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Original Article

Ameliorative effects of watermelon seed oil *(Citrulus lanatus)* on cadmium chloride-induced hippocampal toxicity in adult male Wistar rats

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Abstract

BACKGROUND AND AIM: BACKGROUND AND AIM: Humans and other organism are exposed to a broad spectrum cytotoxic heavy metals in the atmosphere due to their interaction with the environment. The aim of the study was to evaluate the ameliorative effect of watermelon (*citrullus lanatus*) seed oil on cadmium chloride-induced hippocampal damages of male adult Wistar rats.

METHODOLOGY: Twenty-five (25) adult male Wistar rats weighing between (120 – 200g) were used for the study. The animals were divided into five groups of five animals per group (n=5). Group I was designated as the (Control and received Physiological Saline, Group II received 5 mg/kg body weight of Cadmium chloride, Group III received 5 mg/kg body weight of cadmium chloride and 500 mg/kg body weight of *C. lanatus* oil as high dose, Group IV received 5mg/kg body weight of cadmium chloride and 250 mg/kg body weight of *C. Lanatus* oil as low dose while Group V received 5 mg/kg body weight of cadmium chloride and 10 mg/kg body weight of Succimer for the period of 28 days through Orogastric canula.)

RESULTS: No significance difference was recorded in the organ/body weights. The spatial learning and memory showed significant increase ($p<0.033$) in the mean-time to locate the shallow plate form in the Morris water maize test in the second and third week for the toxic groups when compared with the control and the treated groups. There was significant increase ($p<0.091$) in the mean MDA level of $CdCl_2$ group when compared to the control. Histological observation of the hippocampus showed normal cyto-architecture in Group I while Group II showed massive cellular degeneration, Group III showed some degree of cellular regeneration while Group V showed comparable evidence of cellular regeneration when compared to Group III and Group IV.

CONCLUSION: The results shows that Water melon *Citrullus lanatus* oil ameliorated the effects of cadmium on the (morphology), neuro-behavioural activity, histology, and oxidative stress indices in (hippocampus) of adult male Wistar rats.

Keywords:
Hippocampus; *Citrullus lanatus*; Cadmium chloride; Oxidative stress Marker

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INTRODUCTION

Animals and humans interact with their environment on a daily basis as such are exposed to a broad spectrum of chemicals and heavy metals present in the environment through food, air and water (Saikat *et al.*, 2022). With global change and increasing levels of industrial, commercial and agricultural contaminants it is important to track temporal trends and compare species, particularly species of conservation concern, or those living or migrating through unique or sensitive habitats (Muluneh, 2021). Cadmium has been observed to cause oxidative stress and histologically visible membrane disturbances in the central nervous system, with reduction in acetylcholinesterase activity, increase in oxidative stress markers, depletion of glutathione, superoxide dismutase, and other antioxidants, and depletion of catalase, glutathione peroxidase, and glutathione-S-transferase (Branca *et al.*, 2020). The past decade or so of cell death research has been dominated by the discovery of different forms of necrosis. Until recently, necrosis was largely considered to be unregulated from a molecular perspective, and thus could not be targeted for pharmacological blockade. However, it is now understood that there are multiple different mechanisms that drive necrotic death in regulatable way, raising hopes for therapeutic targeting of such forms of death in pathologies such as stroke which feature a high number of neurons dying by necrosis. These changes have apparently led to apoptosis of

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cortical cells in the central nervous system, possibly due to phosphorylation of calcium/calmodulin dependent protein kinase II (Freckers *et al*., 2018; Quin *et al.,* 2022). Cd can also inhibit influx through calcium channels, Cadmium Chloride which is potentially toxic is currently used in industry (Saleemi *et al*., 2019). Cadmium is a potent heavy metal carcinogen to animals (Eze *et al*., 2021) and humans (Niknafs *et al*., 2015). The reproductive potential of species and their survival have been threatened by an increased industrial and environmental contamination (Odewumi, 2015). The gonads, ventral prostate, liver and kidney are target sites for cadmium toxicity in rodents (Bu *et al*., 2014; Ibegbu *et al.,* 2015; Deng *et al*., 2022 and Sifuna, 2022). It has been reported to exert its genotoxicity via the production of reactive oxygen species (ROS) and by inhibiting cell proliferation and DNA replication (Nair *et al.,* 2015).

