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Neuropsychopharmacological Profile of Koju®, a Popular Nigerian Polyherbal Formulation

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Abstract

Koju® (KHM) is a polyherbal formulation consisting of *Xylopia aethiopica* (root bark), *Securidaca longepedunculata* (stem bark), *Magnifera indica* (stem bark), *Allium sativum* (seed), *Citrus aurantifolia* (root bark), *Morinda lucida* (seed) and *Saccharum officinarum* (Bark). In Nigeria, it is usually indicated for a wide range of diseases. This study was undertaken to investigate the psychoneuropharmacological profile of this formulation. We evaluated the acute toxicity of KHM using Lorke's method. Sedative activity was evaluated using thiopental sodium (TS) sleeping time test. Anticonvulsant activity was evaluated using N-Methyl-D-Aspartate (NMDA), aminophylline and strychnine-induced seizures in mice while anxiolytic effect was evaluated in rats using elevated plus maze (EPM), Zero- maze and open field apparatus. The doses of KHM used were 100, 200 and 400 mg/kg. Results of acute toxicity study showed that KHM produced no signs of toxicity or mortality up to a dose of 5000 mg/kg. In the TS sleeping time test, KHM significantly ($p< 0.001$) decreased onset of sleep and increased duration of total sleeping time. Against NMDA-induced seizures, HKM at 200 and 400 mg/kg offered 16.67% protection. KHM also protected the mice by 16.67-3.33% against aminophylline- induced seizures. While against strychnine- induced seizures, KHM offered 16.67% protection at 100 and 200 mg/kg and 33.33% at 400 mg/kg. KHM also significantly ($p< 0.001$) increased time spent in the open arm of EPM and significantly ($p< 0.001$) increased time spent in open arms of the Zero maze. KHM also significantly increased total locomotor activity ($p< 0.001$) and rearing in the open field apparatus. It was concluded

that the polyherbal formulation possess sedative, anticonvulsant and anxiolytic activities. The findings therefore provide some scientific rationale for the use of KHM in the management of neuropsychiatric conditions.

Keywords: scapul Sedative, Anti-convulsant, Anxiolytic, Koju®, Polyherbal, Neuropharmacological a, glenoid cavity, morphology, shoulder arthroplasty.

1.0 Introduction

Neuropsychiatric disorders primarily appear as abnormalities of thought, feeling or behavior, producing either distress or impairment of function (calvo and Cavero, 2015). These pathologies handicap the person concerned and assign people of its circle. Factors causing these disorders are essentially genetic, social, environmental and psychotropic drugs. Mental and neurological disorders represent 13% of the burden of total morbidity in the world (OMS, 2012). Thirteen per cent (13%) to 49% of the world's populations develop neuropsychiatric disorders at some point in their life (Yasamy *et al.*, 2011). These pathologies affect all categories of person, race, sex and age (Fusar-poli *et al.*, 2012).

The most common neurological disorders include epilepsy, depression, anxiety disorders and insomnia. Epilepsy affects more than 50 million persons in the world including 80% in developing countries (WHO, 2008). High prevalence was observed in Africa where about 75% of patients do not receive adequate treatment (Moshi *et al.*, 2005). Seizure is a common feature of epilepsy and it involves the abnormal discharge of a group of neurons in the brain, and may occur in different clinical forms depending on the discharge rate and its spread (Saki *et al.*, 2014). Depression and anxiety are clinic illnesses related to the central nervous system too. Depression is the second reason of disability after cardiovascular diseases, as it causes severe social and economic deficits (Saki *et al.*, 2014). Anxiety disorders are another common types of mental illnesses found in communities. Insomnia is one of the most common disorders that many people are chronically suffering from for different reasons (Neubaur, 2003).

Many natural or synthetic psychoactive molecules such as neuroleptics, antidepressants, anxiolytics are used in modern medicine to treat these pathologies, particularly epilepsy, schizophrenia and the others psychotic disorders (Starling & Feijo, 2012; Diaby & Etude, 2014; Rey-bellet, 2015). However, these modern treatments are expensive, complex and inaccessible for African populations in rural area (WHO, 2000; Diabey & Etude, 2014). The development of new pharmacological agents that can overcome these barriers has become a major goal in research. The plant kingdom, in this regard plays a major role as new herbs/ polyherbal formulations and even conventional drugs of plant origin are now being discovered and used for protection against these debilitating neurological disorders.

