Liver and Renal Cell Damage Following Excess Bee Honey Consumption in Male Wistar Rat

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Abstract

Honey is a widely used natural product with several health benefits. However, there is paucity of information on its excessive usage. The present study investigated the effect of excess honey consumption on hepato-renal functions in male wistar rats. Twenty-eight adult male Wistar rats were selected into four groups (n=7) and treated with distilled water (control) and 1ml, 2ml and 3ml of honey respectively for 5 weeks. Thereafter, the animals were euthanised and blood as well as kidney and liver were collected for further studies. There was a significant increase in Creatinine, Bilirubin, Urea AST, ALP, total protein as well as a significant decrease in RBC, WBC, haemoglobin, lymphocyte and PCV. Histology of the liver and kidney revealed a significant degeneration and necrosis in a dose dependent manner. This study suggest that excess honey consumption causes liver and renal cellular damage as well as haematological alterations.

Keywords: Honey; Excess consumption; liver enzyme; electrolyte; renal function; haematological indices; histopathology.

INTRODUCTION

Natural honey is a sweet, flavourful liquid with high nutritional value and therapeutic potential (Eteraf-Oskouei and Najafi, 2013). It is a natural product made by honeybees (Apis mellifera; Apidae) from nectar collected from flowers (Dashora et al., 2011). Honey has been consumed by humans since almost five centuries ago for both nutritional and therapeutic purposes (Adebolu, 2005; Ashrafi et al., 2005). However, it is the only naturally occurring insect-derived substance with nutritional, aesthetic, medicinal, and industrial benefits (Bansal et al., 2005). Honey has been used as a natural sweetener since ancient times because of its high fructose content and it was reported to be 25% sweeter than tablet sugar (Babacan and Rand, 2007; Pataca et al., 2007). The increasing popularity shown by the usage of honey in beverages is also accounted to its high fructose content (Babacan and Rand, 2007). As of today, approximately 300 different varieties of honey have been identified and many forms of nectar gathered by honeybees are related to these variations (Lay-flurrie, 2008).

Proximate analysis showed that honey’s main components are carbohydrates (95–97% of its dry weight), proteins, vitamins, amino acids, minerals, and organic acids (Betts, 2008; Helmy and El-Soud, 2012). Meanwhile, phytochemical screening of pure honey also revealed that it contains flavonoids, polyphenols, reducing compounds, alkaloids, glycosides, cardiac glycosides, and volatile compounds (White, 1980; Islam et al., 2012). Regardless of its strong phytochemical properties, honey's vitamin content is poor, and it falls far short of the daily requirements but the most abundant is the vitamin C. Honey is a good source of antioxidant and it has been reported to exhibit strong anti-oxidative (Ahmed and Othman, 2013; Kasala et al., 2015), and anti-inflammatory (Khalil et al., 2012) potential. Due to the high polyphenols of honey, various studies reported the pharmacological usage of honey in the treatment and management of pathological conditions like increase blood pressure (Ahmed and Othman, 2013), diabetes (Estevinho et al., 2008), neuropsychiatric symptoms (Ghosh and Playford, 2003; Rahman et al., 2014), bacterial infections (Attia et al., 2008; Kasala et al., 2015) as well as respiratory and gastrointestinal disorder (Abdurhman et al., 2008; Israili, 2014), microbial infection (Israili, 2014; Saikaly and Khachemoune, 2017). The antioxidant properties of honey have been implicated through its reactive oxygen species (ROS) scavenging ability and by increasing the intracellular activity of glutathione (GSH), uric acid, beta-carotene, and vitamin C (Ahmed et al., 2018). Moreover, certain phenolic ingredients of honey were reported to inhibit the activity of nitric oxide synthase, decrease inducible nitric oxide synthase (iNOS) and cyclooxygenase-2...
(COX-2) activities that cause inflammation of cells and tissues in human body (Ahmed et al., 2018). Also, honey displayed very strong anti-inflammatory effect reported in several studies. Reports stated that honey can inhibit or slows down pro-inflammatory cytokine release, nitric oxide synthase (iNOS) expression, generation of ROS, and reduce the level of prostaglandin: which are the major players culminating processes involved in inflammation (Al-Waili and Boni 2003; Candiracci et al. 2012). According to Candiracci et al., (2012), honey exacerbated nitric oxide release in acute and severe inflammation. However, this mechanism was related to COX-2 and iNOS inhibition leading to suppression of mediators of pro-inflammation (PGE2, NO, TNF-α, and IL-6) (Hussein et al. 2012). Another area where honey is adopted is its effect on wound healing. Several preclinical and clinical trials have reported the application of honey in both acute and chronic wounds including injuries resulting from burns (Moore et al. 2001). This reported have demonstrated honey’s ability to reduce the level of edema, enhance granulation and epithelization during the proliferative stage as well as decreased wound healing time and scarring and decreases contractures in cases with burn wounds with no adverse effect (allergy or toxicity) whatsoever (Yaghoobi et al. 2013).