Hippocampus is a component of the limbic system and plays a role in memory and emotion. The name comes from the Greek words hippo, meaning horse, and kampo, meaning monster, as its shape resemble that of a seahorse (Baiomy, 2016).

Since ancient times, natural products from plants, animals, microbial and marine sources have been exploited for treatment of several diseases (Danielle, 2017). Plants play an important role in the treatment of diseases and still remain the foremost alternative for majority of people (Mushtaq *et al*., 2018).

Vegetable oils account for 80% of the world's natural oils and fat supply with increasing importance in nutrition owing to their dietary energy, antioxidant and raw materials potentials for industries (Damilola *et al*., 2015; Branca *et al*., 2020). Growing evidence has suggested that individual fatty acids from seeds may play different roles in human health especially in acute and chronic diseases management (Ibegbu *et al*., 2015; Nair *et al*., 2015). Diets rich in essential specific fatty acid may provide potential prevention of a number of health problems or diseases (Mladenovic *et al*., 2014; Eze *et al*., 2022). However, there has been a global campaign towards the uses of natural phytochemicals present in natural products such as fruits, vegetables and their extracts for the management of various diseases and as useful remedies for the alleviation of human illnesses (Poyodi *et al.,* 2020; Babaiwa *et al.,* 2020; Eze *et al*., 2022). According to (Sifuna, 2022), effective health cannot be achieved in Africa, unless orthodox medicine is complemented with traditional medicine. One of these medicinal plants is the watermelon seed. The watermelon is one of the medicinal plants with a deep green colored which is smooth exteriorly with gray or light green stripes inside while the fruit is pink, red or yellow in color with small black/brown seeds embedded in the middle third of the flesh. The ripe fruits are edible and largely used for making confectionary. Its nutritive values are also useful to the human health. It also reported having analgesic and anti-inflammatory activity of roots and leaves, antimicrobial activity, laxative activity of fruit anti-oxidant and anti-ulcerative activity (Mladenovic *et al*., 2014; Men *et al*., 2020; Sifuna, 2022). Fruits exerted the highest contents of alkaloids and simple phenols whereas seeds were rich in terpenes and steroids as well as flavonoids. All organs were devoid of anthraquinones (Akintunde and Thomas, 2021). Several studies show that alkaloids and terpenes are widely spread in the genus Citrullus (Feiz *et al*., 2017). These secondary metabolites are responsible for the pharmacological activities such as antiulcer, antimicrobial, antioxidant, analgesic, aphrodisiac and many other ethno-medicinal uses (Sebastine, 2016). Cucurbitaceae plants are known to contain bioactive compounds such as cucurbitacin, triterpenes, sterols and alkaloids (Damilola and Adekunle, 2016). The seed is also a good vermifuge and has a hypotensive action. Preliminary research indicates that the consumption of watermelon may have antihypertensive effects (Ibegbu *et al*., [2015]).

MATERIALS AND METHODS

Ethical Clearance

(Ethical approval for the study was sought from the Ethic review Committee for animal use and care of Ahmadu Bello University, Zaria and approval obtained for the study after the procedures met the committee`s satisfaction.)

Purchase of Watermelon Seed Oil

(90 ml) of watermelon seed oil manufactured by Hemani international KEPZ Karachi- Pakistan and licensed by Hemani Herbal LLC, 215 Pineda St Unit121, Longwood, FL 32750, USA were purchased from a (reputable store) in Utako District of Abuja.

Cadmium chloride

(10 g) of Cadmium Chloride manufactured by May and Bakers Chemical Laboratory limited Dagenham England were purchased from a (reputable chemical store) in Zaria, Kaduna state, Nigeria. (It was authenticated in the Department of Chemistry, Faculty of Physical Sciences, Ahmadu Bello University, Zaria.)

Meso 2, 3-dimercaptosuccinic acid (Succimer, DMSA)

(5 g) Meso 2, 3-dimercaptosuccinic acid (Succimer, DMSA) was purchased from Sigma- Aldrich Chemical Limited, Germany and was (authenticated in the Department of Chemistry), Faculty of Physical Sciences, Ahmadu Bello University Zaria. (10 mg/kg body weight was administered to the animals as standard drug.)

