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Toxicological evaluation of the aqueous leaf extract of *Moringa oleifera* Lam. (Moringaceae)

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ABSTRACT

Ethnopharmacological relevance: The rapid increase in consumption of herbal remedies worldwide has been stimulated by several factors, including the notion that all herbal products are safe and effective. However, over the past decade, several news-catching episodes in developed communities indicated adverse effects, sometimes life-threatening, allegedly arising as a consequence to taking herbal products or traditional medicines from various ethnic groups. Despite the popular use of *Moringa oleifera* for treating various disorders, there is limited or no scientific data available regarding safety aspects of this remedy, nor are there any documented toxicological studies that can be used to ascertain the safety index of its herbal preparation. Therefore, this present study aimed to carry out extensive toxicological evaluation of the aqueous leaf extract of *Moringa oleifera*.

Materials and Methods: In an acute toxicity test, male Wistar albino mice were orally administered an aqueous extract up to 6400 mg/kg and intraperitoneally up to 2000 mg/kg. A sub-chronic toxicity test was performed by daily administration with the extract at 250, 500 and 1500 mg/kg orally for 60 days. Control rats received distilled water. Sperm quality was analyzed, haematological and biochemical (liver enzymes, urea and creatinine) parameters were determined and a histopathological examination was carried out.

Results: The LD_{50} was estimated to be 1585 mg/kg. The extract did not elicit any significant difference ($P \geq 0.05$) in sperm quality, haematological and biochemical parameters in the treated rats compared to the control. Moreover, there was no significant difference in weight gain of the control and treated animals although there was a dose-dependent reduction in food consumption of the animals treated with 250 to 1500 mg/kg extract.

Conclusions: Results obtained in this study suggest that the aqueous leaf extract of *Moringa oleifera* is relatively safe when administered orally.

1. Introduction

Herbal medicine is still the most abundant, affordable, reliable, trusted and well understood form of health care in virtually all African villages (Abalaka et al., 2009) and 80% of African populations use some form of traditional herbal medicine (WHO, 2002; Willcox and Bodeker, 2004). Before the advent of orthodox medicine, African people relied on herbs growing in and around them to take care of their health problems and, in some cases, as a simultaneous source of food (Abalaka et al., 2009). Orthodox medicine somewhat minimised the herbal health care system but the development of resistance against orthodox medicine by pathogens, high costs as well as the lack of availability of some of these drugs has, in recent times, begun to reverse this trend (Lee, 2006; Lam, 2007; Ogbunugafor et al., 2008), fortified by the notion that all herbal products are safe and effective (Farnsworth and Soejarto, 1985; Soejarto, 1989). However, several adverse effects, sometimes life-threatening, arose after the consumption of herbal products or traditional medicines from various ethnic groups, putting into question the safety of such herbal remedies (Soejarto, 1989; Elvin-Lewis, 2001). In some cases, adulteration, inappropriate formulations, or a lack of understanding of plant and drug interactions or their uses led to adverse reactions that were sometimes life-threatening or lethal to patients (Ernst, 1998). Therefore, contrary to popular belief, the use of herbal remedies can pose serious health risks (Alastair and Wood, 2002).

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Traditional herbal medicines do not receive sufficient attention in global health debates (Tilburt and Kaptchuk, 2008) even though the worldwide annual market for traditional herbal medicine products approaches US$ 60 billion (WHO, 2002; Adelaja, 2006; Tilburt and Kaptchuk, 2008). China, India, Nigeria, the USA and WHO have all made substantial research investments in traditional herbal medicines (WHO, 2002). Industry has also invested hundreds of millions of US dollars looking for promising medicinal herbs and novel chemical compounds (Zamiska, 2006; Novartis, 2007).

Herbal drugs are often bulky, doses are not quantified and most importantly toxicity is largely unknown (Galati and O'Brien, 2004; Sa'ad et al., 2006). Although a substantial number of scientific research papers have revealed activities of so many African plants, not many venture into studying the toxicity of this plant material (Abalaka et al., 2009). Alastair and Wood (2002) recommended that in the quality assurance research of herbal remedies, determination of the efficacy and safety are important aspects to consider.

