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Research Paper

Allium cepa Peel Extract Plays a Protective Role in Ethanol-Induced Kidney and Liver Toxicity in Balb/C Mice: A Histological Study

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ABSTRACT

Background: *Allium cepa* peels are byproducts obtained from the onion bulb, which has abundant bioactive components that have been used in the treatment of various ailments across the globe. The current study investigates the effect of *Allium cepa* on the histology of the kidney and liver tissue following alcohol toxicity.

Methods: A total of 24 Balb/C mice, three months old and weighing 15-22 g, were grouped into four groups of 6 mice each. They were administered treatment as follows: Group I was considered the positive control and received an equal volume of distilled water; Group II (negative control) was administered 20% ethanol at 10 mg/kg; Group III was administered 50 g/kg of *Allium cepa* peel extract and 20% ethanol at 10 ml/kg; and Group IV received 100 g/kg of *Allium cepa* peel extract and 20% ethanol at 10 ml/kg. The treatment continued for 28 days, after which the mice were sacrificed, and the liver and kidney tissues were dissected for routine histological preparation.

Results: Administration of *Allium cepa* extract caused a non-significant increase in the body weight in treated groups, significantly ($P<0.05$) increased the weight of the kidneys, significantly ($P<0.05$) decreased in the weight of the liver, preserved the hepatocytes in the liver and the renal epithelium and glomerulus of the kidney tissue.

Conclusion: *Allium cepa*, in the present investigation, shows potential as a candidate to protect against ethanol-induced hepatotoxicity through its effects on renal and hepatic tissue. However, further studies are required to determine the exact mechanisms involved and the active biocomponents.

Keywords: *Allium cepa*, Alcohol, Histology, Kidney, Liver

Introduction

Onion (*Allium cepa* L.) is a widely cultivated and consumed vegetable as an ingredient. It is used medicinally to manage or prevent several common diseases, such as atherosclerosis, asthma, bronchitis, and coughs [1]. *Allium cepa* peel or skin is obtained from onions, usually as a byproduct, and has been found to contain abundant phytochemicals, indicating its antioxidant potential. The composition of onion peel/skin differs based on the different varieties, agronomic characteristics of the region where it was cultivated, and method of extraction to obtain the onion peel [2]. Phytochemical analysis of *Allium cepa* peel has revealed the presence of bioactive components, including saponins, aglycones, quercetin, cepaenes, flavonoids, organosulfur, and phenolics which have demonstrated various pharmacological properties and therapeutic effects [3]. The antioxidant properties are attributed to the presence of phenolic acids, flavonoids, thiosulfinates, and anthocyanins [4,5].

In many scientific studies, *Allium cepa* has been proven to have antimicrobial, antithrombotic, antitumor, anti-hyperlipidaemic, anti-arthritic, anti-hyperglycemic anticarcinogenic properties [6], antioxidant, antispasmodic [7], antimicrobial, wound healing, anti-inflammatory [8], antimicrobial, antimutagenic [9], anticancer, antifungal, anti-inflammatory [10,11] amongst several other activities.

Alcohol is a severe hepatotoxicant that causes a variety of liver disorders [12]. Alcohol-related disorder of the liver is an inflammatory condition caused by hepatic steatosis and disorder injuries to the liver tissue secondary to alcohol intake, which is responsible for over 10% of the cases reported globally [13, 14]. This condition leads to a progressive inflammatory disease associated with long-term alcohol intake. Prolonged and excessive alcohol consumption (≥40-80 g/day for men and ≥20-40 g/day for women) could lead to serious ailments, including gastrointestinal ulcers, pancreatitis, alcoholic liver disease, neurologic disorders, diabetes mellitus, and cancers [13,

15]. Above the conditions mentioned above, alcoholic liver disease is significant because of its high morbidity and mortality [13]. Alcoholic liver disease (ALD) can progress over time to cirrhosis and hepatic cancers, and consequently, inevitable death [13,15].

Considering the fact that liver diseases are fast emerging as global health priorities [16], it is imperative to find a solution. Treatment strategies for ALD include lifestyle alterations to reduce alcohol ingestion, cigarette smoking, and obesity; nutrition therapy; and pharmacological therapy [Marsano]. Diagnosis and management of the complications of ALD are necessary for alleviating the symptoms of the disease, improving quality of life, and decreasing mortality. Pharmacotherapeutic interventions in the treatment of ALD include pentoxifylline or prednisone for alcoholic hepatitis, silymarin for cirrhosis and liver transplantation in selected abstinent patients with severe cases [17], pentoxifylline [18], corticosteroids [19], propylthiouracil [20], complementary and alternative medicines have also been used in the treatment and management of alcohol-related liver and kidney disorders in many scientific studies. The current investigation proposes *Allium cepa* as an alternative medication used in the treatment of alcohol-induced hepatic and renal toxicity.