Meanwhile, the side effect of honey consumption has not been well studied and there are major concerns with respect to excessive intake of honey causing increase in blood sugar level. There seems a very little or no report on the excessive or prolonged consumption of honey which might lead to toxicity in the body system. Hence, the goal of this present study is to investigate the high consumption of honey on haematological parameters, liver function indices and kidney function in male Wistar rats.

**MATERIALS AND METHODS**

**Drugs and Chemicals**

Honey was purchased at Gembu local market in Saurdana Local Government area of Taraba State, Nigeria. Creatinin and Urea kit was obtained from Immunometrics Limited (UK) and Total Proteins kit, Albumin kit and Bilirubin kit were all obtained from Sigma Aldrich (St. Louis, MO, USA). Other reagents and solvents were of analytical graded level.

**Experimental Animals**

Twenty-eight adult male Wistar rats (weighing 180-200g) were obtained from the Physiology Department Central Animal House (PDCAH), University of Ibadan, Ibadan, Oyo State, Nigeria and managed under normal laboratory condition according to the University ethical guideline which adheres strictly to the “Principle of Laboratory Animal Care” (NIH Publication No. 85-23). The dosed selected for this study was according to Fasanmade and Alabi, (2008) with slight modifications.

**Treatment Design**

The animals were arranged into four groups (n =7). Group 1 serves as the non-treated animal (control animals) and received distilled water (10 mL/kg) alone. Group 2 was administered with 1ml/100g of body weight while group 3 received 2ml/100g of body weight and group 4 received 3ml/100g of body weight. All treatments were daily administered orally using oral gavage and lasted for 35 days. The animals were carefully observed for change in body weight and blood glucose level evaluated weekly and after overnight fasting on the last day of sacrifice (24 hours after the last day of treatment) using a glucometer (Accu-check Active, Roche diagnostic, Mannheim Germany).

**Preparation of blood samples for biochemical analysis**

After the conclusion of the treatment, all the rats were subjected to ketamine anaesthesia and then sacrificed through cervical dislodge. Cardiac puncture was used for blood collection for haematological variables. Further, plasma was also obtained from the collected blood by centrifugation (3000 rpm; 15 minutes) at room temperature using a bench top centrifuge (Bosch, UK) for the assessment of electrolytes concentration, renal and liver function markers.

**Estimation of liver function markers**

Alanine transaminase (ALT), Aspartate aminotransferase (AST) and Alkaline Phosphatase (ALP) activities for liver injury markers in the plasma was determined according to the protocol previously described by Reitman and Frankel (1957) using Randox test kit.

**Estimation of kidney function markers**

**Assessment of serum creatinine concentration**

Plasma (50 mL) was taken and mixed to a monoreagent (1000 IL) obtained from the assay kit. The mixture was then incubated for 60 seconds. Thereafter the absorbance was read (k 492 nm) twice within the interval of 1 min. Furthermore, the concentration of creatinin was calculated using the kit manufacturer method (Immunometrics Limited UK).

**Assessment of serum urea concentration**

Four parts of monoreagent taken from reagent I and one-part monoreagent taken from reagent II were mixed together and incubated at 15–25°C for 30 minutes. Following incubation, the mixture was kept in amber bottle prior to use. 10 mL of plasma sample and urea standard were further mixed to 1000 IL monoreagent each and then further incubated at 20-25°C for 60 seconds. The absorbance was read at wavelength of 340
nm twice within the interval of 1 minute. Finally, the concentration of urea was determined and calculated as proposed by the kit manufacturer (Immunometrics Limited UK) using the formula:

\[
\text{Urea concentration} = \frac{\text{Change in sample absorbance}}{\text{Change in standard absorbance}} \times \text{Standard concentration/Cal}
\]

Assessment of serum albumin concentration
Plasma albumin was determined using RANDOX reagent kits as according to the instructions and method in the manual further corroborated by Doumas et al. (1971).

