



Safety Evaluation of *Morinda lucida* (L.) Benth (Rubiaceae) Aqueous Stem Bark Extract: A 50-day Oral Toxicity Study in Female Wistar Rats

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Abstract

This present study assessed a 50-day toxicological evaluation of *Morinda lucida* aqueous stem bark extract (MLE) in female Wistar rats. An acute toxicity was used to evaluate the safety. In a separate study, twenty-eight rats (100-120 g) were divided into four groups of 7/group to assess the subchronic toxicity in female rats. Group I received 10ml/kg distilled water, Group II, III and IV received 40 mg/kg, 200 mg/kg and 1000 mg/kg of MLE respectively. All treatment was via the oral route. Animals were sacrificed by cervical dislocation 24 hours following last administration. Weight changes, biochemical, electrolytes and histological changes were assessed in control and treated animals. An up and down procedure of single oral acute toxicity of MLE (2000mg/kg) produced no mortality in mice. MLE (40 mg/kg and 200 mg/kg) significantly reduced ($P < 0.05$) WBC in treated rats. MLE (200 mg/kg) elevated ($P > 0.05$) total bilirubin and amylase levels. MLE dose dependently reduced ($P > 0.05$) Na^+ and K^+ levels. MLE (40 mg/kg and 200 mg/kg) elevated Ca^{2+} level MLE (40 mg/kg and 1000 mg/kg) reduced ($P > 0.05$) urea and creatinine levels while 200 mg/kg elevated ($P > 0.05$) these biomarkers of renal function. Although, the extract did not significantly alter the body and relative organ weights it produced mild to moderate inflammation in liver, lungs, and heart at 1000 mg/kg. All the doses caused cortical-renal pelvical congestion. MLE may be considered relatively safe for consumption.

Keywords: *Morinda lucida*, Traditional medicine, Toxicity study, Safety evaluation

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Introduction

It is estimated that 80% of the world's population uses herbal medicine (Wang *et al.*, 2025). However, without adequate research and safety measures, concerns about potential risks may reduce its use as these hazards become more widely known. Therefore, alongside synthetic medicines, herbal medicines must meet international standards for safety and efficacy in modern healthcare (Adesiyon *et al.*, 2022). Consequently, analysis of herbal products is of immense relevance in order to define their health benefits or risks to consumers (Ayedogba *et al.*, 2026). In most West African countries like Nigeria, a large percentage of the populace depends on herbal medicines because the orthodox medicines are becoming increasingly expensive and out of reach (Ouoba *et al.*, 2022). Amongst the medicinal plants commonly use in Nigeria for management/treatment of various types of ailments is *Morinda lucida* Benth. *Morinda lucida* (Rubiaceae) is a tropical plant in West Africa rainforest commonly known as Brimstone tree. *Morinda lucida* is a medium size tree about 15m tall with scaly grey bark, short crooked branches and shining foliage (Lawal *et al.*, 2012). The leaves are used as “oral teas”, which are usually taken for traditional treatment of malaria, and as a general febrifuge, analgesic, laxative and anti-infections (Lawal *et al.*, 2012). The leaves have also been reported to possess trypanocidal, vasorelaxant, anticancer, hepatoprotective, cytotoxic, genotoxic, antispermatogetic, antileishmaniasis, antimalarial, hypoglycemia and antidiabetic activities (Raji *et al.*, 2005; Oyedare *et al.*, 2009; Olubunmi *et al.*, 2011; Abubakar *et al.*, 2016). The major constituents of *Morinda lucida* extract are the various types of alkaloids, anthraquinones and anthraquinols (Murthy *et al.*, 2023). Despite the profound therapeutic advantages possessed by various parts of this plant, there is paucity of data on the toxicity profile. In view of the prevalence uses of *Morinda lucida* in the management of both human and veterinary diseases and dearth of scientific information on the safety profile of its stem bark, we assessed the oral acute and sub chronic toxicity profile of this plant in experimental female Wistar rats.

Materials and Methods

Plant collection

Fresh stem bark of *Morinda lucida* were collected from deciduous forest of Ilaro town in Egbado Local Government Area of Ogun State, Nigeria, in the month of September, 2015. Plant samples were authenticated by Mr Oyebanji, an Herbarium curator in the Department of Botany and Microbiology, Faculty of Science, University of Lagos, Akoka, Lagos. Voucher

specimens (LUH 5009) were deposited in the herbarium for reference purposes.

