Available online on 15.04.2022 at http://jddtonline.info

Journal of Drug Delivery and Therapeutics

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Research Article

Hepatoprotective Properties of *Sarcocephalus latifolius* Extract in Hyperglycemic Rat Model

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Article Info:

Article History:

Received 21 February 2022
Reviewed 12 March 2022
Accepted 19 March 2022
Published 15 April 2022

Cite this article as:

Chukwudozie KI, Ezeudoka BC, Okechukwu VC, Hepatoprotective Properties of *Sarcocephalus latifolius* Extract in Hyperglycemic Rat Model, Journal of Drug Delivery and Therapeutics. 2022; 12(2-s):72-76

DOI: http://dx.doi.org/10.22270/jddt.v12i2-s.5268

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Abstract

Currently, there is a need for safe, effective, and less costly antidiabetic medications, and investigating medicinal plants for new antidiabetic medication is gaining increased attention. Diabetes mellitus is a chronic metabolic disease associated with hyperglycemia, dyslipidemia, and hepatocellular damage. *Sarcocephalus latifolius (*family Rubiaceae) has been widely explored in ethnomedicine for the treatment and management of various disorders. The biochemical, hepatoprotective, and histological effects of aqueous-ethanolic leaf extract of *S. latifolius* in alloxan-induced diabetic rats were investigated. Thirty (30) juvenile male Wistar rats were placed into six groups, each with five rats: Normal rats made up Group 1, while diabetic rats in Groups 2–4 were given 200, 400, and 800 mg/Kg body weight of aqueous-ethanolic leaf extract, respectively; diabetic rats in Group 5 were given a standard anti-diabetic drug (0.2 mg/kg glibenclamide), and diabetic rats in Group 6 were left untreated. When compared to control rats, Alloxan induction led to a significant elevation in plasma glucose level, liver enzymes, low density lipoprotein (LDL), total cholesterol (TC), and triglycerides (TG), but a significant decrease in high density lipoprotein (HDL). The alterations in the following parameters were returned to normal levels when the diabetic rats were administered *S. latifolius* extract. The results indicate that *S. latifolius* showed hypoglycemic and hypolipidemic potentials, and may serve as a remedy for the management of diabetes.

Keywords: *Sarcocephalus latifolius,* Diabetes, Albino rats, Alloxan, Liver

1. INTRODUCTION

Diabetes mellitus (DM) is a metabolic disorder which is characterized by a persistent rise in blood glucose level. Diabetic patients can utilize many interventions including dietary management and regular exercise to manage their health status[1]. In addition, the use of alternative and complementary medicine for the treatment and management of DM have gained greater importance[2]. Medicinal plants have provided valuable therapeutic agents for treating diseases and disorders, and they are widely employed in many regions of the world, particularly in rural areas where modern medical facilities are limited[3]. Recently, there has been an increase in plant-based therapeutic products in both developed and developing countries because they are mostly non-toxic, have fewer side effects, and are available at affordable prices[4,5] One such medicinal plant is *S. latifolius.* The plant African peach (*S.latifolius*) grows in many tropical and subtropical regions of Africa and Asia and is used for medicinal purposes in folk medicine.

The plant is commonly used in traditional medicine for treating diabetes and malaria[6]. *S. latifolius* is also used to treat various other ailments such as liver diseases[7], stomach disorder and cough[8]Increasingly, diabetes management involves non-conventional drugs. It is estimated that 25 to 57% of people with diabetes have at one time or another resorted to complementary and alternative medicine, including medicinal plants[9].

Hypercholesterolemia and hyperglycemia are on the increase in the human population, and their drugs are not easily affordable to most of the affected individuals [10]. Moreso, undesirable side effects associated with these drugs made it imperative to explore other alternative sources for managing these diseases. The study aimed to provide some scientific support for the use of *S. latifolius* in ethnomedicine to treat diabetes. To achieve this, studies were carried out to evaluate the anti-diabetic, anti-hepatotoxic and anti-hyperlipidemic activities of *S. latifolius* in alloxan-induced diabetic rats, with the goal of determining the plant's acute toxicity implications when used conventionally in diabetes therapy.

2. MATERIALS AND METHODS

2.1 *Collection of Plant Material*

Fresh roots and leaves of *S. latifolius*harvested from a forest in Obukpa, South-eastern Nigeria. The samples were identified by Mr Felix Nwafor, a plant taxonomist at the Department of Pharmacognosy, University of Nigeria.

