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Gallic Acid: A Potential Therapeutic Agent for Managing Diabetes-Associated Neuroinflammation and Cognitive Decline

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ABSTRACT

Recent studies have implicated diabetes as a risk factor for neuroinflammation and cognitive decline, increasing the likelihood of dementia and other neurodegenerative disorders. Gallic acid, a polyphenolic compound extracted from gallnuts, is being studied for its possible therapeutic effects in glucose-related disorders. This study aimed to explore the potential of gallic acid as a therapeutic agent for managing diabetes-associated neuroinflammation and cognitive dysfunction. Thirty-two male Wistar rats used in this experiment were randomly divided into four groups: normal control, diabetic, and two groups receiving gallic acid at doses of 50 mg/kg and 100 mg/kg. The diabetic and gallic acid groups received 65mg/kg b.w. streptozotocin intraperitoneally and were subsequently treated with gallic acid. The open field test was used to assess long-term recognition memory, while brain tissue was collected for histology and biochemical analyses. Gallic acid treatment at a dose of 100mg/kg significantly improved habituation scores ($p<0.05$) and discrimination indices ($p<0.05$) in diabetic rats. Also, treatment with gallic acid prevented neuronal death and microglial depletion caused by diabetes, with mild microglial activation in the cerebral cortex. Furthermore, gallic acid treatment reduced neuroinflammation in a dose-dependent manner, characterised by decreased ($p<0.05$) interleukin-6 at 50 mg/kg and 100 mg/kg) and tumour necrosis factor-alpha levels ($p<0.05$) at 50 mg/kg and 100 mg/kg. The study found that gallic acid significantly protected cognitive function and reduced neuroinflammation in diabetic male Wistar rats. These findings suggest that gallic acid may serve as a therapeutic agent for managing diabetes-associated neuroinflammation and cognitive decline.

Keywords

Gallic acid, Diabetes Mellitus, Neuroinflammation, Cognitive decline

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INTRODUCTION

Gallic acid, an isolate of gallnut, is a polyphenolic compound with potential therapeutic properties in the management of diabetes (Kahkeshani *et al*., 2019; Rahimifard *et al*., 2020; Variya *et al*., 2020; Obafemi *et al*., 2021; Xu *et al*., 2021). It is found in other plant species such as tea leaves and grape seeds (Adefegha *et al*., 2015; Karas *et al*., 2017; Jinrong *et al*., 2021). Gallic acid is composed of 3,4,5-trihydroxybenzoic acid (Fig. 1) (National Center for Biotechnology Information, 2024). There has been extensive research on the antioxidant and anti-inflammatory properties of gallic acid, primarily in the context of glucose metabolism. It has been found to have potent inhibitory effects on enzymes that play a role in glucose metabolism, making it a promising compound for the treatment of glucose-related disorders (Punithavathi *et al*., 2011; Chao *et al*., 2014; Oboh *et al*., 2016; Chao et al. 2021). However, emerging evidence suggests that its potential applications extend beyond glucose regulation. Gallic acid has also

been found to have neuroprotective effects in various models of neurodegenerative disorders, helping to prevent or mitigate the damage caused by oxidative stress and inflammation in the brain (Mansouri *et al*., 2013; Sun *et al*., 2014; Ferk *et al*., 2018; Yu *et al*., 2019; Bhuia *et al*., 2023; Ojo *et al*., 2023).

Studies have shown that diabetes raises the risk of neuroinflammation and cognitive decline, which makes dementia and other neurodegenerative disorders more likely (Chu *et al.*, 2014; Xue *et al*., 2019; Esmaeili *et al*., 2020; Barbiellini *et al*., 2021; Chen *et al*., 2021; Selman *et al*., 2021; Sebastian *et al*., 2023). Diabetes mellitus is characterised by impaired insulin function, glucose metabolism dysfunction, and persistent inflammation (Inzucchi, 2013; Chatterjee *et al*., 2017; Tsalamandris *et al*., 2019; Wondmkun, 2020; Dilworth *et al*., 2021). Besides its established impact on the pancreas and peripheral tissues, research has also shown a connection between diabetes and changes in the central nervous system (CNS) (Seaquist, 2010; Grote *et al*., 2013; Ruud *et al*., 2017; Luna *et al*., 2021; Al-Sayyar *et al*., 2023). Research has found that people with diabetes are more likely to develop cognitive impairment and dementia, with some studies indicating that as many as 70% of type 2 diabetes patients may experience cognitive decline (Kinattingal *et al*., 2023).