Preparation of the aqueous stem bark extract of *Morinda lucida*

Fifty (50 g) of pulverized *Morinda lucida* stem bark was boiled with 500 ml of distilled water under continuous rigorous magnetic stirring on hotplate (JENWAY) for 1 hour before it was sieved using a mucilin cloth. The filtrate was transferred into an aerated oven at 40°C and completely dried to give deep brown, solid, sweet-smelling residue.

Chemicals

The following chemicals were used; Dimethylsulfoxide (DMSO), 3,5-dinitrobenzoic acid, sodium nitrite, aluminum chloride, ascorbic acid, 2,4,6-tripyrindyl-s-triazine, riboflavin, nitroblue tetrazolium and phosphate saline buffer (Sigma Chemical Co. USA). All chemicals and reagents used were of analytical grade.

Animals

A total of twenty-eight adult female Wistar rats (120 - 180 g) were purchased from the Laboratory Animal Centre of the College of Medicine, University of Lagos, Idi-Araba, Lagos State and were kept in the Animal Colony of the Animal House of Lagos State University College of Medicine, Ikeja, Lagos State. They rats were maintained on a rat pelleted diet (Bendel Feed & Flour Mill Ltd., Ewu, Nigeria) and water *ad libitum*. The study was in accordance with the established guidelines for the care and use of Laboratory Animals in Biomedical Research published by the U.S. National Institute of Health (NIH Publication No. 85 – 83, revised 1996) (Kilkenny *et al.*, 2011).

Acute and Sub-chronic oral toxicity studies of MLE

Young adult nulliparous female Wistar rats were randomly divided into four groups consisting of seven rats each. The acute oral toxicity study was conducted using the limit dose test of up and down procedure according to OECD/OCDE (OECD 2001) with a limit dose of 5000 mg/kg. Three female young adult Wistar rats were systematically selected out of a population of 10 Wistar rats (6 - 8 weeks old) by systematic randomization techniques (Adeneye *et al.*, 2006). The rats were fasted overnight but had access to water. Each rat was given the crude extract orally at a dose of 5000 mg/kg. Following administration, the rats were closely observed for signs of toxicity. Observations

were made every 15 minutes during the first 4 hours, and then daily for the remaining 12 days.

For the subchronic toxicity study, the rats were divided into four groups of seven female rats each. Group I (control) received distilled water at 10 ml/kg/day, Group II (low-dose group) received 40 mg/kg, Group III (medium-dose group) received 200 mg/kg, while Group IV (high-dose group) received 1000 mg/kg/day of MLE. The animals were treated for 50 days.

Blood Sample Collection

A day prior to termination of treatment, the rats were fasted but allowed drinking water *ad libitum*. The rats were sacrificed under deep inhaled diethyl ether anesthesia. Blood sample for full blood count was collected into an EDTA- treated bottle while that for serum biochemical (liver and renal functions) assays was collected into plain sample bottles, allowed 2 hours to clot, and centrifuged at 3500 rpm for 10 minutes to obtain the serum.

Measurement of body and relative organ weights

The weights of all the rats were measured using electronic Mettler weighing balance (Mettler Toledo Type BD6000, Mettler-Toledo GmbH, Greifensee, Switzerland) on days 1, 15, 29, 43 and 50, respectively, while the weight of each organ relative to the 100 g of body weight of the rats was calculated as: Organ weight (g) ÷ body weight of rat (g) x100}.

Assessment of Biochemical Indices

Biochemical Indices including liver function (AST, ALT and ALP in plasma), renal function (UA, creatinine), LDL- and HDL- cholesterol, total protein, albumin, were determined using Randox kit.

Determination of sodium (Na⁺) and potassium (K⁺) concentrations

Blood samples were diluted with a solution containing an internal standard (Lithium or Caesium) and aspirated into a prepared air flame. Na⁺, K⁺, Li⁺ and Cs⁺, *Flame emission Spectrophotometry* when excited, emit spectra with sharp bright lines at 589, 768, 671 and 852 nm respectively (Sherwood, Model 410).