Experimental Animals

Twenty-five (25) adult male Wistar rats weighing between (120 - 200g) were procured and housed in the Animal holdings of the Department of Human Anatomy, (A.B.U.,) Zaria. The animals were allowed to acclimatize for 2 weeks under standard laboratory conditions of temperature 27-30^{o}C. Lighting was natural “day-

light" such that the animals were exposed to approximately 12:12 light and dark cycle. The animals were fed with rat pellet (Mae-Syl Agrochemical Company at No 22 Sokoto road, Samaru, Zaria, Kaduna State–Nigeria) with access to drinking water *ad libitum*.

Experimental Protocols

Animals were randomly divided into five groups (I-V) with each group comprising of five (5) rats. Group I serve as the (Control group and (received 2ml/kg body weight), group II received 5mg/kg body weight of cadmium chloride only, group III and IV received high and low dose of *C. lanatus* (500mg/kg body weight and 250mg/kg body weight) with 5mg/kg body weight of cadmium chloride while rats in group V were given 5mg/kg of cadmium chloride with 10mg/kg of Succimer. (A drugs administration was done orally using orogastric canula.)

Animal Sacrifices and Samples Collection

The animals were sacrificed twenty-four (24) hours after the last drug(s) administration (so as to allow complete metabolism of the last administered drug) by anaesthetizing the animals with 20mg/kg ketamine and (silenzing), thereafter the animals were transcardially perfused fixed using Bouin's Fluid. The animal's blood was withdrawn from the left ventricle prior to transcardiac perfusion and appropriately dispensed into heparinized bottles for (haematological analysis). (Hippocampus was extract from the brain prior to perfusion,) weighed with (sensitive weighing balance) and processed for histological analysis.

Haematoxylin and Eosin Staining

The staining was to demonstrate the histo-architecture of the hippocampus. The section were immersed in Haematoxylin for 5 minutes, washed in water, and counter stained with Eosin for two minutes. The sections were the deparaffinized in xylene and cover slipped using (DPX)

Data Analysis

Data from this study were analyzed using Statistical Package for Social Science Students (SPSS version 20.0). Groups were compared with one-way ANOVA, and results expressed as Mean ± S.E.M with significant level set at $P<0.05$.

P-value ≤ 0.05) (while the histological examination, Oxidative stress marker and neurobehavioural (study).

RESULTS

Morphological Observation

The morphometric analysis of the weight changes in the animals showed no significant difference, although, days as shown in **table 1.**

Neurobehavioral Test

To determine the effect of $Cdcl_2$ on the formation of spatial working memory, rats were subjected to 4 trials/day for one week in the MWM test in which a hidden platform was placed in the same location at the virtual quadrant 3. Both the control and treated rats learned the task and performed similarly over the one week of training, manifested as swimming a shorter distance to find the hidden platform, then they were subjected to MWM test Three times per week throughout the experiment. (The result shows no statistical significant difference across all the group as shown in **Table 2.**

Oxidative Stress Marker

(The oxidative stress markers revealed increase in the level of all the parameters (SOD, MAD, GSH) except CAT, and these increase, however, showed a significant different when compared to the control as shown in Figure 1,2,3,4 and 5.

Histomorphology

Histoarchitectures of hippocampus of the animals in the control group showed normal Histoarchitecture of the hippocampal cells as shown in Plate A. Meanwhile the animals in group two which served as the toxic group revealed serious cellular degeneration as shown in Plate B. However, the treated groups showed mild degeneration of pyramidals cells when compared with the toxic group as evidenced in plates C and D. In addition, the animals in group five showed comparable level of cellular degeneration when compared with the treated groups plate E.

