Biochemical and Histopathological Studies on the Efficacy of Camel Milk and Urine against Alloxan Induced Diabetic Rats

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Authors' contributions

This work was carried out in collaboration among all authors. Author AML performed data mining and all experimental work. Author ZS helped author AML in experiments and manuscript writing. Authors ZHB, SMS and HJB managed the analyses of the study and literature searches. All authors read and approved the final version of the manuscript.

Article Information

Original Research Article

ABSTRACT

Background: Camel urine has been extensively used for the treatment of diseases including cancer. However, it uses in the management of diabetes complication has not been explored.
Aim: Present study aimed to access the effect of camel milk and urine on biochemical parameters and histopathological alterations of the liver in alloxan induced diabetic rats.
Methodology: Twenty-five male albino rats were divided into five groups; group 1 served as the Nondiabetic (NDC), group 2 as Diabetic control (DC), group 3, 4 and 5 are animals treated with camel milk (DCM), camel urine (DCU) and metformin (DM) respectively. The treatment was for twenty-one days. The protective role of camel milk and urine was evaluated by determining biochemical parameters and also by studying the histopathological alterations of the liver.
Results: The results indicate a significant increase ($P<0.05$) in aspartate aminotransferase (AST), alanine aminotransferase (ALT) and total protein (TP) in DC rats compared to NDC. However,

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nosignificant difference was observed in the serum level of alkaline phosphate (ALP) between NDC and DC groups (P <0.05). Treatments of diabetic rats with either camel milk, camel urine or metformin significantly (P <0.05) serum activities of AST, ALT and TP. The results of lipid profile show that pretreatment of diabetic rats with camel milk or urine significantly (P<0.05) decreases serum levels of triacylglycerol (TG), low density lipoprotein cholesterol (LDL-C) compared to diabetic control group compared to DC group. Moreover, high density lipoprotein cholesterol (HDL-C) increased remarkably in the groups treated with CM, CU and metformin respectively. Histopathological studies of the liver revealed that all the severe endocrine changes in the endocrine part and localized necrosis present in DC are absent in the Diabetic treated with camel milk (DCM), Diabetic treated with camel urine (DCU) and Diabetic treated with metforming (DM) groups.
Conclusion: Treatment with camel milk or urine has the potential to delay the onset of diabetic complications.

1. INTRODUCTION

Diabetes Mellitus is a metabolic disorder in which there is relative or absolute deficiency of insulin, or resistance of organs to the effect of insulin. It is a condition characterized by disturbances in carbohydrate, lipid and protein metabolism resulting in the elevation of blood glucose, it's also a very serious disease affecting human health and in advanced stages is accompanied by general weakness and alteration in fats, protein and carbohydrates metabolism [1]. The incidence of diabetes has increased dramatically in recent decades. Predominantly due to changes in lifestyle and the increase in the prevalence of obesity in individuals [2,3]. it has been predicted that by the year 2040 the number of diabetes cases would rise to over 640 million [4].

Diabetes is one of the most prevalent and serious chronic diseases to human in nearly all countries. It is the leading cause of new cases of blindness in the world and each year about 12,000 to 24,000 people lose their sight because of Diabetes Mellitus and the leading cause of blindness in adults of about 20-71 years old [5]. In 2011, the disease affected 366 million people worldwide of which 1.6 people lost their lives, the number is expected to have risen to about 552 million by 2030 [5]. Oxidative stress [6], genetic and environmental factors [7], are attributed to the pathogenesis of Diabetes Mellitus. family background, overweight, lack of exercise and poor diet are also key factors that cause Diabetes Mellitus. Its symptoms include; frequent urination, excessive thirst, extreme hunger, unexplained weight loss, increased fatigue, blurred vision, itching of the private parts in women, slow healing of cuts and wounds, presence of ketones in the urine, frequent infection, such as gums or skin infection and vaginal infections, impotence-failure to sustain an erection [8]. It is associated with many consequences such as Kidney damage, coronary artery, heart and peripheral vascular diseases, atherosclerosis, hyperlipidemia, eye damage and obesity if left untreated [9]. Insulin injection has been one of the main treatments for diabetes. However, some patients have a phobia for injection. Hence, they prefer treatment with fewer or no side effects. In the last decade, research has focused on providing a suitable means for insulin delivery [10].