Materials and Methods

Animals

A total of 24 Balb/C mice, three months old and weighing 15-22 g, were obtained from the Biochemistry Animal House at the University of Maiduguri. They were randomly grouped and kept in cages in the animal house for 14 days to allow them to acclimatize. The mice were fed vital hybrid feed and had access to water ad libitum.

Plant Collection

Allium cepa peels were obtained from a local grocer at the Monday market in Maiduguri, Borno State. The peel was authenticated by a botanist in the Faculty of Biological Sciences at the University of Maiduguri, and a sample was deposited in the herbarium of the Pharmacognosy Department, Faculty of Pharmacy, University of Maiduguri, with voucher number (UMM/FPH/ASH/001). The husks were mechanically ground into a fine powder, yielding a total of 2.3 kg of powdered *Allium cepa*, which was carefully stored in an airtight container.

Preparation of Onion Peel Extract

The onion powdered peel was diluted in 2.5 liters of ethanol (Sigma-Aldrich, Missouri). It was covered and agitated vigorously to mix and allowed to steep for 24 hours, after which the resultant solution was filtered using filter paper to obtain the filtrate, which was evaporated at a temperature of 47°C.

Experimental Design

The mice were randomly grouped into four groups, each containing six mice, as seen in the protocol below.

Mice in Group I (positive control) were administered equal doses of distilled water.

Mice in Group II (negative control) were administered 20% ethanol at 10 ml/kg.

Mice in Group III were administered 50 g/kg of *Allium cepa* peel extract and 20% of ethanol at 10 ml/kg.

Mice in Group IV were administered 100 g/kg of *Allium cepa* peel extract and 20% ethanol at 1 ml/kg.

Treatment Protocol

Kidney damage was induced in Groups II, III, and IV by administering 20% ethanol at a dosage of 10 ml/kg, which was performed via the orogastric route 8 hours prior to the administration of *Allium cepa* extract to the same groups, also via the orogastric route. This practice was repeated for a period of 18 days. The mice were weighed throughout this period and were allowed unrestricted access to feed and drinking water.

Animal Sacrifice, Tissue Procurement and Processing

After 18 days, the mice were sedated using ketamine hydrochloride (Pfizer, Esentepe, Istanbul, Turkey) at a concentration of 100 mg/kg, administered as an intramuscular injection in the left thigh of all the mice. A median incision was made on the abdominal wall to expose the intra-abdominal organs. The liver and kidneys were dissected from the posterior abdominal wall, and connective tissue was removed from them and weighed. The left kidney of each mouse was preserved in 10% formalin, dehydrated using a graded series of alcohol, cleared in xylene, impregnated in paraffin wax, sectioned using a microtome at 8 µm, and stained using hematoxylin and eosin.

Statistical Analysis

The collected data were expressed as a mean±S.D and analyzed using the GraphPad Prism (version 8.0) software. One-way analysis of variance (ANOVA) was carried out, and statistical significance was considered at $P<0.05$.

Results

Effect of Ethanol Extract of *Allium cepa* Peel on the Body Weight of Mice With Ethanol-induced Renal and Hepatic Damage

Administration of *Allium cepa* extract caused a non-significant increase in the body weight in treated groups (Groups III and IV) when compared to the control group, as evidenced by a slight increase in the final weight of mice who were administered *Allium cepa* extract. The lower concentration of *Allium cepa* increased the weight of mice when compared to the higher dose of *Allium cepa*. Administration of ethanol caused a decrease in body weight in animals in Group II and the weight difference in this group was the lowest

when compared with all other groups (Figure 1).

Effect of Ethanol Extract of *Allium cepa* Peel on the Weight of the Kidney of Mice with Ethanol Renal and Hepatic Damage

Administration of *Allium cepa* extract significantly increased the weight of the kidneys in mice when compared to the control group (P<0.05). The higher dose (100 mg/kg) of *Allium cepa* caused a significant increase in the weight of the kidney when compared to the lower dose of 50 mg/kg (Figure 2).

