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ORIGINAL ARTICLE

Comparative Effect of Aqueous Extract of Mango Leaves (*Mangifera indica*) and Glibenclamide® on Physiological Indices of Wistar Rats Induced with Type II Diabetes

[1]Ruth A. Agyo✉, [2]Ifeoma Nwuzor, [3]Emmanuel U. Obasi, [4]Paul C. Nweje-Anyalowu, [5]Obumneme C. Ogbonnaya, and [2,6]Felix A. Andong.

[1]Department of Public Veterinary, Public Health and Preventive Medicine, College of Veterinary Medicine, Joseph Sarwuan Tarka University, Makurdi, Nigeria.
[2] Department of Zoology and Environmental Biology, Faculty of Biological Sciences, University of Nigeria, P.O. Box 3146, Nsukka, Enugu State, Nigeria.
[3]Department of Biochemistry, Faculty of Science, Federal University of Medical and Health Sciences, Kwale, Delta State, Nigeria
[4]Department of Chemical Sciences, Faculty of Science, Clifford University, Owerrinta (Ihie Campus), Abia State, Nigeria
[5]Department of Biochemistry, University of Nigeria, Nsukka, Enugu State, Nigeria.
[6]AP. Leventis Ornitological Research University of Jos, Plateau State, Nigeria

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ABSTRACT

The high cost and side effects of synthetic antidiabetic agents necessitate exploring affordable plant-based alternatives. *Mangifera indica* L. (Anacardiaceae) leaves are traditionally used for their antidiabetic properties. The objective of the study was to comparatively evaluate the effects of aqueous extract of *M. indica* leaves and glibenclamide on body weight, blood glucose, liver function enzymes, and hematological indices in alloxan-induced diabetic male Wistar rats. Acute oral toxicity was assessed using the OECD 425 guideline in mice (n=5). Diabetes was induced in 30 male Wistar rats by single intraperitoneal injection of alloxan monohydrate (150 mg/kg). Diabetic rats (fasting blood glucose ≥ 200 mg/dL) were divided into five groups (n=6): Group I (diabetic control, distilled water), Groups II–IV (*M. indica* extract at 100, 200, and 400 mg/kg b.worally), and Group V (glibenclamide 5 mg/kg b.worally). A sixth group (n=6) served as non-diabetic normal control. Treatment lasted 28 days. The oral LD_{50} of *M. indica* aqueous extract exceeded 5000 mg/kg, indicating wide safety margin. *M. indica* extract at 200 and 400 mg/kg b.wsignificantly ($p < 0.05$) reduced fasting blood glucose compared to the diabetic control, with the 400 mg/kg b.wdose showing comparable efficacy to glibenclamide by day 28. Unlike glibenclamide, which caused progressive weight gain, *M. indica*-treated rats maintained stable body weight. Both *M. indica* (200 and 400 mg/kg) and glibenclamide significantly ($p < 0.05$) restored altered hematological parameters (PCV, RBC, Hb) and reduced elevated liver enzymes (ALT, AST, ALP) toward normal levels. Aqueous extract of *M. indica* leaves demonstrates dose-dependent antidiabetic, hepatoprotective, and hematological restorative effects comparable to glibenclamide, with the advantage of weight neutrality. These findings support its potential as an affordable alternative adjunct in diabetes management.

Keywords: Alloxan-induced diabetes; *Mangifera indic*;, Glibenclamide; Blood glucose; Liver function enzymes; Hematological parameters.

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✉**Corresponding Author**: R. A. Agyo. Email. ruth.agyo@uam.edu.ng. **DOI:** https://dx.doi.org/10.4314br.v24i2.32

1.0 INTRODUCTION

Diabetes mellitus is a chronic metabolic disorder characterised by persistent hyperglycemia resulting from defects in insulin secretion, insulin action, or both (ADA, 2023). The global prevalence of diabetes has reached epidemic proportions, with an estimated 537 million adults living with the condition in 2021, a figure projected to rise to 783 million by 2045 (IDF, 2021). Type II diabetes mellitus (T2DM), which accounts for over 90% of cases, is driven by progressive insulin resistance coupled with eventual β-cell dysfunction (Chatterjee et al., 2017). Experimental induction of diabetes in rodents is commonly achieved using β-cell cytotoxins such as alloxan or streptozotocin. Alloxan induces selective necrosis of pancreatic β-cells via a redox cycling mechanism that generates reactive oxygen species, including superoxide radicals and hydroxyl radicals through the Fenton reaction, leading to rapid β-cell destruction and reduced insulin secretion (Rohilla & Ali, 2012; Szkudelski, 2001). While this model more closely resembles Type 1 diabetes, alloxan-induced hyperglycemia in rats is widely employed for preliminary screening of antidiabetic agents (Etuk, 2010). Current pharmacotherapy for T2DM includes oral hypoglycemic agents such as metformin, sulfonylureas (e.g., glibenclamide), thiazolidinediones, and dipeptidyl peptidase-4 inhibitors (Chaudhury et al., 2017). Although effective, these synthetic drugs are associated with adverse effects including weight gain, hypoglycemia, gastrointestinal disturbances, and, in rare cases, hepatotoxicity (Bolen et al., 2007; Stein et al., 2013). Moreover, the rising cost of long-term diabetes management, particularly in low- and middle-income countries, underscores the urgent need for affordable, safe, and effective therapeutic alternatives (Moucheraud et al., 2019).