Camel milk (CM) can serve as an alternative due to its insulin like protein which does not coagulum in the stomach acid environment [11]. It has been used as an adjunct to insulin therapy [12]. CM has been used as food for the management of diseases particularly, diabetes [13]. Previous studies showed that CM improves glycemic content and reduces insulin resistance in diabetic patients [14–16]. The presence of essential minerals and vitamins enables CM to be used as an anti-inflammatory, antidiabetic, hepatoprotective and cardio-protective food [17–19]. It has been shown throughout the history of medical science till today that CM has a profound medical use such as effectiveness against allergies, skin conditions, fever, burns, tuberculosis and fertility [20]. Camel urine (CU) has been reported to contain no ammonia and it has very slight trace urea compared to other animals including humans, these molecules are responsible for bad smell and toxicity of urine [21]. Invitro studies also displayed anticancer properties of camel urine [22]. Camel urine has been reported to be a strong repressor of platelets, like inhibiting both prostaglandin and adenosine diphosphate receptor (ADP) mediated pathway [23]. Increasedplatelet counts has been

seen in diabetic patients with a long duration of the disease [24]. This is a strong indication that camel urine could be a potential candidate for the treatment of diabetes and its complications. The antidiabetic effect of CM and CU has not been fully explored, moreover to the best of authors' knowledge no study has established the antidiabetic effect of camel urine. Therefore, this study aimed at determining the protective effect of CM and CU on liver function biomarker, lipid profile and histopathological alterations of the liver in alloxan induced diabetic rats.

2. MATERIALS AND METHODS

2.1 Collection of Samples

The fresh CM and CU were collected daily early in the morning from Moree camel farm in Sokoto Nigeria. Healthy camels with no visible signs of any illness were hand-milked on an early morning. Milk and urine were collected in sterilized screw bottles and were immediately placed on ice and then transported to the laboratory and were administered to the experimental animals.

2.2 Experimental Design

Twenty-five healthy albino rats (average weight 100g) were purchase from faculty of pharmacy UsmanuDanfodio university teaching hospital Sokoto Nigeria. The animals were housed in rubber cages in an air-conditioned room at 21-23°C and 60-65% relative humidity and kept on a 12hours light/dark cycle under standard conditions. They were maintained on standard pellets and water *ad libitum*. The animals were acclimatized for 14 days before the commencement of the experiment subsequently the animals were grouped into five groups of five (5) rats per each group (Table 1).

2.3 Induction of Diabetes Mellitus and Treatments

Alloxan (powder from B.D.H chemical LTD, England) was dissolved in distilled water prepared. Diabetes was induced in rats (except NDC) by giving intraperitoneal freshly prepared alloxan solution 120 mg/kg body weight. after three days, the blood glucose level was determined by glucometer. Rats with a blood glucose level of 200 mg/dl and above are considered diabetic and are included in the study. The animals were fed daily with either CM or CU (1 ml/24hrs/cage) for 21 days. DM group received 500 mg/ b.wt of metformin for the same duration.

2.4 Biochemical Analysis

At the end of 21 days, the animals were sacrificed by anaesthetizing the animal with chloroform. The blood sample was collected via cardiac puncture. the blood samples were collected in a plain container and centrifuged at 3000rpm for 20 minutes. The Serum samples were used to analyzed liver function biomarkers and lipid profile (Aspartate transaminase (AST), Alanine transaminase (ALT), Alkaline phosphatase (ALP), Total protein (TP), Total Cholesterol (TC), Low density lipoprotein cholesterol (LDL-C, Hight density lipoprotein cholesterol (HDL-C) and triacylglycerol (TG).

2.5 Estimation of Serum AST and ALT Level

For the estimation of serum AST and ALT, a reagent blank was made by mixing 0.5 ml of reagent 1 with 0.1 ml of distilled water. While sample test tubes were prepared by mixing 0.5 ml of reagent 1 with 0.1 ml each of serum samples. The solutions were incubated for 20 minutes at 37°C. This was followed by 0.5 ml of

Table 1. Rats grouping and type of treatment

Group	Title	Treatment
NDC	Non-diabetic control (Normal)	standard feed+ Water ad libtinum
DC	Diabetic Control	standard feed+ Water ad libtinum
DCM	Diabetic treated with CM	standard feed+ 0.2 ml Kg^{-1} BW day^{-1} of CM+ water libitum
DCU	Diabetic treated with CU	standard feed+ 0.2 ml Kg-1 BW day^{-1} of CU+ water libitum
DM	Diabetic treated with metformin	Standard feed + 500 mg/ b.wt of metformin water libitum

reagent 2 in both reagent blank and sample test tubes. The mixture was allowed to stand for 20 minutes at room temperature. Finally, 5 ml of sodium hydroxide was added to terminate the reaction. The absorbance of the sample was read against the reagent blank after 5 minutes at 546 nm [25].

