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Research Article

Neuroprotective Effects of *Cucurbita pepo* Leaves Extracts on Aluminium Chloride-Induced Alzheimer's Disease in Albino Rats

***Bawa Y. Muhammad[1], Abdulkadir H. Lawal[1], Saadiya A. Tukur[1] and Ruqaiyatu M. Adamu[2]**

[1]Department of Biochemistry, Nasarawa State University, Keffi, Nigeria
[2]Drug information Unit, Pharmacy Department, Federal Medical Centre, Keffi, Nigeria
****Corresponding Author's email*:** abuddar@nsuk.edu.ng

ABSTRACT
This study evaluated the neuroprotective effect of *Cucurbita pepo* leaves methanol extract in rat model of Alzheimer's disease induced by Aluminium chloride. Thirty male Wistar rats were divided into six groups (n = 5): normal control, disease control, low dose, high dose, and standard (Vitamin E). Aluminium chloride (100 mg/kg, i.p.) was administered daily for 28 days, except in the normal control. Treatments were given two hours post- $AlCl_3$ injection. Behavioural tests were conducted on days 1, 7, 14, 21, and 28, followed by biochemical analysis of brain tissue. Disease control rats showed elevated amyloid-β and tau proteins, reduced antioxidant enzyme activities (SOD, GPx), increased lipid peroxidation (MDA), and neurotransmitter imbalance (↑AChE, MAO-A, MAO-B; ↓acetylcholine). Administration of *C. pepo* extract significantly reversed these alterations, enhancing antioxidant defences and normalizing neurotransmitter levels. Phytochemical profiling revealed high concentrations of steroids and phenols. In the Elevated Plus Maze Test, disease controls showed reduced open-arm exploration ($p < 0.001$), while extract treated rats showed improved performance comparable to Vitamin E. *Cucurbita pepo* leaves extract revealed strong neuroprotective properties, attenuating Alzheimer's like pathology through modulation of oxidative stress, neurotransmitter regulation, and amyloid-tau burden. These findings suggest its potential as a promising adjunctive therapy for neurodegenerative disorders.

Keywords: Alzheimer's disease; Amyloid-beta; Antioxidants; *Cucurbita pepo;* Elevated Plus Maze; Neuroprotection; Neurotransmitters; Tau protein

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INTRODUCTION

Alzheimer's disease (AD) is a progressive, neurodegenerative condition characterized by cognitive and functional decline, including episodic memory loss, language skills impairment, neuropsychiatric symptoms, and premature death (Zhao *et al.,* 2024). It involves the degeneration of cholinergic neurons in the brain, leading to reduced acetylcholine synthesis and secretion, amyloid-beta (Aβ) deposition, and plaque formation causing dementia (Zhao *et al.,* 2024). Approximately 60–80% of dementia cases are attributed to AD, affecting around 25 million people globally, with projections of 115.4 million cases by 2050 (Abubakar *et al.,* 2025).

Oxidative stress occurs when there is an imbalance between the production of reactive oxygen species (ROS) and the body's ability to detoxify them or repair resulting damage (Ashikaa *et al.,* 2023). In the brain, high oxygen consumption and abundant lipid content make neurons particularly susceptible to oxidative damage. Key contributors to oxidative stress in AD include amyloid-beta (Aβ) plaques Aβ peptides can induce oxidative stress by generating free radicals, affecting lipids, proteins, and nucleic acids (Majid &

Garg, 2024). Lipid peroxidation compromises cell membrane integrity, leading to neuronal dysfunction and cell death. Oxidative modifications of proteins and DNA further exacerbate neuronal damage and disrupt cellular processes (Majid & Garg, 2024).

Inflammation is another critical factor in AD pathogenesis, Chronic neuroinflammation is characterized by sustained activation of microglia and astrocytes (Kakkar *et al.,* 2025), which release pro-inflammatory cytokines and chemokines such as IL-6, TNF-α, and IL-1β in response to Aβ deposition (Nasb *et al.,* 2024). While initially protective, prolonged inflammation becomes detrimental, contributing to a vicious cycle of neuronal injury, increased Aβ production, oxidative stress, and further inflammation (Nasb *et al.,* 2024). These interlinked processes are central to AD progression; Therapeutic strategies targeting both oxidative stress and inflammation hold promise for altering the disease course (Scarano *et al.,* 2025).

