mg there was a significant increase in immobility time as compared to citalopram. At 28 days, *RVRa* 125 mg and *RVRe* 250 mg showed significant decrease in immobility time compared to the control while *RVRa* 125 mg decreased immobility time when compared to *RVRe* 500 mg (Fig. 2).

3.2 Neurobiochemical Parameters in Plasma and Brain

R. vomitoria root extracts (aqueous and ethanol) after 14 days of administration showed no significant ($p<0.05$) difference in plasma serotonin concentration, whereas, after 28 days, *RVRa* 250 mg significantly increased serotonin level when compared to control (Fig. 3). The plasma dopamine concentration was significantly increased in *RVRe* 250 mg treated group as compared to Imipramine group after 14 and 28 days (Fig. 4). In addition, Plasma norepinephrine level in *RVRa* 125 mg treated group, increased significantly relative to the Imipramine treated group. However, *RVRe* 250 mg increased norepinephrine level compared to control and imipramine. *RVRa* 500 mg and *RVRe* 250 mg groups had significantly increased plasma levels as compared to Imipramine and Citalopram respectively (Fig. 5).

However, in the brain, the administration of *RVRe* 250 mg and citalopram for 14 days significantly raised the serotonin concentration compared to control and at 28 days, the concentration in *RVRa* 500 mg group increased significantly as compared to *RVRe* 125 mg groups while in *RVRe* 250 mg group compared to *RVRe* 500 mg, there was an increase in the serotonin level (Fig. 6). Also, the brain dopamine levels in citalopram, *RVRa* 250, *RVRa* 500 and *RVRe* 125 mg treated groups showed a significant increase compared to control. The *RVRa* 125 mg and *RVRa* 250 mg administration decreased the brain dopamine significantly when compared to *RVRa* 500 mg. *RVRe* 500 mg group was significantly increased compared to citalopram and imipramine. The aqueous extract at all concentrations resulted in increased dopamine concentration when compared to *RVRe* 500 mg, whereas, *RVRe* 125 mg caused

an increase when compared to *RVRe* 500, but at 28 days, there was no significant change (Fig. 7).

Nor epinephrine at 14 days in *RVRe* 250 mg treated group showed a significant increase compared to *RVRe* 500 mg. There was a significant increase in the brain norepinephrine levels of *RVRe* 250 mg treatment compared to *RVRe* 500 mg; and also *RVRa* 500 mg and *RVRe* 125 mg compared to imipramine (Fig. 8).

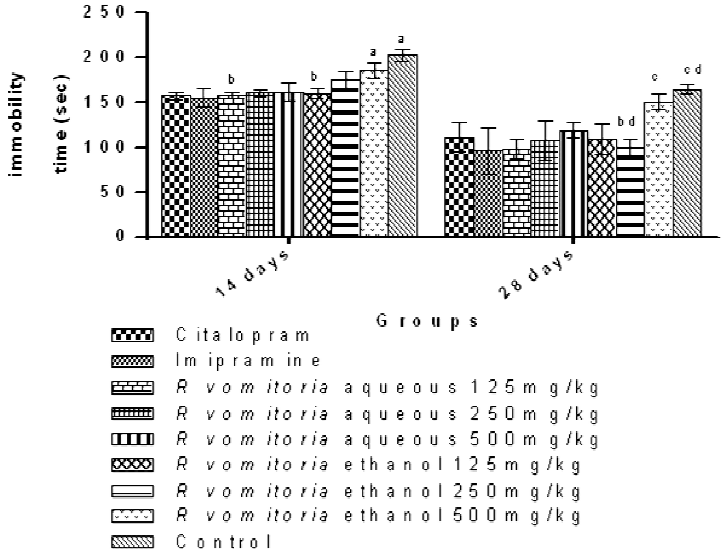

Fig. 2. Immobility time in forced swim test of rat administered plant extracts, antidepressant and normal saline for 14 and 28 days

Values are significant at (p<0.05) when compared to: a=citalopram; b=control; c=RVRa 125 mg/kg and d=RVRa 500 mg/kg

