

# In-Vivo Evaluation of Hypoglycemic Activity of Aqueous Extract of *Vernonia amygdalina* Leaf and its Formulation into Capsule Dosage Form

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## Article Info:

Received: November 2025

Accepted: December 2025

Published online:

February 2026

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## ABSTRACT:

Diabetes mellitus is a chronic metabolic disorder characterised by high blood sugar levels due to the body's inability to produce or effectively use insulin. This condition affects millions of people worldwide and can lead to serious health complications if not properly managed. This study evaluates the hypoglycemic activity of aqueous extracts of *Vernonia amygdalina* leaf and develops a capsule dosage form for its administration. *Vernonia amygdalina*, commonly known as bitter leaf, is widely used in traditional medicine, particularly for its purported antidiabetic properties. The research involved preparing aqueous extracts from the leaves and administering them to male albino Wistar rats to assess their impact on blood glucose levels. Antidiabetic efficacy was measured by comparing blood glucose levels in extract-treated, glibenclamide-treated, and untreated diabetic rats. Additionally, the study involved formulating the leaf extract into a capsule dosage form to enhance stability and patient compliance. The findings suggest that *Vernonia amygdalina* has significant hypoglycemic effects, supporting its use as a potential complementary treatment for diabetes mellitus. The encapsulation of the extract also proved to be a viable method for delivering the active components. This study contributes to phytomedicine by exploring alternative treatments for diabetes, highlighting the therapeutic potential of natural products.

**Keywords:** *Vernonia amygdalina*; Diabetes Mellitus; Capsules; Glibenclamide; Hypoglycemic.

**Please Cite this article as:** Shittu AO, Alimi MO, Njinga NS. In-Vivo Evaluation of Hypoglycemic Activity of Aqueous Extract of *Vernonia amygdalina* Leaf and its Formulation into Capsule Dosage Form. Int. Pharm. Acta. 2026; 9(1):e3.

DOI: <https://doi.org/10.22037/ipa.v9i1.51011>

## 1. Introduction

Diabetes mellitus is a chronic metabolic disease marked by abnormalities in insulin action, production, and metabolism that lead to persistent hyperglycemia, with fasting plasma glucose greater than 7.0 mmol/L or plasma glucose greater than 11.1 mmol/L 2 hours after a meal. An estimated 463 million individuals worldwide were anticipated to be affected by this global health issue in 2019, and forecasts for the next several years point to a continued rise in prevalence [1]. Diabetes mellitus is the third leading cause of death after heart attack and cancer [2]. The major types of diabetes mellitus are: Type 1 diabetes mellitus is an autoimmune disorder in which the body's immune system attacks and

destroys the insulin-producing beta cells in the pancreas. This leads to a complete lack of insulin production, typically diagnosed in children and young adults, but can occur at any age. Thus, lifelong insulin therapy is required for survival.

Type 2 diabetes mellitus is the most common form of diabetes, accounting for around 90-95% of all cases. It is characterised by insulin resistance, where the body's cells cannot effectively use the insulin produced by the pancreas. It is often associated with obesity, physical inactivity, and an unhealthy diet. It is often managed with lifestyle changes, oral medications, and, in some cases, insulin therapy. The insulin hormone facilitates the intracellular transport of glucose from the systemic circulation. The lack of this hormone leads to a buildup of sugar in the blood [3]. Polyuria, polydipsia, polyphagia, and

urinary tract infections are signs of hyperglycemia. These may lead to complications such as cardiovascular disease, nephritis, and retinopathy. Although there is currently no cure for the illness, it may be controlled and managed. Treatment aims to reduce or eliminate symptoms and prevent complications [4].

The pharmacological treatment of diabetes includes both insulin and oral glucose-lowering drugs such as sulfonylureas (glibenclamide, glimepiride, and glipizide), biguanides (metformin), meglitinides, alpha-glucosidase inhibitors, thiazolidinediones (pioglitazone), and, in some instances, complementary and alternative medicine. The management of diabetes mellitus also includes lifestyle modification. The difficulty of obtaining and affording these conventional treatments in developing nations prompted the search for suitable, effective natural substitutes.

Due to their hypoglycemic properties, more than 1,200 plants have reportedly been used in traditional medicine to manage diabetes mellitus [5].

