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Antidepressant and anxiolytic activities of *Maerua angolensis* DC. (Capparaceae) leaves and *Borago officinalis* L. (Boraginaceae) leaves mixture in laboratory animals

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Abstract
Anxiety and depression are two debilitating conditions that are often preceded by a triggering event. The experimental formula which contains an equal portion of *Maerua angolensis* DC. leaves and *Borago officinalis* L. leaves, is used by the Hausa community of Kano state for both depression and anxiety. This study aims to scientifically assess the antidepressant and anxiolytic effects of the mixture and establish its safety profile in laboratory animals. The LD_{50} of the extract was estimated to be approximately 2154 mg/kg in mice. The extract showed neither significant reduction in immobility time in forced swim and tail suspension test, nor impact on line crossing following an open field task. The extract at 600 and 300 mg/kg significantly increased the number of entries and permanence time into open arms in elevated plus maze test and increased both the number of head-dip and upward stairs climbed following hole board and staircase tasks respectively. Following 28-days administration, the extract significantly increased the level of alkaline phosphatase. The findings suggest that the formula has shown some level of anxiolytic activity with no significant effect in animal models of depression. The herbal mixture was also found to be relatively safe in animal model.

Keywords: Antidepressant; Anxiolytic; *Borago officinalis*; *Maerua angolensis;* Neurobehavioral studies; Toxicity

INTRODUCTION

Depression and anxiety are leading causes of disability worldwide with significant impact on individual's quality of life and economic burden to the society [1]. Structural and functional brain changes as well as abnormalities in mood regulating neurotransmitters such as serotonin, dopamine, and norepinephrine account for the aetiologies of these disorder [2,3].

While anxiety accounts for different forms of abnormal and pathological fear, depression presents a state characterised by persistent feelings of desolation, bleakness, and anhedonia. High prevalence and inadequate diagnosis of the disorders coupled with relatively expensive treatment options

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and sometimes unavailability of medications contribute to the rising burden of these disorders [4-7). Several anxiolytics and antidepressants are currently used in the treatment of these disorders; however, these drugs cause numerous side effects to patients affecting patients' compliance. Their associated risks of interaction with other medications also remain a pivotal issue in their selection [8,9].

Medicinal plants still remain a reliable source of medicines to meet the health care needs of developing countries. They provide biologically active lead compounds valuable to drug discovery and development [10]. Most traditional treatments often lack comprehensive documentation of their side effects. A mixture of an equal portion the leaves of both *Maerua angolensis* DC. (Capparaceae) and *Borago officinalis* L. (Boraginaceae) is claimed to be useful in the treatment of several psychiatric disorders as claimed by a trado-medical practitioner. Several plant parts of *Marua angolensis* were traditionally reported to be useful in the management of pain, cancer, fever, malaria, sores, wound and gastrointestinal problems [11,12]. While *Borago officinalis* that is often recommended to be used externally for safety concerns, it is still employed by the community for medicinal purposes [13]. It is native of the Western regions of Mediterranean area including Europe, North America, and it is also found in West African countries like Nigeria.
Gas chromatography connected with mass spectrometry (GC-MS) analysis revealed the presence of about several volatile compounds in the seed oil of *Borago officinalis* such as β-caryophyllene, p-cymene-8-ol, nonadecane, hexanol, oil monoterpens, sesquiterpenes, linoleic acid, α-linolenic acid and γ-linolenic acid etc., majority of whom possesses therapeutic effects [14,15]. Given the growing interest in natural remedies for depression and anxiety [16], there is a pressing need for comprehensive research to assess the antidepressant and anxiolytic potentials and safety profile of the mixture of *Maerua angolensis* DC. and *Borago officinalis* L. in animal models of anxiety and depression.

EXPERIMENTAL METHODS

Albino mice (18–22 g) were obtained from the animal house, Department of Pharmacology and Therapeutics, Bayero University, Kano. The mice were maintained in a well-ventilated room and fed with standard feeds and water *ad libitum*. The mixture of (in powdered form) was obtained from a traditional medical practitioner at Kurmi Market, Kano state, Nigeria. It was macerated with 70% v/v methanol over 72 hours with occasional shaking and stirring, filtered and then dried at 50°C over several days until a constant weight was obtained. Phytochemical analysis of the extract was conducted to detect the presence of secondary metabolites according to standard procedure [17]. Ethical approval was obtained from the Animal Care and Use Research Ethics Committee (ACUREC), Bayero University, Kano.