Estimation of plasma electrolyte concentration
The plasma electrolytes: Sodium, Potassium and Chlorides were assayed using their respective commercial kits. All assays were done using microplate reader SpectraMAX PLUS (a molecular Device product).

Estimation of haematological indices
The haematological parameters were determined using an automated haematology analyzer (ABX Micros 60 from Horiba ABX, France). The red blood cells (RBC), Packed Cell Volume (PCV), haemoglobin and other haematological indices such as, lymphocytes, neutrophils, monocytes, eosinophils and basophils were determined. The mean corpuscular haemoglobin concentration (MCHC), mean corpuscular hemoglobin (MCH) and mean corpuscular volume (MCV) were calculated from RBC, haemoglobin (Hb) and packed cell volume (PCV) values. The white blood cell (WBC) count was also determined.

Histological assessment
The kidney and liver tissues were harvested and fixed in 10% phosphate buffered formalin for histomorphological examination. The kidney and liver tissues were directly fixed through immersion in a 4% paraformaldehyde of 0.1 mol/L phosphate buffers at pH 7.2 for 48 h. All tissues were then further dehydrated and embedded in a paraffin wax and thereafter sliced transversely using the microtome machine into sections (5 μm). After tissue slicing, it was then stained in haematoxylin and eosin solution. Finally, all the sections were examined by using optical microscope for cell condensation and death (Asiwe et al., 2021).

Statistical Analysis
Data are presented as Mean ± Standard Error of Mean and analysed with one-way analysis of variance (ANOVA) and compared by Newman-Keuls test using the GraphPad prism 7.0 (GraphPad software, San Diego, CA, USA). P<0.05 was considered statistically significant.

RESULTS

Honey consumption (HC) maintains blood glucose level and reduced body weight gain in rats
The effect of honey consumption on blood glucose level and body weight was presented in table 1-2. Following administration of honey, there was no significant difference in the glucose level across the treatment group comparative to the control (Table 1). However, there was a significant (p < 0.05) progressive decrease in body weight from the week 2-5 in HC (2ml/100g and 3ml/100g) when compared with control (Table 2).

Honey consumption (HC) induced electrolytes imbalance in rats
Table 3 showed the impact of honey consumption on the plasma level of electrolytes following administration in the rats. The plasma concentration of sodium and chloride ion significantly (p < 0.05; [689 ± 7.98 and 450 ± 3.13 vs 736±3.36] and [29.1 ± 2.61 and 26.1 ± 11.70 vs 31.3 ± 0.92]) decreased in the animals administered HC (1ml/100g and 3ml/100g), but there was significant (p < 0.05; [747 ± 5.29 vs 736±3.36] and [69.8 ± 1.33 vs 31.3 ± 0.92]) increase in the animals administered HC (2ml/100g) relative to the control. The plasma concentration of potassium ion decreased significantly (p < 0.05; [5.88 ± 0.41, 6.08 ± 0.42 and 3.92 ± 0.30 vs 7.58 ± 0.08]) across all the groups administered HC (1ml/100g, 2ml/100g and 3ml/100g) when compared to the control (Table 3).

Honey consumption (HC) exacerbates liver function markers in rats
The data for markers of liver toxicity in rats was presented in Fig. 1A-C. Data showed significant decrease level of ALT in the animals treated with HC (2ml/100g and 3ml/100g) compared to the control (Fig. 1A). However, the animals treated with higher doses of HC (2ml/100g and 3ml/100g) significantly decreases the level AST and ALP comparative to the control (Fig. 1B-C).

Honey consumption (HC) initiates renal toxicity via increased inflammatory markers in rats
The results obtained from this result indicating renal toxicity following honey consumption is represented in figure 2A-E. There was a significant (p < 0.05) increase in the urea and creatinine concentration in the animals treated with HC (2ml/100g and 3ml/100g) when compared to the control (Fig. 2A-B). We also observed significant (p < 0.05) increased total protein and bilirubin level in the animals that were administered HC (1ml/100g, 2ml/100g and 3ml/100g) (Fig. 2C-D), while
a significantly (p < 0.05) decreased albumin level was recorded in them (Fig. 2E).