Numerous diabetes-associated microvascular complications, such as diabetic neuropathy, identify oxidative stress and neuroinflammation as pivotal pathophysiological triggers (Sandireddy *et al*., 2014). Inflammation in the CNS triggers the activation of microglia and astrocytes, which leads to the release of pro-inflammatory molecules like interleukin-6 (IL-6) and tumour necrosis factor-alpha (TNF-α) (Wang *et al*., 2015; Kempuraj *et al*., 2016; Kwon and Koh, 2020; Gąssowska *et al*., 2023; Isik *et al*., 2023). These pro-inflammatory molecules can harm neurons and contribute to cognitive decline. Studies have also shown that diabetic animals display increased programmed cell death (apoptosis) in the brain (Vincent *et al*., 2002; Sadeghi *et al*., 2016), which can also contribute to cognitive impairment.

Cognitive function in animals can be evaluated using a range of behavioural tests, including the novel object recognition (NOR) test, which assesses their ability to recognise and distinguish between new and familiar objects and can also involve measuring habituation and discrimination indices (Gaskin *et al*., 2010; Akkerman *et al*., 2012; Antunes and Biala, 2012; Lueptow, 2017). Habituation refers to an animal's ability to become less responsive to repeated stimuli, while the discrimination index measures their capacity to differentiate between distinct stimuli.

There is a dearth of information on the neuroprotective effect of gallic acid on neuroinflammation in the context of diabetes-associated neuroinflammation. In this study, the brain's histomorphology, levels of inflammatory markers like IL-6 and TNF-α, and cognitive function using NOR tests, including habituation and discrimination index, were assessed. The aim of the present study was to investigate gallic acid as a novel therapeutic agent in managing diabetes-associated neuroinflammation and cognitive dysfunction in a rat model of diabetes.

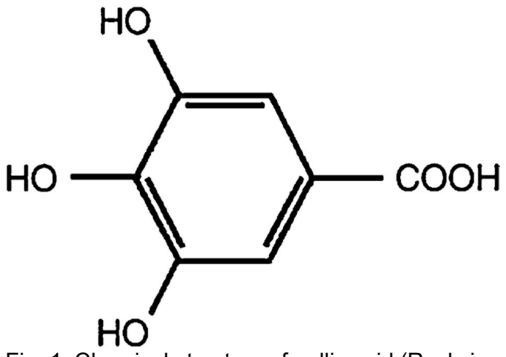

Fig. 1: Chemical structure of gallic acid (Reckziegel *et al*., 2016)

MATERIALS AND METHODS

Animals

Thirty-two male rats of the Wistar strain, weighing 180-220 g, were used in this study. The rats were obtained from the animal breeding facility of the College of Medical Sciences, University of Calabar, Nigeria, where they were also housed and cared for. They were maintained at room temperature with access to food and water ad libitum during a 7-day acclimatisation period and a 21-day experimental period. The experimental procedures were performed in accordance with the National Institutes of Health (NIH) guidelines for the care and use of laboratory animals (National Research Council, 2011). The research was approved by the Institutional Animal Ethics Committee of the College of Medical Sciences, University of Calabar (Ethical Approval Number: 150ANA1024).

Experimental Design

The study was conducted using a randomised control design. The rats were fasted overnight before being administered a single intraperitoneal (i.p.) dose of 50 mg/kg body weight of freshly prepared streptozotocin (STZ) in citrate buffer (0.1 M, pH 4.5) to induce diabetes, as described by Hasanein and Shahidi (2011). The blood glucose levels of rats were read after 72 h using a Finetech glucometer, and levels above 250 mg/dL were considered diabetic. The Wistar rats were randomly divided into four groups of eight animals each, totalling 32 rats: Normal control rats were given food and water ad libitum; diabetic rats (STZ) were administered with 65 mg/kg bw, i.p. of STZ; diabetic rats were administered with 50 mg/kg bw, i.p. of gallic acid (STZ + GA-50); and diabetic rats were administered with 100 mg/kg bw, i.p. of gallic acid (STZ + GA-100) as derived from previous studies (Patel and Goyal, 2011; de Oliveira *et al*., 2016). The study lasted for 21 days following the method of Ojo *et al*. (2023).