Polyherbal formulations are mixtures of many plant parts (which could be roots, leaves, stem, flowers, pods and seeds) obtained from various plant species and families. These plants/ their combinations usually contain an array of bioactive compounds making them suitable for the treatment and management of a variety of disease conditions (Pieme, 2016). By using herbal combinations, nature provides a balance of ingredients that may act as buffers, synergists or counterbalances, which work in harmony to rid the body of diseases and infirmities (Montrale, 1998). Some polyherbal extracts have been scientifically proven for efficacy in the treatment of diseases while many others are yet to be investigated (Idakwoji *et al.*, 2016). One of such polyherbal formulations that is yet to be scientifically investigated for its neuropharmacological benefits is Koju®.

Koju® is a polyherbal formulation consisting of *Xylopia aethiopica* (root bark), *Securidaca longepedunculata* (stem bark), *Magnifera indica* (stem bark), *Allium sativum* (seed), *Citrus aurantifolia* (root bark), *Morinda lucida* (seed)

and *Saccharum officinarum* (Bark). It is usually indicated for a wide range of diseases which include menstrual disorders, pile, diorrhoea, dysentery, waist pain, protruding rectum and diabetes. It was reported by Idakwoji and Uzuazokaro, (2018a) that the herbal formulation possesses anti-hyperglycaemic, anti- bacterial, anti- malarial, analgesic and anti- inflammatory activities. This study was aimed at profiling the polyherbal formulation for its sedative, anticonvulsant and anxiolytic activities.

2.0 Materials and Methods

2.1 Materials

2.1.1Chemicals and drugs

All experimental drugs and chemicals (analytical grade) used were purchased from Sigma Chemical Co. Ltd (USA). Koju® Herbal Mixture (KHM) was purchased from the company vendors around Adankolo area of Lokoja, Kogi State, Nigeria.

2.1.2 Animals

Adult rats (150- 200 g) and mice (18- 30g) were used for this study. They were maintained at 23.0 ± 2.0 ^{o}C, 12h light and dark cycle, fed with standard animal feed (Feeds Masters, Ilorin, Nigeria) and water was provided ad libitum. The animals were used in compliance with the National Institute of Health Guide for the Care and use of Laboratory Animals (Publication nos. 85-23, revised 1985).

2.2 Methods

2.2.1 Drying and reconstitution of the polyherbal formulation

Several bottles of KHF were emptied into a beaker and dried in an oven at 45ºC to a constant weight. Subsequently, the extract was reconstituted using normal saline to the required concentration.

2.2.2 Acute toxicity study

The oral median lethal dose (LD_{50}) of the extracts was determined in rats according to the method of Lorke *et al.* (1983)

2.2.3 Evaluation of sedative activity

Thiopental sodium-induced sleeping time test

The method described by Williamson *et al.* (1996) was adopted in this study with slight modifications. Thirty (30) mice were divided into five groups of six animals each. Group 1 served as control and received normal saline 10 ml/kg, while groups 2, 3 and 4 received 100, 200 and 400 mg/kg, p. o. of KHM respectively. Group 5 received diazepam (1 mg/kg). 30 min post-treatment, thiopental sodium (40 mg/kg, i.p.) was administered to mice in all the groups to induce sleep. The animals were observed for the latent period (time between Thiopental sodium administrations to loss of righting reflex) and duration of sleep (the time between the loss and recovery of righting reflex).

2.2.4 Evaluation of anti-convulsant activity

N-Methyl-D-aspartate (NMDA)-induced seizures in mice

The methods described by Ngo Bum *et al.* (2008) and Schmutz *et al.* (1990) were adopted for this study with modifications. Thirty mice were divided into five groups of six animals each. Group 1 served as control and received normal saline (10 ml/kg). Groups 2, 3 and 4 received 100, 200, and 400 mg/kg i.p. KHM respectively while group 5 received diazepam 10 mg/kg body weight. Thirty minutes after treatment, 75 mg/kg of NMDA was administered s.c to mice in all groups. Animals that did not elicit turning behavior within 30 min period were considered protected (Ngo Bum *et al.*, 2008; Schmutz *et al.*, 1990). Turning behavior was characterized by two consecutive 360^{o} cycles by the same animal (Ngo Bum *et al.*, 2008).