Table 1: The Body and Organ Weight of the experimental animals

Groups	Initial (g)	Final (g)	WD (g)	Brain (g)
2ml/kg distilled water (control)	178.00±17.65	194.25±21.31	16.25±4.52	1.70±0.04
5mg/kg $CdCl_2$	180.25±15.89	175.50±16.32	-4.75±1.44	1.70±0.05
5mg/kg $CdCl_2$ + 500mg/kg *C. lanatus*	179.20±6.89	179.80±10.79	0.20±6.81	1.66±0.03
5mg/kg $CdCl_2$ + 250mg/kg *C. lanatus*	177.00±10.07	173.80±4.31	-2.00±6.25	1.71±0.05
5mg/kg $CdCl_2$ + 10mg/kg succimer	168.75±12.49	182.25±6.66	13.50±7.14	1.65±0.05
F	0.125	0.392	2.494	0.396
P	0.971	0.812	0.082	0.809

Values presented as Mean ± SEM and n=5

Table 2: Morris Water Maze analysis of the experimental animals

Groups	Training (sec)	Week 1	Week 2	Week 3	Week 4
2ml/kg (control) distilled water	3.25±0.30	4.88±0.23	6.00±0.56	3.25±0.25	4.00±0.91
5mg/kg $CdCl_2$	3.38±0.74	2.68±0.50	4.75±0.85	3.50±0.79	5.00±0.54
5mg/kg $CdCl_2$ + 500mg/kg *C. lanatus*	2.10±0.98	4.26±0.90	8.40±2.04	5.80±0.59	5.40±0.93
5mg/kg $CdCl_2$ + 250mg/kg *C. lanatus*	3.00±0.72	2.86±0.64	4.60±0.51	3.20±0.73	4.00±0.87
5mg/kg $CdCl_2$ + 10mg/kg succimer	1.50±0.35	3.13±0.43	5.25±0.25	5.00±0.91	3.25±0.25
F	0.531	0.746	1.289	1.424	0.354
P	0.716	0.574	0.313	0.269	0.838)

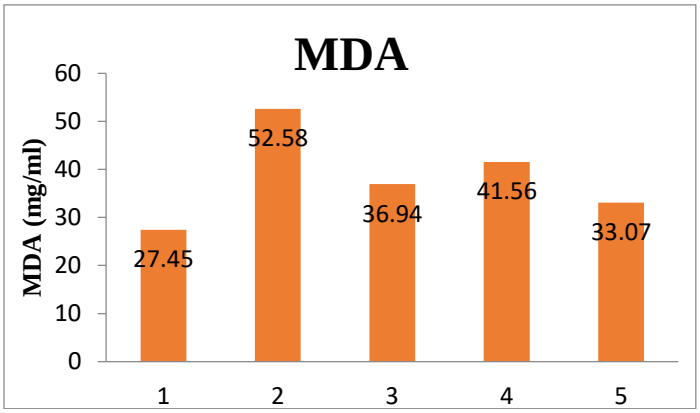

Figure 1: MDA concentration in the hippocampus of animals exposed to cadmium chloride Group 1= Distilled water (H_2O), Group 2 = 5mg /kg bwt CdCl only, Group 3 = 5 mg /kg bwt CdCl 500 mg/kg bwt CLSO. Group 4 = 5 mg /kg bwt CdCl 250 mg /kg bwt CLSO. Group5 = 5 mg /kg bwt CdCl + 10 mg/kg bwt of Succimer.

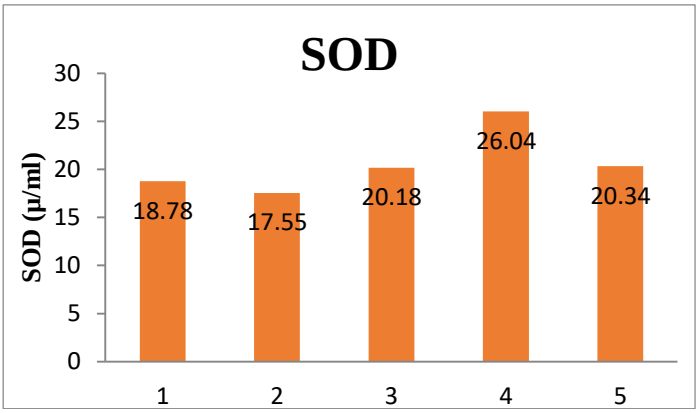

Figure 3: SOD concentration in the hippocampus of animals exposed to cadmium chloride Group 1= Distilled water (H_2O), Group 2 = 5mg /kg bwt CdCl only, Group 3 = 5 mg /kg bwt CdCl 500 mg/kg bwt CLSO. Group 4 = 5 mg /kg bwt CdCl 250 mg /kg bwt CLSO. Group5 = 5 mg /kg bwt CdCl + 10 mg/kg bwt of Succimer.