Moringa oleifera Lam. (Moringaceae) or the horseradish tree is a pan-tropical species known by regional names such as benzolive, drumstick tree, kelor, marango, mlonge, mulangay, nébéday, saijhan, miracle tree, magic tree and sajna. Over the past two and a half decades, many reports have appeared in mainstream scientific journals describing its nutritional, medicinal and other properties (Fahey, 2005). *Moringa oleifera* preparations have been cited in the scientific literature as having antibiotic, antitrypanosomal, hypotensive, antispasmodic, antiulcer, anti-inflammatory, hypocholesterolemic, and hypoglycemic activities, as well as having considerable efficacy in water purification by flocculation, sedimentation and even reduction of *Schistosome cercariae* titer (Eilert, 1978; Eilert et al., 1981; Ezeamuzie and Ambakederemo, 1996; Ferreira et al., 2011; Sreelatha et al., 2011).

Despite the popular use of this herbal preparation for the treatment of various disorders, there is limited or no scientific data available regarding safety aspects of this remedy, nor are there any documented toxicological studies which can be used to ascertain the safety index of the herbal preparation. Therefore, this present study aimed to carry out extensive toxicological evaluation of the aqueous leaf extract of *Moringa oleifera*.

2. Methodology

2.1. Plant collection

The fresh young leaves of *Moringa oleifera* (about 2 years old) were collected from Odofin Agbebi farm, close to Ikire township secondary forest, in the Ikire Local Government Area of Osun State, Nigeria, in July, 2010. Botanical identification and authentication were performed by Prof. J.D. Olowokudejo of the Department of Botany, Faculty of Science, University of Lagos, Lagos, Nigeria and Mr. T.K. Odewo, a Senior Superintendent of the Forestry Research Institute of Nigeria (FRIN), Ibadan, Nigeria. A voucher specimen (LUH 2923) was deposited in the herbarium of the University of Lagos, Akoka, Yaba, Lagos.

2.2. Extract preparation

Fresh leaves of *Moringa oleifera* were air-dried for about 7 days at 30 °C and the dried material was macerated in distilled water (100 g in 2 L). The extract was decanted 24 h later. The filtrate was evaporated to dryness in an oven for 4 days at 40 °C giving a greenish brown colour, with a yield of 22%. The dried extract was weighed and reconstituted in distilled water (pH = 6.8), just before administration to experimental animals to obtain a stock concentration of 200 mg/ml.

2.3. Animals

Male Wistar albino mice (average weight 20 g) and male albino rats (average weight 100 g) used in this study were obtained from the Laboratory Animal Centre of the College of Medicine, University of Lagos, Lagos, Nigeria. The animals were maintained under standard environmental conditions (23–25 °C, 12 h/12 h light/dark cycle) and were fed on Pfizer standard rodent pellet diet and water *ad libitum*. The investigation conforms to *The Guide for the Care and Use of Laboratory Animals* published by the U.S. National Institutes of Health (NIH Publication No. 85-23, revised 1996) for studies involving experimental animals.

The use of mice in the acute toxicity study and rats in the chronic toxicity study is a standard toxicological/experimental procedure. The purpose of the acute toxicity is to investigate the acute lethality of the agent and thus mice are often use because of their nature and strength compare to rats. There is no study that will use rats for the acute toxicity test or mice for the chronic toxicity test (e.g., Frank, 2008; Awodele et al., 2010).

2.4. Acute toxicity study

1. Oral acute toxicity
   Mice were randomly divided into six groups of five animals per group. Graded doses of the extract (400, 800, 1600, 3200 and 6400 mg/kg) were administered to the animals orally *ad libitum*. The control group was administered 0.1 ml distilled water orally. Mice were observed for 24 h post-treatment for mortality, behavioural changes (restlessness, dullness, agitation) and signs of toxicity.
2. Intraperitoneal acute toxicity
   Mice were randomly divided into five groups of five animals per group. Graded doses of the extract 250, 500, 1000 and 2000 mg/kg were administered intraperitoneally. The control group was administered 0.1 ml of distilled water. Mice were observed for 24 h post-treatment for mortality, behavioural changes and signs of toxicity.