**The effect of honey consumption on haematological indices in rats**

Table 4 showed the values of the haematological indices in the rats after administration of honey. The results showed that there were significant (p < 0.05; [3.06 ± 0.54 and 2.05 ± 0.31 vs 5.41 ± 0.39]) decrease in WBC in the HC (1ml/100g and 2ml/100g) treated rats and a significant (p < 0.05; [7.59 ± 0.55 vs 5.41 ± 0.39]) increase in the rats treated with HC (3ml/100g) when compared to the control. The lymphocyte counts decrease significantly (p < 0.05; [1.26 ± 0.17 and 0.42 ± 0.05 vs 2.96 ± 0.22]) in the rats treated with HC (1ml/100g and 2ml/100g) when compared to the control. The concentration of haemoglobin decreases significantly (p < 0.05; [12.5 ± 0.17, 11.4 ± 0.16 and 13.1 ± 0.17 vs 14 ± 0.29]) in the HC (1ml/100g, 2ml/100g and 3ml/100g) treated rats when compared to the control. The value of RBC and PCV decreases significantly (p < 0.05; [6.98 ± 0.16 and 6.42 ± 0.41 vs 8.2 ± 0.18]) and (p < 0.05; [39.5 ± 0.17 and 37.1 ± 2.27 vs 44.9 ± 0.44]) in the HC (1ml/100g and 2ml/100g) treated rats when compared to the control. Additionally, we observed that the value of PCT decreases significantly (p < 0.05; [0.50 ± 0.14 vs 0.64 ± 0.40]) in the HC (3ml/100g) when compared to the control. However, there were no significant (p > 0.05) change MCV, MCH, MCHC and Platelet levels when compared with group (Table 4).

**Honey consumption (HC) induces hepato-renal degeneration in rats**

Figure 3 showed the photomicrograph of the liver and kidney tissues. Histomicrograph of the liver in control rats showed normal cellular architecture with no lesion (Plate 1). However, the rats administered HC (1ml/100g) showed centrilobular, hepatocellular vacuole change while HC (2ml/100g) showed diffused atrophy of hepatic cords and focal hepatocyte vacuolation. Also, those given the higher dose of HC (3ml/100g) showed hepatocellular degeneration and fibroblast reaction as well as diffuse atrophy cords and portal inflammation. The photomicrograph of the kidney showed patchy epithelia degeneration as well as necrosis in HC (1ml/100g and 2ml/100g) while HC (3ml/100g) showed tubular epithelia coagulation as well as necrosis as shown in figure 3.

**Table 1.** Effect of Bee honey consumption on fasting blood glucose (g/dl).

<table>
<thead>
<tr>
<th>Weeks</th>
<th>Control</th>
<th>HC (1ml/100g)</th>
<th>HC (2ml/100g)</th>
<th>HC (3ml/100g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 1</td>
<td>120 ± 2.03</td>
<td>118 ± 2.71</td>
<td>114 ± 2.20</td>
<td>115 ± 2.23</td>
</tr>
<tr>
<td>Week 2</td>
<td>120 ± 2.03</td>
<td>118 ± 2.71</td>
<td>114 ± 2.20</td>
<td>115 ± 2.23</td>
</tr>
<tr>
<td>Week 3</td>
<td>112 ± 1.11</td>
<td>116 ± 1.69</td>
<td>122 ± 2.07</td>
<td>120 ± 1.24</td>
</tr>
<tr>
<td>Week 4</td>
<td>133 ± 1.29</td>
<td>121 ± 2.78</td>
<td>107 ± 2.71</td>
<td>110 ± 2.71</td>
</tr>
<tr>
<td>Week 5</td>
<td>116 ± 3.69</td>
<td>116 ± 3.67</td>
<td>114 ± 1.82</td>
<td>114 ± 2.74</td>
</tr>
</tbody>
</table>

Values are expressed as Mean ± standard error of mean, (n=5). HC = Honey consumption.
Figure 2. (A) Urea (B) Creatinine (C) Total Protein (D) Bilirubin (E) Albumin. Values are expressed as Mean ± standard error of mean, (n=5). *p< 0.05 is significant when compared with control.