2.6 Determination of Serum ALP Level

0.5 ml of alkaline phosphatase substrate was added into each test tubes and equilibrated to 37°C for 3 minutes. At timed intervals, 0.05 ml of each standard, control, and sample were added to test tubes mixture were mixed gently. Distilled water was used as a sample for reagent blank. The mixtures were incubated for 10 minutes at 37°C and 2.5 ml alkaline phosphatase color developer was added to all test tubes and it was mixed. The absorbance of the colored solutions was measured at 590 nm [26].

2.7 Determination of Serum TP

For estimation of total protein. 0.02 ml of each of distilled water, standard and serum were dispensed into the labelled test tubes accordingly, and the 1 ml of TP standard was added to each of the labelled test tubes. The solutions were incubated for 30 miutes at room temperature. Samples absorbance was measured against reagent blank at 540 nm.

2.8 Determination of Lipid Profile

TC was estimated by cholesterol oxidase/peroxidase method (Trinder,1969). TG was determined using enzymatic method as described by (Trinder,1969). HDL– C was determined as described by Burstein (1979). LDL–C and VLDL–C were determined by Friedewald formulae (Friedewald et al.1999).

2.9 Histopathological Studies of the Liver

Liver specimens were collected from all five groups of rats after they were anaesthetized with chloroform, and fixed in 10% buffered formalin. The tissues were embedded in paraffin wax sectioned at 5 µm and were stained routinely with Hematoxylin and Eosin (H & E) using Mayer's Hemalum. Stained sections were examined for histological changes using light microscopy.

2.10 Statistical Analysis

The data analysis was performed using *in vivo* Stat. Before the analyses, a Normality test was perform using a Shapiro-Wilk test. The statistical significance was determined using ANOVA test and specific comparisons were made by the Tukey's Honestly Significant Difference (HSD) test with *p* < 0.05 considered as significant.

3. RESULTS AND DISCUSSION

3.1 Results

3.1.1 Effect of camel milk and urine on biochemical parameters

There was a significant difference ($P<0.05$) in serum level of AST, ALT and TP of DC rats when compared with NDC, while there is no significant difference ($P <0.05$) in serum level of ALP between NDC and DC (Table 2). All the liver function biomarkers analyzed in the present study (AST, ALT, ALP and TP) were remarkably higher in DC compared to DCM and DCU (Table 2) ($P <0.05$). Similarly, there was an appreciable difference in serum AST level in DCU compared to DCM and DM. On the other hand, serum activity of ALT was reasonably lower in DCM compared with respective groups ($P <0.05$). Moreover, no meaningful difference ($P <0.05$) in the serum of ALP in comparison to DCM and DCU. Nonsignificant difference ($P <0.05$) in the serum level of TP among NDC, DCM, DCU and DM (Table 2).

3.1.2 Effect of Camel milk and urine on lipid profile parameters

The results indicated that the treatment of diabetic rats with CM or CU significantly decreases serum level of TG ($P <0.05$) compared to DC group. TC, HDL-C and LDL-C significantly ($P <0.05$) increased as a result of treatment wither either CM or CU when compared with DC group. Moreover, the serum level of all the lipid profile analyzed in this study was remarkably higher in the treated groups (DCM and DCU) compared to NDC ($P <0.05$).