Aminophylline- induced seizures in mice

The method of Mamatha *et al.* (2009) was adopted for this study with modifications. Thirty (30) mice were divided into five groups of six animals each. Group 1 served as control and received normal saline 10 ml/kg i.p. Groups 2, 3 and 4 received 100, 200, and 400 mg/kg of KHM i.p., respectively. Group 5 received phenobarbital 30 mg/kg i.p. Thirty minutes after pretreatment, mice in all groups received aminophylline 300 mg/kg s.c. The animals were observed for about 60 min, for the onset of myoclonic seizures, THLE, and mortality.

Strychnine-induced seizure in mice

The method described by Porter *et al.* (1984) was adopted in this study with slight modifications. Thirty (30) mice were divided into five groups of six animals each. Group 1 served as control and received normal saline 10 ml/kg. Groups 2, 3 and 4 received 100, 200, and 400 mg/kg, i.p. of KHM respectively. Group 5 was given phenobarbital 30 mg/kg, i.p. Thirty minutes post-treatment, mice in all the groups received 1.5 mg/kg of strychnine s.c. The proportions of mice presenting convulsions as well as the onset of tonic convulsions were recorded.

2.2.5 Evaluation of anxiolytic activity

Elevated plus maze

Rats were habituated to the testing room under dim light for at least 1 h before the test and then randomly divided into five groups consisting of 6 animals. The rats that served as control group received 10 ml normal saline/kg body weight orally, while the treated rats received KHM (100, 200 and 400 mg/kg b. w orally) and diazepam (2.5 mg/kg body weight i.p.). One hour after oral treatment with KHM and 30 mins after intraperitoneal administration of diazepam, each rat was placed at the center of the maze, facing one of the open arms and allowed to explore the maze freely for a 5-min testing period. The time spent in open and enclosed arms were recorded. The maze was thoroughly cleaned between tests with a tissue paper moistened with 70% ethanol.

Elevated zero maze

Rats were randomly divided into eleven groups of six rats each. One hour before this test, rats were treated with KHM (100, 200 and 400 mg/kg, orally). The control group received 10 ml normal saline/kg while standard reference drug diazepam (2.5 mg/kg, i.p.) was administered 30 mins before the test. One hour after drug administration, each rat was placed at the center of the open arm (facing toward the closed chamber). The times spent in both open and closed arms of the maze were manually recorded. The maze was thoroughly cleaned between tests with a tissue paper moistened with 70% ethanol.

Open-field test (OF)

Locomotor activity and exploratory behavior were assessed in an open field by the method described by Souza *et al.* (2010). The OF apparatus consist of a clear glass box (45×45 cm^2). The floor was divided by lines drawn into 9 equally sized squares. Thirty (30) rats were randomly divided into 5 groups of 6 rats each. One hour before test session, rats were treated orally with KHM (100, 200 and 400 mg/kg) while the control received 10 ml normal saline/kg orally. One hour later each rat was placed individually in the center of the apparatus and observed for 5 min to record the locomotor (number of squares crossed with four paws) and exploratory activities (indicated by frequency of rearing) (Walsh and Cummins, 1976; Souza *et al.*, 2010).

2.3 Statistical Analysis

Results were presented in tables and expressed as mean ± SEM. The level of significance was tested using One-way ANOVA followed by Dunnett post hoc test. Results were regarded as significant when $p< 0.05$. All statistical analyses were performed using SPSS software, version 21.

3.0 Results

3.1 Acute Toxicity

In the acute toxicity studies (**Table 1**), KHM produced no signs of toxicity and zero mortality up to a dose of 5000 mg/kg. Therefore, The LD_{50} of the extract was taken to be higher than 5000 mg / kg.

Table 1: General State of Animals after Administration of KHM

	Treatment					
Parameters	**10 mg/kg KHM**	**100 mg/kg KHM**	**1000 mg/kg KHM**	**1600 mg/kg KHM**	**2900 mg/kg KHM**	**5000 mg/kg KHM**
Signs of Toxicity	A	A	A	A	A	A
Mortality	A	A	A	A	A	A

Key: A: Absent

3.2 Thiopental Sodium-induced Sleeping Time Test

The result of thiopental sodium-induced sleeping time test is presented in **Table 2**. KHM significantly ($p< 0.001$) decreased the onset of sleep observed compared to control. Additionally, there was also a significant ($p< 0.001$) increase in duration of total sleeping time observed in mice treated with HKM at 100, 200, and 400 mg/kg when compared with the control. KHM at 400 mg/kg produced a similar effect to that of the positive control (diazepam 1 mg/kg).