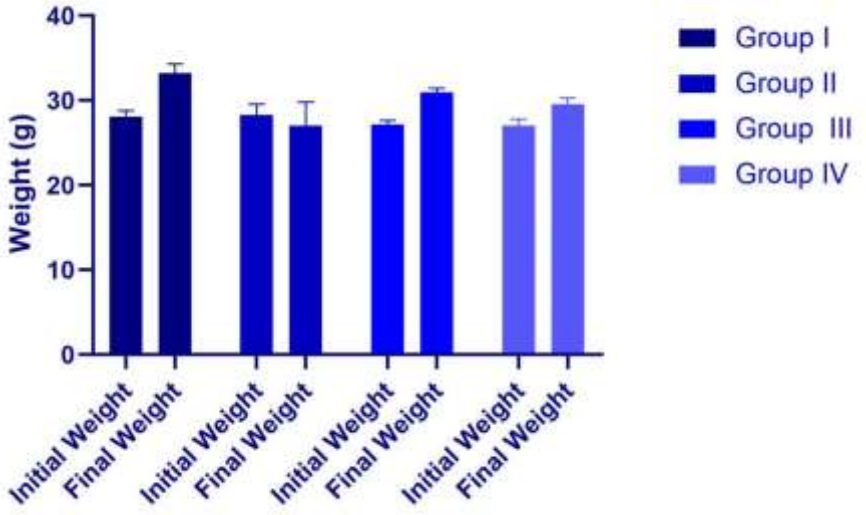

Figure 1. Showing the initial versus final weight of mice in all groups

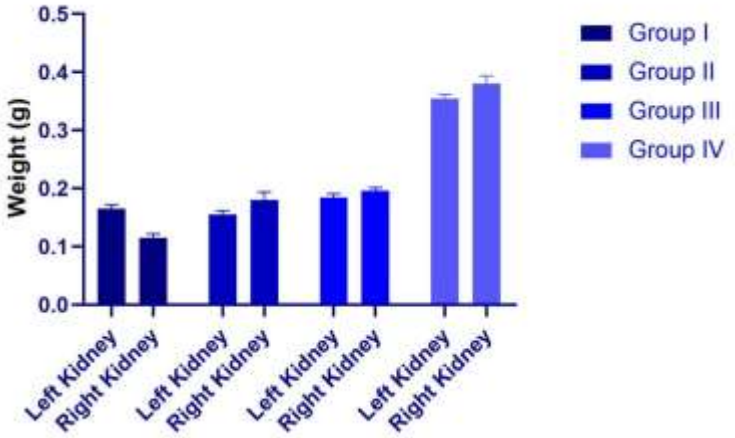

Figure 2. Showing the weight of the difference in weight of the kidneys in all groups

Effect of Ethanol Extract of *Allium cepa* Peel on the Weight of the Liver of Mice with Ethanol Renal and Hepatic Damage

Allium cepa extract caused a significant decrease in the weight of the liver of Balb/C mice when compared to the control group (P<0.05). The weight was lowest in the group administered with the lowest concentration of *Allium cepa* when compared to the higher dose (Figure 3).

Effect of Ethanol Extract of *Allium cepa* Peel on the Histology of the Liver of Mice with Ethanol Renal and Hepatic Damage

Figure 4 (A-D) indicates the histology of the liver of mice in Groups I-IV. Group I revealed normal Hepatic histology with the clear central vein enclosed with a continuous endothelial lining. The polygonal hepatocytes were arranged in cords that radiated from the central vein with sinusoids separating the hepatocyte cords. The basophilic nucleus was darkly stained and surrounded by an eosinophilic cytoplasm. The liver of rats in Group II exhibited ill-defined hepatocytes that appeared distorted. The cytoplasm showed continuity with the sinusoidal spaces, lacking clear demarcation, and the nuclei appeared pyknotic, indicating liver damage. In contrast, administration of *Allium cepa* preserved the liver tissue in Groups III and IV, as these mice did not show the liver damage observed in Group II.