Medicinal plants have historically served as a rich source of antidiabetic agents. The World Health Organization has endorsed the exploration of traditional plant-based therapies for diabetes management, especially in resource-limited settings (WHO, 2013). Among these, *Mangifera indica* L. (Anacardiaceae), commonly known as mango, has garnered considerable attention. The leaves of *M. indica* are traditionally used for the

management of diabetes across various regions of Africa and Asia (Shah et al., 2010; Gondi & Rao, 2015). Phytochemical screening of *M. indica* leaves has revealed the presence of bioactive compounds including mangiferin, flavonoids, tannins, saponins, phenolic acids, and alkaloids, which are implicated in antioxidant, anti-inflammatory, and antihyperglycemic activities (Doughari & Manzara, 2008; Jhaumeer Laulloo et al., 2018; Rodeiro et al., 2013). In particular, mangiferin, a xanthone glycoside abundant in mango leaves, has demonstrated potent glucose-lowering and β-cell-protective effects in diabetic animal models (Sellamuthu et al., 2013; Muruganandan et al., 2005).

Despite these promising reports, comparative studies evaluating the efficacy of *M. indica* leaf extract against a standard sulfonylurea drug (glibenclamide) across multiple physiological indices including glycemic control, body weight regulation, hematological parameters, and liver function remain limited. Furthermore, the safety profile and dose-response relationship of aqueous *M. indica* leaf extract in diabetic models require further elucidation. Therefore, this study was designed to assess the acute oral toxicity of aqueous extract of *M. indica* leaves, and evaluate its comparative effects with glibenclamide on fasting blood glucose, body weight, hematological indices (PCV, RBC, hemoglobin), and liver function enzymes (ALT, AST, ALP) in alloxan-induced diabetic male Wistar rats over a 28-day treatment period.

2.0 MATERIALS AND METHODS

2.1 Plant collection, identification, and extract preparation

Fresh leaves of *Mangifera indica* L. (Anacardiaceae) were collected from the University of Nigeria, Nsukka campus (6°51′21″N, 7°23′45″E). The plant was identified and authenticated at the Department of Plant Science, University of Nigeria, where a voucher specimen was deposited (PCG/UNN/0022). The leaves were thoroughly washed with distilled water, shade-dried at room temperature (25 ± 2°C) for 14 days, and pulverized using a laboratory blender. Thirty grams of the powdered leaf sample was macerated in 300 mL of distilled water for 24 hwith intermittent shaking, then filtered through Whatman No. 1 filter paper. The filtrate was concentrated using a rotary evaporator at 40°C and stored at 4°C until use.

2.2 Phytochemical screening

Qualitative phytochemical screening of the aqueous extract was performed for alkaloids (Mayer's test), flavonoids (NaOHhCl test), tannins ($FeCl_3$ test), saponins (frothing test), glycosides (Fehling's test), and total phenols (Dennis test) following standard procedures (Tijani et al., 2019).

2.3 Determination of extract concentration

The concentration of the aqueous extract was determined gravimetrically as described by Andong et al. (2020). A pre-weighed crucible (Wt1 = 30.77 g) was filled with 2 mL of the aqueous extract and reweighed (Wt2 = 33.33 g). The crucible was oven-dried at 60°C to constant weight and reweighed (Wt3 = 30.94 g). The dry mass per 2 mL aliquot was calculated as Wt3 − Wt1 = 0.17 g. Thus, the extract concentration was 0.085 g/mL, equivalent to 85 mg/mL.

2.4 Acute oral toxicity test (LD_{50})

Acute oral toxicity of the aqueous extract was assessed using Lorke's method (Lorke, 1983). In the first phase, nine adult BALB/c mice were divided into three groups (n = 3) and orally administered 10, 100 and 1000 mg/kg body weight (b.w) of the aqueous extract, respectively. Animals were observed continuously for the first 4 hand intermittently for 24 h for signs of toxicity and mortality. No mortality was observed. In the second phase, three additional mice were individually administered 1600, 2900, and 5000 mg/kg b.w orally and observed similarly. No mortality occurred at any dose; however, mild behavioral alterations (reduced activity, piloerection) were observed in the mouse receiving 5000 mg/kg b.w, which resolved within 10 min. Since no mortality was recorded at the highest dose tested, the LD_{50} was estimated to be greater than 5000 mg/kg, indicating the extract is practically non-toxic via the oral route.

2.5 Experimental animals

Forty-two male Wistar rats (4 weeks old, weighing 100–250 g) were obtained from the animal facility of the Department of Zoology and Environmental Biology, University of Nigeria, Nsukka. Twelve rats were used for the LD_{50} study (Section 2.5). The remaining 30 rats were used for the main experiment. All animals were housed in standard polypropylene cages under controlled environmental conditions (temperature 25 ± 2°C, 12h light/dark cycle, relative humidity 50–60%) and allowed free access to standard pelleted rat chow and water *ad libitum*. The rats were acclimatized for 7 days prior to the experiment.

2.6 Induction of experimental diabetes

After acclimatization, the 30 rats were fasted for 24 h (water provided *ad libitum*). Diabetes was induced by a single intraperitoneal injection of alloxan-monohydrate (Sigma-Aldrich®, Germany) dissolved in distilled water at a dose of 120 mg/kg b.w. Forty-eight hours after injection, fasting blood glucose (FBG) was measured from the tail vein using a glucometer (Omron®, E-OHS-BD) and a sugar strip.