Table 2. Effect of Bee honey consumption on body weight (grams).

<table>
<thead>
<tr>
<th>Honey consumption</th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Week 1</td>
<td>Week 2</td>
<td>Week 3</td>
</tr>
<tr>
<td>Control</td>
<td>203 ± 7.69</td>
<td>226 ± 7.46</td>
<td>223 ± 8.62</td>
</tr>
<tr>
<td>HC (1ml/100g)</td>
<td>206 ± 5.13</td>
<td>219 ± 10.0</td>
<td>220 ± 12.1</td>
</tr>
<tr>
<td>HC (2ml/100g)</td>
<td>205 ± 3.96</td>
<td>210 ± 7.01*</td>
<td>206 ± 5.85*</td>
</tr>
<tr>
<td>HC (3ml/100g)</td>
<td>204 ± 8.22</td>
<td>183 ± 20.6*</td>
<td>198 ± 8.07*</td>
</tr>
</tbody>
</table>

Values are expressed as Mean ± standard error of mean, (n=5). *p< 0.05 is significant when compared with control, HC = Honey consumption.

Table 3. Effect of Bee honey consumption on electrolytes after 35 days (5 weeks).

<table>
<thead>
<tr>
<th>Variables</th>
<th>Honey consumption</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
</tr>
<tr>
<td>Na (g/dl)</td>
<td>7.36 ± 3.36</td>
</tr>
<tr>
<td>K (g/dl)</td>
<td>7.58 ± 0.08</td>
</tr>
<tr>
<td>Cl (g/dl)</td>
<td>31.3 ± 0.92</td>
</tr>
</tbody>
</table>

Values are expressed as Mean ± standard error of mean, (n=5). *p< 0.05 is significant when compared with control, HC = Honey consumption. ml of honey

Table 4. Effect of Bee honey consumption on haematological indices after 35 days (5 weeks).

<table>
<thead>
<tr>
<th>Variables</th>
<th>Honey consumption</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
</tr>
<tr>
<td>WBC</td>
<td>5.41 ± 0.39</td>
</tr>
<tr>
<td>Lymphocyte</td>
<td>2.96 ± 0.22</td>
</tr>
<tr>
<td>RBC</td>
<td>8.2 ± 0.18</td>
</tr>
<tr>
<td>Hb (g/dl)</td>
<td>14 ± 0.29</td>
</tr>
<tr>
<td>PCV</td>
<td>44.9 ± 0.44</td>
</tr>
<tr>
<td>MCV</td>
<td>55 ± 0.41</td>
</tr>
<tr>
<td>MCH</td>
<td>17 ± 0.04</td>
</tr>
<tr>
<td>MCHC</td>
<td>31.3 ± 0.17</td>
</tr>
<tr>
<td>Platelet</td>
<td>761 ± 56</td>
</tr>
<tr>
<td>PCT</td>
<td>0.64 ± 0.40</td>
</tr>
</tbody>
</table>

Values are expressed as Mean ± standard error of mean, (n=5). *p< 0.05 is significant when compared with control, HC = Honey consumption. ml of honey.
DISCUSSION

The constituents of honey make it one of the widely used natural products for treating many diseases. However, our present study evaluated the effect of excess honey consumption on serum electrolyte, liver and renal function markers as well as haematological variable in male Wistar rats. There was a progressive decrease in the body weight of the animals which suggest the antiobesogenic potential of honey as reported by Yaghoobi et al., (2008) and Bahrami et al., (2009). The weight loss was highest in the group fed with 3 ml of honey which corroborated the studies of Chepulis, (2007) that protective effects of honey against obesity and weight gain depend on quantity or duration of exposure. We also observed a decrease in blood glucose level in week 4 and week 5 after an initial increase in week 3. This observation was consistent with the report that administration of honey in STZ-induced diabetic rats and non-diabetic rats for 3 days significantly reduces blood glucose levels (Özta, san et al., 2005; Jansen et al., 2012). However, the antidiabetic effect of honey can be attributed to its ability to modulate adiponectin secreted by adipose tissue which regulate glucose and lipid metabolism as reported by (Li et al., 2009). The adiponectin modulating potential of honey though not within the scope of our present study, could suggest the mechanism of weight loss in a dose depended manner. Electrolytes are essential for survival because of the electrical charges they provide. They interact with each other and the cells in the tissues, nerves and muscles. Imbalance in this electrolyte can alter the normal physiology of the body. Na and K ions are essential contractile tools of excitable tissues such as the heart, muscles and nerves, a decrease in this ions concentration as observed in this study suggest a modulating role of honey in electrolyte balance. The decrease in the levels of haematological components in this study suggests that honey supplementation directly destroy the blood components or disturb the processes involved in their formation. It can also be attributed to loss of blood due to haemorrhage as hematurea was observed during the study. However, this finding was not consistent with the studies of Al-Waili et al., (2006) and Abdelaziz et al., (2012) who reported a protective role of honey against haemorrhagic and anemic conditions. Other studies such as Bazzoni et al., (2005), Al-Qayim et al., (2014), Ghorbel et al., (2015) also showed conflicting results.