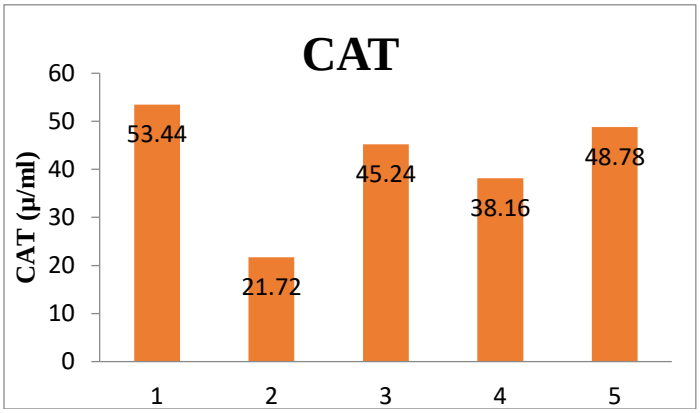

Figure 2: CAT concentration in the hippocampus of animals exposed to cadmium chloride Group 1= Distilled water (H_2O), Group 2 = 5mg /kg bwt CdCl only, Group 3 = 5 mg /kg bwt CdCl 500 mg/kg bwt CLSO. Group 4 = 5 mg /kg bwt CdCl 250 mg /kg bwt CLSO. Group5 = 5 mg /kg bwt CdCl + 10 mg/kg bwt of Succimer.

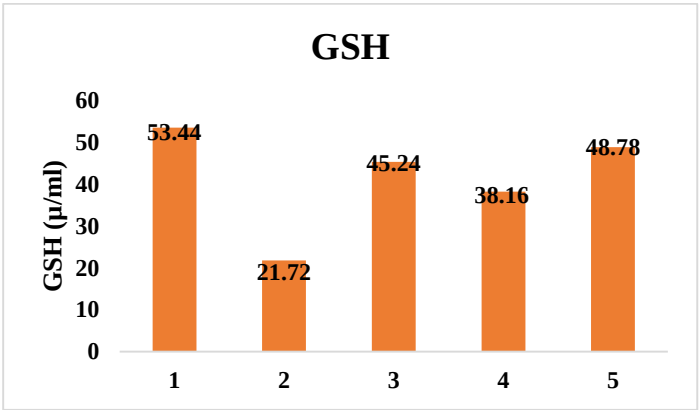

Figure 4: GSH concentration in the hippocampus of animals exposed to cadmium chloride Group 1= Distilled water (H_2O), Group 2 = 5mg /kg bwt CdCl only, Group 3 = 5mg/kg bwt CdCl 500mg/kg bwt CLSO. Group 4 = 5mg/kg bwt CdCl 250mg/kg bwt CLSO Group5 = 5mg/kg bwt CdCl + 10mg/kg bwt of Succimer.

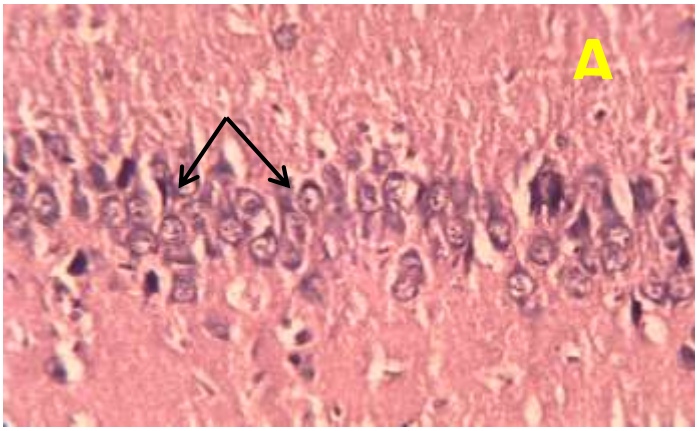

Plate A: Photomicrograph of rat's (hippocampus) of animals in (group 1) showing normal hippocampal histoarchitecture with black arrow demonstrating (Pyramidal Cells) Haematoxylin and Eosin (250x).