2.5. Sub-chronic toxicity study

Rats were randomly allotted to four groups of 6 animals per group. The animals were orally administered *ad libitum* an aqueous leaf of extract of *Moringa oleifera* at doses of 250, 500, and 1500 mg/kg daily for 60 days. The control group was orally administered 0.2 ml of distilled water daily. The rats were weighed weekly throughout the course of the experiment. The animals were closely observed for behavioural such as restlessness, hyperactivity, dullness and general morphological changes.

2.6. Collection of blood and organ sample

The animals were sacrificed by cervical dislocation on the 61st day of the experiment and blood samples were collected via ocular puncture with the aid of a capillary tube into EDTA (ethylenediaminetetraacetic acid) bottles and heparinised bottles for haematological and blood chemistry analysis, respectively. The kidney and liver were carefully isolated for histopathological examination and the epididymis was immediately removed for sperm quality analysis.

2.7. Haematological parameters and serum chemistry and sperm analysis procedures

The white blood cell (WBC), red blood cell (RBC), hemoglobin (HGB), mean cell volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC) and

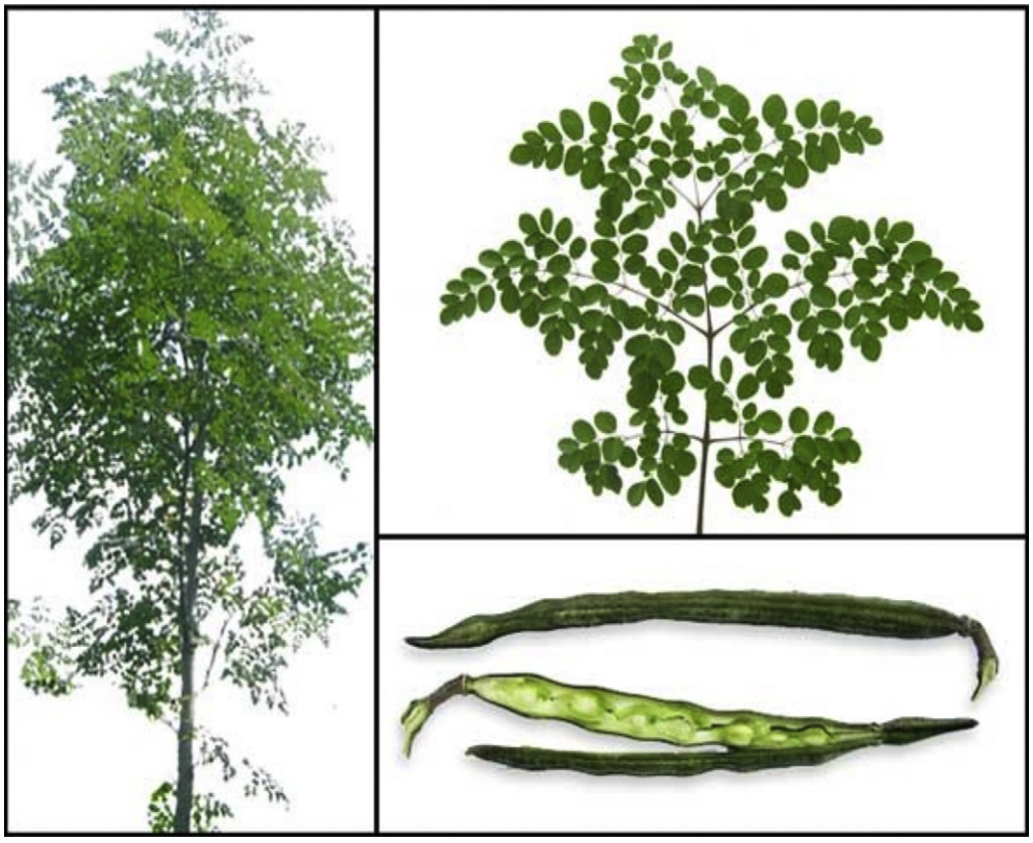

Fig. 1. The tree, leaves and seeds of *Moringa oleifera* Lam. (Adapted [online] from http://www.Stuartxchange.com/ChineseList.html.)