Table 2: Effect of KHM on Thiopental Sodium-induced Sleeping Time in Mice

Treatment	Onset of action (min)	Duration of sleep (min)
Control (10ml/kg NS)	16.38 ± 0.55	60.45 ± 1.49
KHM (100 mg/kg)	14.11± 0.39**	105.86± 2.34***
KHM (200 mg/kg)	9.26± 0.26***	150.23± 1.97***
KHM (400 mg/kg)	9.15 ± 0.79***	160.67 ± 1.78***
Diazepam (1 mg/kg)	8.21 ± 0.46***	168.12 ± 2.16***

Normal saline (NS), KHM, Diazepam were administered 30 min intraperitoneally before the injection of Thiopental sodium (40 mg/kg i.p). Values are the mean ± SEM, n=6. One way ANOVA, ***p<0.001, **p<0.01 and *p<0.05 Dunnett post hoc test

3.3 N-Methyl-D-Aspartame (NMDA)- induced Seizures in Mice

KHM offered 16.67% protection against two consecutive 360^{o} cycles induced by NMDA at 200 and 400 mg/ kg. The standard- phenobarbital 30 mg/kg also offered 16.67% protection. There was no significant increase in the mean onset of mortality between the control and the test groups. Further, the fraction protected the animal by 50% against mortality at doses of 200 and 400 mg/kg and phenobarbital 30 mg/kg (**Table 3**).

Table 3: Effect of KHM on N-Methyl-D-Aspartame (NMDA)- induced Seizures in Mice

Treatment	Quantal protection	Mean seizure onset (min)	Mortality rate	Mean mortality time (min)
Control (10ml/kg NS)	0/6	10.15 ± 1.26	6/6	14.35 ± 1.25
KHM (100 mg/kg)	0/6	13.34± 1.30	6/6	14.12± 1.34
KHM (200 mg/kg)	1/6	12.07± 1.78	3/6	13.88± 1.89
KHM (400 mg/kg)	1/6	12.21 ± 1.13	3/6	13.33 ± 1.54
Phenobarbital (30 mg/kg)	1/6	8.08 ± 0.56	3/6	13.40 ± 1.12

Normal saline (NS), KHM and phenobarbital were administered 30 min intraperitoneally before the injection of NMDA (320 mg/kg) subcutaneously. Values are the mean ± SEM, n=6.

3.4 Aminophylline - induced Seizures in Mice

Table 4 shows the result of aminophylline-induced seizures in mice. KHM offered dose-dependent protection from aminophylline-induced seizures. The standard- phenobarbital 30 mg/kg protected the mice against the seizures 100%. There was no significant increase in the mean onset of myoclonic seizure and THLE/mortality between the control and the test groups.

Table 4: Effect of KHM on Aminophylline - induced Seizures in Mice

Treatment	Mean onset of myoclonic seizure (min)	Quantal protection	Mean onset of THLE/ mortality
Control (10ml/kg NS)	45.16 ± 2.45	0/6	46.87± 2.45
KHM (100 mg/kg)	48.23± 3.29*	2/6	43.16± 3.71
KHM (200 mg/kg)	50.37± 2.14**	3/6	44.48± 4.55
KHM (400 mg/kg)	55.91 ± 4.47***	4/6	46.28± 3.28
Phenobarbital (30 mg/kg)	62.26 ± 4.55***	6/6	-

Data presented as mean ± SEM, n= 6. NS: Normal saline, *p< 0.05 Dunnett's post hoc test of multiple comparisons.

3.5 Strychnine- induced Seizures in Mice

The extract produced protection against strychnine- induced seizures in mice. KHM at 100 and 200 mg/kg gave 16.67% protection while 400 mg/kg offered 33.33% protection against strychnine- induced hind limb extension and death respectively. The standard drug used, Phenobarbital (30 mg/ kg), offered 100% seizure protection. There was no significant difference between the control and the test groups in the mean onset of seizures/mortality (**Table 5**).