Haematological Assays

The blood samples collected by cardiac puncture under inhaled diethyl ether anaesthesia into EDTA (ethylenediamine-tetra acetate) bottles and were analysed for full blood count (FBC) using Hematology Autoanalyser System (Sysmex Hematology-

Coagulation Systems[®], Model KX-21N, Sysmex Incorporation, Kobe, Japan).

Histological Assessment

The tissue blocks were fixed in 10% buffered formalin and placed in a molten wax at a temperature of 56-60°C in an oven. Following hematoxylin and eosin (H & E) staining, mounting of sections was carried out using dimethyl paraffinize xylene (DPX) as a mountant, after which the sections were ready for microscopic studies (mag. ×100).

Statistical Analysis

Data were expressed as mean ± S.D. for body weight and relative organ weights while data for biochemical and hematological assays were expressed as mean ± S.E.M. Significant differences among the group were determined by one-way analysis of variance (ANOVA) and Post Doc test by least significant difference (LSD) using the Statistical Analysis Programme for Social Sciences (SPSS) software. Results were considered to be significant at $P \leq 0.05$.

Results

Extraction yield

Aqueous extraction resulted in dark brown, sweet-smelling and sticky solid residue with an average yield of $8.2 \pm 3.3\%$.

Preliminary Qualitative Phytochemical Analysis of MLE

Preliminary phytochemical analysis of MLE showed the presence of flavonoids, alkaloids, saponin, terpenoids, phenols, tannins and phlobatannins while cardiac glycosides, steroids, glycosides and anthraquinones were absent.

Acute Oral Toxicity Studies

A single oral treatment of rats with 5000 mg/kg body weight of MLE produced no death within the short- and long-term observation period of the limit dose test of Up-and-Down Procedure (Table 1). However, the behavioral toxicity observed included dyspnea, restlessness/agitation, generalized body tremor, feed and water refusal within 24 hours post-treatment which gradually subsided after 24 hours.

Effect of MLE on body and organ weight

There was remarkable increase in the body weight following daily treatment with MLE for 50 days in all the groups, however there was no significant ($P > 0.05$) changes (increase) in the average body weight of the animals across the groups (Table 2). The relative

weights of the liver, kidney, lung, spleen, stomach and heart were not significantly ($P > 0.05$) altered (Table 1, Figure 1).

Table 1: Acute oral toxicity profile of MLE in female Wistar rats

Test sequence	Dose (mg/kg)	Short-term outcome	Long-term outcome
01	5000	Survival	Survival
02	5000	Survival	Survival
03	5000	Survival	Survival
04	5000	Survival	Survival
05	5000	Survival	Survival

Table 2: Changes in body weight (g) following MLE administration

Groups	15 th day	29 th day	43 rd day	50 th day
DW	32.14±8.9	52.71±11.9	58.861±13.5	58.861±13.5
MLE 40	30.00±17.4	38.00±22.3	36.00±17.0	47.14±20.05
MLE 200	25.57±16.5	42.86±24.6	48.43±15.1	39.00±20.13
MLE 1000	45.00±28.7	45.00±28.7	58.20±23.9	60.80±20.25