2.2 *Extraction Procedure*

Extraction was carried out as previously described[11].The roots were washed with clean tap water, and dried for 7 days in the shade, after which they were pulverized into a coarse powder.

A 2 kg portion of powder was cold macerated in 8 liters of 95% (v/v) ethanol (Sigma-Aldrich) at ambient temperature for 48 hours, and then filtered with Whatman No. 1 filter paper. The resulting filtrate was evaporated to dryness under a cool stream of air to obtain the extract.

2.3 *Phytochemical Analysis of Crude Aqueous Extracts*

This was done using standard methods as previously described[12]. The phytochemicals tested for include; alkaloids, saponins, flavonoids, tannis, glycosides and essential oils.

2.4 *Experimental Animals*

A total of 30 juvenile male Wistar rats weighing 150-200 g were obtained from the University of Nigeria, Nsukka's Faculty of Veterinary Medicine. Male rats were selected for this study because they are regarded to be more stable physiologically and less subject to hormonal changes, which could affect the results. The animals were housed under standard laboratory conditions and allowed free access to feed and clean water. The animals were treated in accordance with the National Institutes of Health's (NIH) guidelines for laboratory animal use and care[13].

2.5 *Induction of Diabetes*

Following a 12-hour fast, 25 rats received an intraperitoneal injection of alloxan solution at the dose of 150 mg/kg. Rats with a fasting blood glucose level of greater than 140 mg/dl for 5 consecutive days were judged to have developed diabetes and were selected for the study.

2.6 *Experimental Groups and Treatments*

The experimental rats were randomly divided into 6 different experimental groups of 5 rats per group.

Group 1: normal control (received 1ml distilled water/kg body)
Groups 2: diabetic rats (received 200mg/kg of *S. latifolius* extract).
Groups 3: diabetic rats (received 400mg/kg of *S. latifolius* extract).
Groups 4: diabetic rats (received 600mg/kg of *S. latifolius* extract).
Groups 5: diabetic rats (received 0.2 mg/kg of glibenclamide).
Group 6: diabetic rats (untreated)

The treatments were given orally twice a day, every 12 hours, for 21 days.

2.7 *Measurement of Blood Glucose*

The animals were fasted for 12 hours before blood samples were taken from the rats' tail veins and examined for fasting blood glucose levels using a glucometer (ACON Laboratories Inc, USA). Until the end of the treatment, measurements were taken every seven days.

2.8 *Biochemical Parameters Determination*

The serum levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), albumin, high-density lipoproteins(HDL), low-density lipoproteins (LDL), triglycerides (TG) and total Cholesterol (TC) were determined using assay kits from Randox Laboratories ltd (United Kingdom).

2.7 *Acute Toxicity Study*

This was carried out as previously described[12] The extract was administered to six groups of five rats each at doses of 10, 100, 1000, 1600, 2900 and 5000 mg/kg. The rats were monitored for clinical signs of toxicity and mortality.

2.9 *Statistical Analysis*

The data obtained was to one-way Analysis of Variance (ANOVA), using IBM SPSS Statistics software version 23. Significance was accepted at $p \leq 0.05$.

3. RESULTS AND DISCUSSION

Diabetes mellitus is a public health problem in a large number of countries worldwide. This needs the development of more effective and minimally invasive therapeutic techniques. Plants with anti-diabetic properties may be a rich source of new hypoglycemia compounds. Hyperglycemia and impaired glucose metabolism are the primary markers of diabetes, and alloxan injection dramatically raised the blood glucose of the experimental rats compared to the normal control. Alloxan causes diabetes mellitus by causing the destruction of certain pancreatic cells, which results in hyperglycemia. Treatment with *S. latifolius* extract, on the other hand, corrected the alloxan-induced hyperglycemia (Table 1). This observation is in consonant with the findings of earlier studies that reported the hypoglycemic effects of *S. latifolius* extracts [8].

