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# Antipsychotic Effects of Ethanol Leaf Extract and Fractions of *Milicia excelsa* (*Moraceae*) in Mice

**Lateef Abiola Akinpelu[1,2*], Moses Atanda Akanmu[2] and Efere Martins Obuotor[3]**

*[1]Department of Pharmacology and Toxicology, College of Pharmacy, Igbinedion University, Okada, Edo State, Nigeria.*
*[2]Department of Pharmacology, Faculty of Pharmacy, Obafemi Awolowo University, Ile-Ife, Osun State, Nigeria.*
*[3]Department of Biochemistry, Faculty of Science, Obafemi Awolowo University, Ile-Ife, Osun State, Nigeria.*

***Authors' contributions***

*This work was carried out in collaboration between all authors. Author LAA managed the experimental process, performed the statistical analysis of the study, managed the literature searches and wrote the first and final version of the manuscript. Author MAA designed the study, managed the experimental process and managed the analyses of the study. Author EMO designed the study, managed the experimental process and managed the analyses of the study. All authors read and approved the final manuscript.*

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## ABSTRACT

**Aim:** This study investigated the acute toxicity ($LD_{50}$) and antipsychotic potentials of ethanol leaf extract of *Milicia excelsa* (EME), hexane (HF), ethyl acetate (EAF), butanol (BF) and aqueous (AF) fractions in mice.
**Study Design:** This study used experimental mice models predictive of human psychosis.
**Place and Duration of Study:** Department of Pharmacology, Faculty of Pharmacy, Obafemi Awolowo University, Ile-Ife, Osun State, Nigeria, between January 2014 to February 2015.
**Methodology:** The antipsychotic effect was assessed using swim-induced grooming; apomorphine-induced climbing and ketamine-induced hyperlocomotion behaviours in mice.

**Corresponding author: E-mail: akinpelu_abiola01@yahoo.com;*

**Results:** The results showed that the $LD_{50}$ of the ethanol extract and its various fractions were greater than 5000 mg/kg. EME and all its fractions significantly ($P < 0.05$) decreased the number of grooming while the duration of grooming was significantly ($P < 0.05$) reduced by EME, EAF and AF in swim-induced grooming. EME and EAF significantly ($P < 0.05$) inhibited climbing behaviour in apomorphine-induced climbing. EME and all the fractions significantly ($P < 0.05$) inhibited the hypermotility induced by ketamine while the number of ataxia was significantly ($P < 0.05$) reduced by EME, EAF and AF in ketamine-induced hyperlocomotion, with AF producing a stronger ataxia reducing effect compared to haloperidol, a reference antipsychotic drug. EME and EAF showed consistent antipsychotic activities in all the models used.
**Conclusion:** This study concludes that EME and all its fractions may be safe and contain antipsychotic principles, thus, providing scientific evidence for the suggested ethnomedicinal use of the leaf in treating insanity in traditional medicine.

*Keywords: Milicia excelsa; antipsychotic; swim-induced grooming; apomorphine; ketamine.*

## 1. INTRODUCTION

Schizophrenia is a devastating psychiatric disorder that disrupts cognition, emotion, language, and thought. It affects 0.5%–1.5% of the population [1]. Abnormality in neurotransmitters pathways such as hyperactivity of dopaminergic system [2], hypofunction of glutaminergic pathway via the NMDA receptor [3] and the serotoninergic system, [4] have been implicated in the brain of individuals with schizophrenia.

The poor efficacy and tolerability of the currently available antipsychotic drugs have limited their use. Due to rise in psychiatric disorders and adverse effects associated with the existing therapy; it becomes pertinent and imperative for clinicians to search for alternative remedies for the treatments of this neurobehavioural disorder [5].

Medicinal plants play an essential role in health care delivery and needs of rural populace in Africa, and among other underdeveloped or third world countries. Especially in the treatment of diseases, [6] and also in developed countries, [7] because they are considered more natural, safer, and affordable compared to "manufactured" pharmaceutical products [8,9].