2.7 Assessment of body mass and initial blood levels

The body weight of the rats, to the nearest 0.1 g, was measured using an Electronic compact scale, while initial and final hematological and biochemical indices of individuals that attained the marked diabetic level (i.e. ≥ 200 mg/dL) was assessed.

2.8 Administration of extract and glibenclamide

Positive rats were grouped into 5 and orally administered the aqueous extract of *M. indica* leaves to group one at a dose of 100 mg/kg, group two at 200 mg/kg b.w, and group three at 400 mg/kg b.w. The fourth group is the negative control, and no extract was administered, whereas group five were given a synthetic drug used in the management of diabetes (glibenclamide) at the dose of 4 mg/kg of the body weight.

2.9 Quantification of haematological indices after induction

Blood was collected from the retro-orbital plexus of the rats using a sodium heparinized capillary tube and a plain EDTA bottle (Andong et al. 2021), containing tripotassium ethylenediamine tetracetic acid as an anticoagulant. Blood samples were marked with the rats' markings before being analyzed using a Haematology analyzer (Medonic®Cell Analyser, M32) to determine packed cell volume (PCV in%), red blood cell count (RBC in µL), and haemoglobin concentration (Hb in g/dL).

2.10 Quantification of liver function enzymes

The liver function enzymes alkaline phosphatase (ALP), alanine aminotransferase (ALT), and aspartate aminotransferase (AST) were assess using the Randox® kits. The separation of serum from the blood by the centrifugation machine (Teehmel & Techmel: 800D, USA) at 4000 rpm for 30 min was done twice and the serum decanted into another plain bottle (Andong et al. 2021). Specifically, the ALP involved the use of Bassey et al. (1946) methods, which was modified by Wright et al. (1972). We finally calculated the mean absorbance per minute by the formula enumerated below. [*i.e., ALP activity (IU/L) = 2742 × ΔA 405 nm/min; where: 2742 = Extinction coefficient; ΔA 405 nm/min = change in absorbance per minute for the homogenate sample*]. Meanwhile, both ALT/AST were assessed by method of IFCC (1980). The R1 was the buffer (phosphate buffer 100 mmol/L, pH = 7.4; L-alanine 200 mmol/L; a-oxoglutarate-2.0 mmol/L), then 2, 4-dinitrophenylhydrazine 2.0 mmol/L is the R2. Both R1 + R2 were mixed using NaOH and distilled to form the blank reagent. After conducting the assay, our absorbance was read using the formula enumerated below. [i.e., ALT/ AST activity (nm/min) = 1746 × ΔA 340 nm/min, ΔA 340 nm/min = change in absorbance per minute for the homogenate sample, 1746 = Extinction coefficient].

2.11 Data analysis

All data were expressed as mean ± standard error of the mean (SEM). Statistical analyses were performed using SPSS for Windows (version 23.0; IBM Corporation, Armonk, NY, USA). Data were tested for normality using the Shapiro-Wilk test and for homogeneity of variance using Levene's test prior to parametric analysis. Comparisons among groups were conducted using one-way analysis of variance (ANOVA), followed by Dunnett's posthoc test for pairwise comparisons between each treatment group and the diabetic control group. Differences were considered statistically significant at $p \leq 0.05$. Graphical representations were generated using GraphPad Prism (version 9.0; GraphPad Software, San Diego, CA, USA).

2,12 Ethical approval

Animal handling and experimental procedures were approved by the University of Nigeria Animal Research Ethics Committee (Approval no.

DOR/UNN/19/0006) and conducted in accordance with the National Code of Conduct for Animal Research.

3.0 RESULTS

3.1 Acute toxicity of the aqueous extract of *Mangifera indica* leaves

No mortality or signs of acute toxicity were observed in mice administered the aqueous leaf extract of *Mangifera indica* at doses ranging from 10 to 5000 mg/kg b.wbody weight during the observation period. Consequently, the median lethal dose (LD_{50}) could not be calculated using Lorke's method because no dose produced 100% mortality. The oral LD_{50} of the extract was therefore estimated to be greater than 5000 mg/kg b.w, indicating that the extract is practically non-toxic under the conditions of this study.

3.2 Phytochemical constituents of the aqueous extract of *Mangifera indica* leaves

Qualitative phytochemical screening showed that the aqueous leaf extract contained alkaloids, flavonoids, saponins, and phenolic compounds, whereas cardiac glycosides were not detected (Table 1a). The presence of these phytochemicals was confirmed by the characteristic colour changes and reactions obtained during the qualitative analyses.

3.3 Effect of the aqueous extract of *Mangifera indica* leaves on blood glucose concentration

Treatment with the aqueous extract of *Mangifera indica* leaves reduced blood glucose concentrations in diabetic rats throughout the experimental period (Table 2). Although the reduction generally increased with dose, the response was not strictly linear. Blood glucose levels were significantly lower in extract-treated groups than in the diabetic control group over the treatment period ($p < 0.05$). Rats treated with the reference drug also showed a significant reduction in blood glucose compared with the diabetic control.

3.4 Effect of the aqueous extract of *Mangifera indica* leaves on body weight

Changes in body weight are presented in Table 3. Rats treated with the aqueous extract exhibited increases in body weight during the treatment period, although the response was not dose-dependent. Significant increases were observed in the groups receiving 200 and 400 mg/kg b.w of the extract ($p < 0.05$). The reference drug-treated group also showed an increase in body weight compared with the diabetic control group throughout the study.