platelet (PLT) were determined using a fully automated haematology analyzer (Pentra-XL 80, Horiba ABX, USA). The liver enzymes biomarkers, urea and creatinine were determined using a fully automated clinical chemistry analyzer (Hitachi 912, Boehringer Mannheim, Germany). Measurement of the activity of serum antioxidant enzymes and MDA (malondialdehyde) levels were done according to standard procedures: catalase EC 1.11. 16 (Beers and Seizer, 1952; Beuge and Aust, 1978; Soon and Tan, 2002); MDA EC 202-974-4 (Soon and Tan, 2002; Ebuehi et al., 2009); Superoxide dismutase (SOD EC 1.15.1.1) (Soon and Tan, 2002); and reduced glutathione (GSH EC 2.5.1.18) (Beers and Seizer (1952) and Beuge and Aust (1978). The sperm analysis (motility, count and abnormal morphology) was done using the method of Morakinyo et al. (2008). Briefly, laparatomy was done to expose the reproductive tract. The caudal epididymis was carefully isolated and minced with scissors to release the sperm. Each chamber of the haemocytometer was loaded with 10 microlitres of the diluted sperm (1:20 dilution) and allowed to stand and or settled for 5 min. Counting was done under a light microscope at 400× magnification. Sperm morphology was determined using the eosin and nigrosin stain. Ten microlitres of eosin and nigrosin was mixed with about 40 microlitres of sperm suspension. The sperm suspension was incubated at 40 °C for 5 min and re-suspended with a micro-pipette. About 200 sperm cells per rat were morphologically examined under microscope at 400× magnification. Morphological abnormalities were classified as headless sperm, banana head, bent neck and bent tail. Sperm motility was done by placing 10 μl of sperm suspension on slide for microscopic evaluation at a magnification of 400×. About 200 sperm cells were examined and classified as either motile or immotile. The assessment of the motile sperm was calculated as mean motile sperm number × 100/total number of sperm.

2.8. Histopathology

The liver, kidney, heart, brain and testes of all the animals after 60 days were fixed in 10% formalin in labeled bottles. Tissues were processed routinely and embedded in paraffin wax. Sections of 5 μm thickness were cut, stained with haematoxylin and eosin and examined under the light microscope by a pathologist.

2.9. Statistical analysis

Results were expressed as mean ± SEM. The data were subjected to one-way analysis of variance (ANOVA) test and differences between samples were determined by Dunnett's multiple comparison test, using the Graph Pad Prism (statistical) software. Results were considered to be significant at $p \leq 0.05$.

3. Results

The tree leaves and seeds of *Moringa oleifera* Lam. was shown in Fig. 1. The aqueous leaf extract of *Moringa oleifera* did not produce any mortality when administered orally at various doses of 400 mg/kg to 6.4 g/kg, but reduced locomotion and dullness were observed in some animals treated with higher doses of 3200 and 6400 mg/kg 2 h post-treatment. The intraperitoneal (i.p.) route administration showed 20% and 80% mortality at the higher doses of 1000 and 2000 mg/kg. The LD_{50} was estimated to be 1585 mg/kg using a probit analysis method (Tables 1 and 2). There were no significant differences ($p \geq 0.05$) in the percentage weight gain of rats treated with *Moringa oleifera* (250, 500 and 15000 mg/kg) in comparison with the control rats (Table 3). The 60 days administration of *Moringa oleifera* at all doses investigated revealed no significant effect ($p \geq 0.05$) on the haematological parameters as compared