Liver is an essential organ for food metabolism and detoxification of substances that threatens the normal functions of the body. The biomarkers assayed in this study indicated the state of health of the liver as it was previously reported to indicate toxicity when there is significant increase in their concentration (Murugavel and Pari, 2007; Asiwe et al., 2022). Previous studies by Al-Waili et al. (2006) and Halawa et al., (2009) showed that honey attenuates elevated liver enzymes during acute blood loss and food restriction. However, we observed that honey supplemented diet reduces ALT and increases AST and ALP in a dose dependent manner. Most studies reported the preventive effect against liver
injury due to its free radical scavenging potentials. However, the present study was not consistent with previous studies and the inconsistency can be attributed to the dose and duration of the study. Honey has been reported by Rashed and Soltan, (2004) to contain several trace elements as well as heavy metals such as cadmium (Cd) and lead (Pb) as well as aluminium (Al) which previously has been confirmed to be toxic to liver and kidney functions. This may contribute to the observed dose and time dependent toxicity of honey. On the other hand, kidney is one of the important organs in the body saddled with the responsibility of excreting waste metabolic product from the body and a dysfunction of the kidney has been reported to be characterised by increased serum concentrations of creatinine and urea (Asiwe et al., 2022). Halawa et al., (2009) reported ameliorating effect of honey in environmental toxicant induced kidney dysfunction. However, our present findings suggest that honey supplementation could cause renal damage as both creatinine and urea concentrations were significantly increased when compared to the control group.

The photomicrograph of the liver showed centrilobular, focal hepatocyte vacuolation, hepatocellular degeneration and fibroblast reaction as well as diffuse atrophy cords and portal inflammation. Several trace elements as well as heavy metals such as cadmium (Cd) and Lead (Pb) which was previously confirmed by Asiwe et al., (2022) to be toxic to liver and kidney functions by inducing cellular stress, injury or damage in body tissues was reported by Rashed and Soltan, (2004) to be part of the constituents of honey as contaminants. This could suggest the adverse effect of honey in this study. This observation was consistent with the study of Wilson et al., (2011) who reported adverse effect of excess honey intake on histology of the liver. The renal tissue was not exempted from this effect as the photomicrograph of the kidney showed patchy epithelia degeneration, necrosis as well as tubular epithelia coagulation in a dose dependent manner. This could contribute to the increased creatinine and urea concentrations observed in this study. This observation was in contrast with the study of Onyije et al., (2011) who reported normal renal architecture with increased urea and creatinine levels.

CONCLUSION

In conclusion, this study suggest that excess honey consumption causes adverse effects on liver and renal tissues as well as haematological alterations as shown both in biochemical assays and histological examination. It is therefore recommended that proper awareness should be raised to educate the public as well as agencies regulating food and drug intake of these possible adverse effect of excess consumption of honey or honey products.

**Ethics approval and consent to participate:** Ethical approval was given by the College of Medicine Ethics Committee. Animal handling was done in accordance to established guidelines by the National Institute of Health for care and use of laboratory animals as adopted by the College of Medicine, University of Ibadan, Nigeria.

**Consent for publication:** Not applicable

**Availability of data and materials:** All data produced and analyzed during this study are included in this article.

**Competing interest:** The authors declare that they have no competing interests.

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**Authors’ contributions:** AA and AJN designed the study. AJN, AA and AOG performed the experiments, analyzed the data, and wrote the manuscript. All authors read and approved the final manuscript.

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