3.5 Effect of the aqueous extract of *Mangifera indica* leaves on hematological parameters

The effects of the aqueous extract on packed cell volume (PCV), red blood cell (RBC) count, and haemoglobin concentration are presented in Tables 4, 5 and 6. Diabetes induction reduced PCV, RBC count, and haemoglobin concentration in the untreated diabetic rats. Treatment with the aqueous extract significantly improved these hematological parameters in a dose-related manner ($p < 0.05$). The highest dose (400 mg/kg) produced the greatest improvement in PCV, RBC count, and haemoglobin concentration. The reference drug also significantly improved these parameters compared with the diabetic control group, although the response at 400 mg/kg b.wof the extract was comparable to or greater than that observed with the reference drug.

3.6 Effect of the aqueous extract of *Mangifera indica* leaves on liver enzyme activities

The effects of the aqueous extract on serum liver enzyme activities are presented in Tables 7 to 9. Treatment with the extract significantly reduced serum alkaline phosphatase (ALP) activity in a dose-related manner compared with the diabetic control group (Table 7; $p < 0.05$). Similar reductions were observed for alanine aminotransferase (ALT) activity (Table 8), with the 200 and 400 mg/kg b.w doses producing greater reductions than the reference drug. Aspartate aminotransferase (AST) activity was also significantly reduced following treatment with the extract, with the 400 mg/kg b.wdose showing the greatest reduction among the extract-treated groups (Table 9; $p < 0.05$).

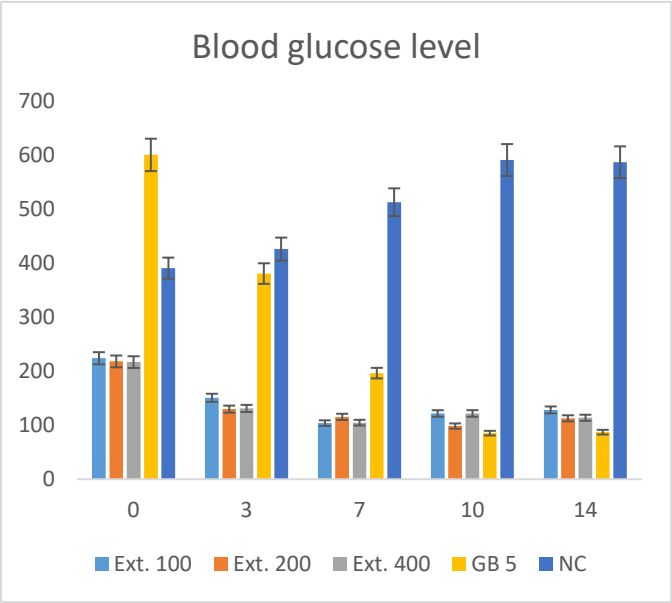

*Figure **1**. The effect of the aqueous extract of M. indica and glibenclimide on the blood glucose level of the diabetic rats. Although not dose-dependently, the aqueous extract of M. indica abruptly improved by decreasing the blood glucose level than the synthetic drug administered (glibenclimide) and the control.*

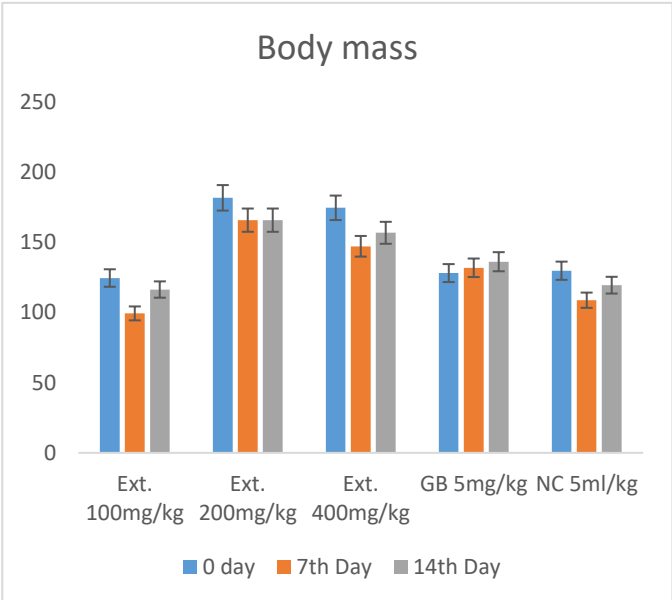

*Figure **2**. The effect of the aqueous extract of M. indica and glibenclimide on the body mass of the diabetic rats. The aqueous extract of M. indica unsteadily influenced the body mass of the rats when compared to the synthetic drug and the control group.*

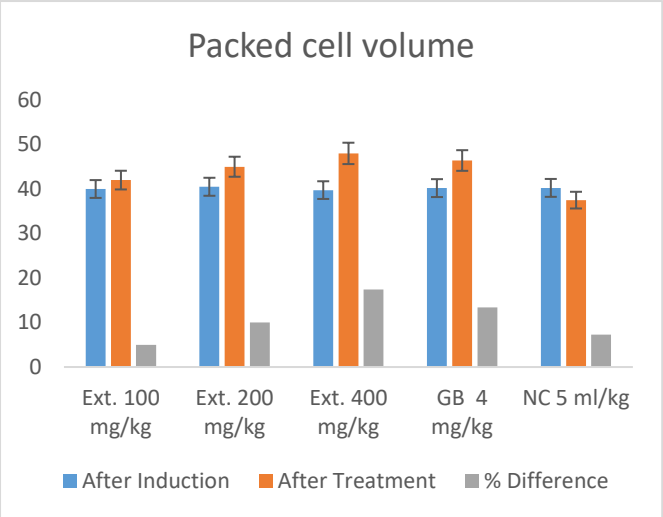

*Figure **3**. The effect of the aqueous extract of M. indica and glibenclimide on the packed cell volume of the diabetic rats. There was a dose-dependent improvement by increasing the packed cell volume after treatment with M. indica. Although the synthetic drug effectively improved the packed cell volume than the control group but not as much as the 400 mg/kg of the M. indica extract..*