*Milicia excelsa* (welw.) C.C. Berg belongs to the family of Moraceae, popularly known as Iroko tree or African teak. It is a large deciduous tree 30 to 50 m high occurring naturally in humid forests of West Africa [10]. Its latex, leaf, stem bark, root, fruit, and ashes are used in African traditional medicines to prepare traditional remedies for the treatment of malaria [11], rheumatism [12], sexual dysfunction [13], mental illnesses [14,15,16], anaemia, [17] among other diverse folkloric uses. Pharmacologically, the leaf has been reported to have wound healing effects [18], while the anti-inflammatory effect of the stem bark has also been reported [19].

This study was therefore designed, to provide scientific evidence, for the traditional claim of the leaf in the treatment of insanity [14], coupled with its widespread use among the Yoruba speaking tribe of South Western Nigeria as an antipsychotic herbal drug (Personal communication). To the best of our knowledge; the antipsychotic effect of the leaf has not been reported upon comprehensive literature search.

## 2. MATERIALS AND METHODS

### 2.1 Plant Identification and Authentication

*Milicia excelsa* leaves were collected within the campus of the Obafemi Awolowo University (OAU) Ile Ife Nigeria. It was identified and authenticated by Mr. G. A. Ademoriyo of the Herbarium Unit, Department of Botany, Faculty of Sciences, OAU, Ile-Ife and herbarium number Ife-17482 was obtained.

### 2.2 Preparation of Plant Materials

The leaves of *Milicia excelsa* were air dried at room temperature. The dried leaves were pulverized and 1.0 kg of the powder was extracted with 3 liters of ethanol (70%) for 72 h. The marc was re-extracted once and the combined extract was concentrated *in vacuo* at a temperature of 40ºC to yield 70 g (7.0%) crude extract and coded (EME). Sixty gram (60 g) of the crude extract was successively partitioned into n-hexane (HF), ethyl acetate (EAF), n-butanol (BF) and aqueous (AF) fractions. The fractions were again concentrated *in vacuo* to give n-hexane, ethyl-acetate, n-

butanol and aqueous fractions (Personal communication).

## 2.3 Drugs

Haloperidol, Apomorphine, Tween 20 (Sigma Chemicals Co, St. Louis, Missouri, U.S.A.), Ketamine hydrochloride (Rotexmedica, Germany) and physiological saline (Unique Pharmaceutical Limited, Lagos, Nigeria). EME and fractions were dissolved with 2% Tween 20 and made up to the required volume with normal saline. The drugs, crude extract and fractions were freshly prepared on each day of the experiments.

## 2.4 Laboratory Animals

Adult male albino mice (18–25 g) were obtained from the Animal House, Department of Pharmacology, Faculty of Pharmacy, OAU, Ile-Ife. The animals were acclimatized for one week in a cage lined with wood shavings at room temperature, under 12 h of light/12 h of darkness cycle. The animals were fed on standard animal pellets and water *ad libitum*. Experimental protocols were carried out in accordance with the National Institute of Health [20]. The experiments were carried out between 9.00 am and 3.00 pm on each day of the experiment.

## 2.5 Acute Toxicity Study

As a follow up to the preliminary acute toxicity studies of EME and BF, which were determined using Lorke's method (Personal communication), acute oral toxicity assessment of HF, EAF, and AF were also carried out using Lorke's method [21]. The experiments were carried out in two phases. In the first phase, HF was administered via an orogastric route to three groups of mice (n=3) at the doses of 10, 100 and 1000 mg/kg respectively. In the following phase, another three groups of mice (n=1) were again administered 1600, 2900 and 5000 mg/kg of HF via an orogastric route. After oral ingestion of HF in each of the two phases, each mouse was observed for obvious toxic symptoms and mortality for 24 h post administration. These procedures were repeated for EAF and AF.

## 2.6 General Experimental Design

Male mice were randomly divided into 5 groups (n = 5). Group I (Vehicle), the animals in this group received 2% Tween 20 in normal saline (10 mL/kg, p.o.), Group II-IV (Treatment groups), the animals received 250, 500 and 1000 mg/kg, p.o of the extract and fraction(s), Group V (Reference drug). Male mice were used for this study because of the psychoprotective effect of oestrogen and progesterone in females [22,23,24,25].