Table 5: Effect of KHM on Strychnine- induced Seizures in Mice

Treatment	Onset of seizure/mortality (min)	% Seizure/mortality protection
Control (10ml/kg NS)	6.45 ± 0.67	0.00
KHM (100 mg/kg)	6.23± 0.88	16.67
KHM (200 mg/kg)	7.83± 0.38	16.67
KHM (400 mg/kg)	7.45 ± 0.45	33.33
Phenobarbital (30 mg/kg)	0.00	100.00

Normal saline (NS), KHM and Phenobarbital were administered 30 min intraperitoneally before the injection of strychnine (2.5 mg/kg) subcutaneously. Values are the mean ± SEM, n=6.

3.6 Effect of KHM on elevated plus maze (EPM)

KHM significantly (p<0.05, 0.01) decreased the time spent in the closed arm of the elevated plus maze (EPM) in a dose- dependent manner. KHM (400 mg/ kg) and Diazepam produced comparable effect in reducing the time spent in closed arm of the EPM (Figure 1). Similarly, KHM significantly (p<0.05, 0.01, 0.001) and dose-dependently increased the time spent in the opened arm of the elevated plus maze (Figure 2).

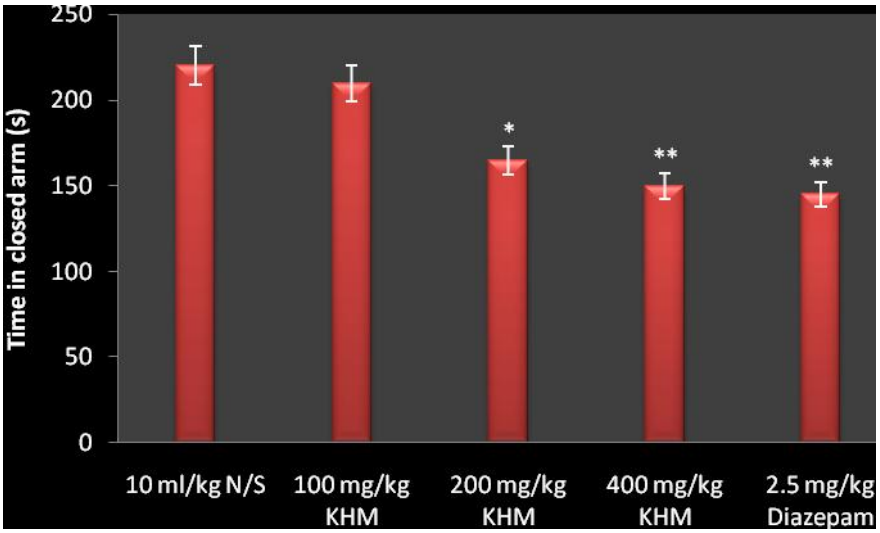

Figure 1: Effect of KHM on time spent in closed arm of the EPM. One way ANOVA, ***p<0.001, **p<0.01 and *p<0.05 Dunnett post hoc test

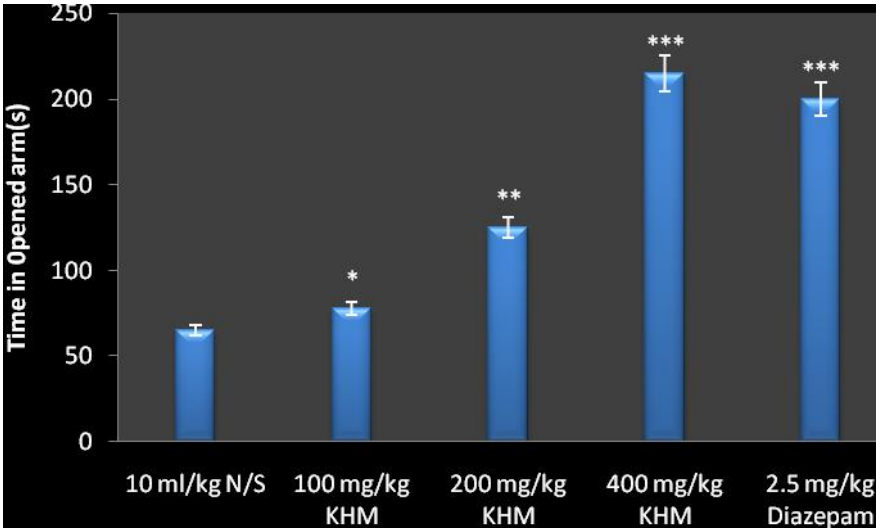

Figure 2: Effect of KHM on time spent in opened arm of the EPM. One way ANOVA, ***p<0.001, **p<0.01 and *p<0.05 Dunnett post hoc test