DW = 10 ml/kg of distilled water; MLE = *Morinda lucida* Extract

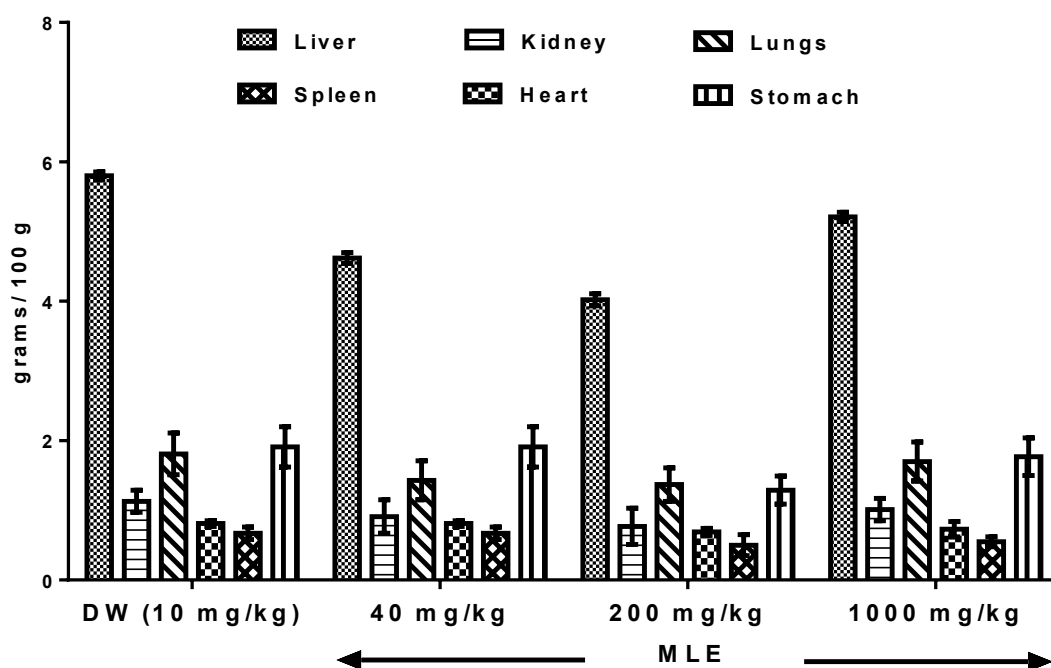


Figure 1: Effect of MLE on the relative weights of liver, kidney, lung, spleen, heart and stomach per 100g of treated rats. DW = Control (10 ml/kg of distilled water). MLE- *Morinda lucida* aqueous extract

Effect of the extract on liver enzymes level, total bilirubin (TBIL) and amylase (AMY) activity.

Daily oral treatment with 40-1000 mg/kg of MLE for 50 days did not result in any significant ($P > 0.05$) alterations in the serum levels of liver enzymes, total bilirubin and amylase when compared to the control group (Figure 2), however 200 mg/kg of MLE caused non-significant ($P > 0.05$) elevations in the serum TBIL and AMYL levels when compared with control values (Figure 2).

Effect the extract on albumin (ALB), total protein (TP), glucose (GLU), triglyceride (TG), total cholesterol, urea and creatinine.

Daily oral treatment with MLE for 50 days caused a significant ($P < 0.05$) reduction in the serum TC, particularly at 1000 mg/kg/ when compared to the control values (Figure 3). MLE did not cause significant ($P > 0.05$) alterations in the serum levels of ALB, TP, and GLU levels when compared to the control (Figure 3). Both 40 mg/kg and 1000 mg/kg MLE decreased urea level by 9.2% each, although, 200 mg/kg MLE slightly elevated urea levels by 2.6% (Figure 4).