Most plants have phytochemicals, such as flavonoids, tannins, and antioxidants, which stimulate and regenerate pancreatic beta cells. They improve glucose absorption in tissues and increase insulin secretion. Usually, combinations of these herbal therapies are used to manage the disease [5].

*Vernonia amygdalina* (*V. amygdalina*) is a member of the Asteraceae family and has small, stalk-like flowers and dark green leaves. This plant is mainly found in tropical Africa and is utilised as a vegetable and herb. It is commonly referred to as "Olugbu," "Ewuro," and "Fetefete" in the Igbo, Yoruba, and Hausa tribes of Nigeria, respectively [6]. It is commonly called a "bitter leaf" due to its characteristic bitter taste, which may be attributed to its anti-nutritional contents [7].

A variety of methods, including microwave-assisted extraction (MAE), Soxhlet extraction [8], liquid chromatography with tandem mass spectrometry (LCMS/MS) analysis [9], and others, have been used to extract and study these bioactive compounds. Lutein, luteolin 7-O- $\beta$ -glucuronide, and luteolin 7-O- $\beta$ -glucoside are among the flavones that were isolated from the flavonoids found in *V. amygdalina* [10].

Capsules are a pharmaceutical dosage form containing solid, liquid, or semi-solid active ingredients enclosed in a two-piece hard shell. The shell is made of gelatin or other suitable materials, and it is designed to protect the contents from moisture, light, and air, ensuring the stability and efficacy of the active ingredients. Capsules are commonly used for oral administration and offer several advantages over other dosage forms.

Additionally, capsules can mask the taste and odour of the active ingredients, making them more palatable for patients who have difficulty swallowing tablets or are sensitive to specific tastes or smells.

There are two main types of capsules: hard-shell and soft-shell. Hard-shell capsules are made of two halves that are snapped together to form a sealed unit. The contents of hard-shell capsules can be either powdered or pelletised, commonly used for dry, free-flowing materials. On the other hand, soft-shell capsules are made of a single piece of flexible material filled with a liquid or semi-solid formulation. Soft-shell capsules are often used for oily or viscous materials that cannot be easily encapsulated in a hard-shell capsule.

### Antiobesity effect

examined the antiobesity potential of *V. amygdalina* in diet-induced obese rats. They treated the rats with extracts of *V. amygdalina* at concentrations of 5% and 15%, along with a cafeteria diet. A control group on the cafeteria diet received 5.14 mg/kg of Orlistat. The study showed that the *V. amygdalina* treatment groups experienced reductions in body weight gain of 12.78% and 38.51%. Also, total body fat decreased by 28.04% and 30.02% in the 5% and 15% *V. amygdalina* groups, respectively. The intake of 15% *V. amygdalina* also led to decreased levels of serum triglycerides and total cholesterol in both the serum and brain [11].

Egedigwe et al. [12] also investigated the antiobesity effects of *V. amygdalina* in rats fed a high-fat diet. They administered aqueous extracts of *V. amygdalina* at doses of 100 mg/kg and 500 mg/kg body weight. The results indicated weight loss in the rats attributed to the phytochemicals in *V. amygdalina* and reduced insulin and leptin levels in the treated groups.

### Antidiabetic activity

Several studies have reported the antidiabetic activity of *V. amygdalina*. A study by Tekou et al. [13] showed that oral administration of *V. amygdalina* for four weeks improved type 2 diabetes in rats induced with streptozocin. IfedibaluChukwu et al. [14] also demonstrated that specific compounds isolated from methanolic extracts of *V. amygdalina*'s stem bark, such as 6 $\beta$ ,10 $\beta$ ,14 $\beta$ -trimethylheptadecan-15  $\alpha$ -olyl-15-O- $\beta$ -D-glucopyranosyl-1,5  $\beta$ -olide, significantly lowered blood glucose levels in rats with streptozocin-induced diabetes.

Erukainure et al. [15] observed that a hot water infusion of *V. amygdalina* leaves inhibited  $\alpha$ -glucosidase activity, reduced glucose absorption in the intestines, and improved muscle glucose uptake. Also, Ong et al. [16] demonstrated that the extract

protected  $\beta$ -cells, leading to increased insulin levels, and its beneficial impact on the antioxidant system contributed to its antidiabetic effects. *V. amygdalina* also enhanced glucose uptake in skeletal muscles by promoting the movement of GLUT 4 transporters (glucose transporter) to the cell membrane.