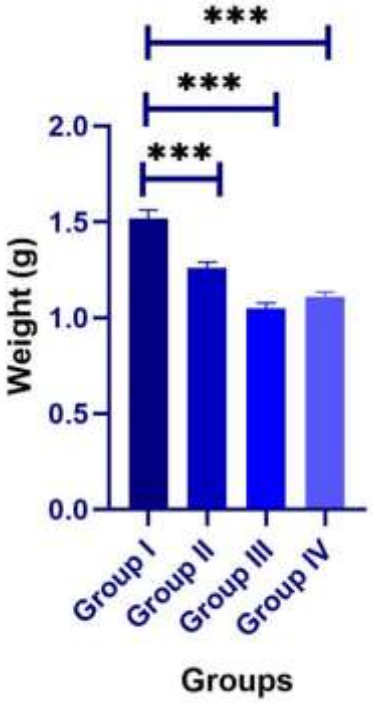

Figure 3. Showing the weight od the liver in all groups (*= significance p<0.05)

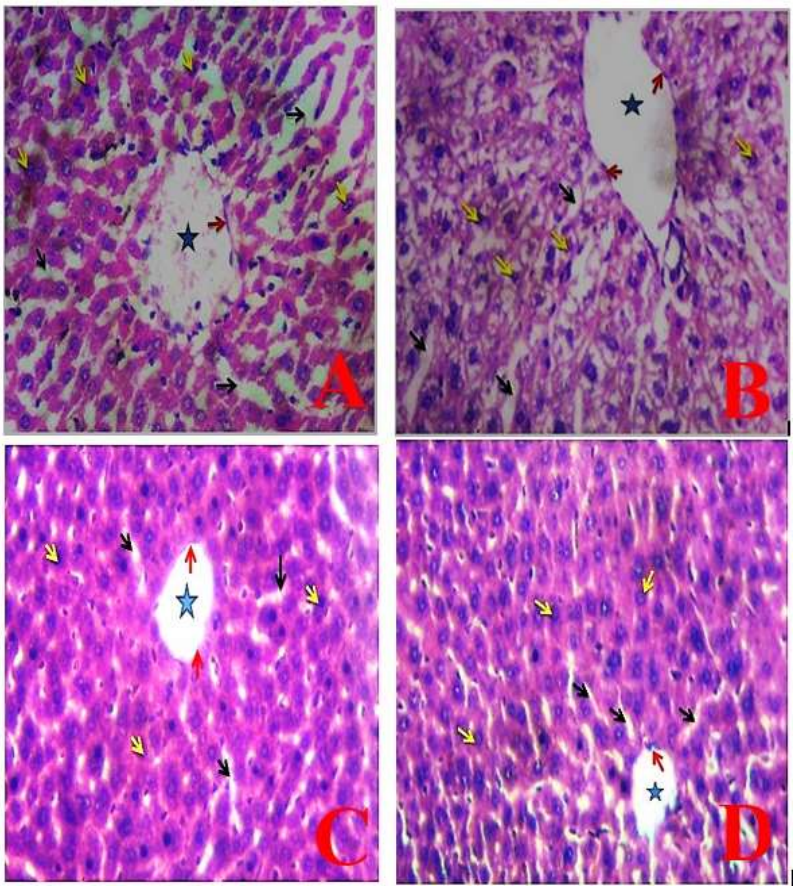

Figure 4. A-D showing the photomicrogragh of the liver of mice in groups I-IV showing the normal hepatic histology showing the central vein (blue star) which is bordered by the squamous endothelia (red arrow). The hepatocytes (yellow arrow) are clearly observed in Group I radiating towards the central vein with clear sinusoidal spaces (black arrow). In Group II, the arrangement of the hepatocytes are disorganized with the sinusoids mostly obliterated (4B). Administration of Alium cepa to the rats in Group III and IV preserved the sinusoids and hepatocytes (4C and D). H and E X 200.

Effect of Ethanol Extract of *Allium cepa* Peel on the Histology of the Kidney of Mice with Ethanol Renal and Hepatic Damage

Figure 5 (A-D) shows the histology of the kidneys of mice in Groups I-IV. The kidneys of rats in Group I showed the glomerular tuft surrounded by the glomerular space. Bowman's capsule surrounded the glomerulus. The proximal and distal convoluted tubules surrounded the glomerulus with the basophilic nuclei of the simple cuboidal epithelial cells observed. The luminal spaces were also clear. The kidney tissue of mice in group II demonstrated collapsed and dilated luminal spaces when compared to the control group. The luminal epithelial cells, however, were preserved as they were in the groups treated with *Allium cepa* extract (Groups III and IV). The lumen in these groups was also clear, and glomerulus intact.