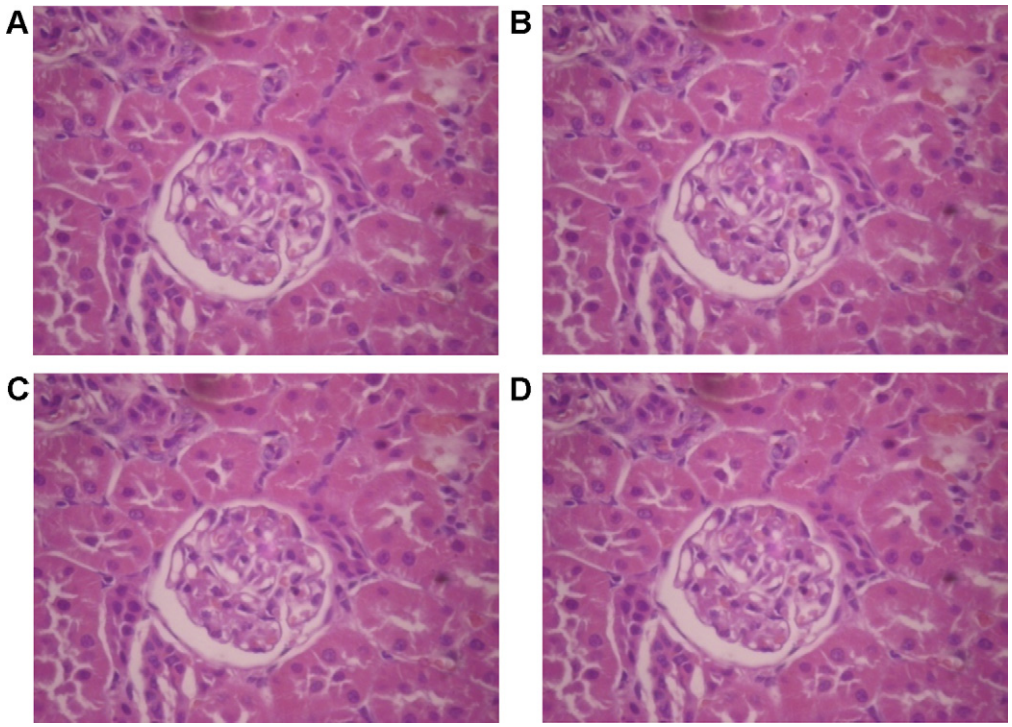

Fig. 2. Micrographs of the kidney sections obtained from rats untreated and rats treated with various doses of aqueous leaf extract of *Moringa oleifera*. Magnification 40×. (A) Rats untreated (control). (B) Rats treated with 250 mg/kg. (C) Rats treated with 500 mg/kg. (D) Rats treated with 1500 mg/kg.

Table 1
Acute (oral) toxicity study in mice after 24 h of administration of aqueous extract of *Moringa oleifera* leaf.

Group	Dose (mg/kg)	D/T[a]	Signs of toxicity observed
A	0.2 ml (H_2O)	0/5	No toxic changes observed
B	400	0/5	No toxic changes observed
C	800	0/5	No toxic changes observed
D	1600	0/5	Slight dullness was observed in 2 animals in the first 2 h
E	3200	0/5	Slight dullness was observed in 2 animals in the first 2 h
F	6400	0/5	Slight dullness was observed in 2 animals in the first 2 h

[a] D/T: Number of mice deaths/total number of mice ($n = 5$).

Table 2
Acute (i.p.) toxicity study in mice after 24 h of administration of aqueous extract of *Moringa oleifera* leaf.

Group	Dose (mg/kg)	D/T[a]	Signs of toxicity observed
A	0.25 ml (H_2O)	0/5	No toxic changes observed
B	250	0/5	No toxic changes observed
C	500	0/5	No toxic changes observed
D	1000	1/5	Slight dullness observed in 2 mice in the first 2 h
E	2000	4/5	Slight dullness observed in 3 mice in the first 2 h

LD_{50} = 1585 mg/kg.
[a] D/T: number of mice deaths/total number of mice ($n = 5$).

with the control (Table 4). The results (Table 5) obtained with urea and creatinine showed no significant difference ($p \geq 0.05$) in comparison with the control group however, there were slight elevation in the values of these renal function markers in all the doses (250, 500 and 15000 mg/kg) with highest level of creatinine (2.27 ± 0.62) and urea (71 ± 17.34) at the 1500 mg/kg dose as compared to the creatinine (1.26 ± 0.17) and urea (46.20 ± 5.32) of the control animals. The histology results of the kidneys at all doses revealed no destruction to the kidneys architecture (Fig. 2). The results further showed that the hepatic enzymes markers (SGOT, SGPT, ALP) were not significantly different from the control. However, slight reductions in the values of SGOT were observed at all the doses compared with the control (Table 5). The liver histology results showed no destruction to the hepatocyte and the architecture except slight congestion of the hepatocytes in the treated groups (Fig. 3).

