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Maerua angolensis DC: evaluation of the oral acute and sub-chronic toxicity profile of its freeze-dried leaves infusion extract

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ABSTRACT

Maerua angolensis is a shrub/small tree that grows up to about 10 m tall. The plant is widely distributed in tropical Africa and used in various ethnomedicinal applications across the region. The objective of this study is to investigate the oral safety profile of the infusion extract of *Maerua angolensis* (IEMa) in laboratory animals. Hippocratic screening was adopted to evaluate the acute toxicity profile using 2000 mg/kg of IEMa, p.o. in mice. The sub-chronic toxicity was performed by daily oral administration of IEMa (800 mg/kg) in Wistar rats for 28 days and clinical observations and toxicological related parameters were recorded. After the treatment period, blood was collected for hematological and biochemical analysis, and organs were removed for macroscopic analysis. The agent exhibited mild symptoms and no mortality recorded in the Hippocratic screening. In the sub-chronic test, few changes in urine output, platelets counts and alkaline phosphatase were observed, but are within the physiological ranges for this animal specie. The results shows that IEMa does not present oral toxicity thereby displaying a wide safety margin for therapeutic use.

Keywords: *Maerua angolensis*, Phytochemistry, Hippocratic screening, sub-chronic toxicity.

INTRODUCTION

Maerua comprises about 50 species mostly found in the drier areas of tropical Africa, Middle East and tropical Asia. *Maerua angolensis* is a shrub or small tree up to about 10 m tall, widely distributed in continental tropical Africa. The plant materials have been used for various ethnomedicinal applications across the region. In Senegal, the powdered leaves are added to food to cure anorexia and asthenia; extract of the stem bark applied to wounds to promote healing in Mali and Nigeria; decoction of leafy twigs is administered to children suffering from amoebic dysentery, and jaundice in Benin; decoction prepared from the stem bark is used to treat malaria, and leaf decoction is used for rheumatism and to relieve stomach-ache in Sudan; leaves known locally as 'Lebaaibu' are used to prevent/treat diabetes among the Fulani ethnic group of northern Nigeria; and the root and stem bark used as an aphrodisiac, and to

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cure diarrhoea and epilepsy in Tanzania (Diallo et al., 2002 ; Akoègninou et al., 2006 ; Maroyi et al., 2020).

Scientific evaluation shows that extracts of the plant materials have been reported to exhibit antimicrobial activity against clinical isolates (Ayo et al., 2013; Yusuf et al., 2017), anti-nocicepive activity against chemical-induced pain model in mice (Iliya et al., 2014), anti-inflammatory (Adamu et al., 2007), antioxidant (Meda et al., 2013), anti-seizure (Malami et al., 2014; Benneh et al., 2018) and anti-diabetic (Mohammed et al., 2007; Iliya et al., 2014; Benneh et al., 2018) activities.

Despite these widespread usages scientific data is limited on the safety profiles other than attempts by Iliya et al. (2014) and Malami et al. (2014) on extracts obtained using organic solvents. In series of studies in our laboratory, we prepared the leaves infusion extract of *Maerua angolensis* and freeze-dried it. The pharmacognostic and phytochemical characterization of the extract have been reported (Adigwe et al., 2021a). In this report, the oral acute and sub-chronic toxicity profiles of the freeze-dried extract was evaluated using standard models in mice and rats.

MATERIALS AND METHODS

Plant material and preparation of extracts

Maerua angolensis DC., Prodr. [A. P. de Candolle] 1: 254 (1824) (IPNI, 2021) was collected at Sabuwar Gayan, Chikun Local Government Area of Kaduna State, Nigeria in March 2021. The plant material was identified at the Taxonomy Unit, Department of Medicinal Plant Research and Traditional Medicine, National Institute for Pharmaceutical Research and Development (NIPRD), Abuja, Nigeria. It was checked at www.theplantlist.org, and a voucher specimen (NIPRD/H/7211) kept. The leaves were cleaned and air-dried under shade, and the dried material was milled into powder. Infusion of the powdered material (200 g) was prepared by incubating in multiples 50 g/L in boiled distilled water for 15 min. The mixture was then filtered, kept frozen and freeze-dried to obtain the infusion extract of *Maerua angolensis* (denoted IEMa).