3.1.3 Effect of camel milk on the histopathology of the liver

The histopathological studies of the liver revealed that in untreated normal rats (NDC) it indicates a normal distribution of hepatocyte and normal orientation of sinusoid with a normal clear central vein (Fig. 1a). Induction of diabetes by alloxan result in severe necrotic cells with a congested central vein in the localized area

indicating that alloxan damages the hepatocyte (Fig 1b). Treatment of diabetic rat with CM reduces localized necrotic cells and it also clears the central vein, the hepatocyte looked active and healthy with active vesicular nuclei similar to those observed in the NDC (Fig 1c). However, treatment with CU results in a normal distribution of hepatocyte with slight disorientation of sinusoid and slight congested central vein (Fig 1d). Moreover, treatment of diabetic rats with metformin indicates a normal distribution of hepatocyte with a prominent orientation of sinusoid and normal clear central vein similar to that of NDC and DCM.

3.2 Discussion

In the present study, the protective role of CM and CU on preventing the onset of diabetic complications was evaluated by analyzing the biochemical biomarkers and observing the histopathology of the liver against alloxan induced diabetic rats. Liver is one of the important organs that are well known to be affected by diabetes [27]. Biochemical changes that reflect function of the hepatocyte were performed in this study. These include AST, ALT, ALP and TP. The liver function test revealed a significant increase in serum AST, ALT and TP

Table 2. Liver function of different groups of rats during the experiment and after the induction of diabetes by alloxan

Rats groups	Aspartate AminoTransferase (U/L)	Alanine Amino Transferase (U/L)	Alkaline Phosphatase (U/L)	Total Protein (U/L)
Group 1: Nondiabetic control (NDC)	117.28 ± 1.10[a]	62.50 ± 0.50[a]	212.8 ± 0.73[a, c]	3.85 ± 0.25[a]
Group2: Diabetic control (DC)	151.21± 0.18[b]	84.50 ± 1.10[b]	217.38 ± 0.80[a]	8.09 ± 0.23[b]
Group 3: Diabetic and camel milk (DCM)	98.81 ± 3.73[c]	38.60 ± 0.678[c]	190.80 ± 1.83[c]	4.33 ± 0.17[a, c]
Group 4: Diabetic and camel milk urine (DCU)	114.30 ± 10.38[a]	63.20 ± 2.24[a]	62.80 ± 1.88[c]	5.29 ± 0.42[c]
Group 5: Diabetic andmetformin (DM)	82.89 ± 1.66[e]	74.50± 1.12[a, b]	313 ± 1.26[d]	4.36 ± 0.57[a, c]

Data was expressed as mean±standard error of mean (SEM). Values with different superscript are significant at P <0.05

Table 3. Lipid profile of different groups of rats during the experiment and after the induction of diabetes by alloxan

Rats groups	Total Cholesterol (mmol/L)	High-density lipoprotein (mmol/L)	Low-density Lipoprotein (mmol/L)	Triacylglycerol (mmol/L)
Group 1: Nondiabetic control (NDC)	184.9 ± 1.09[a]	128.350 ± 0.82[a]	28.30 ± 2.53[a]	139.2 ± 0.62[a]
Group2:Diabetic control (DC)	74.98 ± 1.00[a, b]	103.90 ± 1.17[b]	119.65 ± 1.38[b]	259.55 ± 1.36[b]
Group 3: Diabetic and camel milk(DCM)	247.98 ± 1.20[c]	194.18 ± 1.71[c]	16.58 ± 3.75[c]	186.25 ± 0.78[c]
Group 4: Diabetic and camel milk urine (DCU)	262.52 ± 1.70[d]	164.57 ± 1.43[d]	55.05 ± 2.00[d]	187.77 ± 1.38[c]
Group 5: Diabetic andmetformin (DM)	249.95 ± 1.05[bc]	209.18 ± 0.52[e]	11.38 ± 0.58[e]	147.45 ± 1.24[d]