Heavy metals, especially Aluminium (Al), have been linked to neurodegenerative diseases such as AD (Kumar, 2025). Al exposure from diet, water, cosmetics, or medications; leads to AD-like symptoms, including memory deficits and neuronal loss (Kumar, 2025).

Herbal medicine has shown efficacy in treating neurodegenerative diseases; phytochemicals improve cognitive function (Sani, *et al.,* 2023). Cucurbita pepo (pumpkin) leaves have gained interest for their bioactive compounds, offering therapeutic benefits for oxidative stress-induced conditions (Abubakar *et al.,* 2025)

Existing pharmacologic treatments for AD provide only symptomatic relief without mitigating the root causes, seldom with side effects and partial efficacy (Cummings, 2021), There's a pressing need for safe, effective new therapies. Thus, this research investigates the Neuroprotective Effects of Cucurbita pepo Leaves Extracts on Aluminium Chloride-Induced Alzheimer's Disease in Albino Rats

MATERIALS AND METHODS

Chemicals and Reagents

Why Some chemicals and reagents used were of analytical grade and they include: Concentrated Hydrochloric Acid, Acetic Anhydride, Wagner's Reagent/ Mayer's Reagent, Sodium Hydrochloride (NaOH), Glacial acetic acid, Ethanol, Sodium Chloride (NaCl), Glutathione reductase solution, Phosphate buffer, n-butanol, Diethyl ether, Sodium Azide Solution, Hydrogen Peroxide, ß-Nicotinamide Adenine Dinucleotide Phosphate.

Preparation and extraction of pumpkin leaves extract

The pumpkin leaves (obtained from the farm), being fleshy and moist, was initially washed to remove impurities and then cut into smaller pieces to increase the surface area for extraction. The pieces were blended into a smooth paste to facilitate the extraction process. Approximately 500 g of the leaves paste was weighed accurately and placed in a maceration container. Methanol was added in a 1:10 ratio to the leaves paste, ensuring complete submersion. The mixture was allowed to macerate for 72 hours at room temperature, with occasional stirring to enhance the extraction process. Following maceration, the mixture was filtered through cheesecloth to separate the liquid extract from the solid residues. The filtrate was then concentrated under reduced pressure at 45°C using a rotary evaporator to remove the solvent. The concentrated extract was subsequently stored at 4°C in airtight containers for future use.

Experimental Animals

Thirty adults Wister albino rats (250-265g body weight) were obtained from Nasarawa State University Keffi, Nasarawa State. Ethical approval was obtained from Ethical Committee for Animal Studies, Nasarawa state University, Keffi. The animals were handled in accordance with principles of Planning Research and Experimental procedures on Animals: The rats were housed in the animal's house of the Department of Biochemistry, Nasarawa State University, Keffi. They were maintained on standard rat vital feed and water which were made available ad libitum for the period of experiment.

Experimental Design

A randomized block design was employed to ensure that variability within the blocks is minimized and to increase the precision of the experiment. The study involved six groups of thirty male Wister rats (n = 5 per group) that were equally distributed. Aluminium chloride (AlCl3) at a dose of 100 mg/kg was administered intraperitoneally to all animals, except for the normal control group, daily for 28 days prior to treatment initiation.

The experimental groups were designed as follows:

Group I: Normal Control (Standard feed and water)

Group II: Disease Control (Feed, water, and 10 mg/kg of $AlCl_3$)

Group III: low dose (Feed, water, $AlCl_3$, and 100 mg/kg of pumpkin leaves extract)

Group IV: High dose (Feed, water, $AlCl_3$, and 200 mg/kg of pumpkin leaves extract)

Group V: Standard (Feed, water, $AlCl_3$, and Vitamin E)

All treatments were administered two hours after the $AlCl_3$ injection. Behavioural parameters were evaluated on days 1, 7, 14, 21, and 28. On the 28th day, the animals were euthanized, and brain tissues were collected for neuro-inflammatory, neurochemical, and biochemical analyses

Quantitative Analysis of the Plant Extract

Phytochemical constituents of the Cucurbita pepo leave methanol extract were quantified using established spectrophotometric assays. Total phenolic and tannin contents were determined with the Folin–Ciocalteu method (Muhammad *et al.,* 2019) while flavonoids were estimated by the aluminum chloride colorimetric assay with rutin as standard. Alkaloids and terpenoids were analysed following the previous method standardized (Tiwari & Chanda, 2016) and sterols were measured using the Liebermann–Burchard reaction (Araújo et al., 2013). Cardiac glycosides and saponins were assessed according to Sofowora (Sofowora & Medicine, 1996), Quantification was performed against appropriate calibration standards, and all analyses were conducted in triplicate.