Experimental animals

Wistar rats (*Rattus norvegicus*) and Swiss albino mice (*Mus musculus*) were bred at uniform condition (John-Africa et al., 2009) at the Animal Facility Centre (AFC), NIPRD, Abuja. The animals were maintained, used and handled in accordance with the International Guiding Principles for Biomedical Research Involving Animals (CIOMS/ICLAS, 2012). The protocol for their usage was approved in line with NIPRD Animal Care and Ethic's standard procedures on laboratory animal usage (NIPRD/05:3:05 – 15).

Evaluation of oral safety

Hippocratic screening

The method described by Neyres et al. (2012) was adopted with little modification as earlier described (Sudi et al., 2021). Briefly, mice were fasted overnight (with water *ab libitum*) and randomized by weight into two groups of 3 male and female mice each. They were all treated orally (p.o.) with 2000 mg/kg (Kunyima et al., 2018). A mouse was given the vehicle (distilled water, 10 mL/kg) to serve as the control in each of the groups. All the mice were individually observed for signs of toxicity or mortality at 15 min, 30 min, 1, 2, 4, and 8 h, and then once daily for 14 days.

Subchronic toxicity test

The subchronic toxicity profile of IEMa was evaluated in rats using the method described by Pavan et al. (2018) with little modification. The rats were randomized by weight keeping the mean weight as near as possible, and then grouped into four groups of 5 rats in the following manner: Group 1, male (treatment); Group 2, male (control); Group 3, female (treatment); and Group 4, female (control) rats. The rats were first acclimatized individually in metabolic cages (Techniplast, Buguggiate, Italy) used for the study for five days. The treatment groups received 800 mg/kg, p.o. daily for 28 days, while the control received the vehicle (distilled water, 10 mL/kg) daily for 28 days. The animals' biophysical (body weights, water intake, food consumption, feces, and urine output) were measured occasionally (2 – 3 days) and grouped every seven days (D_7, D_{14}, D_{21}, and

D_{28}) throughout the observation period. The animals were anesthetized at the end of the treatment and blood was collected for biochemical and hematological analysis.

Hematological parameter

The blood used for the hematological analysis was collected in Vacutainer® tubes containing EDTA and centrifuged at 2500 x g (Beckman GS-15, Brea, California, USA) for 10 min. The plasma was collected and analysed using an automated haematology analyser YNH7021 (Wincom Company Ltd. Hunan, China).

Biochemical parameter

The biochemical analysis was performed using blood collected without anticoagulant and centrifuged at 2500 x g for 10 min. Serum was separated and analysed using appropriate assay kits from Randox Laboratories Ltd, Crumlin, United Kingdom; Agape Diagnostics, Cham, Switzerland; Spectrum Diagnostics, Hannover, Germany; Teco Diagnostics, Anaheim, USA: and Fortress Diagnostics Ltd, Antrim, United Kingdom.

Gross and relative organ weights

The rats were then sacrificed to remove the major internal organs such as the brain, liver, spleen, left kidney, right kidney, heart, stomach, and testes (male) or uterus (female) for analysis as described by Adigwe et al. (2021b).

Data analysis

The results were expressed as the mean ± standard error of the mean (SEM) of 5 – 6 animals. One-way analysis of variance (ANOVA) was used to compare the means between groups. It was followed by the Student-Newman-Keuls test using GraphPad Prism software for Windows (San Diego, California, USA). $P < 0.05$ was considered statistically significant.

RESULTS

Physicochemical parameters

The yield = 20.95% w/w; pH = 4.64 (1 mg/mL at 29.4^{o}C); and solubility >500 mg/mL in distilled water.

Hippocratic screening

Treatment with IEMa (2000 mg/kg, p.o.) initially produced a mild CNS effect characterized by decrease motility, paw licking, mouth scratching and jumping within 30 min lasting between 4 – 8 h. The animals presented no behavioural changes or clinical signs and symptoms of toxicity throughout the 14 days observation.