Acute toxicity study was carried out to determine the median lethal dose (LD_{50}) of the extract in mice according to the method of Lorke [18]. In phase 1, nine (9) mice were grouped into three (3) groups (n=3). Group i, ii and iii received 10, 100 and 1000 mg/kg respectively of the mixture and were observed for 24 hours for signs of toxicity (including changes in behaviour patterns, eyes, mucous membranes, skin, and fur) and mortality. The result from phase 1 determined specific doses used in the next phase. In phase 2, four (4) separate mice received 600, 1000 and 1600 \and 2900 mg/kg of the mixture respectively. Mortality was observed after 24 hours. The LD_{50} was then calculated by taking geometric mean of the minimum dose that caused mortality and maximum dose that does not cause mortality.

Forced swim test (FST). Forced swim test is widely used to assess antidepressant effects of

substances in rodents. The method previously described by Porsolt et al. [19] was employed. Mice were randomly divided into five (5) groups (n=6). Group i received distilled water (10 mL/kg *i.p.*), groups ii, iii and iv, received the mixture (at dose of 150, 300 and 600 mg/kg *i.p.* respectively), while group v received imipramine (10 mg/kg *ip*) as previously used by Meti et al [20]. Thirty (30) minutes later, animals were forced to swim individually in a transparent open glass container (30 cm length and 20 cm in diameter) containing fresh water of 15 cm depth that was maintained at 25±1°C. After initial period of energetic activity (an average of 2 minutes), the animals assumed a characteristic immobile posture. The total duration of immobility was then recorded in the next 4 minutes of the total 6 minutes allocated as the testing period. A decrease in immobility time is indicative of antidepressant activity [19].

Tail suspension test (TST). The method previously described by Steru et al. [21] was adopted. Mice were randomly divided into five (5) groups (n=6). Group i received distilled water (10 mL/kg *i.p.*), groups ii, iii, and iv received the mixture (150, 300 and 600 mg/kg *i.p.* respectively), while group v received Imipramine (10 mg/kg *i.p.*). Thirty (30) minutes later, each mouse was individually suspended 50 cm above the floor by means of an adhesive tape (placed 1 cm from the tip of the tail). After the initial 2 minutes of energetic activity, the time taken during which the animal assumed immobile posture (hung passively or became motionless) within the last 4 minutes testing period allocated was noted. A decrease in the immobility time is indicative of potential antidepressant activity [21].

Open field test (OFT). The method described by Rex et al. [22] was adopted. Mice were randomly divided into five (5) groups (n=6). Group i received distilled water (10 mL/kg *i.p.*), groups ii, iii, and iv received the mixture (150, 300, and 600 mg/kg *i.p*. respectively), while group v received diazepam (0.5 mg/kg *i.p.*) as previously employed by Guragi et al [23]. Thirty (30) minutes post treatment, each mouse was placed in the centre of a white wooden open field apparatus (70 X 70 X 50 cm of length x breath x height) and allowed to explore for 6 minutes, with 2 minutes for acclimation. The exploratory behaviour including the number of squares crossed by each mouse was recorded for five (5) minutes. The apparatus was cleaned with 10% ethanol before and after each mouse to remove olfactory cue [22].

Elevated plus maze test (EPM). Mice were randomly divided into five (5) groups (n=6). Group i received distilled water (10 mL/kg *i.p.*), groups ii, iii, and iv received the mixture (150, 300, and 600 mg/kg *i.p*. respectively), while group v received diazepam (0.5 mg/kg *i.p.*). Thirty (30) minutes post treatment, each mouse was placed at the center of the maze and observed 5 minutes. The time spent and numbers of entries in the open and closed arms was noted [24].

Hole-board test (HBT). Mice were randomly divided into five (5) groups (n=6). Group i received distilled water (10 mL/kg *i.p.*), groups ii, iii, and iv received the mixture (150, 300, and 600 mg/kg *i.p*. respectively), while group v received diazepam (0.5 mg/kg *i.p.*). Thirty (30) minutes post treatment, each animal was placed singly at the center of the board facing away from the observer and its behavior including the total number of head-dips were recorded for 5 min [25].

Staircase test (ST). Mice were randomly divided into five (5) groups (n=6). Group i received distilled water (10 mL/kg *i.p.*), groups ii, iii, and iv received the mixture (150, 300, and 600 mg/kg *i.p*. respectively), while group v received diazepam (0.5 mg/kg *i.p.*). Thirty (30) minutes post treatment, each animal was placed singly facing away from the observer and its behaviour including the total number of stairs climbed and number of rearing performed were recorded for 3 minutes [26].