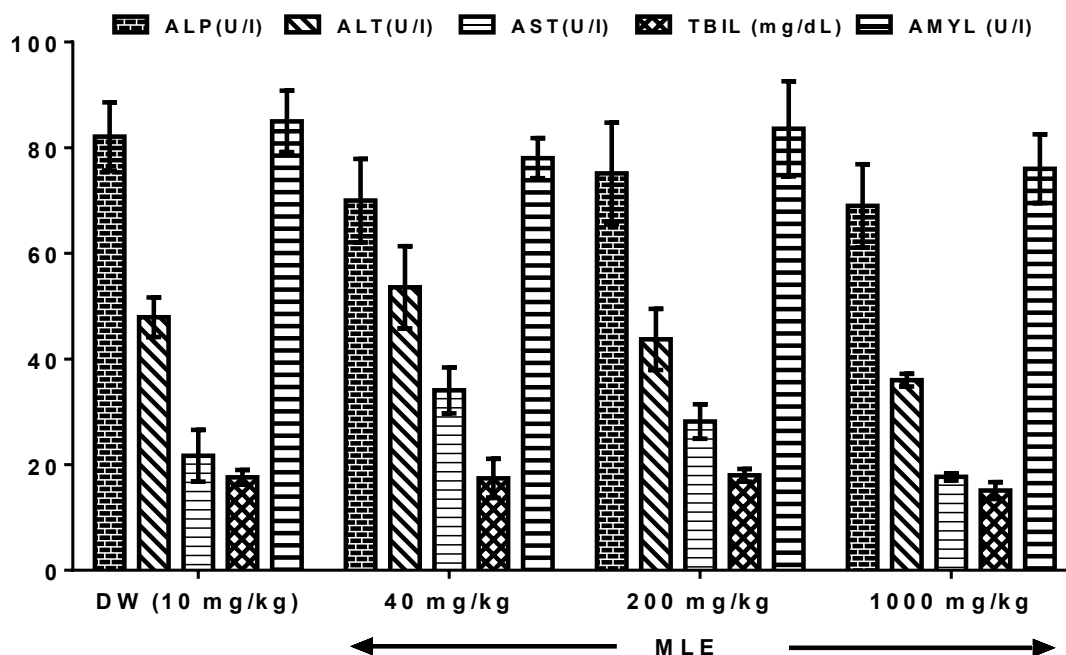


Figure 2: Effect of MLE on the serum liver enzymes (alkaline phosphatase, alanine and aspartate aminotransferases), total bilirubin and amylase of treated rats. DW = Control (10 ml/kg of distilled water). MLE-*Morinda lucida* aqueous extract.

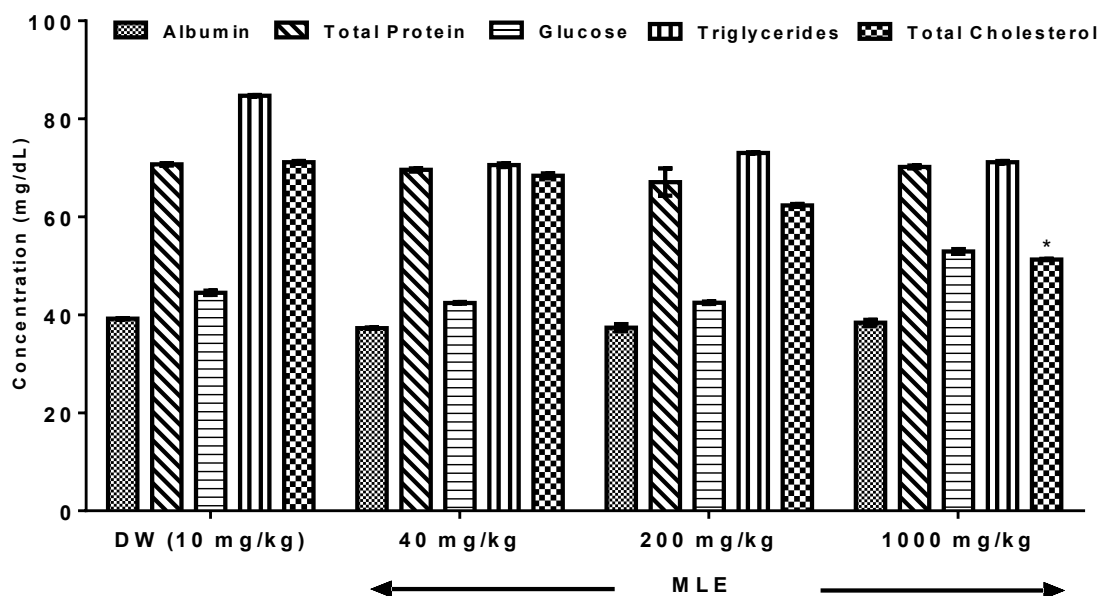


Figure 3: Effect of oral treatment with 40-1000 mg/kg/day of MLE on the serum albumin, total protein, glucose, triglyceride and total cholesterol *P < 0.05 when compared with control distilled water group. DW = Control (10 ml/kg of distilled water). MLE- *Morinda lucida* aqueous extract