Sub-chronic toxicity

Biophysical parameters

IEMa (800 mg/kg, p.o.) did not cause significant changes in body weight, water intake, food consumption, and excretion of faeces after daily treatment for 28 days when compared to the vehicle group (Table 1). There was, however, a significant decrease in food consumption and excretion of faeces in male treatment groups, and urine output in the female treated group on the twenty eighth day (D_{28}), when compared to the vehicle group.

Haematological parameters

Daily treatment with IEMa (800 mg/kg, p.o.) for 28 days did not significantly alter most of the parameters investigated. It however, presented a 15.46% increase ($p < 0.05$) in the absolute value of platelets counts of the male group when compared to the vehicle group (Table 2).

Biochemical parameters

There was no significant change in the biochemical parameters investigated in the male group. However, a significant decrease in alkaline phosphatase was observed in both male and female group in relation to the vehicle following daily treatment with IEMa (800 mg/kg, p.o) for 28 days (Table 3).

Gross and relative organ weights

As shown in Table 4, daily treatment with IEMa (800 mg/kg, p.o) for 28 days did not cause macroscopic changes in the organs analyzed. Also, no significant changes were observed in the relative organ weight in all the tested animals in relation to the vehicle group.

Table 1: Effect of 28 days daily oral administration of IEMa (800 mg/kg, p.o.) in rats on body weight, water intake and food consumption, and excretion of faeces and urine.

Parameters	Periods of treatment (Days)			
	D_7	D_{14}	D_{21}	D_{28}
Male (IEMa, 800 mg/kg)				
Cumulative weight gain (g)	13.53±3.54	29.32±4.12	39.23±6.04	45.15±5.78
Water intake (mL)	94.00±3.06	84.67±3.33	84.33±10.22	84.76±7.23
Food consumption (g)	22.33±0.88	27.33±1.67	29.00±2.52	21.33±2.60*
Feces output (g)	17.67±1.76	21.33±0.67	27.00±1.53	22.00±1.53*
Urine output (mL)	1.93±1.76	1.33±0.52	1.93±0.86	3.60±0.64
Male (Vehicle 10 mL/kg)				
Cumulative weight gain (g)	15.33±2.36	30.548±4.87	44.34± 7.13	50.17±6.46
Water intake (mL)	94.00±7.21	87.00±6.08	82.33±7.22	74.67±3.71
Food consumption (g)	21.67±4.49	26.33±2.67	24.67±2.19	14.00±0.58
Feces output (g)	20.00±5.03	22.67±4.01	26.00±4.00	15.00±0.89
Urine output (mL)	0.97±0.23	1.60±0.20	1.80±0.61	2.60±0.46
Female (IEMa, 800 mg/kg)				
Cumulative weight gain (g)	13.21±2.34	31.00±7.86	38.64±8.12	42.97±9.54
Water intake (mL)	77.33±5.81	79.00±4.04	81.00±3.22	85.33±4.06
Food consumption (g)	17.33±2.67	25.00±2.08	46.00±3.26	22.00±2.52
Feces output (g)	12.67±1.45	21.33±1.33	25.33±1.76	18.00±3.06
Urine output (mL)	6.03±2.62	4.33±1.18*	5.53±1.99*	7.93±0.64*
Female (Vehicle 10 mL/kg)				
Cumulative weight gain (g)	17.33±3.29	31.35±4.56	42.33±5.23	48.20±6.98
Water intake (mL)	90.00±5.29	76.67±6.33	83.67±3.84	72.00±5.57
Food consumption (g)	47.34±4.66	24.67±2.40	26.00±2.65	18.00±2.00
Feces output (g)	18.33±4.33	21.00±2.00	21.67±1.33	14.33±1.86
Urine output (mL)	4.33±1.92	2.73±1.71	2.53±2.16	3.13±1.16

The values represent the mean ± SEM. One-way ANOVA, followed by the Student-Newman-Keuls test.
*$p < 0.05$ vs vehicle.