28-day oral toxicity studies. Upon completion of the neurobehavioral studies, a separate set of animals were utilized for the toxicity study. A total of twenty-four (24) rats (Wistar rats of either sex) were divided into four groups (n=6). The doses chosen herein are those that do not cause any harm as evident during the acute toxicity period. Group i received distilled water (1 mL/kg). Group ii, iii and iv received the mixture (600, 300, and 150mg/kg orally respectively). The animals received the extract once daily for 28 days. The body weights of all the animals before the experiment and then weekly within 28 days of treatment were recorded.

Twenty-four (24) hours after the last treatment, the animals were humanely euthanized by cervical dislocation after mild anaesthesia using chloroform. Four (4) milliliters of blood sample were collected from each rat. Whole blood was collected in plain bottles for each rat. The blood samples were then centrifuged at 2500 rpm for 10 minutes with a Centurion centrifuge machine, model 4040 series to obtain the sera. The sera separated from the cells were utilized for assessment of biochemical parameters such as liver function tests (alanine aminotransaminase (ALT), aspartate aminotransaminase (AST), alkaline phosphatase (ALP), total protein (TP) and albumin. The kidney function (urea, creatine, sodium, potassium, bicarbonate and chloride), They were all assayed using the biobased chemistry analyser. The organ weights (of brain, liver, kidney and heart) were removed and weighed from the sacrificed animals. The weights were documented.

Statistical analysis. The data were expressed as mean ± standard error of the mean (SEM) in figures and tables were appropriate. The statistical analysis was carried out by a one-way analysis of variance (ANOVA) followed by Dunnett's post hoc test (to compare the multiple treatment groups against the distilled water group) using IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp. The $p \leq 0.05$ values were taken as significant.

RESULTS

Phytochemical screening of the mixture revealed the presence of alkaloids, anthraquinones, cardiac glycosides, flavonoids, saponins, steroids, tannins, and terpenoids (Table 1).

28-day oral administration. The median lethal dose (LD_{50}) of the mixture administered intra-peritoneally was determined to be 2154 mg/kg in mice. The mixture at all doses produced no significant effect on organ bodyweight of rats following 28 days oral administration (Table 2). The mixture at the lowest dose of 150 mg/kg significantly increased the concentration of alkaline phosphatase (ALP) in rats following twenty-eight days daily oral administration (Table 3). A significant increase in urea concentration was also observed at the lowest dose of 150 mg/kg (Table 4).

Antidepressant and anxiolytic studies. The mixture across all doses tested did not produce any significant effect on the mean immobility time in forced swim (Figure 1) and tail suspension test (Figure 2) compared with distil water group. The mixture across all doses tested did not produce any significant effect on the mean number of central and peripheral crossing compared with distilled water group. However, the standard drug diazepam, significantly increased the mean number of peripheral crossings compared with distilled water group (Figure 3). The mixture at doses of 600 and 300 mg/kg and the standard drug at 0.5 mg/kg increased the mean number of entries and mean time spent in the open arm compared with distilled water group (Figures 4a & 4b). The mixture at all doses and the standard drug at 0.5 mg/kg significantly increased the number of head dips count

compared with distilled water group (Figure 5). The mixture at doses of 600 and the standard drug at 0.5 mg/kg significantly increased the mean number of upward stairs climbed and mean number of rearing compared with distilled water group (Figure 6).

Table 1: Phytochemical constituents of mixture of *Maerua angolensis* DC. and *Borago officinalis* L.

Phytochemical constituents	Test carried out	Inference
Alkaloids	Dragendoff's/ Wagner's	+
Anthraquinones	Bontrager's test	-
Cardiac glycosides	Keller-Killiani test	+
Flavonoids	Alkaline reagent test	+
Saponins	Frothing test	+
Steroids	Salkwoski test:	+
Tannins	Ferric chloride test	+
Terpenoid	Liebermann Buchard test	+

+ Present, - Absent

Table 2: Effect of the methanol extract of mixture of *Maerua angolensis* DC. and *Borago officinalis* L. on organ weight of rats following twenty-eight days daily oral administration

Organ	DW 1 mL/Kg	MIX 600	MIX 300	MIX 150
Brain	1.20±0.25	1.44±0.07	1.50±0.14	1.54±0.13
Liver	4.80±0.21	4.91±0.30	4.65±0.17	4.90±0.16
Kidney	0.90±0.05	0.87±0.07	0.88±0.12	0.93±0.07
Heart	0.80±0.03	0.44±0.05	0.46±0.03	0.56±0.02

Data presented as Mean ± SEM, analysed using one-way ANOVA followed by Dunnet's post-hoc test. DW= Distilled water, MIX= Mixture of *Maerua angolensis* DC. and *Borago officinalis* L.