## 2. Materials & Methods

### 2.1. Chemicals and Materials

Glibenclamide tablet (Vixa Pharmaceuticals) was procured from PS General Drug Store; Streptozocin (ELK Biotechnology), citric acid monohydrate, trisodium citrate anhydrate, and Nicotinamide were obtained from Bridge Biotech Ltd, Ilorin; HPMC Hard Capsule Shell (Torpac Fairfield, USA); and starch. Fresh leaves of *Vernonia amygdalina* Del.

White albino male rats (*Rattus norvegicus*) was used as test animals. Equipments were glucometer, test strips (Finetest Auto-coding™ Premium, Infopia Co., Korea), water bath, analytical weighing balance, needle and syringe, and oral cannula. Beakers (Pyrex), measuring cylinders. Filter paper, animal cages, animal feeds, gloves, cotton wool, glucose-D, lancets, distilled water, Normal saline, and Methylated spirit.

### Collection of plant material

The fresh leaves of *Vernonia amygdalina* were obtained from an individual farm in the Basin area, at latitude 8.50744 ° N and longitude 4.59814 ° E, Ilorin, Kwara State, in April 2024. The leaves were identified and authenticated at the Department of Plant Biology Herbarium, University of Ilorin, Kwara State. A voucher specimen number was collected, UILH/001/972/2024.

### Preparation of leaf extracts

Large quantities of the fresh specimens of *V. amygdalina* leaves were separated from the stems and air-dried for seven days. The dried leaves were pulverised using a domestic blender. 150 grams of the powdered leaves were macerated in 500ml of lukewarm distilled water for 48 hours, then filtered through a muslin cloth; the filtrate was then collected on a number 1 Whatman filter paper. The filtrate obtained was concentrated in a water bath at 50 °C. The dried, concentrated extract was then used to formulate the granules.

The percentage yield was determined according to the formula;

$$\% \text{ Yield of } Vernonia \text{ amygdalina} = \frac{\text{Weight of extract}}{\text{Weight of plant leaves}} \times 100$$

### Induction of diabetes mellitus

Streptozocin-nicotinamide was used to induce hyperglycemia in male albino Wistar rats. Nicotinamide (95mg/kg) was dissolved in saline solution and injected intraperitoneally 15 minutes before the administration of streptozocin.

Streptozocin 50mg/kg was dissolved in citrate buffer (0.01M, pH 4.5) and administered intraperitoneally. The citrate buffer was prepared by dissolving 1.05g of citric acid monohydrate into 50 ml of distilled water and 1.47g of trisodium citrate monohydrate in 50 ml of distilled water. The solutions were added together to obtain the citrate buffer. The injected rats were returned to their cages and given a 5% glucose solution for 6 hours to overcome Streptozocin-induced hypoglycemia.

### Animals

A total of 24 adult albino male rats (100g-150g) were used for the study. The animals were obtained from an animal house in Ibadan. The animals were acclimatised for 7 days and housed under standard laboratory conditions (29 ± 2°C, 40-45% humidity and good ventilation). The rats had free access to water and a diet *ad libitum* before the commencement of the experiment. The ethical regulations, following National and Institutional guidelines for animal welfare, were strictly adhered to during the experiment.

### Experimental Design

The twenty-four (24) rats were randomly assigned to six groups of four animals each.

The animals received treatment as follows:

**Group A:** Normoglycemic, untreated control rats orally treated with 10mg/kg/day of distilled water.

**Group B:** Hyperglycemic rats were orally treated with 0.5ml of distilled water as a control group.

**Group C:** Hyperglycemic rats were orally treated with 1mg/kg/day of glibenclamide.

**Group D:** Hyperglycemic rats were orally treated with 100mg/kg/day of *Vernonia amygdalina*.

**Group E:** Hyperglycemic rats were orally treated with 200mg/kg/day of *Vernonia amygdalina*.

**Group F:** Hyperglycemic rats were orally treated with 300mg/kg/day of *Vernonia amygdalina*.

The daily oral treatment was given from 10 to 11 a.m. for 14 days, using distilled water at 100mg/ml as the vehicle.

### Determination of blood glucose

The test animals' blood glucose was determined using a glucometer (Finetest glucometer). Blood samples were collected using a lancet to puncture the animals' tail veins and added to the test strip to determine blood sugar with the glucometer. The glucose levels were determined every 2 days of treatment with the leaf extract for up to 2 weeks. Hence, 0, 2, 4, 6, 8, 10, 12, 14.