### 2.6.1 Swim induced grooming (SIG)

Grooming behaviour was induced in mice by a short period of swimming as previously described [26]. The control mice were pretreated with 2% Tween 20 in normal saline (10 mL/kg, p.o.), EME (250, 500 and 1000 mg/kg, p.o.). One hour post treatments, mice were individually placed in a swimming cylinder (8 x 8 x 18 cm high) filled with fresh water maintained at 32°C and allowed to swim for three minutes. The reference, haloperidol ($D_2$ receptor antagonist) treated positive control group received a dose (1 mg/kg, i.p.), 30 minutes before being subjected to swimming for three minutes. After an expiration of 3 minutes swimming session, each mouse was then removed and dried with a towel for 30 seconds and placed immediately into single Perspex boxes. The number and the total duration of grooming episodes were recorded for 15 minutes. The water in the cylinder was changed after each mouse had swum. The procedures were repeated using HF (250-1000 mg/kg, p.o.), EAF (250-1000 mg/kg, p.o.), BF (250-1000 mg/kg, p.o.) and AF (250-1000 mg/kg, p.o.).

### 2.6.2 Ketamine-induced hyperlocomotion

The exploratory activity of mice was assessed using open field test (OFT) as adapted from earlier studies [27,28]. The control animals were treated with 2% Tween 20 in normal saline (10 mL/kg, p.o.), EME (250, 500 and 1000 mg/kg, p.o.). One hour after treatments, each mouse received ketamine (10 mg/kg i.p.) and was immediately put in the open field, and observed for the number of squares crossed (locomotor activity) and ataxia (the frequency of staggered movements and number of falls) during three minutes, after one minute for acclimatization. The positive control group received haloperidol (0.2 mg/kg, i.p.) 30 min before ketamine (10 mg/kg, i.p.). The procedures were repeated using HF (250-1000 mg/kg, p.o.), EAF (250-1000 mg/kg, p.o.), BF (250-1000 mg/kg, p.o.) and AF (250-1000 mg/kg, p.o.).

## 2.7 Statistical Analysis

Results are expressed as mean ± S.E.M. The significance of difference between groups were

analysed using one way analysis of variance (ANOVA), followed by post hoc analysis using the Student- Newman-keuls test. Non parametric tests were analysed by Kruskal Wallis followed by Dunn test using GraphPad InStat® Biostatistics software (GraphPad Software, Inc., La Jolla, USA). The level of significance for all tests was set at $P < 0.05$.

## 3. RESULTS

### 3.1 The Results of Acute Toxicity Study

The acute toxicity ($LD_{50}$) of HF, EAF and AF were greater than 5000 mg/kg, p.o.

### 3.2 Effects of the EME, HF, EAF, BF and AF on Swim-induced Grooming Behaviour in Mice

The results obtained showed that EME, HF, EAF, BF and AF at all the doses used (250, 500 and 1000 mg/kg, p.o.) significantly [F (4, 25) = 22.345, $P < 0.0001$)], [F (4, 25) = 22.876, $P < 0.0001$], [F (4, 25) = 36.101, $P < 0.0001$], [F (4, 25) = 21.942, $P < 0.0001$] and [F (4, 25) = 39.899, $P < 0.0001$] respectively decreased the number of grooming activity compared to the vehicle treated control. The effect was most pronounced in AF in a dose-dependent manner, followed by EAF, HF with BF having the lowest activity. However, EME, EAF and AF at all the doses used (250, 500 and 1000 mg/kg, p.o.) significantly [F (4, 25) = 178.72, $P < 0.0001$)], [F (4, 25) = 93.227, $P < 0.0001$], and [F (4, 25) = 88.747, $P < 0.0001$] decreased the duration of grooming activity respectively compared to the vehicle treated control group. This effect was more pronounced in EAF than AF. BF and HF at all aathe doses used showed no significant effect on duration of grooming when compared to the vehicle treated group. The standard drug, haloperidol significantly ($P < 0.05$) decrease both the number and duration of behaviour (Fig. 1) (Panel A and B).