Table 1: Blood sugar levels in rats before and after treatment with different doses of *S. latifolius* extract

Stages	Treatment groups					
	Control (Normal rats)	200 mg/kg bw	400 mg/kg	600 mg/kg	Standard control	Diabetic control
Baseline	81.25±4.91^{A1}	73.82±5.37^{A1}	79.70±6.13^{A1}	85.72±7.14^{A1}	86.62±67.09^{A1}	77.40 ± 8.10^{b}
After induction	79.51±9.01^{A1}	258.58±60.41^{B45}	291.57±68.85^{B3}	349.40±26.61^{B3}	279.49±34.06^{B3}	294.14± 46.27^{b}
Day 7	87.47±8.57^{A1}	160.63±30.45^{A234}	132.60±94.14^{A}	135.70±25.31^{A12}	96.43±3.87^{A1}	409.63± 43.72^{b}
Day 14	78.79±3.70^{A1}	112.94±33.49^{A123}	94.20±8.61^{A1}	93.80±22.10^{A12}	84.61±2.41^{A1}	432.53± 45.30^{b}
Day 21	74.63±5.86^{A1}	79.21±7.31^{A12}	75.60±8.20^{A1}	82.70±5.75^{A1}	80.29±7.24^{A1}	487.60± 36.12^{b}

Values are represented as Mean (±) standard deviation. Values with different figures as superscripts in a row differ significantly ($p \leq 0.05$). Values with different alphabets as superscripts for a parameter in a column differ significantly ($p \leq 0.05$

The hypoglycemic activity of *S. latifolius* leaves extract could be related to phytochemicals found in the leaves. Alkaloids, flavonoids, and saponin are among the phytochemicals present, and they are believed to have a hyperglycemic effect[14,15]. Also, it is known that these phytochemical constituents can stimulate insulin actions on the beta cells of the pancreas[16]. The preliminary phytochemical screening revealed the presence of glycosides, saponins, tannins, alkaloids, and flavonoids in the crude aqueous-ethanolic leave extracts of *S. latifolius*. These bioactive compounds are present in varying concentrations in the plant extract, as shown in Table 6.

Table 6: Results of Phytochemical Analysis

Phytochemicals	Amount
Alkaloids	+++
Flavonoids	+++
Tannins	+++
Saponins	+++
Glycosides	++
Fats and Oil	+

Key: + slightly present, ++ moderately present, +++ Abundantly present

In the present study, alloxan-induced diabetic rats developed dyslipidemia. The increased TG, TC, and LDL levels, and reduced HDL levels in alloxan-induced diabetic rats seen in this study are consistent with prior studies on changes in these markers in diabetic animals [17–19]. Diabetes-induced hyperlipidemia could be caused by increased mobilization of fat from adipose tissue due to glucose underutilization. However, treatment with *S. latifolius* extracts significantly ($P<0.05$) reduced the TC, TG and LDL when compared to the diabetic untreated rats. Similarly, the HDL which was reduced in the diabetic untreated rats was significantly increased ($P<0.05$) in the groups administered the *S. latifolius* extracts (Table 4 and 5), and this is consistent with previous studies that reported hypolipidaemic properties of *S. latifolius* extracts [20]

Table 4: Effect of oral administration of leaf extract on HDL and LDL of Alloxan induced diabetic rats