Table 6 results showed a non-significant ($p \geq 0.05$) decrease in the values of SOD and CAT at 500 mg/kg and 1500 mg/kg while non significant increase were observed in the values of MDA at 500 mg/kg and 1500 mg/kg as compared with the control group.

There were no significant differences in the sperm motility and abnormality between the control group and the treated groups. However, there was significant ($p \leq 0.05$) reduction in the sperm

Table 3
Effects of aqueous extract of *Moringa oleifera* leaf on the body weights of rats after 60 days administration ($n = 6$).

Parameters	Control	250 mg/kg	500 mg/kg	1500 mg/kg
Weight at day 0 (g)	91.00 ± 13.87	101.67 ± 22.95	100.00 ± 17.61	96.67 ± 14.38
Weight at day 60 (g)	214.50 ± 20.70	207.50 ± 36.43	232.50 ± 34.28	225.00 ± 24.46
Weight gain (g)	123.00	105.83	132.50	128.33
Weight gain (%)	57.48	51.00	56.99	57.04

The t-test at $\alpha = 0.05$ showed no statistically significant differences between doses within each parameter.

Table 4
Effects of aqueous extract of *Moringa oleifera* leaf on the haematological parameters of rats after 60 days administration ($n = 6$).

Parameters	Control	250 mg/kg	500 mg/kg	1500 mg/kg
WBC ($\times 10^9$/L)	8.14 ± 0.85	8.90 ± 1.10	9.02 ± 1.33	8.58 ± 1.34
HGB (g/dL)	12.06 ± 0.73	13.87 ± 0.39	12.15 ± 0.42	12.47 ± 0.71
RBC ($\times 10^{12}$/L)	6.54 ± 0.53	7.74 ± 0.22	6.80 ± 0.22	6.94 ± 0.35
MCV (fL)	64.68 ± 2.39	54.43 ± 0.93	58.78 ± 0.35	57.00 ± 1.29
MCH (pg)	18.58 ± 0.64	17.85 ± 0.14	17.82 ± 0.16	17.90 ± 0.32
MCHC (g/dL)	28.76 ± 0.17	31.23 ± 0.54	30.22 ± 0.39	31.47 ± 0.22
PLT ($\times 10^9$/L)	496.80 ± 50.90	476.33 ± 79.27	593.67 ± 54.21	480.50 ± 34.81

The *t*-test at $\alpha = 0.05$ showed no statistically significant differences between doses within each parameter.

Table 5
Effects of aqueous extract of *Moringa oleifera* leaf on the hepatic and renal function markers of rats after 60 days administration ($n = 6$).

	Urea	Creatinine	SGOT	SGPT	ALP
Control	46.20 ± 5.32	1.26 ± 0.17	55.60 ± 9.82	41.00 ± 11.73	23.80 ± 3.90
250 mg/kg	60.83 ± 9.99	1.83 ± 0.54	49.50 ± 9.37	41.67 ± 8.55	19.33 ± 4.37
500 mg/kg	57.33 ± 5.73	1.83 ± 0.45	30.22 ± 0.39	48.83 ± 28.69	16.50 ± 2.40
1500 mg/kg	71 ± 17.34	2.27 ± 0.62	31.47 ± 0.22	35.00 ± 6.61	24.67 ± 6.89

The *t*-test at $\alpha = 0.05$ showed no statistically significant differences between doses within each marker.

Table 6
Effects of aqueous extract of *Moringa oleifera* leaf on antioxidants enzymes and lipid peroxidation of rats after 60 days administration ($n = 6$).