3.7 Effect of KHM on zero maze

KHM significantly (p<0.01, 0.001) and dose-dependently decreased the time spent in the closed arm of the maze (Figure 3) and significantly (p< 0.05, 0.01, 0.001) and also dose-dependently increased the time spent in the open arm of the elevated zero maze, while diazepam increased time spent on open arm of the maze (Figure 4).

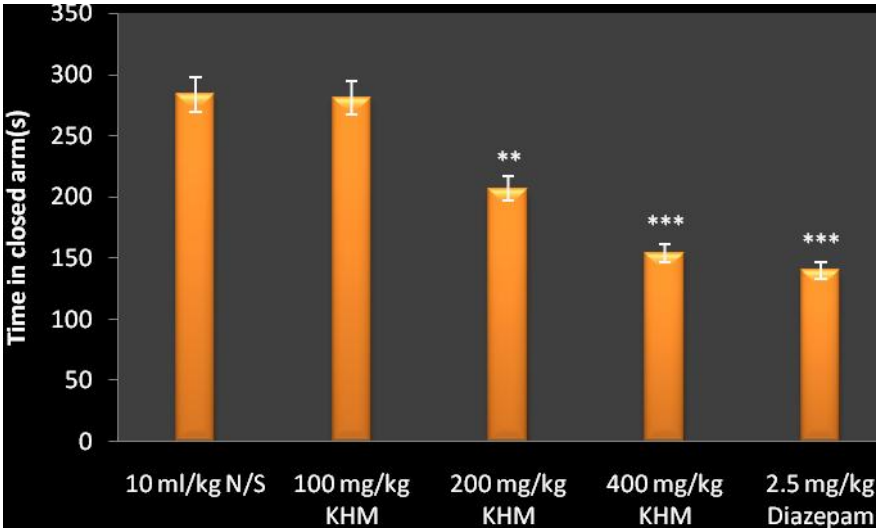

Figure 3: Effect of KHM on time spent in closed arm of zero maze. One way ANOVA, ***p<0.001, **p<0.01 and *p<0.05 Dunnett post hoc test

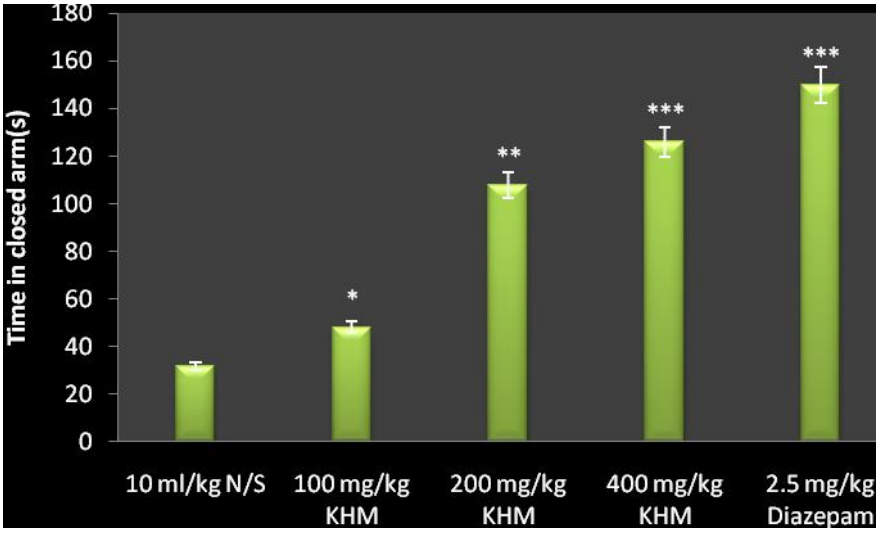

Figure 4: Effect of KHM on time spent in open arm of zero maze. One way ANOVA, ***p<0.001, **p<0.01 and *p<0.05 Dunnett post hoc test

3.8 Effect of KHM on total locomotive activity

The extract significantly (p< 0.05, 0.01, 0.001) and dose- dependently increased the total locomotive activity of rats on open field apparatus (Figure 5). Also, the extract significantly (p< 0.05, 0.01, 0.001) increased the frequency of rearing. The effect of KHM at 400 mg/ kg was similar to that of diazepam- the standard drug used (Figure 6).