Table 3: Effect of the methanol extract of mixture of *Maerua angolensis* DC. and *Borago officinalis* L. on liver function indices in rats following twenty-eight days daily oral administration

	Treatment (mg/kg)			
Liver function parameters	DW 1 mL/Kg	MIX 600	MIX 300	MIX 150
ALT (u/L)	09.25 ± 0.60	10.75 ± 0.80	09.50 ± 0.70	11.75 ± 1.70
AST (u/L)	15.30 ± 2.10	14.50 ± 1.80	27.00 ± 1.20	26.80 ± 2.60
ALP (u/L)	21.30 ± 1.90	24.00 ± 1.10	26.60 ± 2.10	38.60 ± 1.40*
TP (g/dl)	03.90 ± 0.20	05.40 ± 0.60	05.78 ± 0.30	05.56 ± 0.20
ALB (g/dl)	01.20 ± 0.10	01.20 ± 0.30	01.50 ± 0.30	01.40 ± 0.20

Data presented as Mean ± SEM, analysed using one-way ANOVA followed by Dunnet's post-hoc test. DW= Distilled water, MIX= Mixture of *Maerua angolensis* DC. and *Borago officinalis* L.. *P<0.05, ALT=Alanine transaminase, AST= Aspartate transaminase, ALP= Alkaline phosphatase, TP=Total protein, ALB= Albumin

Table 4: Effect of the methanol extract of mixture of *Maerua angolensis* DC. and *Borago officinalis* L. on kidney function indices in rats following twenty-eight days daily oral administration

Kidney function parameters	Treatment (mg/kg)			
	DW 1 mL/Kg	MIX 600	MIS 300	MIX 150
Urea (mg/dl)	032.0 ± 02.40	050.3 ± 11.00	051.3 ± 11.10	057.0 ± 17.10*
Sodium (mmol/L)	270.8 ± 11.30	373.9 ± 40.20*	302.1 ± 19.00	300.8 ± 17.00
Potassium (mmol/L)	010.1 ± 00.30	020.7 ± 04.20	030.3 ± 04.00	023.3 ± 05.00
Creatinine (mg/dL)	001.5 ± 00.10	001.0 ± 00.10	001.0 ± 00.20	001.2 ± 00.20
Chloride (mg/dl)	032.5 ± 01.80	036.8 ± 09.50	029.8 ± 04.60	036.0 ± 04.80
Bicarbonate (mg/L)	115.8 ± 04.60	092.3 ± 03.80	092.5 ± 05.40	093.8 ± 03.80

Data presented as Mean ± SEM, analysed using one-way ANOVA followed by Dunnet's post-hoc test. DW= Distilled water, MIX= Mixture of *Maerua angolensis* DC. and *Borago officinalis* L.

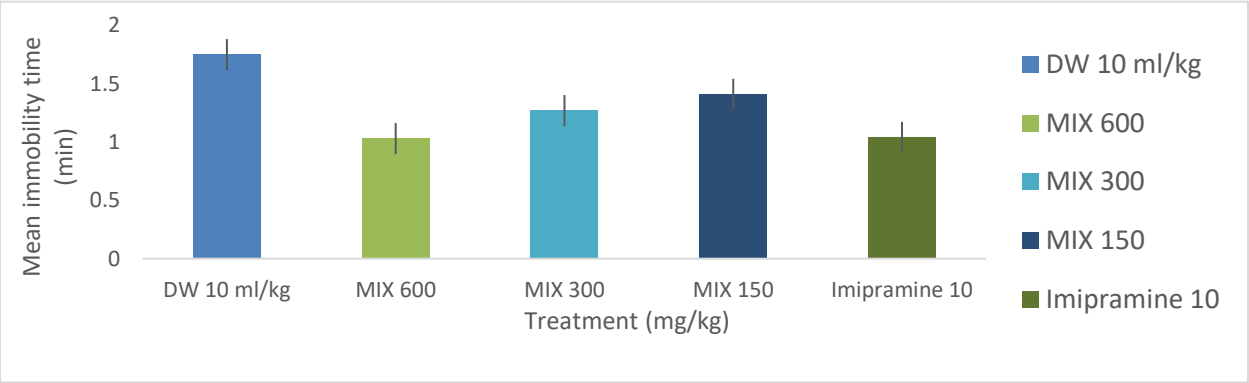

Figure 1: Effect of the mixture of *Maerua angolensis* DC. and *Borago officinalis* L. on immobility time in forced swim test in mice