### 3.3 Effects of EME, HF, EAF, BF and AF on Apomorphine-induced Climbing Behaviour in Mice

The results obtained showed that EME and EAF at 1000 mg/kg and 250 mg/kg respectively significantly ($P < 0.05$) attenuated the climbing behaviour in apomorphine-induced climbing behaviour in mice when compared to the vehicle treated control group. However, HF, BF and AF did not significantly inhibit climbing behavior when compared to the vehicle treated control group. The standard drug haloperidol significantly ($P < 0.05$) reduced the number of climbing behaviour when compared to vehicle treated group (Fig. 2).

### 3.4 Effects of EME, HF, EAF, BF and AF on Ketamine-induced Hyperlocomotion in Mice

Ketamine (Ket 10 mg/kg, i.p.) significantly ($^{\ddagger}P < 0.05$) increased the number of locomotion while the standard drug haloperidol significantly ($P < 0.05$) decreased the hyperlocomotion induced by ketamine when compared to the vehicle treated control group. The hyperlocomotion induced by ketamine (10 mg/kg, i.p.) was significantly [F (4, 25) = 56.658, $P < 0.0001$)], [F (4, 25) = 65.154, $P < 0.0001$] and [F (4, 25) = 29.128, $P < 0.0001$] reduced by the pretreatment with EME, EAF and AF respectively at all doses (250, 500 and 1000 mg/kg, p.o.) when compared to ketamine treated group.

HF at the doses of 250 and 1000 mg/kg, p.o significantly [F (4, 25) = 52.436, $P < 0.05$] and BF at the doses of 250 and 500 mg/kg, p.o. significantly [F (4, 25) = 52.309, $P < 0.001$] decreased hyperlocomotion induced by ketamine (10 mg/kg, i.p.) when compared to ketamine treated control group. EME, HF, EAF, BF and AF produced significant ($P < 0.05$) increase in locomotion when compared to the vehicle treated group without ketamine administration (Fig. 3) (Panel A).

### 3.5 Effects of EME, HF, EAF, BF and AF on Ataxia in Ketamine-induced Hyperlocomotion in Mice

Ketamine significantly ($P < 0.05$) increased the number of ataxia but standard drug haloperidol significantly ($P < 0.05$) decreased the number of ataxia when compared to the vehicle control group. The number of ataxia induced by ketamine was significantly [F (4, 25) = 30.046, $P < 0.0001$)], [F (4, 25) = 41.582, $P < 0.0001$)] and [F (4, 25) = 29.128, $P < 0.0001$)] decreased by pretreatment with EME, EAF and AF respectively at all the doses used (250, 500 and 1000 mg/kg, p.o.) when compared to ketamine treated control group. HF and BF did not affect the number of ataxia behaviour. The results are presented in Fig. 3 (Panel B).

## 4. DISCUSSION

This study investigated the oral acute toxicity ($LD_{50}$) of HF, EAF and AF while the antipsychotic

effect of EME, HF, EAF, BF and AF were also investigated. The $LD_{50}$ of HF, EAF, and AF were found to be greater than 5000 mg/kg suggesting that the fractions may be safe in mice, since no acute toxicity may be considered above 5 g/kg body weight [29]. Preliminary investigations from our laboratory have also shown that the $LD_{50}$ of EME and BF were greater than 5000 mg/kg per body weight. EME and EAF showed antipsychotic effects in all the models of swim-induced grooming (SIG), apomorphine-induced climbing test (AIC) and ketamine-induced hyperlocomotion models (KIH) used in this study.