Novel Object Recognition Test

The NOR test was used to assess memory and cognitive function in the rats. It was conducted in an open box apparatus measuring 72 × 72 × 36 cm, with a plexiglass wall for visibility. The floor of the arena was divided into 25 squares (20 × 20 cm), facilitating the observation of the rats' exploratory behaviours. The test consisted of three

phases: The habituation phase, where rats were allowed to explore an empty arena for 10 min to acclimate and minimise stress; the familiarisation phase, occurring 24 h later, where two identical objects differing were placed in the arena for the rats to explore for another 10 min; and the NOR phase, conducted one day after familiarisation, in which one familiar object and a novel one were presented to the rats for 10 min to assess recognition memory.

The habituation score, which is the ratio of the time animals spent exploring the new object to the total time they spent exploring both objects, and the discrimination index, which is the ratio of the time animals spent exploring the novel object to the total time they spent exploring both objects, were two important metrics that were evaluated. The following parameters were recorded: time spent exploring each object and discrimination index percentage. Based on the method adopted by Adebiyi *et al*. (2022), the test was done 16 days after the gallic acid treatment started.

Animal Sacrifice and Tissue Collection

Twenty-four hours after behavioural testing, rats were humanely euthanised by intraperitoneal injections of a ketamine hydrochloride (50 mg/kg) and xylazine hydrochloride (7 mg/kg) cocktail, as described by Struck *et al*. (2011). The whole rat brains were removed following division into two portions, left and right hemispheres: One part was placed in a 10% neutral buffered formalin solution for histological analyses, while the other was rinsed in phosphate-buffered saline to remove excess blood and stored at -70°C for biochemical assay.

Homogenisation and Biochemical Assays

Five cerebral cortices of the brain samples per group were homogenised in chilled Tris-HCl buffer at a ratio of 1:10 (w/v) and centrifuged at 3,000 g for 10 min. The resulting supernatant was used for the analysis of various biochemical parameters.

Enzyme-Linked Immunosorbent Assay (ELISA)

The assays used rat-specific ELISA kits (MBS760693, MyBioSource Biotechnology Company, San Diego, U.S.A.) for IL-6 and TNF-α. The assays were performed according to the manufacturer's instructions. The intra-assay coefficients of variation for the IL-6 and TNF-α kits were 5.7% and 5.1%, respectively.

Histological Examination

Following sacrifice, rat brains were fixed in a 10% formalin solution and processed for paraffin embedding. Histological sections of 5 µm thickness were obtained at the level of the cerebrum and stained with haematoxylin and eosin. Sections were then examined under a light microscope to assess histological changes (Bancroft and Layton, 2013).

Statistical Analyses

The data were analysed using a one-way analysis of variance followed by a post-hoc Tukey's test to compare the means between groups with the Statistical Package for Social Science (SPSS) IBM SPSS Statistics V. 29. The level of significance was set at $p < 0.05$. The results are presented as mean ± standard error of the mean (SEM).

RESULTS

Behavioural Assessment

Habituation Score

The behavioural assessment showed a significant decrease in the habituation index in diabetic rats compared to normal controls. The gallic acid-treated groups administered 50 mg/kg and 100 mg/kg had significantly higher habituation scores compared to the untreated diabetic group ($p < 0.05$), but not with the control group (Fig. 2).

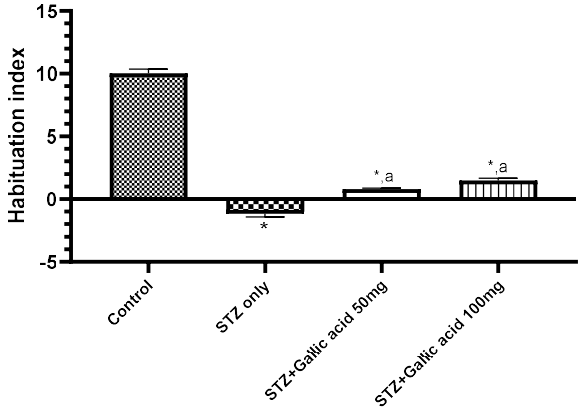

Fig. 2: Habituation score of the experimental groups
* - Significantly different from control at $p < 0.05$; a - Significantly different from the untreated diabetic (STZ) group at $p < 0.05$

Discrimination Index

The behavioural assessment showed a significant decrease in the discrimination index in diabetic rats compared to normal controls. The gallic acid-treated groups administered 50 mg/kg and 100 mg/kg had significantly higher discrimination indices compared to the untreated diabetic group ($p < 0.05$), but not with the control group (Fig. 3).