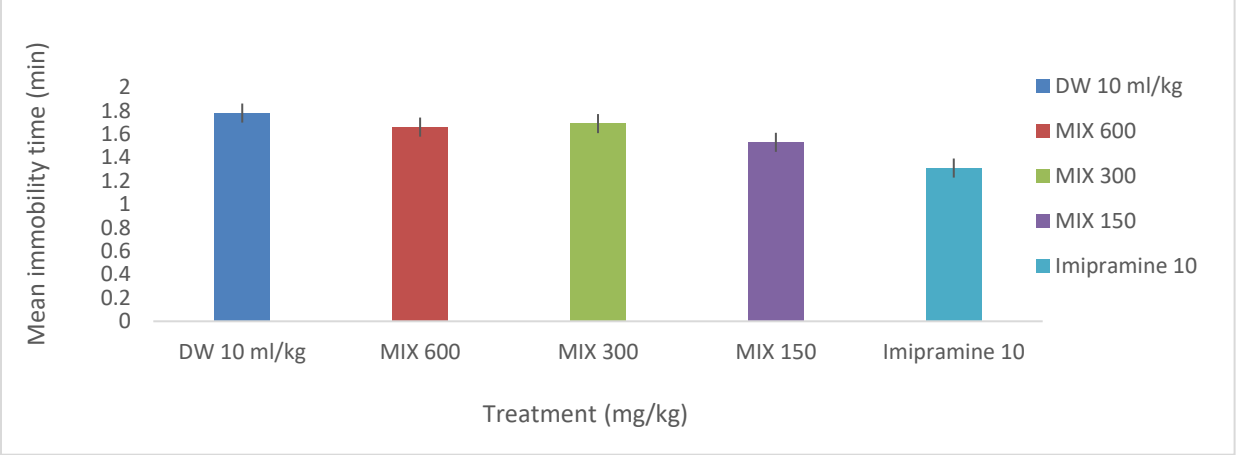

Figure 2: Effect of the mixture of *Maerua angolensis* DC. and *Borago officinalis* L. on immobility time in tail suspension test in mice.

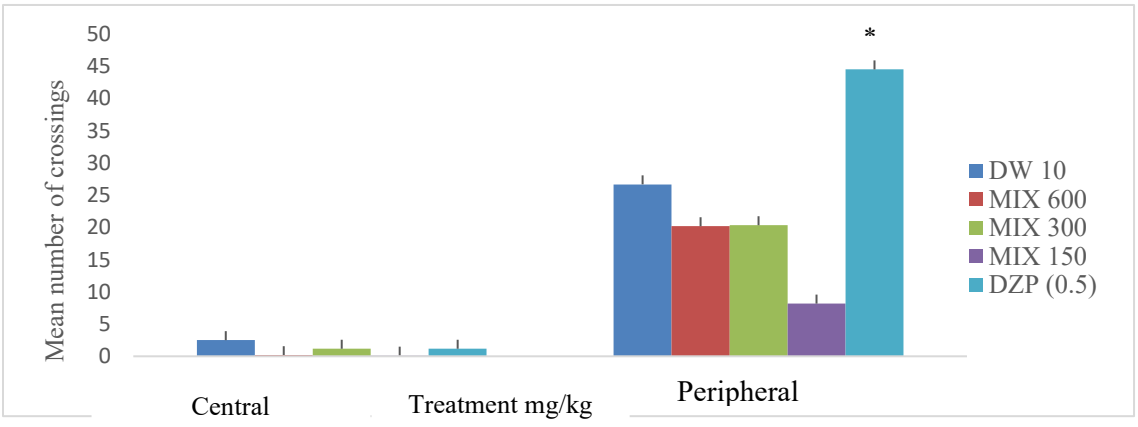

Figure 3: Effect of the mixture of *Maerua angolensis* DC. and *Borago officinalis* L on number of central and peripheral crossing in open field test in mice