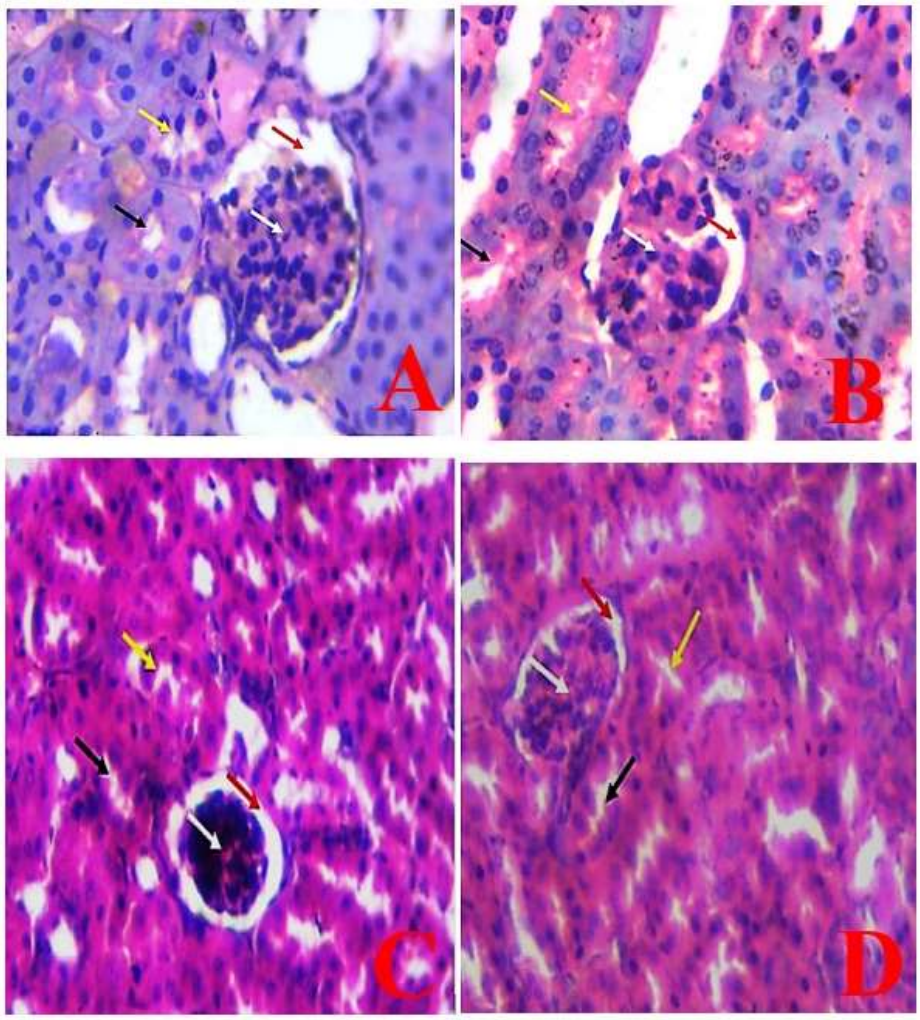

Figure 5. A-D showing the histology of the kidney in mice in groups I-IV showing administered Alium cepa extract. The control group showed normal histology with the glomerular tuft(white arrow) surrounded by Bowman's space (red arrow). The cuboidal cells of the rental tubules surrounded the luminal region (yellow arrow). The tubular luman were clouded and dilated in the ethanol treated group when compared to the control group (5B). Administration of Alium cepa extract preserved the cuboidal cells of the rental tubules and Bowman's capsule (5C and D). H and E X 200.

Discussion

Alcohol-induced renal and hepatotoxicity has been modeled in many scientific studies [12,13, 21,22], and the mechanism for liver injury has been described by Thurman et al. [23]. Alcohol treatment and administration resulted in an increase in the liberation of endotoxins from gut bacteria and may enhance the membrane permeability of the gastrointestinal tract to endotoxins or both. This process can lead to systemic inflammation and contribute to various organ damage, including liver injury. Increased levels of endotoxin activate Kupffer cells to discharge substances such as eicosanoids, TNF-alpha, and free radicals. Prostaglandins increase oxygen uptake and are postulated to be most likely responsible for the hypermetabolic state in the liver. This increase in oxygen demand leads to hypoxia in the liver, and on reperfusion, alpha-hydroxyethyl free radicals are formed, which lead to tissue damage in oxygen-poor pericentral regions of the liver lobule [23].