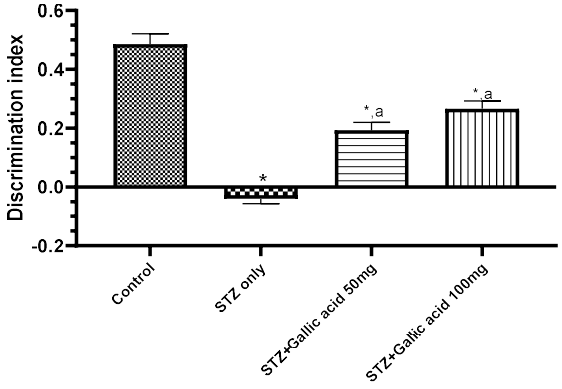

Fig. 3: Discrimination index for the experimental groups
* - Significantly different from control at $p < 0.05$; a - Significantly different from the untreated diabetic (STZ) group at $p < 0.05$

Histological Study

In the control group, the histology of the rats' cerebral cortex showed normal neuronal cell bodies that were round or oval-shaped and had clear nuclei. The microglia had small cell bodies with small nuclei and lightly stained cytoplasm. The diabetic group showed marked changes in the morphology of pyramidal neurones and microglia. These include severe neuronal death characterised by pyknosis, karyorrhexis, fragmentation of the nucleus, vacuolation, eosinophilia of the pyramidal neurons, and microglial depletion (Fig. 4).

In contrast, the cerebral cortex of gallic acid-treated diabetic rats at 50 mg/kg showed mild neuronal damage, characterised by neuronal swelling and moderate microglial death. Gallic acid-treated diabetic rats at 100 mg/kg exhibited a different profile, with normal neurons showing no signs of swelling or nuclear change. Instead, mild microglial activation was observed, characterised by enlargement of microglial cells and the presence of vacuoles (Fig. 4).

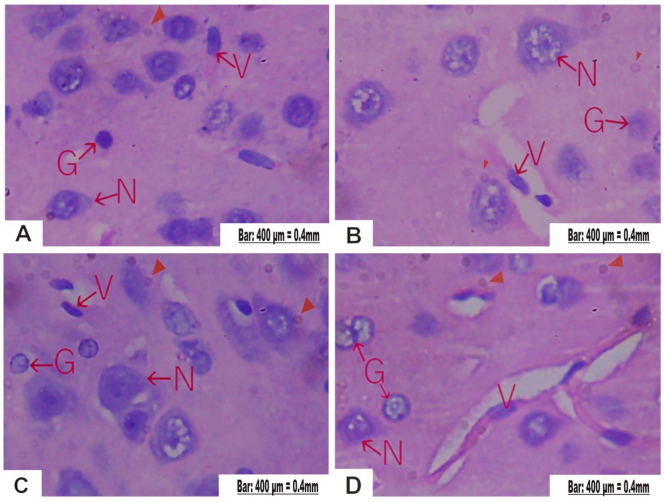

Fig. 4: Photomicrographs of the histomorphology of the cerebral cortices in the experimental groups: A: The cerebral cortex showing pyramidal neurons (N) and microglia (G) in control rats. B: The cerebral cortex showing pyramidal neurons (N) and microglia (G) in diabetic rats; C: The cerebral cortex showing pyramidal neurons (N) and microglia (G) in gallic acid-treated diabetic rats at 50 mg/kg; D: The cerebral cortex showing pyramidal neurons (N) and microglia (G) in gallic acid-treated diabetic rats at 100 mg/kg. arrow head – granule cells; V- blood vessels; H&E; Mag. x 400

Biochemical Assay

Interleukin-6 Levels

The biochemical test showed that diabetic rats treated with gallic acid had less neuroinflammation. This was shown by a significant decrease in IL-6 levels. Gallic acid-treated groups (both 50 mg/kg and 100 mg/kg) had significantly higher levels of IL-6 compared to the untreated group (Fig. 5).

Tumour Necrosis Factor (TNF-a) Levels

The biochemical assay showed an anti-inflammatory effect, characterised by a significant reduction in the TNF-a level in diabetic rats treated with gallic acid. The gallic acid-treated groups, at both 50 mg/kg and 100 mg/kg doses, showed increased levels of TNF-a, which were significantly higher than those in the diabetes-untreated group (Fig. 6).