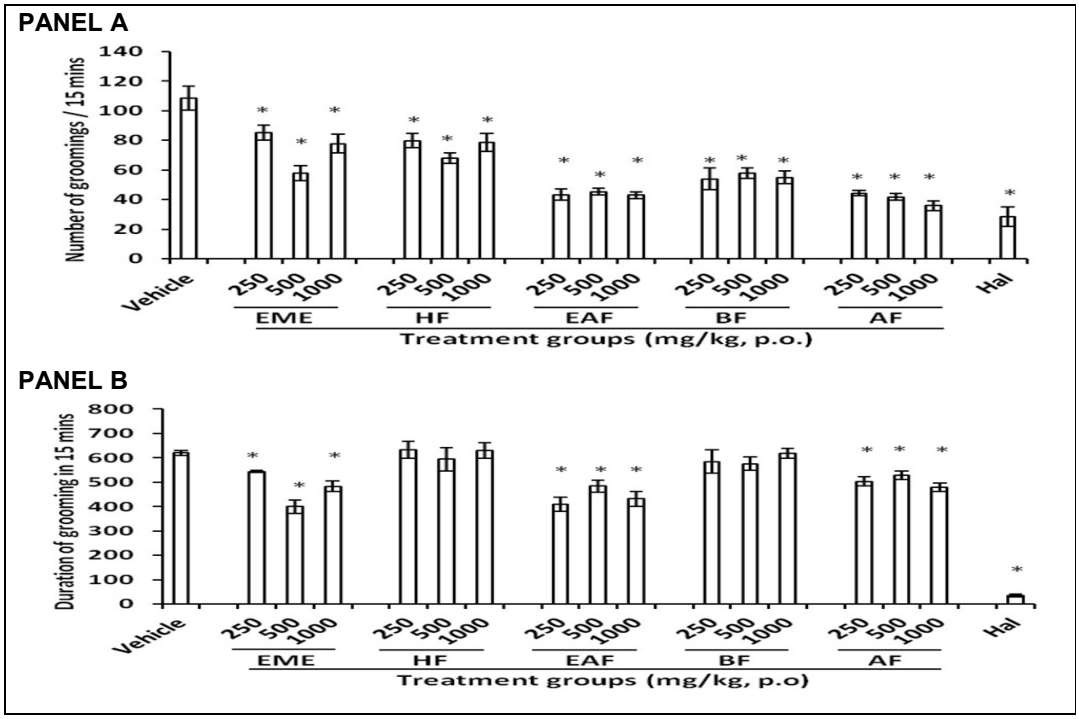


**Fig. 1. Antipsychotic effect of EME, HF, EAF, BF and AF on the number of grooming (Panel A) and the duration of grooming (Panel B) in SIG in mice**

*Vehicle; 2% Tween 20 in Normal saline (10 mL/kg, p.o.), Hal; Haloperidol (1 mg/kg, i.p.), SIG; swim induced grooming, EME, HF, EAF, BF and AF represent ethanol leaf extract, hexane, ethyl acetate, butanol and aqueous fractions of Milicia excelsa respectively. Each bar represents Mean ± SEM, ANOVA; one way analysis of variance followed by Student-Newman Keuls Test, n=6, *P < 0.05 compared to the vehicle treated group*

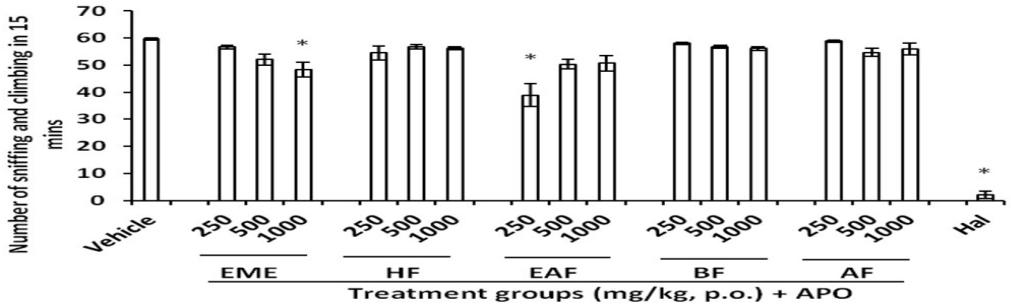


**Fig. 2. Antipsychotic effect of EME, HF, EAF, BF and AF on apomorphine-induced climbing test**

*Vehicle; 2% Tween 20 in Normal saline (10 mL/kg, p.o.), Hal; haloperidol (2 mg/kg, i.p.), APO; apomorphine (1.5 mg/kg, s.c.), EME, HF, EAF, BF and AF represent ethanol leaf extract, hexane, ethyl acetate, butanol and aqueous fractions of Milicia excelsa respectively. Each bar represents Mean ± SEM, Kruskal-Wallis followed by Dunn test, n=6, *P < 0.05 compared to the vehicle treated control*