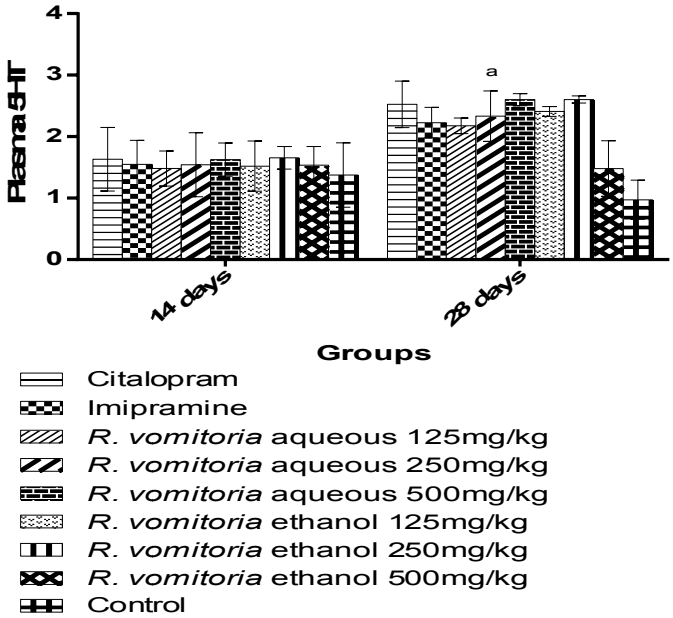

Fig. 3. Concentration of serotonin (5HT) (nmol/g) in plasma of rats administered plant extract, antidepressant and normal saline for 14 and 28 days

Values are significant at P<0.05 compared to: a= control

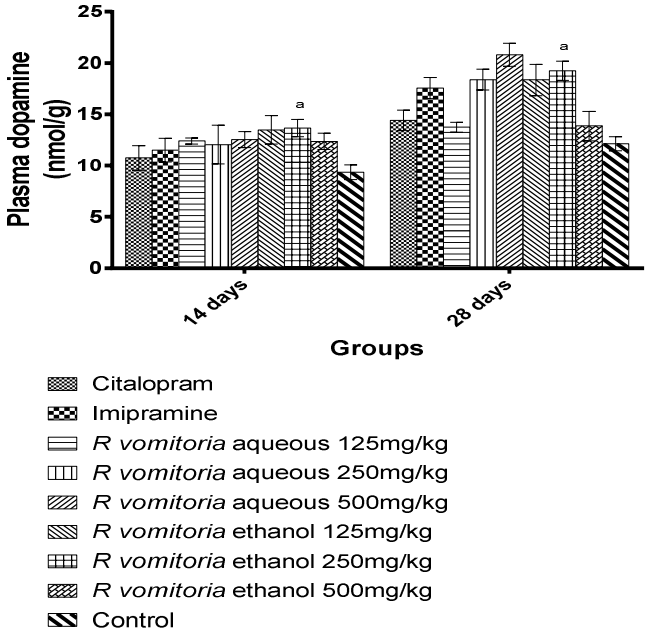

Fig. 4. Concentration of dopamine (nmol/g) in plasma of rats administered plant extract, antidepressant and normal saline for 14 and 28 days

Values are significant at P<0.05 compared to: a=Imipramine control

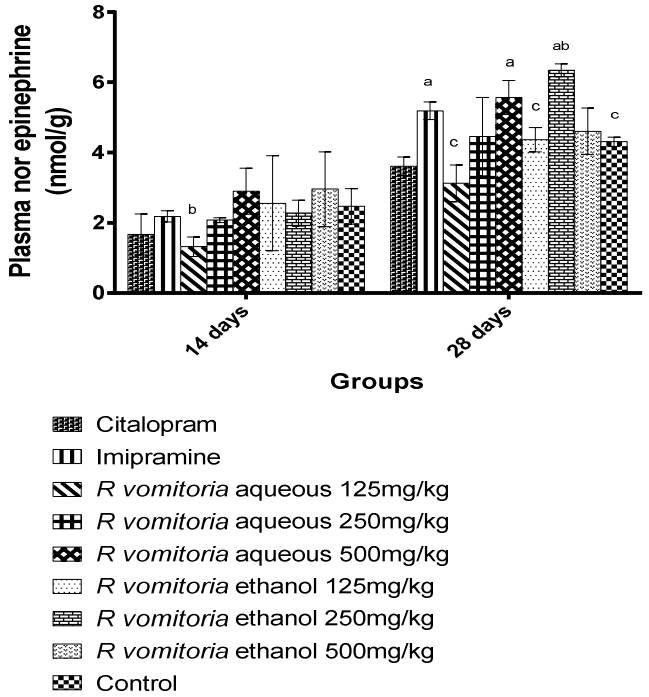

Fig. 5. Concentration of nor epinephrine (nmol/g) in plasma of rats administered plant extracts, antidepressant and normal saline for 14 and 28 days