Table 2: Effect of 28 days daily oral administration of IEMa (800 mg/kg, p.o.) in rats on haematological parameters.

Parameters	Treatment			
	Male (800 mg/kg)	**Male (Control)**	**Female (800 mg/kg)**	**Female (Control)**
Red blood cells (10^{12}/L)	5.87±0.45	6.44±1.14	4.88±0.99	4.50±1.30
Hemoglobin (g/L)	220.33±20.37	240.33±24.88	191.00±28.84	154.67±38.40
Hematocrit (%)	30.42±2.67	32.33±5.72	25.22±5.61	29.59±4.79
MCV[a] (fL)	51.67±1.14	50.17±5.72	51.17±2.17	48.10±3.57
MCH[b] (Pg)	37.56±1.90	38.18±2.56	40.48±3.30	44.26±4.01
MCHC[c] (g/L)	728.67±50.97	760.67±48.83	793.67±77.93	788.67±40.47
Platelets (10^9/L)	458.33±11.87*	381.00±51.00	403.50±77.12	430.00±43.23
Neutrophils: Relative (%)	79.27±0.28	80.42±1.23	77.18±2.87	77.08±24.97
Absolute (10^9/L)	10.77±8.74	10.56±3.88	10.39±0.22	10.77±3.29
Lymphocytes: Relative (%)	15.07±0.37	15.30±2.43	19.77±4.01	15.47±1.52
Absolute (10^9/L)	19.45±0.09	15.49±2.30	22.52±4.20	19.92±1.31

The values represent the mean ± SEM. One-way ANOVA, followed by the Student-Newman-Keuls test. *$p < 0.05$ vs. vehicle. [a]MCV: mean corpuscular volume; [b]MCH: mean corpuscular hemoglobin; [c]MCHC: mean corpuscular hemoglobin concentration; *$p < 0.05$ vs vehicle.

Table 3: Effect of 28 days daily oral administration of IEMa (800 mg/kg, p.o.) in rats on biochemical parameters.

Parameters	Treatment			
	Male (800 mg/kg)	**Male (Control)**	**Female (800 mg/kg)**	**Female (Control)**
Glucose (mg/dL)	184.20±3.27	169.01±4.01	219.1±5.07	180.10±15.12
Urea (mg/dL)	68.23±4.18	65.80±1.25	66.66±2.11	71.01±4.86
Creatinine (mg/dL)	2.14±0.27	1.50±0.17	1.26±0.12	2.08±0.09
Uric acid (mg/dL)	7.45±1.41	8.60±0.52	8.59±0.91	9.98±1.20
Alanine AT[a] (UI/L)	59.01±5.32	63.42±3.44	57.50±2.36	64.36±2.21
Aspartate AT (UI/L)	153.50±5.62	160.20±10.90	150.50±4.54	178.40±10.36
Alkaline phosphatase (UI/L)	662.40±94.82*	934.00±31.75	569.50±81.5*	944.8±23.32
Total Cholesterol (mg/dL)	104.10±4.22	113.30±5.73	117.30±5.99	121.90±13.07

Triglycerides (mg/dL)	125.30±13.13	113.92±21.03	107.27±19.79	95.24±17.26
Total proteins (mg/dL)	6.46±0.36	7.32±0.28	6.98±0.25	7.53±0.57
Ɣ-glutamyl transferase (UI/L)	9.26±2.00	13.12±1.39	5.02±0.77	6.18±1.02
Albumin (mg/dL)	3.92±0.65	3.02±0.59	2.43±0.68	5.93±1.82
D-bilirubin (mg/dL)	12.87±3.00	10.91±1.01	12.63±4.14	16.32±5.72
T-bilirubin (mg/dL)	16.09±0.55	14.74±0.59	15.85±1.50	19.92±2.41
HDL[b] (mg/dL)	65.11±5.21	61.10±2.32	64.44±2.61	71.78±4.92
LDL[c] (mg/dL)	395.80±15.23	347.40±21.99	299.00±20.50	259.40±89.25
Chlorine (mg/L)	85.60±9.41	85.74±8.24	89.22±2.12	90.42±4.52
Sodium (mg/L)	165.00±4.01	168.40±2.82	171.80±3.23	166.50±2.21
Potassium (mg/L)	8.20±0.11	7.78±0.75	9.40±0.32	17.27±7.14

The values are mean ± SEM, $n = 5$. One-way ANOVA, followed by the Student-Newman-Keuls test. *$p < 0.05$ vs vehicle. [a]AT – aminotransferase; [b]HDL - High-density lipoproteins; [c]LDL - Low-density lipoproteins.