GROUPS	BASELINE	AFTER INDUCTION	7 DAYS	14 DAYS	21 DAYS	HDL/LDL (mg/dl)
Group 1	73.22± 8.65^{A1}	75.24 ± 5.90 ^{B1}	72.60± 3.13^{C1}	70.88 ± 1.47^{C1}	71.21 ± 4.72^{B1}	**HDL**
	14.73 ± 1.36^{A1}	17.69±2.72 ^{A1}	15.92±9.13 ^{A1}	14.21 ±7.21^{A1}	16.50±3.50^{AB1}	**LDL**
Group 2	80.44 ± 2.71 ^{A4}	20.21 ± 1.74^{A2}	32.25 ± 1.21^{B2}	49.40 ± 1.52 ^{B3}	71.30 ± 1.03^{B4}	**HDL**
	16.66 ±3.74^{A1}	83.17 ±6.13 ^{B4}	59.42 ±2.51 ^{B3}	37.75±3.33 ^{BC2}	22.17 ±5.31 ^{B1}	**LDL**
Group 3	72.92 ±4.16^{A4}	21.76 ± 1.31 ^{A1}	36.81 ± 6.76 ^{B2}	63.22 ± 7.21 ^{B3}	70.19 ± 4.06 ^{B4}	**HDL**
	13.10 ±1.02 ^{A1}	88.67 ±2.12 ^{B4}	60.31±3.53 ^{B3}	38.05 ±2.03 ^{B2}	11.10 ±3.50^{A1}	**LDL**
Group 4	83.45 ± 2.50 ^{A4}	28.10 ± 4.20^{A1}	39.63± 6.02 ^{B2}	57.80 ± 2.03 ^{B3}	79.39 ± 1.60 ^{B4}	**HDL**
	15.71±6.52 ^{A1}	80.92±3.35^{B4}	52.71 ±4.90 ^{B3}	34.13±7.04 ^{C2}	17.30±1.63 ^{AB1}	**LDL**
Group 5	76.42 ± 3.10 ^{A4}	23.46 ± 3.14^{A1}	42.61± 5.23 ^{B2}	65.11± 5.71 ^{B3}	78.25± 4.15^{B4}	**HDL**
	12.52 ±4.50^{A1}	78.82 ±1.46 ^{B4}	50.31 ±8.36^{B3}	31.68 ±9.31 ^{B2}	13.12±1.33 ^{AB1}	**LDL**
Group 6	78.15 ± 1.56 ^{A2}	25.79 ± 5.42 ^{A1}	21.31± 7.27^{A1}	23.87± 6.22 ^{A1}	19.68 ± 5.17 ^{A1}	**HDL**
	18.41 ±6.72^{A1}	85.65±1.74 ^{B2}	82.70 ±7.13 ^{C2}	87.16±1.59 ^{D2}	84.15 ±6.17^{C2}	**LDL**

Values are represented as Mean (±) standard deviation. Values with different figures as superscripts in a row differ significantly ($p \leq 0.05$). Values with different alphabets as superscripts for a parameter in a column differ significantly ($p \leq 0.05$

Table 5: Effect of oral administration of leaf extract on Triglycerides (TG) and total cholesterol (TC) of alloxan induced diabetic rats

GROUPS	BASELINE	AFTER INDUCTION	7 DAYS	14 DAYS	21 DAYS	TG/TC (mg/dl)
Group 1	74.67 ± 2.51^{A1}	73.28 ± 2.04 ^{A1}	75.90 ± 9.13 ^{A1}	72.13 ± 3.04 ^{A1}	76.30 ± 7.14 ^{A1}	**TG**
	102.60 ± 2.19^{A1}	99.18 ±4.32 ^{A1}	101.50 ±3.10 ^{A1}	104.50 ±4.21 ^{A1}	100.26 ±1.39 ^{A1}	**TC**
Group 2	71.70± 1.23^{A1}	109.00 ± 4.12^{B4}	103.10 ± 5.36 ^{B3}	89.21± 6.02 ^{B2}	75.16 ± 6.15 ^{A1}	**TG**
	96.67 ± 2.15 ^{A1}	132.71 ±2.19 ^{B3}	112.14 ±7.03 ^{B2}	105.98 ±3.12 ^{A1}	98.31 ±6.06 ^{A1}	**TC**
Group 3	68.16 ± 2.21 ^{A1}	115.4 ± 7.32 ^{B3}	99.87 ± 2.19 ^{B2}	77.62 ± 1.69 ^{B2}	66.20 ± 2.33 ^{A1}	**TG**
	108.20 ± 7.09 ^{A12}	128.21 ±9.12 ^{B4}	118.42 ±1.98 ^{B3}	112.64 ±3.34 ^{A2}	105.21 ±4.14 ^{A1}	**TC**
Group 4	73.32 ± 1.55 ^{A1}	118.30 ± 3.20 ^{B3}	97.96 ± 3.03 ^{B2}	89.52 ± 2.14^{B2}	72.23 ± 5.07^{A1}	**TG**
	101.70 ± 3.61 ^{A1}	126.26 ±2.13 ^{B3}	114.22 ±3.17 ^{B2}	107.51 ±5.12 ^{A12}	103.25 ±5.16 ^{A1}	**TC**
Group 5	77.32± 7.11 ^{A1}	108.63 ± 4.23 ^{B3}	96.66 ± 2.61 ^{B2}	85.16 ± 7.35 ^{B2}	76.21 ± 4.21^{A1}	**TG**
	105.26 ± 2.51^{A1}	122.43 ±1.20 ^{B2}	110.20 ±5.46 ^{B1}	104.27 ±3.35 ^{A1}	106.11 ±2.67 ^{A1}	**TC**
Group 6	76.21 ± 2.42 ^{A1}	104.21± 6.37 ^{B2}	109.45 ± 7.22 ^{C2}	111.62 ± 1.41^{C2}	108.32 ± 2.67 ^{B2}	**TG**
	99.78 ± 2.15 ^{A1}	130.40 ±3.37 ^{B2}	127.83 ± 6.71 ^{C2}	131.34 ±6.21 ^{B2}	133.22 ±7.31 ^{B2}	**TC**