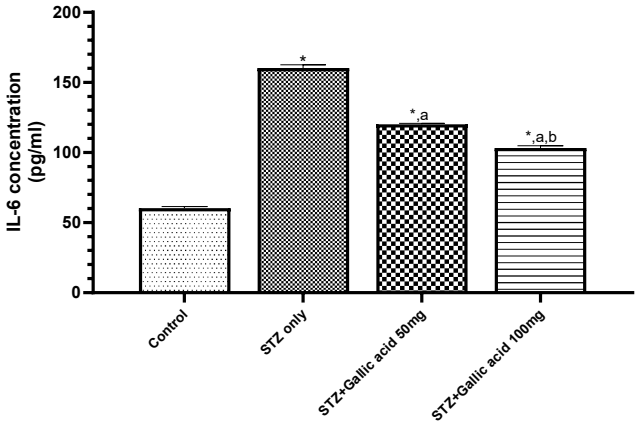

Fig. 5: Interleukin-6 (IL-6) levels among the experimental groups
* - Significantly different from the control at $p < 0.05$; a - Significantly different from the diabetes (STZ) group at $p < 0.05$; b - Significantly different from STZ+ Gallic acid 50 mg/kg group at $p<0.05$

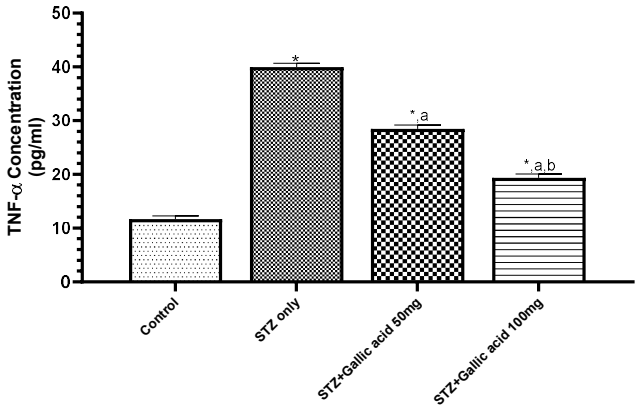

Fig. 6: TNF-α levels from the experimental groups
* - Significantly different from control at $p < 0.05$; a - Significantly different from the diabetes (STZ) group at $p < 0.05$; b - Significantly different from STZ+ Gallic acid 50 mg/kg group at $p<0.05$

DISCUSSION

This study aimed to evaluate the efficacy of gallic acid as a therapeutic agent for mitigating diabetes-associated neuroinflammation and cognitive dysfunction. The present study reveals that treatment with gallic acid at a dose of 100 mg/kg significantly improved neurobehavioural outcomes, specifically habituation and cognitive function, in a rat model of diabetes. Behavioural assessment showed that the gallic acid-treated diabetic rats exhibited notably higher habituation scores compared to the untreated diabetic group, suggesting a preserved cognitive ability. Poor

habituation in diabetic rats could be associated with chronic neuroinflammation and may reflect underlying neurological damage, highlighting the need for effective therapeutic strategies in this population. This finding indicates that gallic acid might mitigate the cognitive impairments commonly associated with diabetes, which has been linked to chronic neuroinflammation and functional deficits in the CNS (Selman *et al*., 2021; Sebastian *et al*., 2023).

The discrimination index also supports the cognitive protection ability of the rats observed, as gallic acid-treated groups displayed increased capacity to differentiate between new and familiar objects. The improvement in the discrimination indices observed in gallic acid-treated groups further underscores these cognitive enhancement effects. These behavioural improvements can be attributed to the compound's anti-inflammatory effects, as both habituation and discrimination are critical indicators of cognitive flexibility, memory, and spatial awareness in animals (Akkerman *et al*., 2012; Lueptow *et al*., 2017).