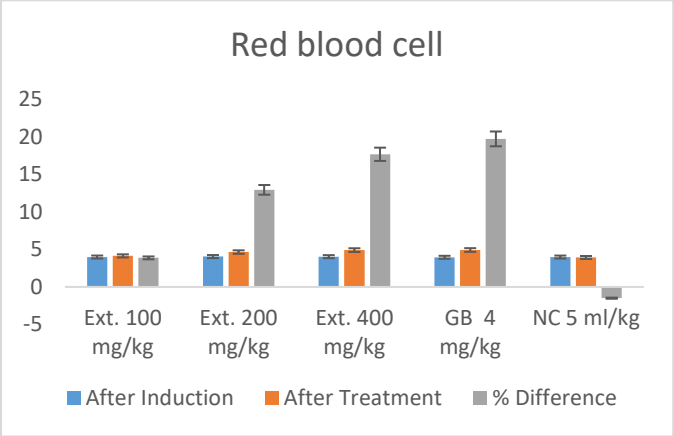

*Figure **4**. The effect of the aqueous extract of M. indica and glibenclimide on the red blood cell of the diabetic rats. There was a slight dose-dependent improvement by increasing the red blood cell after treatment with M. indica.*

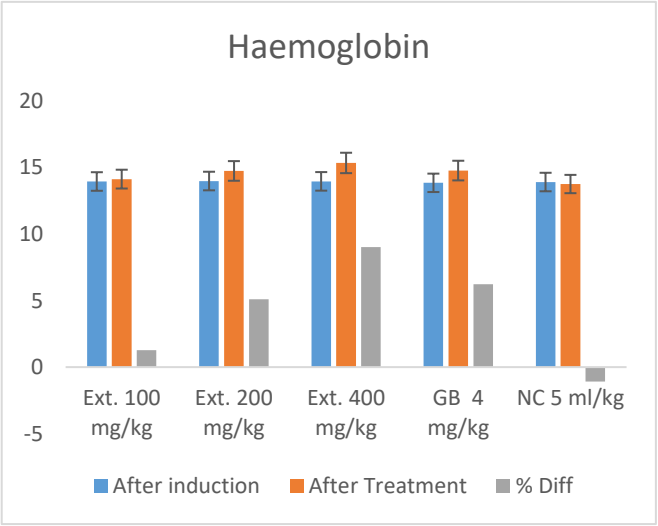

*Figure **5**. The effect of the aqueous extract of M. indica and glibenclimide on the haemoglobin of the diabetic rats indicates a dose-dependent improvement by the extract of M. indica than the synthetic drug and the control group after treatment. Values and error bars are the mean ± SE of raw data.*

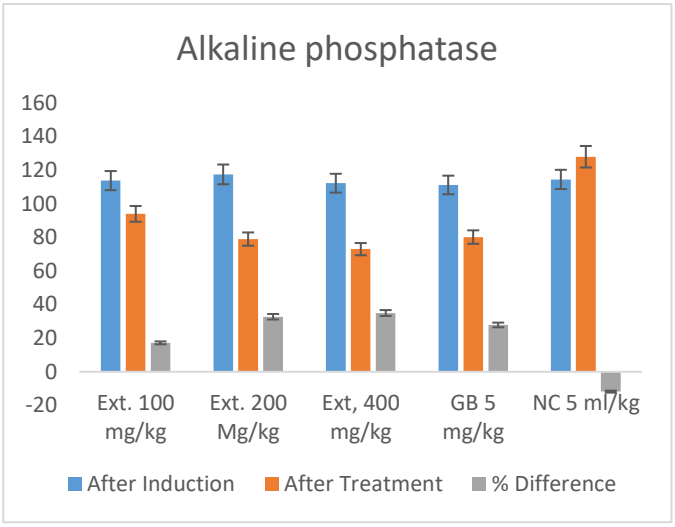

*Figure **6**. The effect of the aqueous extract of M. indica and glibenclimide on the alkaline phosphatase of the diabetic rats indicates a dose-dependent decrease in the serum level by M. indica extract compared with the synthetic drug and the control group.*