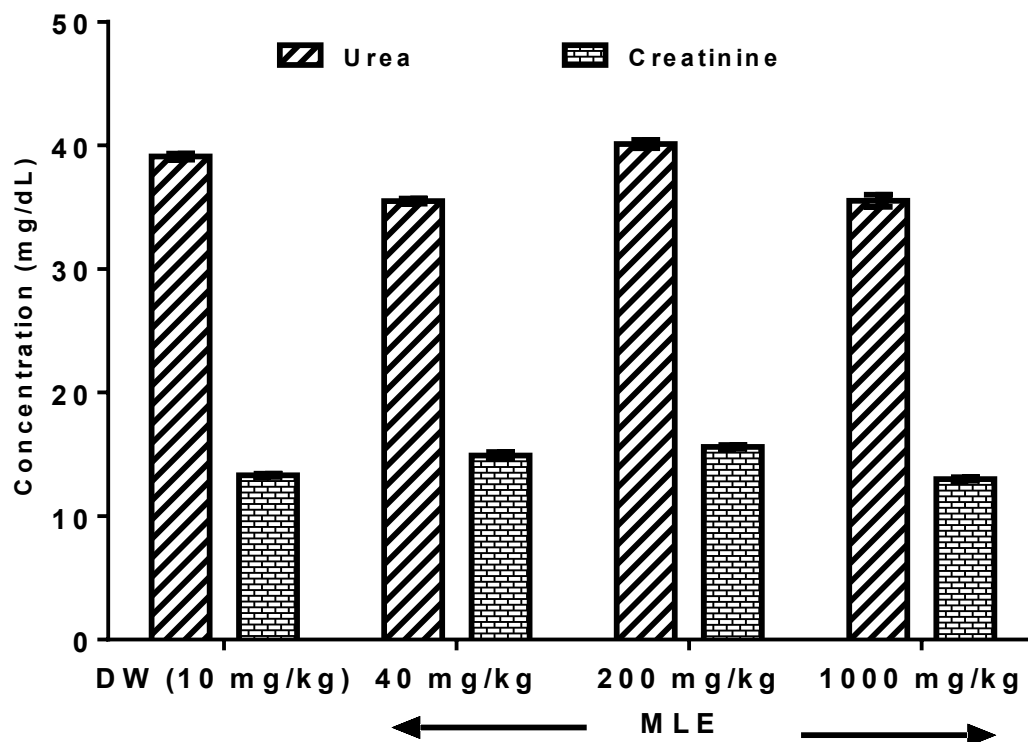


Figure 4: Effect of oral treatment with 40-1000 mg/kg/day of MLE on the serum urea and creatinine DW = Control (10 ml/kg of distilled water). MLE -*Morinda lucida* aqueous extract

Effect of the extract on serum electrolytes

Treatment of rats with MLE for 50 days caused a non-significant ($P > 0.05$) reduction in the serum Na^+ levels when compared to the control value (Table 3). MLE also caused non-significant ($P > 0.05$) reductions in the serum K^+ , Ca^{2+} and Cl^- levels.

*Hematology***Table 3:** Effect of MLE on the serum electrolytes

Groups	Na^+ (mmol/l)	K^+ (mmol/l)	Cl^- (mmol/l)	Ca^{2+} (mmol/l)
DW	148.29±1.34	12.63±0.54	100.86±0.34	4.95±0.42
MLE 40	148.43 ± 2.03	16.83±14.19	101.00±0.87	5.31±0.30
MLE 200	145.14±0.46	11.89±0.76	101.14±0.67	5.09±0.24
MLE 1000	144.20 ± 0.73	11.60±0.38	101.20±0.58	4.77±0.12

Results are expressed as mean±SEM; DW=Control (10 ml/kg of distilled water); MLE -*Morinda lucida* aqueous stem bark (mg/kg/day)

There was a significant ($P < 0.05$) non-dose related reduction in the total white blood cell counts (WBC) (Table 4) while causing non-significant ($P > 0.05$) alterations in the red blood cell count (RBC), hemoglobin (Hb), hematocrit (Hct), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), platelet counts (PLT), differential lymphocyte and neutrophils counts (Table 4).

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Table 4: Effect of MLE on the full blood count parameters of treated rats

Parameters	DW	MLE 40	MLE 200	MLE 1000
RBC	8.04±0.23	8.01±0.14	8.40±0.16	7.71±0.12
WBC	14.49±1.06	11.04±0.66*	10.83±1.53*	11.30±0.60*
HB	14.43±0.34	14.27±0.34	14.73±0.83	13.80±0.16
Hct	45.59±0.93	45.29±0.90	46.47±0.88	44.00±0.85
MCV	56.83±1.41	55.93±0.45	55.39±0.53	57.06±0.87
MCH	17.99±0.44	17.61±0.21	17.54±0.14	17.88±0.14
MCHC	31.7±0.20	31.50±0.30	31.7±0.20	31.40±0.40
PLT	742.1±71.30	685.60±76.0	681.0±83.78	31.40±72.60
LYM	11.07±0.80	8.07±0.50	8.21±1.20	8.92±0.40
NEUT	0.71±0.38	0.94±0.39	0.41±0.28	0.86±0.36