Data was expressed as mean ± standard error of mean (SEM). Values with different superscript are significant at P <0.05
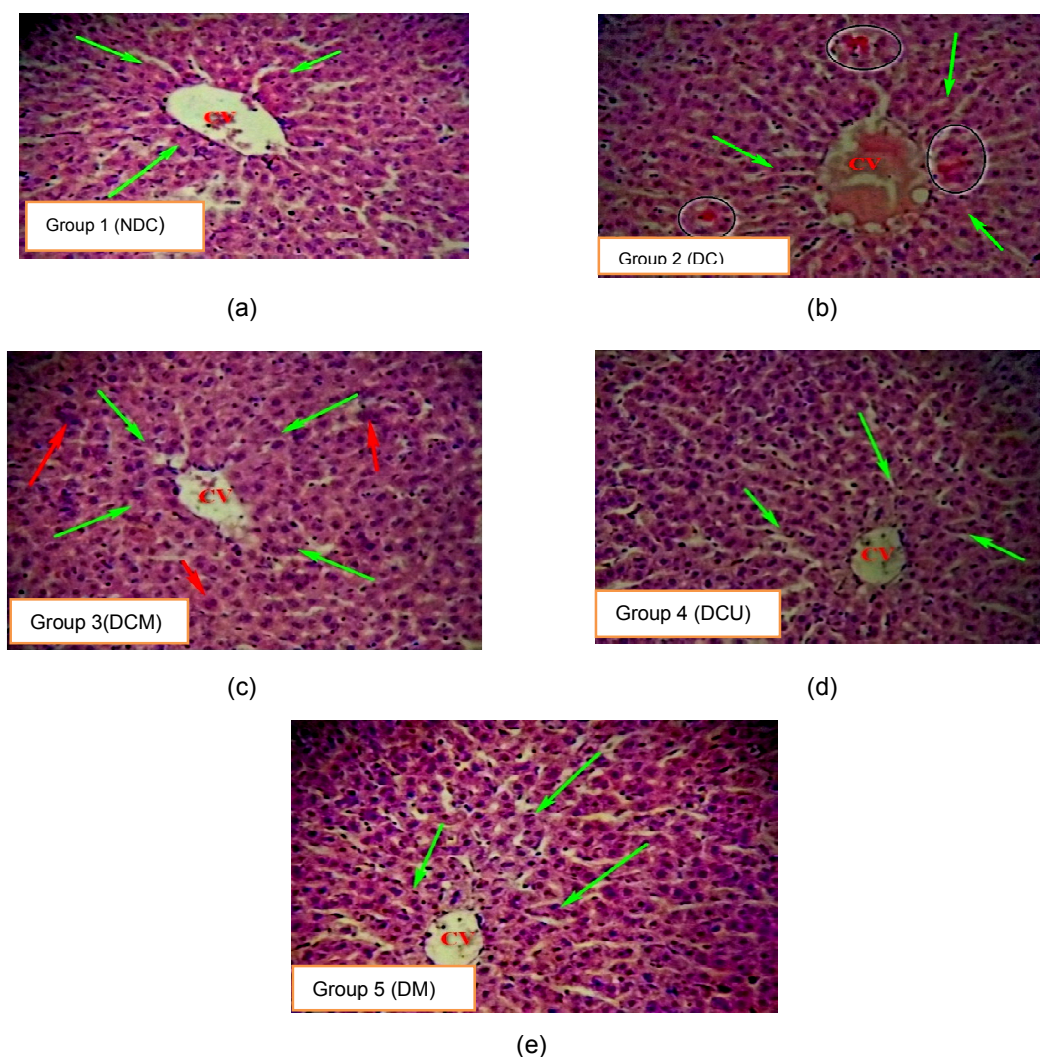
Fig. 1. Photomicrographs of a section of the rats liver: (a—group 1: NDC) normal distribution of hepatocyte with a normal orientation of sinusoid (green arrow) and a clear normal central vein (CV). (250 x magnification. (b—group 2: DC) normal distribution of hepatocyte with a normal orientation of sinusoid (green arrow), localized area of severe necrotic cells (black circle) with a congested central vein (CV) (250 x magnification). (c—group 3: DCM) normally distribution of hepatocyte with a normal orientation of sinusoid (green arrow), minimal localized necrotic cells (red arrow) and a clear normal central vein (CV) (250 x magnification). (d—group 4: DCU) normal distribution of hepatocyte with slight disorientation of sinusoid (green arrow) and slight congested central vein (CV) (250 x magnification). (e—group 5: DM) normal distribution of hepatocyte with a prominent orientation of sinusoid (green arrow) and normal clear central vein (CV) (250 x magnification)

activities in DC compared to NDC. An increase in aminotransferases activities is a good signal of mitochondrial and/or cytoplasmic membranes damage. Increased serum transaminase levels is an indicator of liver cells damage induced by drug or toxin [28]. Increase in serum activities these enzymes observed in this study may be as a result of damage to the hepatocyte by the alloxan which is probably diabetic induced hepatic damage. AST and ALT are the best hepatic damage biomarkers in which their elevated levels indicate damage to the hepatocyte. We observed that treatment with either CM or CU significantly reduces the elevated serum activities of AST and ALT. This may be as result of repairing of damaged hepatocyte by the CM and CU. The ability of these enzymes (AST, ALT and TP) to bounce