Values are significant at P<0.05 compared to: a=Citalopram; b=imipramine and c= RVRe 250 mg/kg

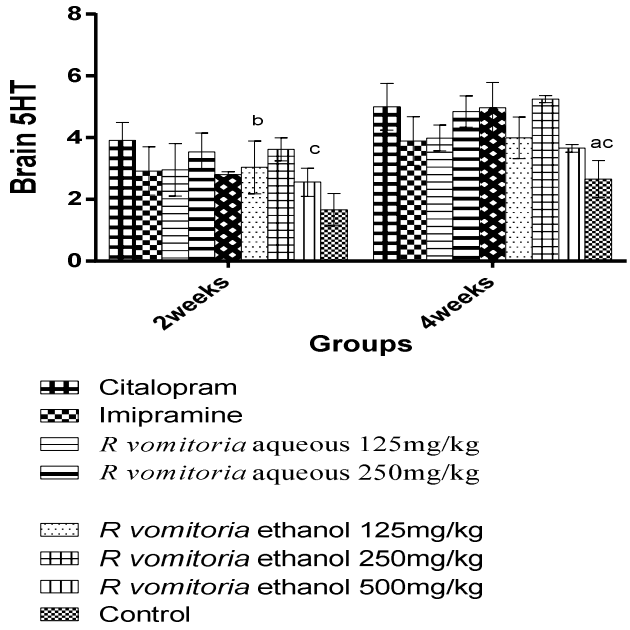

Fig. 6. Concentration of serotonin 5HT (nmol/g) in brain of rats administered plant extract, antidepressant and normal saline for 14 and 28 days

Values are significant at P<0.05 compared to: =Citalopram; b=RVRa 500 mg/kg and c= RVRe 250 mg/kg

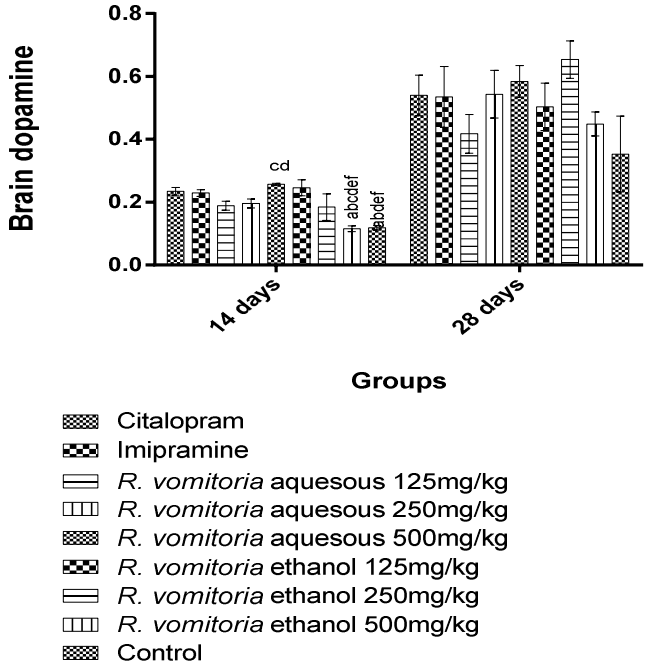

Fig. 7. Effect concentration of dopamine (nmol/g) in brain of rats administered plant extract, antidepressant and normal saline for 14 and 28 days

Values are significant at P<0.05 compared to: a=citalopram; b=RVRe 500 mg/kg

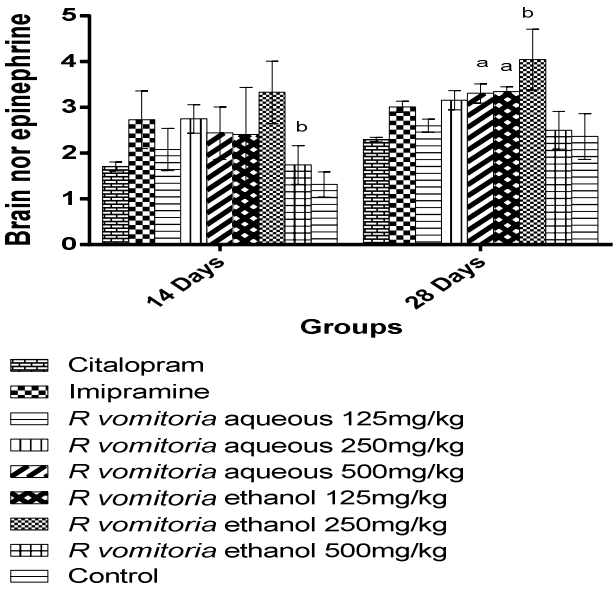

Fig. 8. Concentration of nor epinephrine (nmol/g) in brain of rats administered plant extract, antidepressant and normal saline for 14 and 28 days