Administration of *Allium cepa* extract caused a non-significant increase in the body weight in treated groups. Obesity-related studies carried out using *Allium cepa* by several researchers revealed that it increased body weight in obese rats. Moon et al. [24] demonstrated that *Allium cepa* peel significantly reduced the weight of treated rats. Lee et al. [25] reported that Allium cepa extract decreased body mass index (BMI) and body weight. Significant reductions were observed in weight, BMI, waist, hip, and thigh circumferences, as well as skinfold thickness in studies conducted by other researchers [26, 27]. *Allium cepa* extracts and their fractions with their identified bioactive components induce effects through various mechanisms of action, including pancreatic lipase inhibition, adipogenesis inhibition, and energy expenditure increase in the above research studies. Moreover, a substantial number of studies have proven that in non-obese rats, *Allium cepa* did not increase the weight of rats; the reason for this could be due to the phytochemical composition of investigated samples which vary consistently. These differences should be taken into account in further investigations on the potential use of onion in effective formulations intended for weight control and/or treatment [28,29].

The efficacy of *Allium cepa* in the treatment of pathological conditions linked to obesity is linked to the presence of the biomolecule quercetin and organosulfur compounds, which are responsible for the antiobesity potential of *Allium cepa*.

In the present study, *Allium cepa* significantly increased the weight of the kidney and decreased the weight of the liver in treated animals. Similar to the results obtained above, research on the effect of *Allium cepa* extract on cadmium-induced toxic effects showed that the extract ameliorated toxic effects of cadmium on body, liver, and renal weight [30]

In the present study, necrosis and infiltration of inflammatory cells in the liver parenchyma were attenuated by treatment with *Allium cepa*, as it preserved the liver tissue in both low and high doses; the liver tissue in these mice did not show the liver damage present in the liver of mice demonstrating ethanol-induced hepatic toxicity. In the kidney tissue, luminal epithelial cells of the renal tubules and glomeruli were preserved with *Allium cepa* extract treatment. Ozoegwu and Eyo [31] demonstrated the effect of *Allium cepa* on liver tissue following paracetamol-induced toxicity, and at a concentration of 200 mg/kg, they showed distorted hepatic architecture, severely congested central veins, moderately degenerated hepatocytes, and severely congested sinusoids. At 300 mg/kg, the same histopathological features were observed, and at 450 mg/kg, the hepatic tissue showed severely congested central veins, moderately degenerated hepatocytes, and severely congested sinusoids following the administration of *Allium cepa*. Similar to this study, treatment with silymarin (100 mg/kg) showed mildly congested central veins, moderately degenerated hepatocytes, and moderately congested sinusoids, ameliorating the effects of paracetamol-induced injuries. Consistent with the present study, treatment with *Allium cepa* on liver histology showed a remarkable enhancement in lobular and portal inflammation, hepatic steatosis, and ballooning degeneration [32]. Administration of *Allium cepa* resulted in histopathological changes in acute tubular necrosis of the kidney after high doses of *Allium cepa* extract (600 mg/kg), while only mild focal tubular necrosis was present in the low doses (300 mg/kg) used [33]. *Allium cepa* is as effective as vitamin E in helping tissues, such as the liver and kidney, to regenerate [34, 35].

Conclusions

The findings of the current study showed that *Allium cepa* protects against ethanol-induced kidney and liver injury and may be an acceptable candidate to protect against ethanol-induced hepatotoxicity; the results obtained deserve consideration and further investigation to determine the main components that can be considered as potentially therapeutic and protective agents against other toxicities.

Conflict of Interests

The authors declare that there is no conflict of interests.

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Compliance with Ethical Guidelines

For the current research work, the authors adhered to the ethical guidelines outlined by the Declaration of Helsinki: Statement of Ethical Principles for Medical Research, the University of Maiduguri Research and Ethical Committee, and the National Institutes of Health (NIH) guide for the Care and Use of Laboratory Animals (NIH Publications No. 8023, revised 1978), conforming to Directive 2010/63/EU. The research was approved by the Ethical Committee of the Department of Human Anatomy, University of Maiduguri, with code number UM/HA/UGP 23.24 049/085.

Authors' Contributions

Study conception and design: EW, LJ, LLM, MOOA, NID, and HIB. Data collection and processing, performing experiments: EW, LJ, LLM, MOOA, NID, and HIB. Analysis and interpretation of the results: EW, LJ, and NID. Writing the manuscript: MOOA, NID, LLM, and HIB. Critical revision and editing of the manuscript: MOOA, NID, LLM, and HIB. Final approval of the manuscript prior to submission for publication: EW, LJ, LLM, MOOA, NID, and HIB. Supervision: LLM, NID, HIB, and MOOA. Funding

administration: EW, LJ, LLM, MOOA, NID and HIB.

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