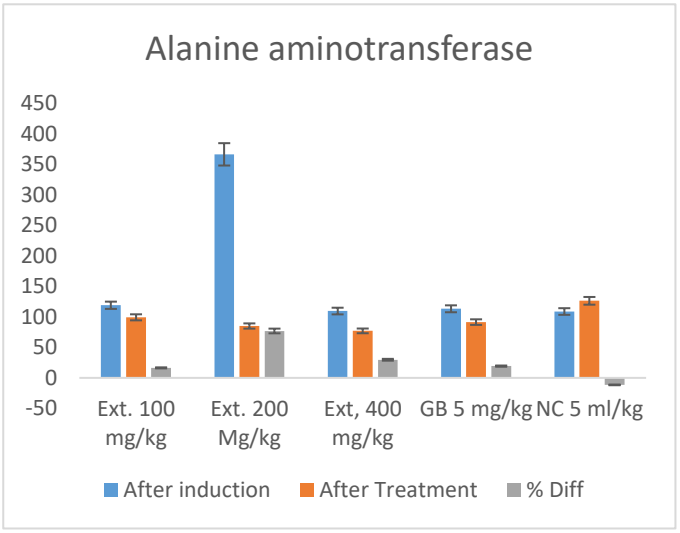

*Figure **7**. The effect of the aqueous extract of M. indica and glibenclimide on the alanine aminotransferase of the diabetic rats indicates a decrease in serum level by M. indica after treatment. However, the decrease was lower at concentrations of 200 and 400 mg/kg when compared to the synthetic drug and the control group. Values and error bars are the mean ± SE of raw data.*

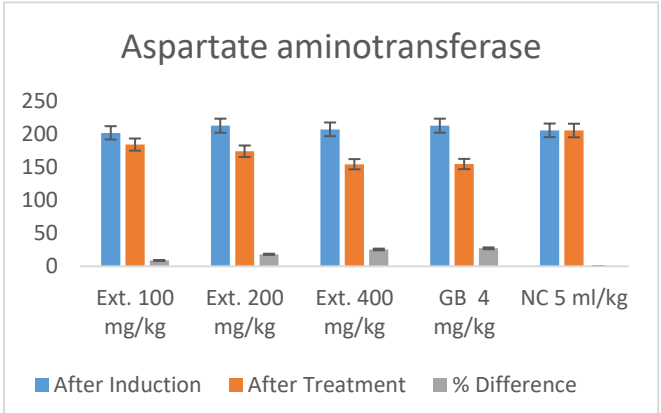

*Figure **8**. The effect of the aqueous extract of M. indica and glibenclimide on the aspartate aminotransferase of the diabetic rats indicates a dose-dependent decrease by M. indica. However, the effect by the synthetic drug and 400 mg/kg of the M. indica was the same and better that the control group. Values and error bars are the mean ± SE of raw data.*

Table **1**. Effect of aqueous extract of *M. indica* leaves and glibenclimide on BGL (mg/dl) of diabetic male albino rats

Sample	Dose	0 Day	3rd Day	7Th Day	10th Day	14th Day
Extract	100 mg/kg	223.8 ± 0.02	150.6 ± 0.08***	103.8 ± 0.73***	121.6 ± 0.69***	128.2 ± 0.33***
Extract	200 mg/kg	218.0 ± 0.51	129.7 ± 0.68***	115.3 ± 0.17***	98.3 ± 0.67***	112.7 ± 0.18***
Extract	400 mg/kg	216.7 ± 0.85	131.0 ± 0.01***	104.7 ± 0.74***	121.7 ± 0.02***	113.7 ± 0.48***
GB	5 mg/kg	600.0 ± 0.00	380.5 ± 0.62***	196.3 ± 0.53***	85.3 ± 0.432***	87.0 ± 0.53***
N.C	5 ml/kg	390.5 ± 0.14	425.8 ± 0.33	512.5 ± 0.83	590.5 ± 0.17	586.5 ± 0.50

* $p \leq 0.05$: significant, ** $p \leq 0.01$: highly significant, *** $p = 0.00$ very highly significant.

Table **2**. Effect of extract of *M. indica* leaves and glibenclimide on the body weight (g) of the experimental animals

Drug sample	Dose	0 day	7th day	14th day
Extract	100 mg/kg	124.5 ± 6.00	99.3 ± 5.10	116.3 ± 5.90
Extract	200 mg/kg	189.6 ± 11.30***	165.7 ± 0.19**	165.7 ± 11.10***
Extract	400 mg/kg	174.5 ± 6.60**	147.1 ± 6.50*	156.7 ± 7.80*
GB	5 mg/kg	128.0 ± 2.20**	131.8 ± 2.00**	136.10 ± 2.10**
NC	5 ml/kg	129.7 ± 9.80	108.7 ± 12.70	119.4 ± 11.10

*$p \leq 0.05$: significant, **$p \leq 0.01$: highly significant, ***$p = 0.00$ very highly significant.

Table **3**. Effect of aqueous extract of *M. indica* leaves and glibenclimide on the PCV (%) of diabetic albino rats

Sample	Dose	After Induction	After Treatment	Diff	% Diff.
Ext.	100 mg/kg	40.0 ± 0.71	42.0 ± 0.70*	2.00	5.00
Ext.	200 mg/kg	40.5 ± 0.65	45.0 ± 1.20**	4.50	10.00
Ext.	400 mg/kg	39.8 ± 0.63	48.0 ± 1.60***	8.35	17.40
GB	5 mg/kg	40.2 ± 0.59	46.4 ± 1.00**	6.20	13.40
NC	5 ml/kg	40.3 ± 0.63	37.5 ± 1.40	2.70	7.30

*$p \leq 0.05$: significant, **$p \leq 0.01$: highly significant, ***$p = 0.00$ very highly significant.