	SOD (μ/mg)	CAT (μ/mg)	MDA (μ/mg)	GSH (μ/mg)
Control	20.39 ± 2.624	94.056 ± 12.110	0.142 ± 0.030	0.414 ± 0.103
250 mg/kg	20.858 ± 4.760	96.213 ± 21.960	0.135 ± 0.025	0.4033 ± 0.036
500 mg/kg	12.004 ± 7.414	55.382 ± 34.205	0.174 ± 0.045	0.308 ± 0.059
1500 mg/kg	19.777 ± 3.903	91.232 ± 18.010	0.293 ± 0.171	0.460 ± 0.051

The *t*-test at $\alpha = 0.05$ showed no statistically significant differences between doses within each enzyme system.

count in the 250 mg/kg treated group (31.75 ± 10.100) as compared with the control group (42.00 ± 5.274) (Table 7).

The microscopic examination of the heart, brain and testis showed no physical and architectural changes.

4. Discussion

The result of acute oral toxicity (LD_{50}) study of aqueous leaf extract of *Moringa oleifera* showed no mortality at the maximum dose of 6400 mg/kg/body weight. In an acute oral toxicity study by Adedapo et al. (2009), *Moringa oleifera* leaf extract was documented to be non-lethal in animals at 2000 mg/kg body weight and thus added that "at doses above this level, the animals may exhibit some toxic changes" (Adedapo et al., 2009). More so, the report of Diallo et al. (2009) revealed that the aqueous extract of *Moringa oleifera* leaf is safe at dosage as high as 5000 mg/kg. These results may indicate that aqueous leaf extract of *Moringa oleifera* is safe orally (non-lethal) during acute administration as 2 g/kg dose was reported to be the ceiling point for medicinal plants toxicity when administered orally in acute toxicity study (Lu et al., 1965). However, this safety assertion may not be applicable to medicinal plants taken for a long period. Slight dullness was observed in the animals at above 1600 mg/kg acute dose administration. This observation is in agreement with the work of Adedapo et al. (2009) that showed that above 2000 mg/kg the animals exhibited some toxic changes. The LD_{50} of acute oral intraperitoneal toxicity study of *Moringa oleifera* leaf extract was determined to be 1585 mg/kg. This lower value of intraperitoneal LD_{50} as compared with the acute oral administration may be due to the route of administration and the presence of particulate matter in the extract which may cause toxicity in the animals during intraperitoneal administration. Based on the oral acute LD_{50} result, doses of 250, 500, 1500 mg/kg were selected for sub chronic toxicity study.

Table 7
Effects of aqueous extract of *Moringa oleifera* leaf on sperm quality of rats after 60 days administration ($n = 6$).

	Motility (%)	Abnormality (%)	Sperm count ($\times 10^6$)
Control	81.600 ± 4.057	7.700 ± 1.497	42.00 ± 5.274
250 mg/kg	76.500 ± 2.473	7.667 ± 1.116	31.75 ± 10.100**
500 mg/kg	77.167 ± 3.208	8.667 ± 1.054	39.17 ± 4.787
1500 mg/kg	83.1677 ± 3.208	7.167 ± 1.400	43.53 ± 3.9124

** $p \leq 0.05$ compared with the control.

There were no statistically significant differences ($p \geq 0.05$) in the % weight gain by the animals throughout the course of extract administration in all the doses compared with the control animals. This observation may indicate that the extract did not alter the metabolic processes of the treated animals which may subsequently affect the hormones and body weight (Cajuday and Poscidio, 2010). It was observed that the food intake of all the treated animals was reduced compared with the control animals without subsequent reduction in body weight of animals. The previous studies of D'souza and Kulkarni (1993), Anwar and Bhanger (2003), Anwar et al. (2005) have all shown that *Moringa oleifera* may serve as food supplements. It has also been reported to contain a profile of important minerals and a good source of protein, vitamins, β-carotene, amino acids and various phenolics (Siddhuraju and Becker, 2003; Holist, 2011).