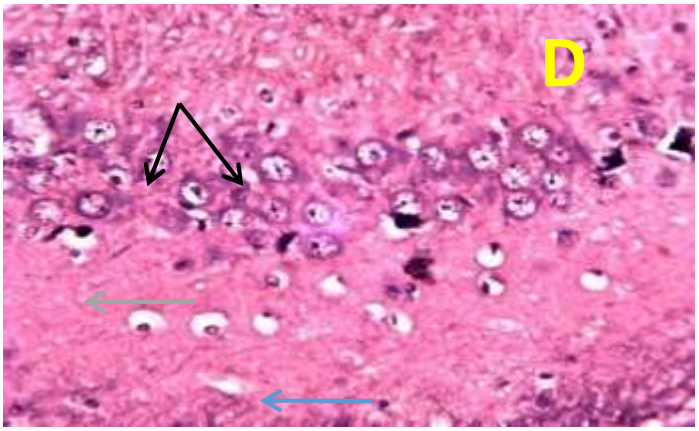

Plate D: Photomicrograph of rat's (hippocampus) of animals in (group 4) showing (mild) degenerating of Pyramidal Cells) (Black Arrows), (Vacuolated cell body) (Green Arrows) and (Ectopic cells) (Blue Arrows). Haematoxylin and Eosin (250x).

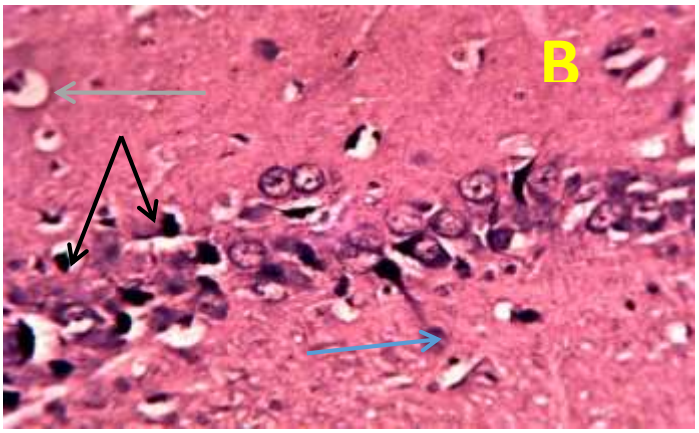

Plate B: Photomicrograph of rat's (hippocampus) of animals in (group 2) showing (severe degeneration Pyramidal Cells) (Black Arrows), (Vacuolated cell body) (Green Arrows) and (Ectopic cells) (Blue Arrows). Haematoxylin and Eosin (250x).

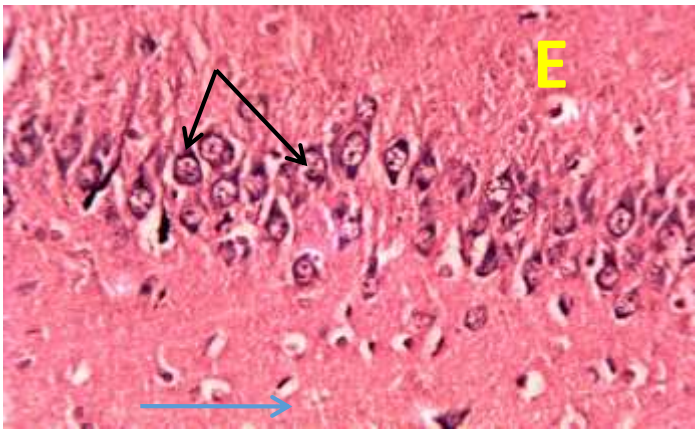

Plate E: Photomicrograph of rat's (hippocampus) of animals in (group 5) Showing (mild) degenerating Pyramidal Cells) (Black Arrows) and (Ectopic cells) (Blue Arrows). Haematoxylin and Eosin (250x).