Behavioural Parameter Assessment: Elevated Plus Maze Test (EPMT)

The elevated plus maze test (EPMT) was employed to evaluate anxiety-like behaviour and long-term spatial memory. The apparatus consisted of two closed arms and two open arms of equal dimensions, extending from a central platform. The closed arms were enclosed by high black walls, while the open arms lacked walls. The apparatus was elevated 40 cm above the ground. Each rat was placed in one of the open arms, facing away from the central platform. Over a 3-minute period, the number of entries into the closed arms and the time spent in the open arms were recorded. Behavioural assessments were conducted on days 1, 7, 14, 21, and 28, following the methodology described recently (Madden *et al.,* 2020)

Preparation of Tissue Homogenate for biochemical analyses

Following a 4-week administration period, the rats were decapitated, and their brains were promptly excised and placed in ice-cold saline. Brain tissue homogenates were prepared from the dissected brains of rats in each experimental group. The tissues were homogenized using a mechanical homogenizer and diluted in a 1:9 (w/v) ratio with phosphate buffer (pH 7.4). The homogenates were centrifuged at 6000 rpm for 15 minutes, and the resulting supernatants were collected for use in the estimation for subsequent biochemical analyses. For estimation of monoamine oxidase, A and B. The supernatant was then centrifuged at 12,000 rpm for 20 minutes. The resulting pellet was washed twice with 100 ml of the sucrose-Tris-EDTA buffer and resuspended in 50 ml of the same medium. The protein concentration of the final preparation was adjusted to 1 mg/ml.

Determination of Antioxidant Parameters

The concentrations of malondialdehyde (MDA), glutathione peroxidase (GPx), and superoxide dismutase (SOD) were determined using ELISA kits obtained from Sunlong Biotech Co., Ltd. (China), following the manufacturer's protocols. Optical density (OD) was measured using a microplate reader, and enzyme activities were calculated based on standard calibration curves supplied with the kits.

Determination of Neurochemical and Enzymatic Biomarkers

The activities of monoamine oxidase A (MAO-A) and B (MAO-B), acetylcholinesterase (AChE), and acetylcholine, as well as the levels of β-amyloid and tau proteins, were quantified using commercial assay kits purchased from Solarbio Life Sciences (Beijing, China) in accordance with the manufacturers' instructions. Optical density (OD) values were read on a microplate reader, and concentrations or enzyme activities were derived from the standard calibration curves provided with the respective kits.

Ethical approval

Ethical approval for the study was obtained from the Ethical Committee of the Research and Publication, Nasarawa State University, Keffi, Nigeria (Approval No. RP/ETH/2025/10), in accordance with institutional regulations and in strict compliance with the ARRIVE guidelines for the care and use of laboratory animals.

RESULTS

Quantitative Phytochemical Analysis of Cucurbita pepo Leaves Methanol Extracts

The quantitative analysis results presented in Table 1 indicate that steroids (19.55±0.83b) and phenols (14.70±0.05b) were the predominant phytochemicals in Cucurbita pepo leaves methanol extract. Flavonoids (10.33±0.06b) and saponins (7.62±0.36b) were detected in moderate concentrations, whereas tannins (1.00±0.05a), cardiac glycosides (3.64±0.20a), and glycosides (3.25±0.18a) were present in relatively lower amounts. These findings suggest that *C. pepo* leaves is a rich source of bioactive compounds, with steroids and phenols being the most abundant constituents.

Effects of C. pepo Leaves Methanol Extracts on Aluminium Chloride-Induced Alzheimer Rats on

Time Spent in Open Arms (s) at Different Days of Treatment (Elevated Plus Maze Test)

All experimental animals underwent the Elevated Plus Maze Test (EPMT) to assess anxiety-related behaviours and memory performance on days 1, 7, 14, 21, and 28. A marked reduction ($p < 0.05$) in the duration spent in the open arms was observed in the disease control group when compared with the normal control group. In contrast, animals treated with Cucurbita pepo leaves extract demonstrated a significant increase ($p < 0.05$) in time spent in the open arms relative to the disease control group. Similarly, the standard treatment group exhibited a significant enhancement ($p < 0.05$) in open arm duration compared to the disease control group.