Table 4: Effect of 28 days daily oral administration of IEMa (800 mg/kg, p.o.) in rats on the relative weight of the internal organs.

Organs	**Male (800 mg/kg)**	**Male (Control)**	**Female (800 mg/kg)**	**Female (Control)**
Brain (g)	1.37±0.13	1.29 ± 0.14	1.30±0.09	1.43±0.10
Liver (g)	4.44±0.25	4.44 ± 0.42	3.7±0.36	4.14±0.27
Spleen (g)	0.37±0.03	0.36± 0.07	0.39±0.04	0.35±0.05
Right kidney (g)	0.38±0.01	0.34±0.03	0.37±0.03	0.37±0.02
Left kidney (g)	0.36±0.01	0.37±0.03	0.33±0.04	0.36±0.01
Lung (g)	1.18±0.11	1.53±0.14	1.55±0.46	1.58±0.72
Heart (g)	0.49±0.01	0.38±0.06	0.47 ±0.05	0.49±0.03
Pancreas	0.39±0.09	0.36±0.01	0.37 ±0.13	0.44±0.05
Testes (g)	2.22±0.13	2.06±0.40	-	-
Uterus (g)	-	-	0.86±0.06	0.67±0.09

The values are mean ± SEM ($n = 6$).

DISCUSSION

This study investigated the oral safety (acute and subchronic) profile of the infusion extract of *Maerua angolensis* (IEMa). Issues of safety of herbal remedies have to be established to enhance their therapeutic benefits. This is usually performed in animals in which correlation of toxicological effects in humans has been reported (Olson et al., 2000). The Hippocratic screening gives a broad knowledge of the parameters evaluated and their descriptions and therefore, used as a general qualitative screening (Neyres et al., 2012). IEMa showed mild symptoms (decrease motility, paw licking, mouth scratching and jumping) that resolved between 4 - 8 h. No treatment-associated abnormality was recorded in all mice throughout the 14 days duration of the study. Test agents that produce no mortality at that dose are considered of use (OECD, 2001) and have a large margin of maneuverability (Bayala et al., 2019).

IEMa was also subjected to sub-chronic test by daily administration of the test agent for 28 days. The test can predict toxicological effects, and by extrapolation (Reagen-Shaw et al., 2007) gives a high predictive value of the toxicological profile of a test agent on several parameters on target organs in humans (Tugwood et al., 2003). IEMa did not significantly alter the parameters related to weight, water intake, food consumption, and faeces output, except for an increase in urine excretion. This is an indication that IEMa does not alter the normal growth and development of the animals.

The haematological assay showed that treatment with IEMa did not significantly alter all the parameters tested from normal, but there was a marginal increase in the platelet's value in the male group. This was the same with the biochemical assay, except for the decrease in alkaline phosphatase in both groups. Despite these observations, the resultant values are still within the physiological ranges of Wistar rats (Melo et al., 2012; Pavan et al., 2018). There was also no alteration macro, and in the relative organ weight analysis. These comparisons of organ weights between treated and untreated groups of animals are used to evaluate the toxicity effect of the test substance (Bailey et al., 2004; Sudi et al., 2021).

Conclusion

This study indicates that the infusion extract of *Maerua angolensis* is safe for therapeutic applications.

COMPETING INTERESTS

The authors declare that they have no conflict of interest.

AUTHORS' CONTRIBUTIONS

The project conception was by OPA and HOE, HOE and BA designed the experimental scheme, generated and analysed the data. AHB provided the provided the ethnomedicinal knowledge. All authors revised and approved the manuscript.

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