back to normal levels in the treated groups (DCM, DCU and DM) is a clear indication of protective effect of CM and CU against diabetic induced hepatic damage. Our results are inconsistent with the study of Al-Humaid et al [24]. who reported that treatment of rats with CM that were poisoned with lead acetate, increased activities of liver function biomarkers (AST and ALT) which were returned to normal levels after treatment with CM. Similarly, Amjad et al., [29] reported that treatment of rats with fresh CM resulted in dramatical reduction of liver diagnostic enzymes to near normal in streptozotocin induced diabetic rats. Previous studies indicate that the administration of CM filtrate in alloxan induced diabetic rats result in the reduction of serum activities of AST and ALT[27].

Diabetes causes a wide change in lipids, TC, and lipoprotein profiles and also enhances the chances of developing cardiovascular diseases. This study shows that treatment of diabetic rat with CM or CU significantly ($P<0.05$) reduces serum level of TG and LDL-P in comparison with DC group. CM has been reported to contains conjugated linoleic acid which decreases TG, TC, LDL cholesterol and LDL/HDL ratio [30]. Current study shows a significant increase in TC in diabetic rats treated with either CM or CU. This is contrary to the previous study which shows CM is effective in reducing TC in diabetic subjects [30] also it was proven in other studies [15,30-31]. This inconsistent finding shows that there is a need for further research to explore the effect of CM and CU on the lipid profile in diabetic subjects. Treatment of DC group with either CM or CU or Metformin significantly ($P<0.05$) increases HDL-C levels. It was reported that CM normalized the alteration in HDL and TG levels in diabetic rats [32]. Mansour et al., reported CM supplementation to diabetic rats increased HDL-C levels which is similar to that found in diabetic rats treated with metformin [33]. Furthermore, the current study shows a significant decrease in LDL-C in diabetic rats treated with either CM, CU or metformin compared to diabetic untreated (DC). Similarly, LDL-C in DC is significantly higher compared to that of NDC. LDL-C is regarded as the bad cholesterol which can build up in the walls of arteries and increases the chances of developing cardiovascular diseases. While HDL cholesterol is regarded as good cholesterol it has protection against heart disease through the removal of LDL from the blood and preventing it from building up in the arteries. Our results are in agreement with previous studies that show an increase in serum HDL-C in alloxan induced diabetic rats treated with synthetic vitamins and minerals [34]. Oxidative stress is firmly related to LDL-C while unrelated to HDL-C [19]).

Liver is one of the vital organs that is affected by diabetic complications. The impact of treating diabetic rats with fresh CM or CU on the histopathology of the liver is shown in Fig 1c and 1d, histopathological examination of the liver indicates that diabetic untreated group (DC) show severe changes in the pathology of the liver compared to normal structure in NDC. In the DC group, there is a severe degenerative change in the Endocrine part (islets of Langerhans) and localized zone of liquefactive necrosis with a congested central vein. Treatment of diabetic rats with CM, CU and metformin respectively, restore the normal structure of the liver in alloxan induced diabetic rats to near that of the NDC group. This shows that both CM and CU has a protective effect against hepatic damage in diabetic rats. The hepatic changes observed in the present study are similar to those reported by [27]. Similarly, Althnaian et al. reported CM to be positive in protecting the liver against injury in CCl_4-treated rats [35].

4. CONCLUSION

The result of the histopathological alteration of the liver and biochemical parameters in this study strongly indicate that both CM and urine can serve as an adjuvant remedy to delay the onset of diabetic complications. Further studies should be done on humans to determine the effect of CM and CU on other body tissues, furthermore, research should be carried out to determine the synergistic effect of CM and CU on vital organs in diabetic subjects and also to isolate and characterized the active component present in the camel urine.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

ETHICAL APPROVAL

This study was conducted in accordance with the standard set for the Care and Use of Laboratory Animals. The protocol was approved by the Ethics Committee on Animal Use of the Sokoto State University, Sokoto Nigeria.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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