Table 1 Quantitative Phytochemical Analysis of the *C. pepo* Leaves Extract

Phytochemical	Concentration (mg/g)
Phenols	14.70±0.05[b]
Tannins	1.00±0.05[a]
Saponins	7.62±0.36[b]
Alkaloids	ND
Steroids	19.55±0.83b
Cardiac glycosides	3.64±0.20[a]
Glycosides	3.25±0.18[a]
Flavonoids	10.33±.0.06[b]

Result presented as Mean ± Standard deviation, a = p>0.05, b = p<0.05.

Table 2. Alzheimer Rats on Time Spent in Open Arms (s) at Different Days of Treatment (Elevated Plus Maze Test)

Day	Normal Control (s)	Disease Control (s)	Low dose (s)	High dose (s)	Standard (s)
1	77 ± 4.18	33 ± 3.65	55 ± 4.90***	58 ± 4.70***	62 ± 34.16***
7	76 ± 4.50	30 ± 3.58	62 ± 3.52***	67 ± 5.60***	72 ± 6.52***
14	79 ± 4.40	28 ± 3.48	61 ± 3.24***	77 ± 4.90***	79 ± 5.13***
21	74± 4.40	27 ± 4.10	62 ± 4.24***	73 ± 4.80***	74 ± 4.13***
28	76 ± 5.90	30 ± 3.99	60 ± 3.17***	71 ± 5.61***	81 ± 4.15***

Values are presented as mean ± SEM (Standard Error of Mean). ***p < 0.001, **p < 0.01 compared to disease control group

Antioxidant Effect of C. pepo Leaves Methanol Extracts

The results presented in Table 3 indicate a significant reduction in SOD and GPx levels in the disease control group (II), accompanied by a marked increase in MDA concentration compared to the normal control group. However, administration of both low and high doses of Cucurbita pepo extract, as well as vitamin E, led to a significant increase in SOD and GPx levels, with a concomitant reduction in MDA concentration relative to the disease control group. Particularly, while the low-dose C. pepo extract showed a greater enhancement in SOD and GPx activity compared to the high dose, the difference was not statistically significant.

Effect *C. pepo* Leaves Methanol Extract on Brain Neurotransmitters

The findings presented in Table 4 demonstrate a significant ($p < 0.05$) increase in acetylcholinesterase (AChE), monoamine oxidase A (MAO-A), and monoamine oxidase B (MAO-B) activities, with concomitant significant ($p < 0.05$) decrease in acetylcholine (ACh) levels in Disease control group compared to the Normal control. Nevertheless, administration of *Cucurbita pepo* leaves extract caused in a significant ($p < 0.05$) reduction in AChE, MAO-A, and MAO-B activities, accompanied by a notable ($p < 0.05$) elevation in ACh levels at higher doses relative to the induced untreated group. This neuroprotective effect was analogous to that observed with the standard drug, vitamin E.

The chart demonstrates the concentration of Aβ (µg/g tissue) across the experimental groups: Normal Control (I), Disease Control (II), Low Dose (III), High Dose (IV), and Standard (V). Group II revealed a significant increase in Aβ levels compared to group I. Administration of Cucurbita pepo extract at both low and high doses, as well as the standard treatment, resulted in a reduction in Aβ levels relative to the Disease Controll group. Similarly, A significant increase in Tau levels was observed in group II compared to the Normal Control (I). Treatment with

Cucurbita pepo extract at both doses (III & IV) and the standard treatment (V) caused a reduction in Tau protein levels, suggesting a potential neuroprotective effect. The error bars denote SEM, and statistical differences between groups are indicated by superscripts.

The chart in Figure 1 demonstrates the concentration of Aβ (µg/g tissue) across the experimental groups: Normal Control (I), Disease Control (II), Low Dose (III), High Dose (IV), and Standard (V). Group II revealed a significant increase in Aβ levels compared to group I. Administration of Cucurbita pepo extract at both low and high doses, as well as the standard treatment, resulted in a reduction in Aβ levels relative to the Disease Control group. Similarly, A significant increase in Tau levels was observed in group II compared to the Normal Control (I). Treatment with *Cucurbita pepo* extract at both doses (III & IV) and the standard treatment (V) caused a reduction in Tau protein levels, suggesting a potential neuroprotective effect. The error bars denote SEM, and statistical differences between groups are indicated by superscripts.