Values are represented as Mean (±) standard deviation. Values with different figures as superscripts in a row differ significantly ($p \leq 0.05$). Values with different alphabets as superscripts for a parameter in a column differ significantly ($p \leq 0.05$)

The phytochemical constituents of *S. latifolius* could have contributed to the capacities of the plant extract to reverse diabetic dyslipidemia. Previous empirical investigations showed that phytochemicals such as saponins, flavonoids and tannins can ameliorate dyslipidemia [9,15]. The liver is severely damaged in patients with diabetes mellitus. These damages include abnormal liver enzymes levels, necrosis, inflammation, hepatocellular damage and acute liver failure. Liver enzymes are essential biomarkers in the body that are used to diagnose and measure whether the liver is functioning normally or not. Changes in liver enzyme levels are caused by major or subtle changes in the integrity of cellular membranes in liver tissues. Increased levels of ALP, AST, and ALT, as observed in the alloxan-induced diabetic rats are indicators of hepatocellular damage (Table 2 and 3), and it is mainly due to exudation of these enzymes from the cytoplasm of liver cells into the bloodstream[21,22]. Since these enzymes are undeniably, markers of liver injury, the elevated levels of these enzymes in diabetes conditions were attributed to harm induced to the hepatocytes by alloxan, which now disrupts the normal activities of the liver[23,24]. Following treatment with the plant extract, the activities of these marker enzymes were significantly reduced in the *S. latifolius* extract treated diabetic rats (Table 2 and 3), indicating the plant's hepatoprotective properties, which is consistent with some studies reporting the plant's hepatoprotective properties [20]. The ability of *S. latifolius* to exert a protective effect on the liver and lower the level of liver enzymes in the blood could be related to flavonoids' hepaprotective characteristics, which serve as membrane stabilizers to protect the liver cells from harm [25,26].

Table 2: Effect of oral administration of *S. latifolius* leaf extract on aspartate transaminase (AST) and alkaline phosphatase (ALP) of alloxan induced diabetic rats

GROUPS	BASELINE	AFTER INDUCTION	7 DAYS	14 DAYS	21 DAYS	AST/ALP (IU/L)
Group 1	66.28 ± 4.53^{A1}	62.71 ± 2.32^{A1}	64.49± 1.47^{A1}	70.21± 2.15^{A1}	63.26 ± 9.12^{A1}	**AST**
	84.23 ± 3.57^{A1}	87.56± 3.28^{A1}	86.22±2.02^{A1}	87.13± 2.91^{A1}	83.83 ± 2.11^{A1}	**ALP**
Group 2	70.69 ±3.06^{A1}	101.29 ±4.87^{B3}	91.41 ±2.61^{B2}	81.26 ±3.56 ^{C1}	75.18 ±2.24^{A1}	**AST**
	78.23 ±4.37^{A1}	137.31±2.21^{C4}	118.63±3.23^{B3}	108.41 ±1.55^{C2}	80.42 ±2.97^{A1}	**ALP**
Group 3	70.25 ±5.76^{A1}	103.45 ±8.04^{B3}	89.13 ±9.47^{B2}	72.62 ±2.41^{BC1}	68.84 2.90^{A1}	**AST**
	73.81 ±9.64^{A1}	125.21±6.44^{BC4}	113.74±2.69^{B3}	80.93 ±2.41^{BC2}	71.63 ±2.10^{A1}	**ALP**
Group 4	74.28 ±2.15^{A1}	111.50 ±3.00 ^{B3}	92.12 ±4.26^{B3}	72.40 ±9.22 ^{C2}	71.59 ±4.00 ^{A12}	**AST**
	89.19 ±8.12^{A1}	131.14±5.27^{C4}	112.70±8.00^{B3}	92.81 ±3.03^{C2}	85.26 ±5.74^{A1}	**ALP**
Group 5	72.65 ±5.96^{A1}	99.08 ±6.12^{B2}	83.28±2.35^{B2}	70.20 ±6.21^{B1}	71.54 ±5.69 ^{A1}	**AST**
	85.49 ±7.27^{A1}	123.50±2.92^{BC2}	112.63±6.00^{B2}	84.11 ±4.18^{AB1}	81.22 ±3.63^{A1}	**ALP**
Group 6	67.80±5.45^{A1}	106.40 ±5.77^{B2}	113.80±6.36^{C2}	108.50±4.76^{D23}	116.21 ±7.28^{B3}	**AST**
	80.90 ±4.15^{A1}	133.90±2.41^{B2}	126.20±6.17^{C2}	125.20 ±4.10^{D2}	131.54 ±5.14^{B2}	**ALP**