Table **4.** Effect of aqueous extract of *M. indica* leaves and glibenclimide on the RBC (µl) of diabetic albino rats

Sample	Dose	After Induction	After Treatment	Diff	% Diff.
Ext.	100 mg/kg	3.9 ± 0.04	4.1 ± 0.02**	0.15	3.87
Ext.	200 mg/kg	4.0 ± 0.04	4.6 ± 0.17***	0.60	12.93
Ext.	400 mg/kg	4.0 ± 0.08	4.9 ± 0.16***	0.87	17.76
GB	5 mg/kg	4.0 ± 0.07	4.9 ± 0.06***	0.97	19.72
NC	5 ml/kg	4.0 ± 0.05	3.9 ± 0.04	-.0.06	-1.50

*$p \leq 0.05$: significant, **$p \leq 0.01$: highly significant, ***$p = 0.00$ very highly significant.

Table **5.** Effect of aqueous extract of *M. indica* leaves and glibenclimide on the Hb (g/dl) of diabetic albino rats

Sample	Dose	After Induction	After Treatment	Diff	% Diff.
Ext.	100 mg/kg	13.9 ± 0.05	14.1 ± 0.07**	0.18	1.27
Ext.	200 mg/kg	14.1 ± 0.06	14.7 ± 0.12***	0.75	5.09
Ext.	400 mg/kg	14.0 ± 0.06	15.3 ± 0.47***	1.38	9.02
GB	5 mg/kg	13.8 ± 0.06	14.8 ± 0.11***	0.92	6.23
NC	5 ml/kg	13.9 ± 0.04	13.8 ± 0.16	0.15	-1.09

*$p \leq 0.05$: significant, **$p \leq 0.01$: highly significant, ***$p = 0.00$ very highly significant.

Table **6.** Effect of aqueous extract of *M. indica* leaves and glibenclimide on serum ALP (ng/dl) of diabetic albino rats

Sample	Dose	After Induction	After Treatment	Diff.	% Diff.
Ext.	100 mg/kg	113.8 ± 4.42	94.0 ± 6.61**	19.60	17.22
Ext.	200 mg/kg	117.5 ± 2.96	79.0 ± 2.65***	38.50	32.77
Ext.	400 mg/kg	112.3 ± 5.22	73.0 ± 8.50***	39.30	35.00
GB	5 mg/kg	111.2 ± 3.15	80.2 ± 5.31***	31.00	27.88
NC	5 ml/kg	114.5 ± 8.92	128.0 ± 4.55	-13.50	-11.79

*$p \leq 0.05$: significant, **$p \leq 0.01$: highly significant, ***$p = 0.00$ very highly significant.

Table **7.** Effect of aqueous *M. indica* leaves extract and glibenclimide on serum ALT (ng/dl) of diabetic albino rats

Sample	Dose	After Induction	After Treatment	Diff.	% Diff.
Ext.	100 mg/kg	119.0 ± 0.55	99.2 ± 4.51**	19.80	16.39
Ext.	200 mg/kg	366.3 ± 0.25	85.0 ± 5.51***	281.50	76.85
Ext.	400 mg/kg	109.5 ± 7.08	77.0 ± 3.21**	32.50	29.69
GB	4 mg/kg	113.2 ± 0.50	91.4 ± 3.33**	21.80	19.26
NC	5 ml/kg	108.8 ± 0.65	126.3 ± 6.00	-12.50	-11.49

*$p \leq 0.05$: significant, **$p \leq 0.01$: highly significant, ***$p = 0.00$ very highly significant.

Table **8.** Effect of aqueous *M. indica* leaves extract and glibenclimide on serum AST (ng/dL) of diabetic albino rats

Sample	Dose	After Induction	After Treatment	Diff.	% Diff.
Ext.	100 mg/kg	202.2 ± 5.88	184.4 ± 4.13**	17.80	8.80
Ext.	200 mg/kg	213.0 ± 8.72	174.3 ± 3.84**	38.67	18.16
Ext.	400 mg/kg	207.5 ± 5.12	154.6 ± 3.18***	52.83	25.52
GB	4 mg/kg	213.0 ± 4.25	155.0 ± 17.87***	58.00	27.23
NC	5 ml/kg	206.3 ± 10.09	205.8 ± 8.54	0.55	0.27

*$p \leq 0.05$: significant, **$p \leq 0.01$: highly significant, ***$p = 0.00$ very highly significant.