Table 3: Effects of *C. pepo* Leaves Methanol Extracts on Antioxidants Biomarkers

Group	SOD (U/ml)	GPx (U/ml)	MDA (nmol/mg protein)
Group I: Normal Control	18.56±0.26^{b}	42.26±5.14^{b}	0.64±0.02^{b}
Group II: Disease Control	16. 72±0.05^{a}	30.43±1.04^{a}	2.53±0.18^{a}
Group III: low dose	19.19±0.24^{b}	49.52±4.71^{b}	1.62±0.30^{b}
Group IV: High dose	18.65±0.33^{b}	51.33±5.36^{b}	0.56±0.14^{b}
Group V: Standard	18.84±0.56^{b}	42.32±3.02^{b}	2.05±0.37^{a}

Results are expressed as means ± standard deviation. Different alphabets at superscript of the means indicates significant differences down the group at P<0.05.

Table 4 Effect *C. pepo* Leaves Methanol Extract on Brain Neurotransmitters

Group	AChE (µ moles/min/mg protein)	ACh (ng/mg protein)	MAO-A (nmoles/ mg protein)	MAO-B (nmoles/ mg protein)
Group I: Normal Control	0.20±0.07^{b}	10.00±0.56^{b}	0.47±0.04^{b}	0.20±.05^{b}
Group II: Disease Control	0.78±0.16^{a}	5.27±0.93^{a}	0.62±0.04^{a}	0.43±0.11^{a}
Group III: low dose	0.24±0.10^{b}	6.77±0.65^{a}	0.53±0.04^{a}	0.20±0.01^{b}
Group IV: High dose	0.48±0.10^{b}	8.73±0.68^{b}	0.51±0.04^{a}	0.28±0.05^{b}
Group V: Standard	0.16±0.03^{b}	7.26±1.68^{a}	0.19±0.09^{b}	0.17±0.01^{b}

Result presented as Mean ± Standard Deviation, a = p>0.05, b = p<0.05.

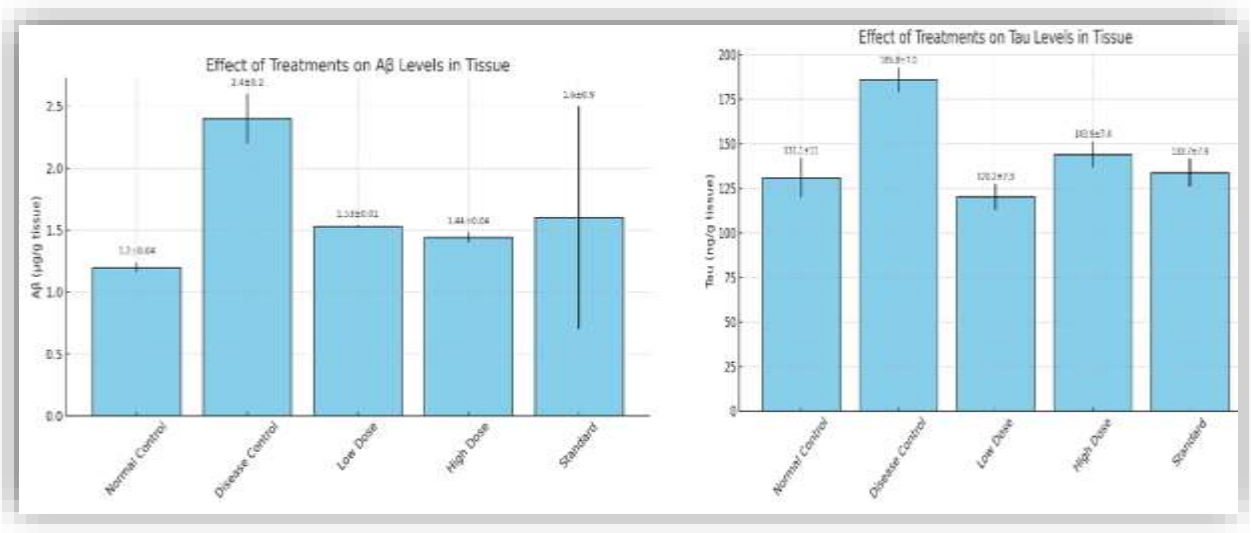

Figure 1: Amyloid-β (Aβ) and Tau Protein Levels in Different Experimental Groups

DISCUSSION

The phytochemical profile of Cucurbita pepo leaves extract revealed steroids (19.55 ± 0.83 mg/g) and phenols (14.70 ± 0.05 mg/g) as the most abundant constituents, followed by flavonoids (10.33 ± 0.06 mg/g) and saponins (7.62 ± 0.36 mg/g), with tannins, cardiac glycosides, and glycosides in lower amounts. These bioactive compounds are relevant to Alzheimer's disease (AD), where oxidative stress, neuroinflammation, and amyloid-beta (Aβ) accumulation drive pathology.