### Determination of body weight

The weight of the Wistar rats was determined and recorded every 2 days for 14 days using a weighing balance. The weights of the rats were recorded in grams and expressed as mean  $\pm$  standard error of mean (SEM).

### Statistical analysis

The data were summarised as mean  $\pm$  standard error of mean (SEM). The data were analysed using a Two-Way ANOVA followed by Dunnett's multiple comparisons test, performed in GraphPad Prism version 10.2.3 (430) for Windows (GraphPad Software, Boston, Massachusetts, USA). Results were considered statistically significant when  $p < 0.05$ . The mean  $\pm$  SEM of the blood glucose and body weight was recorded in mg/dl and grams (g), respectively.

### Preparation of *Vernonia amygdalina* leaf extract granules

The aqueous leaf extract granules were prepared by adding starch as the bulking agent to the concentrated leaf extract. The starch was added in geometric proportions to obtain granule particles. The mixture was then dried using a water bath to obtain dry granules. The granules obtained were weighed, and the percentage concentration of the extract in the triturate (48%) was obtained. The granules were then transferred to an airtight container and labelled accordingly.

### Preformulation studies

Preformulation studies were carried out to investigate the physicochemical characteristics of *V. amygdalina* granules. The overall objective of preformulation testing was to generate information useful for developing a stable dosage form.

### Angle of Repose

A funnel was kept vertically in a stand at a specified height above a paper placed on a horizontal surface. The funnel bottom is closed, and 10 g of sample powder (*V. amygdalina* granules) is filled in the funnel. Then, the funnel was opened to release the powder onto the paper, forming a smooth conical heap, as measured in different directions. The heap's height was measured with a scale. The value of the angle of repose is calculated by using the following formula:

$$\tan \theta = h/r \quad 2$$

Where h is the height of the heap and r is the radius of the heap.

### Bulk Density

A known quantity of powder was carefully poured into the measuring cylinder. The *V. amygdalina* was levelled without compacting, if necessary, and read the unsettled apparent volume,  $V_o$ , to the nearest graduated unit. Bulk

density was calculated in g/mL using the following formula:

$$\text{Bulk density of } V. amygdalina = \text{mass/Volume} \quad 3$$

### Encapsulation procedure

The encapsulation process of *V. amygdalina* dry aqueous leaf extract granules was carried out by weighing and transferring 625mg of the granules into a Hydroxymethylcellulose (HPMC) Hard capsule shell using a manual capsule-filling machine, size 00. The empty capsules were filled into the loading tray and placed over the bed. By opening the handle, the bodies of the capsules were locked, and caps were separated in the loading tray itself, which is then removed by operating the lever. The weighed amount of the *V. amygdalina* granules to be filled into the capsules positioned over the bed. The granules were spread using a powder spreader to fill the capsules uniformly, resulting in 100 capsules. The excess granules were collected on the tray's platform. The pin plate was lowered downward to press the powder into the bodies. The powder tray was removed, and the caps on the holding tray were in position. The caps were pressed with the help of a plate with a rubber top, and the lever operated to unlock the capsules. The loading tray was removed, and the filled capsules were collected in a tray. 625mg of the granules is equivalent to 300mg of the aqueous leaf extract of *V. amygdalina*. The encapsulated product was transferred into an appropriate container for storage and labelled correctly (Tables 1 and 2).

**Table 1.** Description and size of capsules.

| Description                         | Size '00' VEG         |
|-------------------------------------|-----------------------|
| Capsule body capacity               | 0.93 ml               |
| Fill weight                         | 750 mg                |
| External diameter maximum           | 2.65 mm               |
| Length when locked maximum          | 23.6 mm               |
| Weight empty (cap and body) average | 17 mg                 |
| Colours available                   | Clear and transparent |

**Table 2.** Table of formulation of *V. amygdalina* capsules.

| Ingredients          | mg/capsules | g/100 capsules |
|----------------------|-------------|----------------|
| <i>V. amygdalina</i> | 300 mg      | 30 g           |
| Starch               | 325 mg      | 32.5 g         |

### Quality Control Parameters for Capsule

Each formulated capsule contains 625mg of the granules, which is equivalent to 300mg of the dry aqueous leaf extract of *V. amygdalina*.