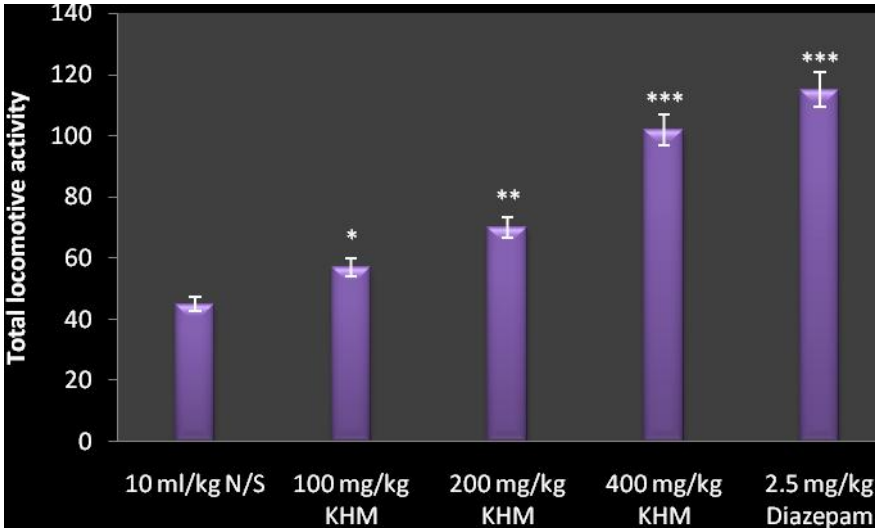

Figure 5: Effect of KHM on total locomotive activity on open field apparatus. One way ANOVA, ***p<0.001, **p<0.01 and *p<0.05 Dunnett post hoc test

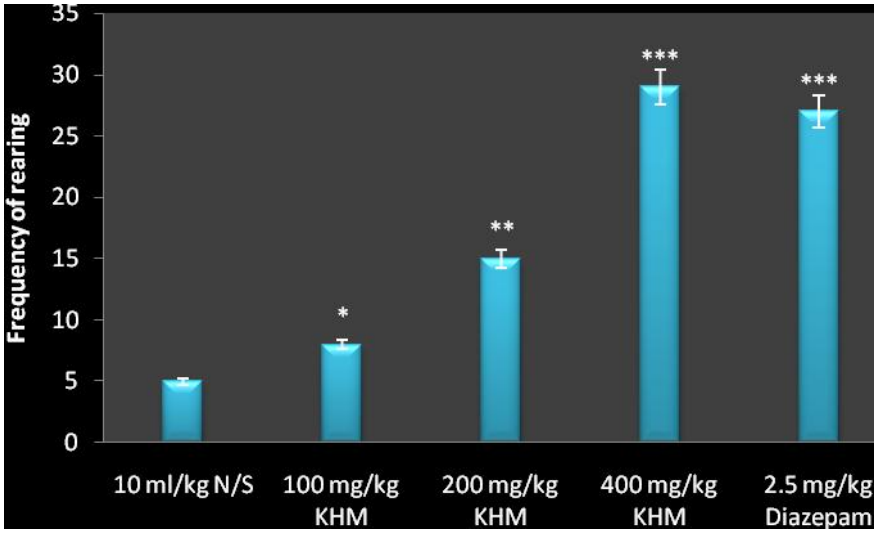

Figure 6: Effect of KHM on rearing. One way ANOVA, ***p<0.001, **p<0.01 and *p<0.05 Dunnett post hoc test

4.0Discussion

Administration of KHM at the doses of 10–5000 mg/kg did not show any visible sign of toxicity-behavioral changes, allergic manifestations (skin, rash, itching) or mortality during the period of observation. Therefore, it indicates that the LD_{50} is greater than 5000 mg/kg. This observation is in agreement with Idakwoji and Uzuazokaro, (2018a) who reported similar value of LD_{50}. Idakwoji and Uzuazokaro, (2018b) also reported that sub-chronic administeration of the polyherbal formulation had no significant effects on the biochemical, hematological and histopathological parameters of rats. From these observations, it is safe to say that the polyherbal formulation possess low toxicity profile.