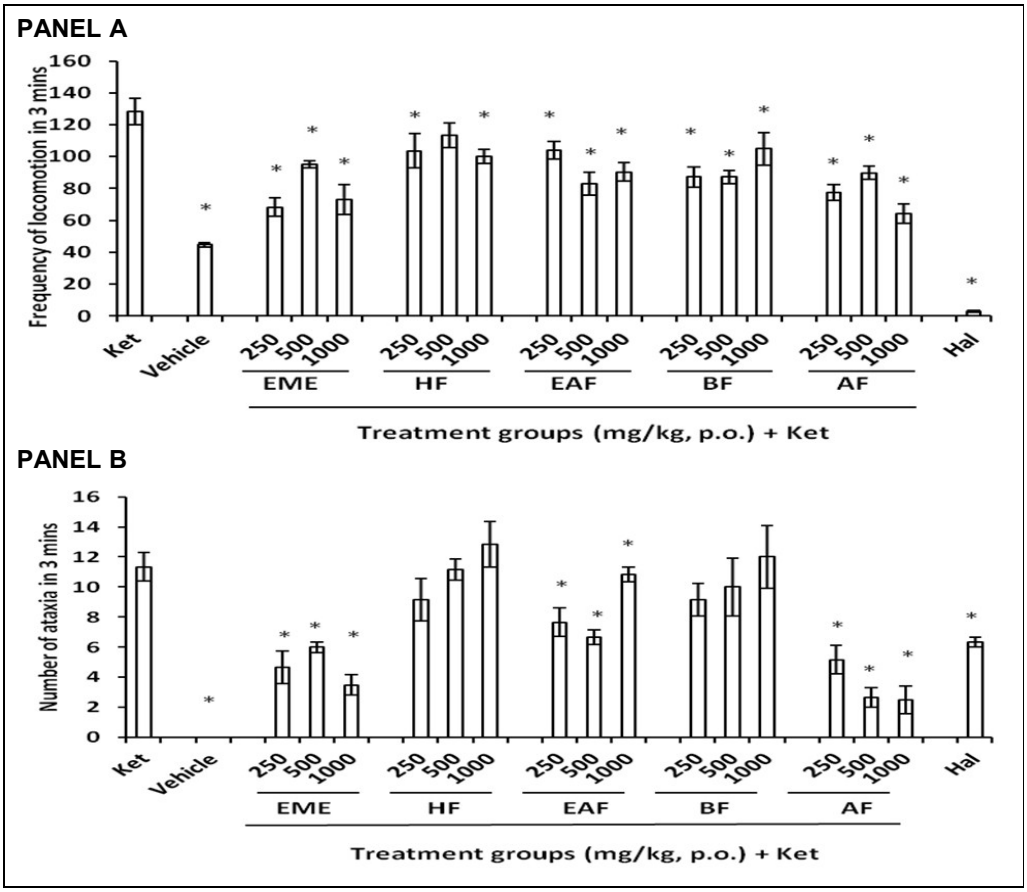


**Fig. 3. Antipsychotic effect of EME, HF, EAF, BF and AF on frequency of locomotion (Panel A) and number of ataxia (Panel B) in Ketamine-induced hyperlocomotion test in mice**

*Vehicle; 2% Tween 20 in Normal saline (10 mL/kg, p.o.), Ket; ketamine (10 mg/kg, i.p.), Hal; haloperidol (2 mg/kg, i.p.), EME, HF, EAF, BF and AF ethanol leaf extract, hexane, ethyl acetate, butanol and aqueous fractions of Milicia excelsa respectively. Each bar represents Mean ± SEM, ANOVA; one way analysis of variance followed by Student-Newman Keuls Test, n=6, *P < 0.05 compared to the vehicle treated group*

In SIG, EME, EAF, and AF reduced the number of grooming and duration of grooming. Swim-induced grooming is one of the widely used models for screening antipsychotic drugs which are mediated through dopamine $D_1$ receptor blocking actions [26]. This finding suggests that they may possess antipsychotic effect which is probably mediated via dopamine $D_1$ receptor blocking action. A number of reports have shown that agents that reduced grooming elicited by immersion in water of mice showed antipsychotic effects [26]. A previous study [30] showed that reduction in Swim-induced grooming behaviour inferred that there was an antipsychotic effect. Thus, the result obtained from this study showed that the plant extract and fractions reduced grooming behaviour and it could, therefore, be inferred that EME, EAF, and AF possessed antipsychotic effect as well. Of all the fractions in swim-induced grooming, AF produced the most potent antipsychotic effect.