In alignment with the behavioural results, the histological examination of the cerebral cortex demonstrated that gallic acid treatments ameliorated diabetic-induced neuronal death and microglial depletion. The presence of pyknosis, karyorrhexis, and pronounced vacuolation in the untreated diabetic group reflects neurodegeneration: This is because diabetes triggers neuroinflammation, leading to neuronal apoptosis and cognitive decline (Wang *et al*., 2015; Gąssowska *et al*., 2023). These findings substantiate the behavioural impairments observed, suggesting that untreated diabetes leads to irreversible neuronal damage and underscoring the importance of early intervention. The cerebral cortices of the gallic acid-treated groups revealed normal neuronal morphology, characterised by rounded or oval-shaped neuronal cell bodies with distinct nuclei. These observed histological preservations coincide with established literature suggesting the protective effect of gallic acid on neuron morphology, indicating its potential in counteracting the neurodegenerative changes associated with diabetes (Díaz *et al*., 2020).

The biochemical assays provided further insight into the mechanism by which gallic acid exerts its neuroprotective effects. IL-6 and TNF-α levels significantly increased in the untreated diabetic group, suggesting activated neuroinflammatory processes. The fact that IL-6 and TNF-α levels dropped significantly in the groups that were treated with gallic acid shows that it had a strong anti-inflammatory effect. Notably, treatment with gallic acid resulted in significant reductions in these pro-inflammatory cytokines. The reduction of these cytokines is particularly meaningful, as IL-6 and TNF-α are known contributors to neuroinflammatory processes that can exacerbate neuronal damage and cognitive impairments in diabetic conditions (Kempuraj *et al*., 2016; Isik *et al*., 2023).

The correlation between decreased levels of these inflammatory markers and the observed behavioural and histological improvements emphasises gallic acid's role as a potent anti-inflammatory agent. In fact, studies have indicated that chronic inflammation in the CNS can lead to increased neuronal apoptosis, further supporting the importance of managing neuroinflammation in diabetes (Vincent *et al*., 2002; Sadeghi *et al*., 2016).

Diabetic conditions have serious effects on neurological health (Rojas-Carranza *et al*., 2018). If they are not treated, they can cause cognitive problems and strong neuroinflammatory responses. Conversely, gallic acid demonstrated a noteworthy capacity to ameliorate these deleterious effects, particularly at a dosage of 100 mg/kg, which appeared more effective compared to the lower 50 mg/kg dose. Future studies should explore the dosage response further and assess potential translational outcomes in human models of diabetes.

The mechanism of action for gallic acid could involve its antioxidant and anti-inflammatory properties, which may alleviate oxidative stress and chronic inflammation in diabetes (Chao *et al*., 2014; Oboh *et al*., 2016). By reducing pro-inflammatory cytokines such as IL-6 and TNF-α, gallic acid may inhibit the activation of microglia and astrocytes in the CNS, thereby mitigating neuroinflammation and preserving neuronal integrity (Wang *et al*., 2015; Gąssowska *et al*., 2023). Additionally, gallic acid may reduce programmed cell death (apoptosis), further enhancing cognitive performance (Vincent *et al*., 2002; Sadeghi *et al*., 2016). Thus, gallic acid may target both metabolic dysfunction and neuroinflammatory pathways associated with cognitive decline in diabetes, supporting its potential as a therapeutic intervention (Variya *et al*., 2020; Xu *et al*., 2021).

Conclusion

This study highlighted the neuroprotective effects of gallic acid against diabetes-associated neuroinflammation and cognitive dysfunction. The substantial improvements observed in neurobehavioural outcomes in habituation and discrimination indices highlight its efficacy in mitigating cognitive decline associated with diabetes. The changes seen in the brain's histology and biochemistry also support gallic acid's neuroprotective role. This suggests that it could be a useful way to treat cognitive problems caused by diabetes. The connection between neuroinflammation and cognitive decline makes it clear that gallic acid should be studied more as a possible way to prevent or improve the cognitive problems that come with diabetes.

DECLARATION

Acknowledgements

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Grants and Financial Support

None was received

Conflict of Interest

None declared.

Ethical Approval
Every effort was made to minimize the number of animals used and their suffering in this study. We followed the National Institutes of Health (NIH) guidelines for the care and use of laboratory animals in the experiments. The Institutional Animal Ethics Committee (IAEC) of the College of Medical Sciences, University of Calabar, Cross River, Nigeria, gave the ethical approval (Ethical Approval Number: 150ANA1024).

Consent to Participate and Publish Data
Not Applicable.

Authors' Contribution
TEI, EME, MEO: Study design and conceptualization. NMU, EP, PNU: Data collection and statistical analysis. TEI, EIO: Literature review. EIO: Writing and editing.

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