Phenolic compounds, abundant in the extract, are recognized for their antioxidant and anti-inflammatory effects. By scavenging reactive oxygen species (ROS), they reduce lipid peroxidation and neuronal apoptosis, while also modulating amyloid precursor protein (APP) processing to limit toxic Aβ aggregates (Sani*, et al*., 2023; Rojas-García *et al*., 2023)

Flavonoids, though present in moderate amounts, are potent neuroprotectants. They inhibit β-secretase (BACE1), thereby lowering Aβ production, and enhance synaptic plasticity and neuronal survival via brain-derived neurotrophic factor (BDNF) signalling, supporting memory and learning (Meshginfar *et al.,* 2021).

Steroids, the dominant phytochemicals, may attenuate chronic neuroinflammation by downregulating microglial and astrocytic activation, reducing cytokines such as TNF-α, IL-1β, and IL-6. Plant-derived phytosterols have been linked to neuroprotection and cognitive resilience (Meshginfar *et al.,* 2021).

Saponins contribute through dual mechanisms: enhancing Aβ clearance via neprilysin activation and supporting cholinergic transmission by maintaining acetylcholine levels, which are typically depleted in AD (Zhang *et al.,* 2023). Collectively, these findings suggest that C. pepo leaves extract exerts multi-targeted neuroprotective effects, antioxidant, anti-inflammatory, anti-amyloid, and cholinergic positioning it is a promising candidate in AD management.

The significant elevation of Aβ levels in the Disease Control group (II) compared to the Normal Control (I) (Figure 1) is consistent with previous reports that aluminium chloride ($AlCl_3$) exposure induces Aβ deposition, oxidative stress, and neuroinflammation key contributors to AD pathology (Muhammad *et al.,* 2021). Excessive Aβ aggregation disrupts synaptic function, triggers neurotoxicity, and promotes neuronal apoptosis, ultimately impairing cognitive function. However, treatment with C. pepo extract at both low and high doses significantly reduced Aβ accumulation, indicating its potential to mitigate Aβ-induced neurotoxicity. Similarly, Tau protein levels followed a similar trend (Figure 1), with a marked increase in the Disease Control group and subsequent reduction following treatment with *C. pepo* extract. Hyperphosphorylated tau aggregates into neurofibrillary tangles, disrupting axonal transport, leading to neuronal degeneration and synaptic dysfunction in AD (Dhapola *et al.,* 2024). The observed decline in tau levels upon administration of *C. pepo* extract suggests that its bioactive compounds may interfere with tau phosphorylation pathways, preventing its pathological accumulation.

CONCLUSION

This study highlights the neuroprotective potential of Cucurbita pepo leaves extract in combating Alzheimer's disease (AD)-like symptoms. Rich in phytochemicals such as steroids, phenols, flavonoids, and saponins, the extract demonstrated strong antioxidant, anti-inflammatory, and anti-amyloid effects. It significantly reduced oxidative stress markers, inhibited key enzymes like AChE and MAOs, and lowered Aβ and tau protein levels. These findings suggest that C. pepo may serve as a natural and effective therapeutic agent for managing AD-related neurodegeneration.

Declaration: "This manuscript submitted has not been previously published, nor is it before another journal for consideration".

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Contribution of Authors: We declare that this work was done by Bawa Y. Muhammad, Abdulkadir H. Hassan, Saadiya A. Tukur and Pharm. Ruqaiyatu M. Adamu. In this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors". **DR. Bawa Y. Muhammad**: conceived the idea, designed and supervised the work as well as wrote the first draft of the manuscript. **Mr. Abdulkadir H. Hassan**: carried out the experiment reviewed the first draft and performed statistical analysis. **Mrs. Saadiya A. Ahmed**: performed laboratory analysis, took care of the rats and reviewed the first draft. all authors have read and approved this manuscript for publication

Pharm. Ruqaiyatu M. Adamu: calculated the therapeutic dosage, performed statistical analysis,

and reviewed the final draft of the manuscript. all authors have read and approved this manuscript for publication.

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