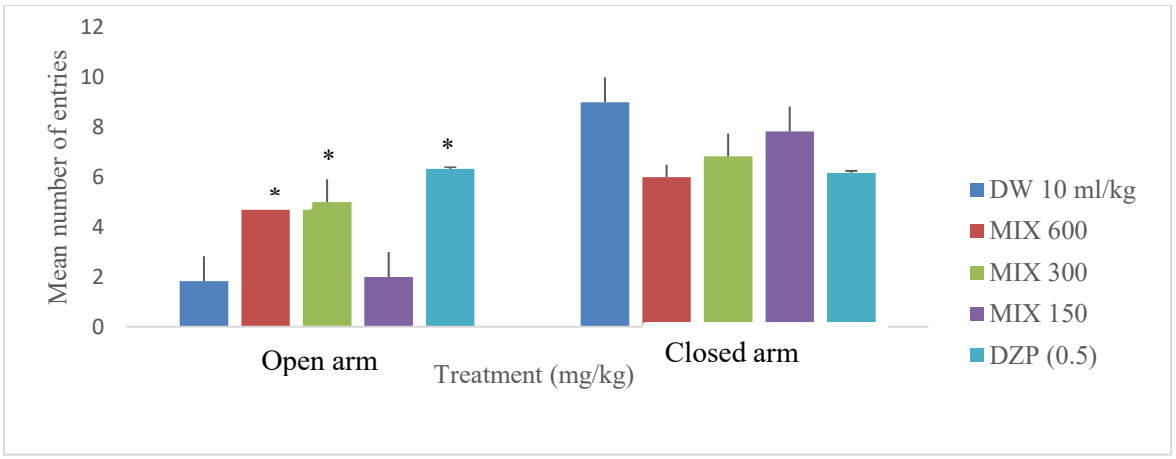

Figure 4a: Effect of the mixture of *Maerua angolensis* DC. and *Borago officinalis* L on number of entries in open and closed arms in elevated plus maze task in mice

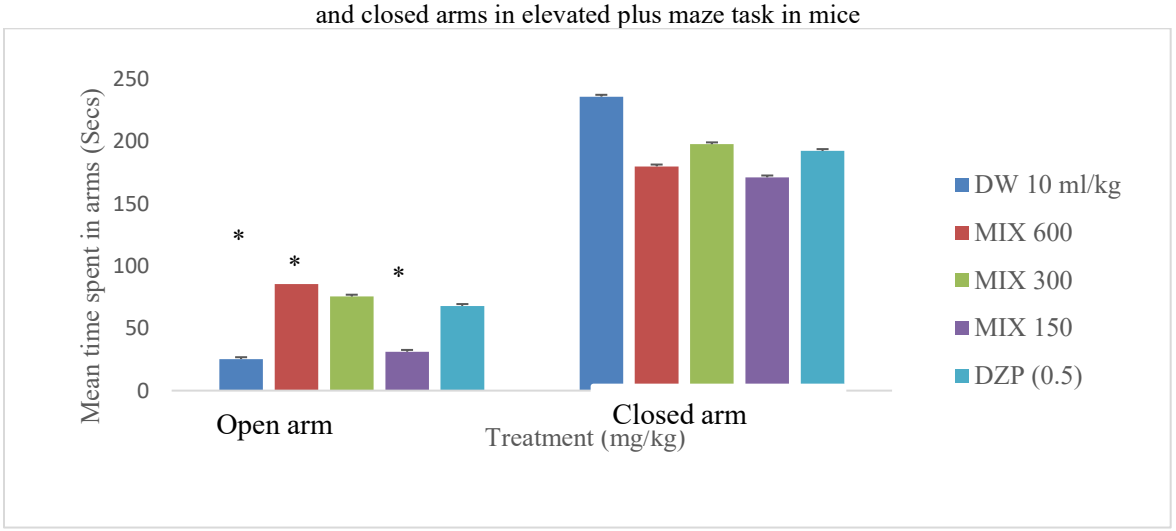

Figure 4b. Effect of the mixture of *Maerua angolensis* DC. and *Borago officinalis* L on time spent in open and closed arms in elevated plus maze task in mice