### Determination of Moisture Content

The test was performed using the KF instrument by Electro Lab. The sample was prepared by mixing the contents of four capsules. For low water concentrations (< 0.1 %), a titrant with a factor of < 5 mg/mL is recommended. An alternative to direct volumetric titration is both the external extraction as well as the KF oven technique: during external extraction, the sample is dissolved; during analysis by the KF oven technique, the water is released by heating the sample to an appropriate temperature and then transferred into a volumetric cell.

### Determination of pH

The solution's pH value was determined potentiometrically using a glass electrode, a reference electrode, and a digital pH meter. The meter was operated according to the manufacturer's instructions. First, the apparatus was calibrated with buffers at pH 4, 9, and 7. One empty capsule was taken and dissolved in 100 ml of demineralised water. The electrodes were immersed in the solution, and the pH was measured.

### Uniformity of Weight

Twenty filled capsules were randomly selected and weighed to determine the average weight, which was then compared with the individual capsule weight. The percentage weight variation was calculated.

### Disintegration Test for Capsule

The disintegration test was performed using the Eweka disintegration test apparatus. One capsule was added to each tube, and a disc was added to each.

The apparatus was operated and maintained at  $37.50 \pm 0.5^\circ\text{C}$ . The time taken for each capsule to dissolve and release the particles to pass through the wire mesh was recorded as the disintegration times.

## 3. Results & Discussion

Streptozocin- Nicotinamide induced hyperglycemia in rats. The percentage yield of *V. amygdalina* leaf extract was 8.67 % w/v. The aqueous leaf extract caused a significant ( $p < 0.05$ ) reduction in blood glucose levels in treated rats compared with the diabetic control and glibenclamide-treated groups. This reduction was also comparable to that in the normoglycemic group (Figure 1). Also, the extract-treated groups showed a significant ( $p < 0.05$ ) increase in weight compared with the normoglycemic and diabetic control groups. The disintegration time for the capsules was obtained to be 10 minutes (Tables 3 and 4).

Diabetes mellitus is a significant burden, particularly in developing economies, and is characterised by high blood sugar levels. This condition disrupts the metabolism of carbohydrates, fats, and proteins due to

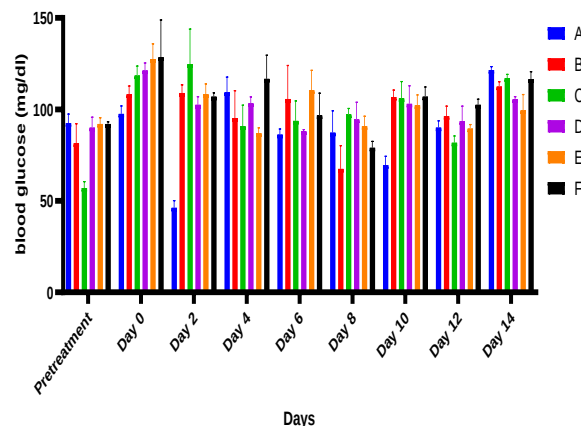


**Figure 1.** Effect of glibenclamide and *V. amygdalina* on blood glucose levels of diabetic Wistar rats. in mg/dl.

Keys: Normoglycemic (A), Streptozocin (B), Glibenclamide (C), *Vernonia amygdalina* 100 mg/kg (D), *Vernonia amygdalina* 200 mg/kg (E), *Vernonia amygdalina* 300 mg/kg.

**Table 3.** Evaluation parameters for *V. amygdalina* dry aqueous leaf extract powder.

| Parameters            | Values       |
|-----------------------|--------------|
| Flow Rate             | 0.28 g/sec   |
| Angle of Repose       | $30.5^\circ$ |
| Bulk Density          | 0.49g/ml     |
| Tapped Density        | 0.53 g/ml    |
| Compressibility index | 1.1          |

**Table 4.** Drug release profile of *V. amygdalina* capsules.

| Weight of capsule $\pm$ gm | Disintegration Time (min.) n=3 | Content Uniformity n=3 | Dissolution $T_{90}$ % (min.) |
|----------------------------|--------------------------------|------------------------|-------------------------------|
| $0.625 \pm 0.045$          | $17.0 \pm 2.5$                 | $98.5 \pm 0.5$         | $25.0 \pm 2.0$                |

issues with insulin secretion or action. It is a widespread disease, especially prevalent in Africa [17, 18]]. Uncontrolled high blood sugar can lead to increased production of free radicals, such as reactive oxygen species (ROS) and nitrogen oxides (NOx), which can further damage tissues [19].