4.0 DISCUSSION

The present study demonstrated that the aqueous extract of *Mangifera indica* leaves possesses significant antihyperglycemic activity in streptozotocin-induced diabetic rats. Treatment with the extract significantly reduced blood glucose concentrations throughout the experimental period, with the higher doses producing greater reductions than the diabetic control. Although the response was not strictly dose-dependent at all-time points, the overall trend supports the antihyperglycemic potential of *M. indica* leaves and is consistent with previous reports describing their efficacy in experimental diabetes (Sellamuthu et al. 2008; Anthony & Adebimpe 2009; Ngo et al. 2019). The antihyperglycemic effect observed in this study may be explained by the phytochemical composition of the extract. Qualitative screening confirmed the presence of alkaloids, saponins, flavonoids, tannins, and phenolic compounds, while cardiac glycosides were absent, corroborating the findings of Ali et al. (2020). These phytochemicals have previously been associated with improved glycemic control through complementary mechanisms, including inhibition of carbohydrate-digesting enzymes such as α-amylase, enhancement of insulin sensitivity, stimulation of glucose uptake, and attenuation of diabetes-associated oxidative stress (Yang et al. 2012; Marrelli et al. 2016; Kato et al. 2017; Ngo et al. 2019). Consequently, the significant reduction in blood glucose observed in the present study is likely attributable to the synergistic action of these bioactive constituents rather than to a single phytochemical component. The proximate analysis showed that carbohydrate was the predominant constituent of the extract, followed by moisture, ash, fat, protein, and crude fibre. Although proximate composition was not the primary focus of this study, the presence of dietary fibre and protein may complement the pharmacological activity of the extract. Previous studies have shown that pectin, a major polysaccharide in *M. indica*, can improve glucose tolerance, reduce insulin resistance, and lower blood glucose concentrations in diabetic animals (Bello-Pérez et al. 2007; Liu et al. 2016). Similarly, adequate dietary protein has been associated with improved metabolic regulation in individuals with type 2 diabetes (Campbell & Rains 2015). These nutritional constituents may therefore contribute to the overall biological activity of the extract. Treatment with the aqueous extract also improved body weight compared with the diabetic control group. Weight loss is a common consequence of uncontrolled diabetes due to impaired glucose utilization and increased catabolism of fat and protein reserves. Therefore, the partial restoration of body weight observed in the treated groups suggests an improvement in metabolic status following administration of the extract. However, the response was not clearly dose-dependent, indicating that the selected doses may have approached a plateau of physiological response or that biological variability existed among the experimental animals. Similar improvements in body weight following treatment with *M. indica* have been reported previously (Furuse et al. 1993; Ngo et al. 2019; Sellamuthu et al. 2008). Diabetes-induced hematological alterations were also ameliorated by treatment with the extract. Significant dose-related increases in packed cell volume, red blood cell count, and haemoglobin concentration were observed, with the highest dose producing responses comparable to or greater than those of the reference drug. Diabetes mellitus is frequently associated with reductions in erythrocyte indices due to oxidative damage, impaired erythropoiesis, and shortened erythrocyte lifespan. The improvements observed in the present study therefore suggest that *M. indica* may alleviate diabetes-associated hematological impairment. Although the increase in these parameters may indicate improved erythropoietic activity and oxygen-carrying capacity, dedicated studies using established anemia models are required before therapeutic conclusions regarding the treatment of anemia can be drawn. The extract also significantly reduced serum alkaline phosphatase, alanine aminotransferase, and aspartate aminotransferase activities compared with the diabetic control group. Elevated serum liver enzyme activities are widely recognized as indicators of hepatic injury in diabetes. Consequently, the reductions observed following treatment suggest that the extract may exert hepatoprotective effects against diabetes-induced hepatic dysfunction. The greater reductions observed at the higher extract doses, particularly for ALP and ALT, further support this possibility. Similar hepatoprotective effects of *M. indica* have been attributed to its rich polyphenolic and flavonoid composition (Bahadoran et al. 2013; Irondi et al. 2014; Iwalokun et al. 2006). However, because liver histopathology was not performed, these findings should be interpreted as indirect evidence of hepatoprotection rather than definitive proof.

Limitations

This study has several limitations. The mechanisms responsible for the antihyperglycemic activity were inferred from previous studies because insulin concentration, oxidative stress biomarkers, inflammatory mediators, and pancreatic or hepatic histopathology were not evaluated. Furthermore, only three extract doses were investigated over a relatively short treatment period. These factors limit definitive conclusions regarding the molecular mechanisms of action of the extract. Future studies should incorporate mechanistic investigations, oxidative stress assays, histopathological analyses, and longer treatment durations to further elucidate the therapeutic potential of *M. indica* leaves. Nonetheless, the present findings demonstrate that the aqueous extract of *Mangifera indica* leaves possesses significant antihyperglycemic activity and improves hematological and hepatic biochemical indices in streptozotocin-induced diabetic rats. These beneficial effects are likely mediated by the combined action of the flavonoids, phenolic compounds, saponins, alkaloids, and other bioactive constituents identified in the extract. While the results support the traditional use of *M. indica* in diabetes management, further mechanistic and long-term studies are required before its therapeutic application can be fully established.

Conclusion

The present study demonstrated that the aqueous leaf extract of *Mangifera indica* possesses significant antidiabetic activity in streptozotocin-induced diabetic Wistar rats. Treatment with the extract reduced blood glucose concentrations and improved selected hematological parameters (RBC, PCV, and Hb) as well as liver function biomarkers (ALT, AST, and ALP), indicating potential hematoprotective and hepatoprotective effects. These biological activities are likely attributable to the rich phytochemical composition of the leaves, including flavonoids, phenolics, tannins, saponins, and alkaloids, which have recognized antioxidant and antihyperglycemic properties. Although the hypoglycemic effect was less pronounced than that of glibenclamide, the findings support the potential of *M. indica* leaves as a promising natural adjunct for the management of diabetes and its associated metabolic complications. Nevertheless, the underlying mechanisms of action remain to be fully elucidated. Future studies should include larger sample sizes, extended treatment periods, dose-optimization experiments, histopathological evaluation of the liver, kidney, and pancreas, and molecular investigations of insulin secretion, oxidative stress, and inflammatory pathways. Such studies will help establish the long-term**.**

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Data availability statement

The datasets generated and analyzed during the current study are not publicly available. However, it may be available from the corresponding author on reasonable request.

IRB approval

The University of Nigeria National Code of Conduct for Animal Research Ethics Committee approved this study

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Conflict of interest
The authors have declared that know competing interests exist.

Authors' contribution
FAA, RAA, JCN conceived and designed the study; FAA, JCN, ILN performed the study; JCN, RAA, ILN performed the laboratory analyses; FAA statistically designed and analyzed the data; FAA, RAA, JCN, ILN wrote the manuscript; FAA, RAA edited the manuscript.

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