Values are significant at P<0.05 compared to: a=citalopram; b=RVRe 500 mg/kg

4. DISCUSSION

Depression is a heterogeneous affective disorder which particularly affects the mood and is associated with high rates of recurrence, relapses, and premature deaths. Globally, up to 20% of population is affected with major depression [21]. Open Field Test is a locomotor activity test that measures the exploratory behaviour and general activity of animals. It is a mechanism used to assess the sedative, toxic or stimulatory effects of compounds [22]. In this present study, the excitatory and locomotor activities which were not affected by oral administration of the aqueous and ethanol extracts suggest that the extract has no stimulatory effect on the central nervous system. This result agrees with earlier report by Eluwa et al. [23].

In screening potential antidepressant effects of agents, the indicator for depression is immobility time in the force swimming test [24]. This behavioural change is sensitive to major classes of antidepressants drugs. Immobility time is recorded when the rats continued floating in water without struggling and only makes movements to keep nose or head above water [25]. Therefore, increase in immobility time implies a weak or non-antidepressant activity of a compound. In this study, both aqueous and ethanol extracts of *R. vomitoria* showed good antidepressant activity by decreasing the immobility time in rats especially at 125 and 250 mg/kg while the ethanol extract at 500 mg/kg displayed high immobility time. This suggests that *R. vomitoria* antidepressant like activity may be dose dependent. Studies have shown that imipramine and SSRI's (citalopram) significantly reduced immobility time and reduced locomotor activities [26]. Low levels of monoamines in the synapses have been linked to depression. Classical antidepressants like imipramine inhibits reuptake of monoamines, thereby making these neurotransmitters continually available for neurotransmission [27]. Most antidepressants in clinical use promote an increase in 5HT, dopamine and nor epinephrine [28]. In this study, *R.vomitoria* extracts may exhibit its antidepressant- like effect by inhibition of monoamine neurotransmitter re-uptake which is evidenced in the increase in both plasma and brain neurotransmitter levels following the administration of *RVRa* 125-500 mg/kg and *RVRe* 125-250 mg/kg. However, higher dose of ethanol extract (*RVRe* 500 mg/kg), in most cases which reduced the levels of the monoamine neurotransmitters, suggest a dose-dependent effect which could be due to the increase in specific alkaloids such as reserpine. Reserpine in high doses can permanently inhibit the vesicular uptake of monoamines thereby depleting

monoamines in the brain and ultimately lead to depression, while at low dosage shows anti-depresant effects [29,30]. The NE and 5-HT neurotransmitter systems are mutually interacted in the central nervous system [31]. Studies have shown that antidepressants that act on more than one neurotransmitter are better [32]. Most clinically employed antidepressants exert their effects on one monoaminergic system, although it is unlikely that use of a single neurotransmitter in relative isolation would effectively remedy severe neurochemical dysfunction [24]. Therefore, *R. vomitoria* which had showed antidepressant effect in more than one monoaminegic system, may provide a better therapeutic index. Previous studies found that serum 5-HT concentrations in patients with major depressive depression (MDD) were significantly lower than those in healthy controls, suggesting 5-HT deficiency in patients with MDD [33].

5. CONCLUSION

The present study suggests that the aqueous and ethanol extracts of *R. vomitoria* has the ability to reduce immobility time in the forced swimming test which is not due to stimulatory effect as confirmed by open field test. Data of this study suggest that the antidepressant-like effect of *R. vomitoria* is mediated by increase in monoamine levels.

CONSENT

It is not applicable.

ETHICAL APPROVAL

All authors hereby declare that "Principles of laboratory animal care" (NIH publication No. 85-23, revised 1985) were followed, as well as specific national laws where applicable. All experiments have been examined and approved by the Health Research Ethics Committee of the College of Medicine of the University of Lagos, Lagos, Nigeria. Approval number: CMUL/HREC/19/01810.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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