EME and EAF inhibited AIC behaviour which is suggestive of $D_1$ and $D_2$ action. Numerous reports have shown that the ability of substances to antagonize apomorphine-induced climbing behaviour have been correlated with their neuroleptic potentials which are mediated via the activation of both $D_1$ and $D_2$ receptors [31]. For example, some researchers reported that *Securinega virosa* extract inhibited the climbing elicited by apomorphine in apomorphine-induced climbing behaviour in mice [31]. Likewise, others observed reduction in apomorphine-induced climbing test following the administration of *Morinda citrifolia* in mice [5], thus, they both suggested that these extracts may have

antipsychotic effects, the mechanism of which involved antagonism of $D_1$ and $D_2$ receptors. Since, EME and EAF inhibited apomorphine-induced climbing behaviour, it could therefore be suggested as well that they have antipsychotic effects mediated via the same mechanism.

EME, HF, EAF, BF, and AF reduced the hyperlocomotion induced by ketamine in KIH at varying degrees. The potency of EME and AF is comparable to that of haloperidol (a standard neuroleptic drug). These findings suggest that EME and the various fractions may have varying degrees of antipsychotic actions that could probably be mediated via dopaminergic neurotransmission [32]. This is in tune with earlier finding [27].

A competitive antagonist of NMDA receptor such as ketamine has been shown to induce behavioural effects that mimic positive, negative and cognitive schizophrenic symptoms in healthy humans [33,34,35] as well as behavioural activation in experimental animals [36]. Neuroleptics, such as haloperidol and risperidone have been reported to decrease locomotor activity due to the acute depressant effect of this class of drugs [37]. This hypomotility caused by neuroleptics may be as a result of reduced central nervous system excitability or through sedative effect [37]. A number of research findings have shown the ability of some agents to reduce hypermotility induced by ketamine [27,37,38]. For example, the antipsychotic effect of *Alpinia zerumbet* has been ascribed to its hypomotility effect in ketamine-induced hyperlocomotion in mice [39]. EME, EAF, and AF reduced ataxia induced by ketamine suggesting that the antipsychotic effect of these substances may also involve amelioration of glutaminergic neurotransmission as dysfunction of glutaminergic neurotransmission mediated via the NMDA receptor has been implicated in the pathophysiology of the psychotic illness such as schizophrenia [40,41]. AF produced stronger ataxia reducing effect compared to haloperidol, a reference antipsychotic drug.

Although the antipsychotic activity elicited by EME, EAF, and AF is less comparable to haloperidol in this study, but the use of medicinal plants in treating diseases has been an integral part of every culture [42] and a major part of Africa heritage [43]. Despite advances in and availability of orthodox medicine, there is still a high patronage of traditional/herbal medicine for treatment of mental and other disorders in Africa/Nigeria [44,45]. For example, *Rauwolfia vomitoria* has been used in Nigeria to manage psychiatric disorders despite orthodox medicine [46]. Therefore, conducting scientific findings into the efficacy and safety of medicinal plants is pertinent and imperative. Moreso, that World Health Organisation encourages the incorporation of valuable elements of traditional medicine into national health care systems [47]. This study, therefore, is worthwhile because of the widespread belief that “green medicine” is cheap, safe, more dependable and accessible than the costly synthetic drugs many of which are associated with intolerable effects [48,49].

## 5. CONCLUSION

This study concludes that *M. excelsa* leaf extract and fractions may have biologically active antipsychotic principles. The magnitude of potency of the fractions may be of the order EAF > AF > HF > BF. Thus, lend pharmacological credence to the suggested ethnomedicinal uses of the leaf in treating insanity in traditional medicines. However, further studies may be warranted to investigate the effect of EME and its fractions on drug-induced catalepsy and ptosis in mice.

## 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 appropriate ethics committee.

## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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