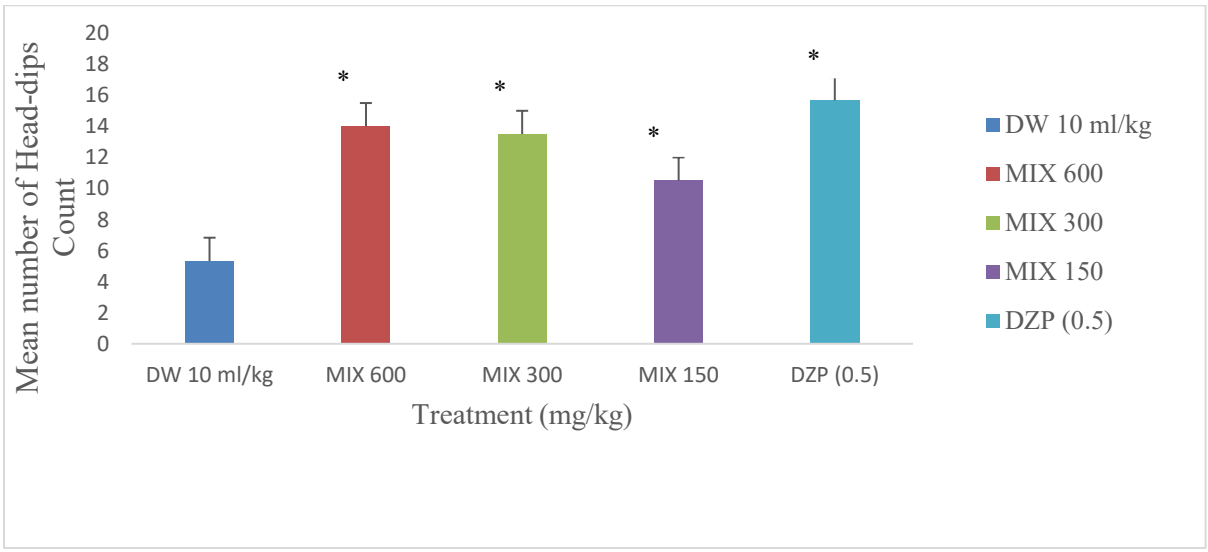

Figure 5: Effect of the mixture of *Maerua angolensis* DC. and *Borago officinalis* L on number of head dips in hole board test

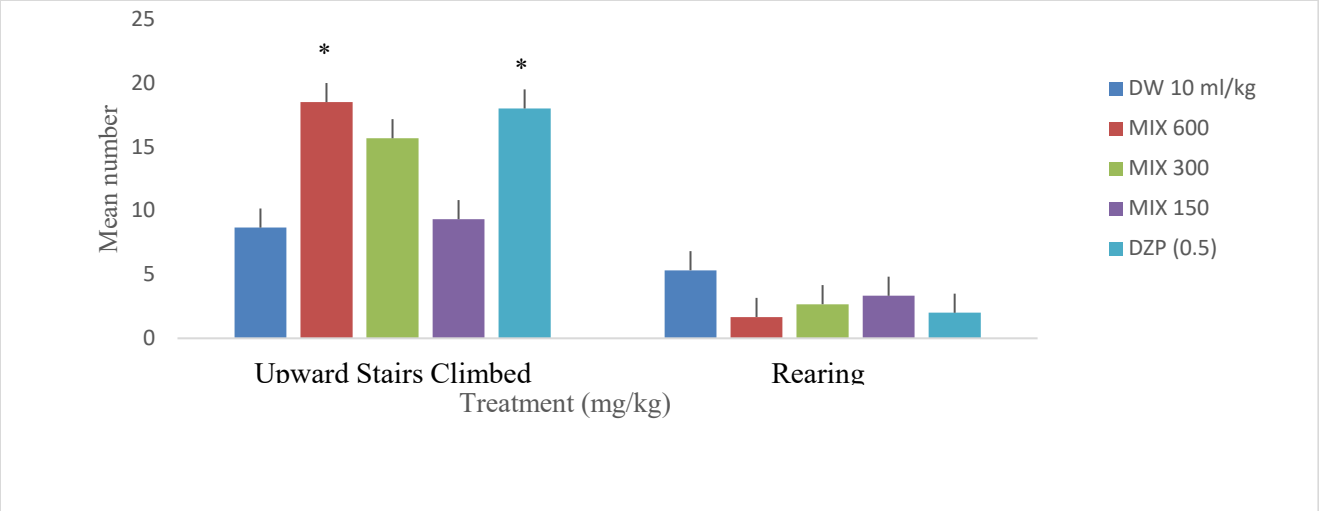

Figure 6: Effect of the mixture of *Maerua angolensis* DC. and *Borago officinalis* L on number of climbing and rearing in staircase test in mice

DISCUSSION

Depression and anxiety are unpleasant emotional state of the mind with identifiable causes that are often overwhelming and inevitable [27]. Dysregulation of the GABAergic, serotoninergic, dopaminergic and adrenergic neuro-systems have all been implicated in the pathophysiology of anxiety and depression [28]. Antidepressant such as the selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), Tricyclic antidepressants (TCAs) and Monoamine oxidase inhibitors (MAOIs) work by restoring balance to neurotransmitter levels in the brain [29]. Recently, the selective serotonin reuptake inhibitors (SSRI) and serotonin norepinephrine reuptake inhibitors (SNRI) are used as first-line agent for such treatment [30].