The results further showed that there were no significant differences ($p \geq 0.05$) in all the haematological parameters of the test animals compared with the control. The urea and creatinine results also showed no significant differences ($p \geq 0.05$) in all groups of experimental animals compared with the control animals. The blood chemistry results corroborate the histological report of the kidney which showed no damage to the renal cells. However, there were slight increase in the levels of the urea and creatinine of the treated animals. Thus, there is need to exercise caution in the long-term consumption of this medicinal plant as it may exhibit long term nephrotoxicity. It was also revealed in this study that

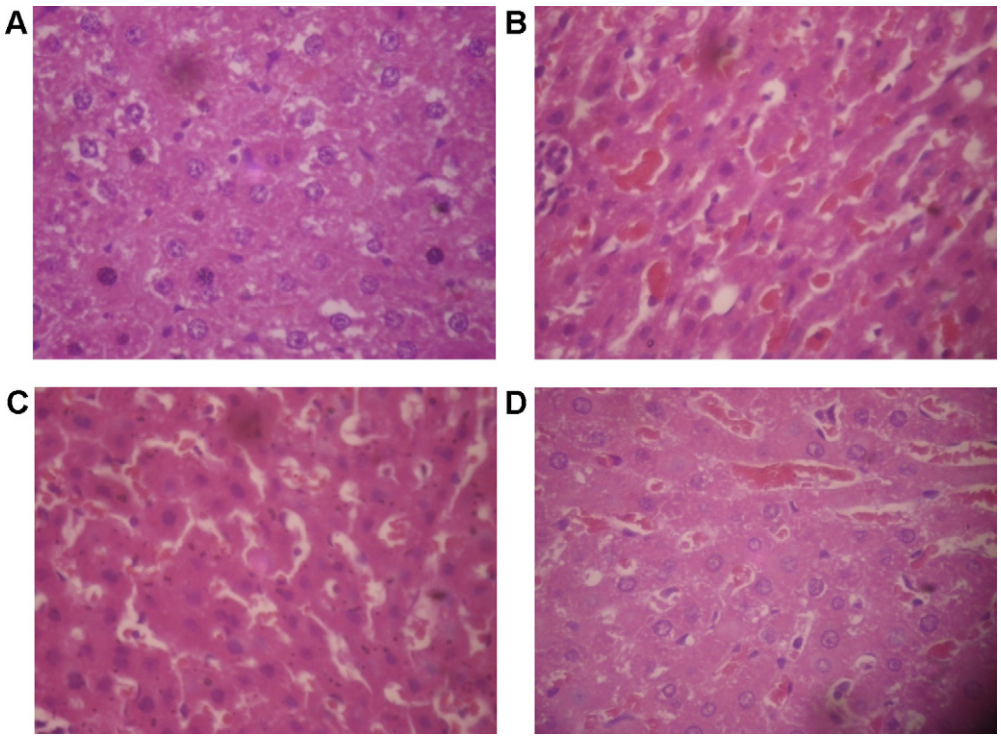

Fig. 3. Micrographs of the liver sections obtained from rats untreated and rats treated with various doses of aqueous leaf extract of *Moringa oleifera*. Magnification 40×. (A) Rats untreated (control). (B) Rats treated with 250 mg/kg. (C) Rats treated with 500 mg/kg. (D) Rats treated with 1500 mg/kg.

the liver enzymes biomarkers were not significantly altered by the extract. Though, the histopathology results showed unremarkable sinusoidal congestion in the hepatic cells of the treated animals. The sperm quality examination revealed no toxic effect on the sperm count, motility and morphology as shown in this study.

The results of lipid peroxidation and antioxidants level of treated rats as shown in this study revealed non-significant increase ($p \geq 0.05$) in the level of MDA and decrease in the levels of SOD and catalase at higher doses of 500 mg/kg and 1500 mg/kg. This may indicate that *Moringa oleifera* has the potential to induce free radical generation and this may be the rational for slight increase in the values of urea and creatinine of the treated animals.

5. Conclusion

It can be concluded that *Moringa oleifera* is relatively safe for human consumption. However, caution must be taken during long term administration. Further investigations in the areas of mutagenic, teratogenic and carcinogenic effects of *Moringa oleifera* are advocated.

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