Sedatives are known for their inhibitory effect on the CNS, which is caused by either augmentation of GABA inhibitory effect by binding to $GABA_A$ receptor like benzodiazepines, or antagonizing the effect of glutamate by blocking glutamate receptors such as N-methyl-D- aspartate (NMDA) AMPA, kainate, glycine or metabotropic receptors (Kahnberg *et al.*, 2002; Ebert *et al.*,

2006; Moniruzzaman, 2015). KHM significantly ($p< 0.001$) decreased the onset of sleep and also significantly ($p< 0.001$) increased the duration of total sleeping time. The decrease in onset of sleep and prolongation of sleeping time are indications of sedative activity of KHM.

Epileptic seizures arise from an excessive synchronous and sustained discharge of a group of neurons due to the alterations of synaptic transmission and/or intrinsic properties of neurons (Engelborghs *et al.,* 2007). It could also be related to imbalance between elements that excite and those which depress the nervous system. In any case, anti-epileptic drugs (AEDs) could be able to reestablish the equilibrium. HKM antagonized the seizures induced by aminophylline and strychnine. These observations suggest that the extract has considerable potentiating effect on adenosine and glycine receptors. Glycine and adenosine act as inhibitory neurotransmitters in the central nervous system, the inhibition of which has been implicated in convulsions. Strychnine, a toxic alkaloid causes hyper-excitability and hyper-reactivity of neuron by his fixation on glycine receptors. It is a potent spinal cord convulsant that blocks glycine receptors selectively to induce excitatory response in the central nervous system. The inhibition by HKM of strychnine- induced seizures suggests the presence of anticonvulsant properties (Trailovic & Varagic, 2007; Park *et al.,* 2007) and the involvement of glycine receptors (Findlay *et al.,* 2002). Seizures induced by theophylline could be due to adenosine receptor antagonism or due to inhibition of cerebral 5-nucleotidase activity (Chu, 1981). Apart from these findings, phosphodiesterase-3 (PDE- 3) inhibition by theophylline causes transmembrane influx of $Ca^{2+.}$ This influx of Ca^{2+} is as a result of the phosphorylation processes of intracellular proteins, such as ion channels, receptors, enzymes, and transcription factors, which exhibit significant neuronal excitability and epileptic seizures (Butler *et al.,* 1995). The anticonvulsant activity of KHM against aminophylline-induced seizure may be due to the potentiation of adenosine receptor and/or phosphodiesterase 3 activities. KHM also showed anticonvulsant effects in the NMDA- induced seizure model. This implies that KHM might also have an antagonizing effect on NDMA receptors.

Results showed that KHM significantly ($p< 0.001$) decreased the time spent in the closed arm of the elevated plus maze and increased the time spent in the open arm. This observation is not consistent with standard anxiolytic behaving similar to benzodiazepines with anxiolytic effect at low doses and anxiogenic or sedative effect at higher doses (Madara *et al.,* 2013). The indices of anxiety (percentage of open-arm entries, and percentage of time spent in the open arm) are sensitive to agents and are thought to act via the GABA receptor complex. The anxiolytic effect of the extract was further confirmed by the results obtained from the use of the elevated zero maze. HKM produced anxiolytic-like effect which is clearly defined by the increased time spent in the open quadrant of the zero -maze. This observation may be due to the extreme spectrum of anxiolytic sedative effects characterized by sedation-like behavior. This is consistent with the effect of sedative anxiolytics. The open-field apparatus provides information on anxiety-related behaviour characterized by natural aversion of rodents to an open brightly lit area (Choleris *et al.,* 2001). Animals are thus afraid of the centre and spend more time in the protective corners and in freezing state. Anxiolytics increase total locomotive activity resulting in a reduction of time spent in corners, an increased time spent in the center and a decreased time spent in freezing state. KHM increased total locomotive activity and increased rearing of treated rats hence, further confirming its anxiolytic potential.

5.0 Conclusion

Results showed that the polyherbal formulation (KHM) possesses sedative, anticonvulsant and anxiolytic activities. The findings therefore provide rationale for indication of KHM in some neurological disorders such as epilepsy, anxiety and insomnia.

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