Values are represented as Mean (±) standard deviation. Values with different figures as superscripts in a row differ significantly ($p \leq 0.05$). Values with different alphabets as superscripts for a parameter in a column differ significantly ($p \leq 0.05$)

Table 3: Effect of oral administration of *S. latifolius* leaf extract on Alanine transaminase (ALT) of alloxan induced diabetic rats.

GROUPS	BASELINE	AFTER INDUCTION	7 DAYS	14 DAYS	21 DAYS	ALT (mg/dl)
Group 1	33.25±5.22^{A1}	36.80±3.15^{A1}	30.11±6.80^{A1}	28.39±7.20^{A1}	37.00±3.13^{A1}	**ALT**
Group 2	31.62±5.15^{A1}	68.78±1.73^{B4}	62.00±9.37^{B3}	51.00±3.10^{C2}	31.76±1.40^{A1}	**ALT**
Group 3	36.88±3.67^{A1}	73.41±6.80^{B4}	67.40±4.60^{B3}	42.76±4.50^{BC2}	34.28±2.50^{A1}	**ALT**
Group 4	34.22±2.03^{A1}	62.68±2.90^{B4}	51.20±7.20^{B3}	40.89±2.72^{C2}	32.56±3.86^{A1}	**ALT**
Group 5	40.05±5.27^{A1}	70.33±6.98^{B3}	59.60±3.61^{B2}	43.61±3.60^{AB1}	39.35±2.65^{A1}	**ALT**
Group 6	39.37±4.32^{A1}	66.37±5.16^{B2}	70.30±0.67^{C2}	73.22±2.13^{D2}	72.12±3.01^{B2}	**ALT**

Values are represented as Mean (±) standard deviation. Values with different figures as superscripts in a row differ significantly ($p \leq 0.05$). Values with different alphabets as superscripts for a parameter in a column differ significantly ($p \leq 0.05$)

In acute toxicity study, a scale proposed by [27] roughly classifies substances administered via the oral route according to their LD_{50} as follows: Very toxic (LD_{50}< 1.0 mg/kg bw), toxic (LD_{50} up to 10.0 mg/kg bw), less toxic (LD_{50} up to 100.0 mg/kg bw) and only slightly toxic (up to 1000.0 mg/kg bw). Substances with LD_{50} values greater than 5,000 mg/kg bw are practically non-toxic. Acute toxicity evaluation revealed that *S. latifolius* extract did not produce any mortality in the animals up to a dose of 5000 mg/kg. Hence LD_{50}> 5000 mg/kg. The high oral LD_{50} (> 5000 mg/kg) obtained suggested that the extract is practically non-toxic when administered via the oral route in ethnomedical use.

4. CONCLUSION

This study revealed that *S. latifolius* ethanolic extract have hypolipidemic, hypoglycemic and hepatoprotective effects in alloxan-induced diabetic rats. As a result, plant extracts may contribute beneficially in the treatment and management of diabetes mellitus and its associated complications. The plant extract was demonstrated to be non-toxic when taken orally in the acute toxicity study. However, more research on chronic toxicity is needed to determine the long-term effects of using this plant extract.

Declaration of Competing Interest

The authors declare no conflicts of interest.

Acknowledgement

The authors express their gratitude to Mr. Agbo Anthony of the Faculty of Veterinary Medicine, University of Nigeria, for his technical help.

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