DW = Control (10 ml/kg of distilled water); MLE 40 mg/kg/day MLE= 200 mg/kg/day MLE= 1000 mg/kg/day. MLE: *Morinda lucida* aqueous stem bark extract; WBC: White Blood Cell; RBC: Red Blood Cell; Hb: Hemoglobin; Hct: Hematocrit; MCV: Mean Cell Volume; MCH: Mean Cell Hemoglobin; MCHC: Mean Cell Hemoglobin Concentration; PLT: Platelets; LYM: Lymphocytes; NEUT: Neutrophil. * $P < 0.05$ when compared to control values (Group DW), MLE -*Morinda lucida* aqueous extract (mg/kg/day)

Histopathological investigation

Histopathological examination revealed that MLE produced minimal tissue alterations at lower and intermediate treatment levels (40 and 200 mg/kg),

with the liver (Figure 4 A, B, C), heart (Figure 6 A, B, C), and lungs (Figure 7 A, B, C), largely maintaining normal architecture similar to the control group. However, higher exposure (1000 mg/kg) was associated with mild to moderate inflammatory changes in the liver (Figure 4 D), heart (Figure 6 D), and lungs (Figure 7D), indicating possible tissue

irritation at elevated concentrations. In the kidneys, vascular congestion was observed across treatment groups (Figure 5 B, C, D), suggesting that the renal tissue may be more sensitive to the extract than other organs.

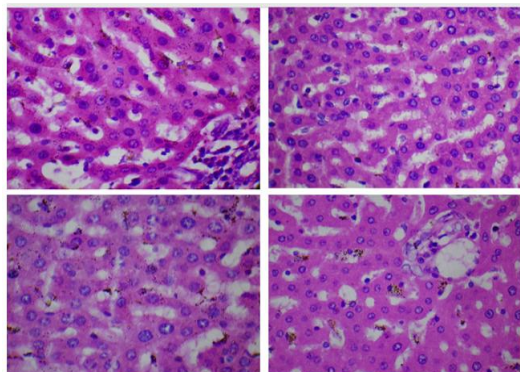


Fig. 5: Photomicrograph of the Liver, control, 10 ml/kg distilled water: normal (A), 40 mg/kg MLE: normal (B), 200 mg/kg MLE: normal (C), 1000 mg/kg MLE: Mild to Moderate periportal Inflammation (D). MLE= *Morinda Lucida* Aqueous Stem Bark Extract (H & E stain, Mag. X 100).

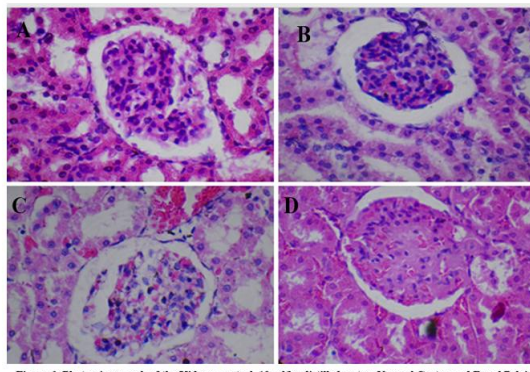


Figure 6: Photomicrograph of the Kidney, control, 10 ml/kg distilled water: Normal Cortex and Renal Pelvis (A), 40 mg/kg MLE: Normal Cortex Mild Renal Pelvis congestion (B), 200 mg/kg MLE: Severe Cortical and Renal Pelvis Congestion (C), 1000 mg/kg MLE: Normal Cortex and Renal Pelvis Moderate Cortical and Renal Pelvis Congestion (D). MLE= *Morinda Lucida* Aqueous Stem Bark Extract (H & E stain, Mag. X 100).

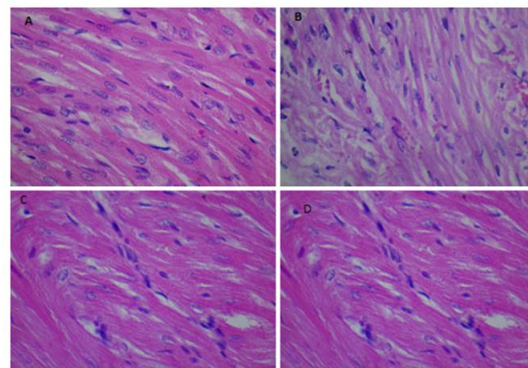


Figure 7: Photomicrograph of the Heart, control, 10 ml/kg distilled water: normal (A), 40 mg/kg MLE: normal (B), 200 mg/kg MLE: normal (C), 1000 mg/kg MLE: Mild to Moderate Cardiac Inflammation (D). MLE= *Morinda Lucida* Aqueous Stem Bark Extract (H & E, Mag. X 100).