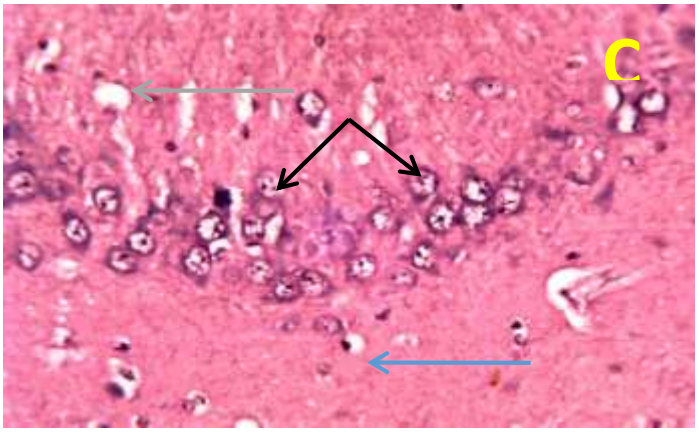

Plate C: Photomicrograph of rat's (hippocampus) of animals in (group 3) showing (mild) degenerating Pyramidal Cells (Black Arrows), (Vacuolated cell body) (Green Arrows) and (Ectopic cells) (Blue Arrows). Haematoxylin and Eosin (250x).

DISCUSSION

This study was designed to look at the ameliorative effects of *C. lanatus* on the cadmium chloride induced hippocampus toxicity of adult male Wistar rats. The morphometric data obtained from this study indicate no significant increase in the animal's body weight changes throughout the experiment and the reason for this insignificant increase in animal's body weight may be due to the low fat content in the *C. lanatus* (Nurjannah, 2020; Deng *et al*., 2022). This result suggested that consumption of watermelon seed could not cause gain in body weight. Research in recent time revealed that exposure to the toxic heavy metals decreased the density of memory and learning-related dendritic spines in the hippocampus during the precarious period of brain development which subsequently lead to hippocampus-dependent spatial memory deficits (Monica *et al*., 2022). The neurobehavioral test did not show any significant difference when compared with the

control. This findings is in agreement with the work of (Monica *et al*., 2022; Eze *et al*., 2022).

The oxidative stress result from this study showed a statistical significance increase in the mean MDA, SOD and GSH, but significance decrease in CAT when compared with the control. However, there was a significant increase in the mean MDA in the toxic group when compared with the rest of the groups. The results however, shows that the antioxidant property C. *lanatus* mitigated the oxidative mediated tissue damage of cadmium (Omoboyowa and Ajayi, 2016; Reetapa *et al*., 2017; Wang *et al*., 2018). This suggest that *Citrullus lanatus* rich antioxidant potential and can help to reduce oxidative stress. The reduction in the level of CAT may have to do with the dosage of *C. lanatus* oil used.

The observation from the present study revealed that cadmium chloride caused degenerative changes. Loss of pyramidal cells with vacuolated cell bodies of cells in adult male Wistar rats treated with cadmium chloride. These neurodegenerative changes could invariably affect learning and memory abilities associated with CA3 region of hippocampus. The hippocampus and the cerebral cortex are the key structures of memory formation because the hippocampus is especially indispensable in the integration of spatial information (Aissi *et al*., 2013; Saikat *et al*., 2022). In addition, administration of *Citrullus lanatus* oil has a clear improvement in preventing total degeneration of brain cells when compare with animals exposed to cadmium chloride only (Omoboyowa and Ajayi, 2016; Oghagbon *et al*., 2016). This finding agrees with the work of Eze *et al.*, 2022 who in their research revealed that *C. lanatus* significantly improved the cytotoxic effects of cadmium in the pre-frontal cortex of experimental rats.

Conclusion: In conclusion, the results from the present study (demonstrated the consequences of cadmium chloride exposure) and *Citrullus lanatus* seed oil has potential ameliorative effect on the histology, (neurobehavioural characteristic) (spatial learning and memory) and (oxidative stress) and histoarchitecture on cadmium chloride-induced hippocampal toxicity in adult Wistar rats in a dose dependent manner.

Recommendation: It is recommended that *C. lanatus* oil be subjected to further studies to ascertain its mechanism of action. Further studies at different dosages with other heavy heavy metals could revel further reveal the oxidative stress scavenging strength of C. *lanatus*.

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