Many traditional plant treatments have been used to manage diabetes. Scientific research has shown that several of these herbal remedies possess properties that can counteract diabetes and its complications [20]. The therapeutic properties of these plants are attributed to the bioactive compounds they contain. Studies by Akoko et al. [21] and Asante et al. [22] have specifically highlighted the antidiabetic effects of *Vernonia amygdalina* in diabetic rat models. Monitoring blood

glucose levels is crucial in assessing glycemic status, as elevated levels are a hallmark of diabetes and can lead to various health complications.

The study investigated the effects of *Vernonia amygdalina* leaf extract on diabetic Wistar rats over 14 days, focusing on body weight and blood glucose levels. The blood glucose levels decreased significantly in the *V. amygdalina*-treated groups, with reductions comparable to those in the normoglycemic control group. The groups receiving 100 mg/kg, 200 mg/kg, and 300 mg/kg of extract showed 13%, 21.96%, and 28% reductions in blood glucose, respectively. The decrease observed was dose-dependent, with the highest dose yielding results similar to those of the standard antidiabetic drug glibenclamide. Previous studies, such as those by Asante et al. [22] and Atangwho et al. [11], have demonstrated the plant's ability to lower blood sugar levels and improve insulin sensitivity. Ong et al. [16] demonstrated that *V. amygdalina* protects pancreatic  $\beta$ -cells, thereby increasing insulin levels. They also noted that the plant enhances the body's antioxidant system, which may contribute to its antidiabetic properties.

Additionally, their study highlighted that *V. amygdalina* facilitates glucose uptake in skeletal muscles by promoting the movement of GLUT4 transporters to the cell surface. Similarly, Michael et al. [23] found that combining *V. amygdalina* extract with metformin effectively treated diabetes induced by alloxan in mice. This suggests that *V. amygdalina* could be used alongside conventional diabetes treatments for better efficacy. Wu et al. [24] provided further evidence of the plant's antidiabetic potential, showing that treatment with different doses of *V. amygdalina* (50, 100, 150 mg/kg) over six weeks significantly lowered fasting blood glucose levels. They also observed improved glucose and insulin resistance, increased adenosine monophosphate kinase activity, and decreased activity of critical enzymes involved in glucose production. These consistent findings across multiple studies reinforce the efficacy of *V. amygdalina* in managing diabetes. The present study's results, which showed a significant reduction in blood glucose levels and improved metabolic outcomes in diabetic rats, align well with these earlier reports.

Additionally, all groups experienced weight gain, with the *V. amygdalina*-treated groups showing a greater increase than the normoglycemic and hyperglycemic control groups. This suggests that the extract positively affects weight gain. The *V. amygdalina*-treated groups also showed a greater weight increase than the glibenclamide group, suggesting that the plant extract may offer additional benefits, such as preventing diabetic-associated weight loss.

Formulating the leaf extract into capsules may further enhance the plant's stability and bioavailability, offering

a more practical and potentially more effective treatment option for diabetes management.

#### 4. Conclusion

The study concludes that *Vernonia amygdalina* leaf extract has beneficial effects on both weight gain and blood glucose reduction in diabetic rats. The plant extract may serve as a potential natural treatment for diabetes, offering advantages over glibenclamide, particularly in preventing weight loss associated with the disease. Diabetes mellitus, characterised by hyperglycemia, can lead to various metabolic disturbances and complications. While traditional plant treatments have been used to counteract these effects, scientific research has validated the therapeutic properties of many of these remedies, including *V. amygdalina*. Also, encapsulating the leaf extract is a strategic approach that enhances its stability and bioavailability, paving the way for the development of innovative delivery systems and ensuring optimal efficacy and patient compliance.

#### Acknowledgements

None.

#### Conflict of interest

There is no conflict of interest.

#### Funding

This study has no specific Fund.

#### Ethical statment

Approval for the use of test animals was requested from the University of Ilorin's ethical review committee (FPS-ERC ASN/2023/6).

#### Author contribution

Abiodun Oyetunji Shittu: Conception and design of the study, drafting of article, data analysis.

Mariam Opeyemi Alimi: acquisition of data.

Ngaitad Stanilaus Njinga: revising the article for intellectual content.

#### Using AI declarations

The authors declare that no artificial intelligence (AI) tools or technologies were used in the writing, editing, or preparation of this manuscript.

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