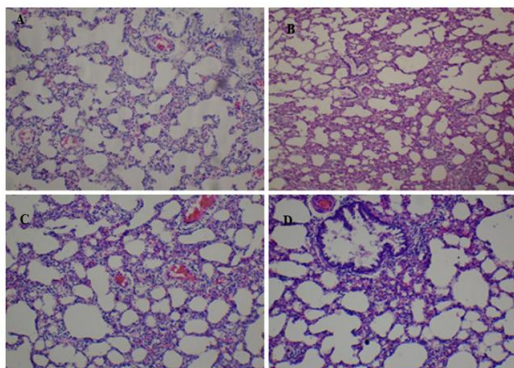


Figure 8: Photomicrograph of the Lung, control, 10 ml/kg distilled water: normal (A), 40 mg/kg MLE: normal (B), 200 mg/kg MLE: normal (C), 1000 mg/kg MLE: Mild to Moderate Inflammation (D). MLE= *Morinda Lucida* Aqueous Stem Bark Extract (H & E stain, Mag. X 100).

Discussion

This study investigated the acute and a 50-day toxicity of the aqueous stem bark extract of *Morinda lucida* (MLE) in rodents using anthropometric, biochemical, hematological and histopathological methods. The findings suggest that the extract possesses a favorable safety profile following oral administration. Although transient signs of toxicity such as breathing difficulty, agitation, tremors, and reduced food and water intake were observed shortly after treatment, these effects were temporary and resolved completely within a short period. The absence of mortality and full recovery of the animals indicate low acute toxicity. Furthermore, prolonged administration did not

produce marked changes in liver function indicators, suggesting that the extract did not adversely affect hepatic integrity or function. Overall, the results support the oral safety of the extract under both acute and extended exposure conditions.

Liver is known to be the main organ of detoxification for most drugs and alterations in its enzyme markers are considered strong indicator of toxicity (Tamber *et al.*, 2023). The fact that MLE caused no significant alterations in hepatic enzyme markers suggests that MLE is not hepatotoxic. The serum triglyceride and total cholesterol lowering effects are suggestive of the hypotriglyceridemic and hypocholesterolemia

activities. Previous studies have also reported glucose and lipids lowering effects of the ethanol *Morinda lucida* leaf extract and its solvent fractions in both normal and experimental hyperglycemic rat models (Adeneye, 2013; Lolok *et al.*, 2023). Results of this study corroborate some of these findings. Similarly, on the renal function parameters, oral treatments with MLE for 50 days did not induce any profound alterations in the kidney indices which is indicative of the safety of the extract on renal function integrity. These biochemical findings are corroborated by the histological findings of minimal histological changes in the rat livers and kidneys. The hematological findings indicate that the extract had minimal effects on blood parameters. While a significant reduction in total white blood cell count was observed, changes in red blood cell count, hemoglobin concentration, and hematocrit were mild and not statistically significant, suggesting limited hematological toxicity.

The leucopenia induced by MLE is suggestive of immunosuppressive tendency of the extract, bearing in mind that, white blood cells otherwise known as leucocytes are the “defense guards” of the body (Kale *et al.*, 2019; Amin *et al.*, 2024). Histopathological evaluation revealed the presence of mild to moderate inflammatory changes in several organs, including the liver, lungs, and heart. These findings suggest that prolonged exposure to the extract may induce localized tissue responses despite the absence of marked alterations in most biochemical and hematological parameters. In addition, cortical and pelvicalyceal congestion observed in the kidneys indicates vascular changes that may reflect increased renal workload or tissue irritation. The findings indicate a generally favorable safety profile, although prolonged or high-level exposure may elicit mild organ-specific histological changes. While the extract demonstrated a relatively favorable safety profile, the observed microscopic tissue changes highlight the need for caution regarding potential organ-specific effects during extended use.

Conclusion

Morinda lucida aqueous stem bark extract may be considered safe for consumption. However, cautions are needed as the extract showed tendency to induce anemia and leucopenia on prolonged oral exposure.

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