Anxiety disorders are ranked among the most frequently occurring mental disorders [30], with an estimated prevalence of 4.05% [31]. Approximately one third of the population living in Africa and Asia lack access to essential medicines, hence resorting to traditional medicines such as the present herbal mixture for their health care needs. The constituents of the mixture; *Maerua angolensis* DC and *Borago officinalis* are used ethnobotanically for several neuropsychiatric and neurodegenerative disorders [32,33].

The phytochemical analysis of the mixture revealed the presence of several secondary metabolites. Such constituents have been previously reported to be responsible for several pharmacological activities [34]. Notably, the sedative and anxiolytic activity of alkaloid and saponins have been reported [35,36], which may be responsible for the observed pharmacological activities/ Other phytochemicals reported to have sedative, anxiolytic and health-promoting uses include phytosterols [37,38], and phenolic compounds such as flavonoids and tannins [39].

The LD_{50} value of the mixture administered intraperitoneally indicates that the mixture is relatively less toxic according to previous classification [40]. This is comparable to similar LD_{50} values of extracts obtained from other medicinal plants that are useful for similar disorders [34]. The behavioural models employed in this study assess immobility, curiosity and increase or reduced exploration by the rodents as indicative of either antidepressant or anxiolytic effects. The mixture at all doses tested showed no significant difference in immobility time in both forced swim and tail suspension tasks compared to the distilled water group.

Similarly, in open field test which measures general locomotor activity, depressive and anxiety-related behaviour, mixture did not produce any significant differences which further showcased no antidepressant activity within the range of doses tested. These findings are similar to those reported by Perampanel (used for monotherapy and/or adjunctive therapy of partial-onset and tonic-clonic seizures) in patients aged 4 years and older respectively [41], and are in contrast to results obtained when Phytol, a branched chain unsaturated alcohol isolated from essential oils of different medicinal plants was administered to mice [42].

Despite no significant antidepressant activity being recorded, administration of the mixture at 600 mg/kg and 300 mg/kg, significantly increased ($p < 0.05$) the number of entries and permanence time into open arms in elevated plus maze task, compared with distilled water group. These increases which represent anxiolytic effects are in conformity with literature reports that anxiolytic agents do increase the frequency of entries and time spent in open arms in EPM task [43-45]. The increase in frequency of entry is a measure of increased locomotor activity commonly observed with standard anxiolytic drugs.

When the animals were subjected to the hole-board test which measures several responses including curiosity and exploratory behaviours of the rodents to an unfamiliar environment [46], the mixture significantly increased the number of head-dip counts made by the animals. Similar neurobehavioral activity has been recorded reported by the administration of the methanol extract of *Achyranthes aspera* [47]. A significant increase in number of upward stairs climbed and reduced number of rearing was also recorded (at 600 mg/kg) in staircase task performed by the mice. Substances with anxiolytic properties increase the number of head-dips and upward stairs climbed by rodents which is indicative of anxiolytic effects [48].

In this study, rats treated daily with mixture for 28 days did not show any abnormal changes in their behaviour compared to the distilled water group. No significant change was observed in organ weights relative to body weight such as that of the heart, kidney, liver and brain suggesting that the herbal formula at the tested doses is not associated with toxicity. A previous study by Julde et al. [49] also found no significant change in organ weights in rats that were treated with ethanol leaf extract of *Laggera Aurita* Linn for 90 days while 28 days administration of *Combretum hypopilinum* significantly reduced the relative kidney weight at the higher doses [50].

Liver enzymes are valuable indicators of liver damage useful in the diagnosis of acute hepatic injury. Although many drugs, toxins, and herbal medicines are believed to cause liver and renal injury, no significant effect was observed except for the alkaline phosphatase at the lowest dose tested. The increase observed herein may be due to stress of daily administration of the extract.

A slight rise (though not significant) in renal parameters such as sodium and urea levels were observed in the rats after 28-days administration of the mixture. This increase might be associated with stress (Table 4). A similar study showed a significant increase in potassium after a sub-acute administration of *Combretum hypopilinum in rats*

Conclusion. From the results obtained in this study, it can be concluded that the mixture of *Borago officinalis* and *Marua angolensis* do not exhibit antidepressant activity at the doses tested. However, the mixture showed some anxiolytic activity in mice with increased doses without inducing substantive sedative side effects. Also, the mixture is nontoxic at the doses tested, yet, it should be used with caution in the presence of hepatic or renal impairment.

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