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Original Research Article

Ethanol Extract of*Anacardiumoccidentale* Leaves and *Musa sapientum* Peels Co-Treatment Enhanced Cognitive and Olfactory Functions via Antioxidant Mechanism in Cadmium-Induced Brain Damage in Female Wistar Rats

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ABSTRACT

Dementia, one of today's most important public health problems, affects cognitive function, resulting in memory loss. This research investigated the impact of co-administration of ethanol extract of *Anacardiumoccidentale* (AO) leaves and ripe *Musa sapientum* (MS) peels on cognitive and olfactory functions in cadmium-induced brain insult in female Wistar rats. Thirty mature female Wistar rats weighing between 75 and 154 g were randomly divided into six groups (n=5) for this study. Group 1 received 1 mL of distilled water. Group 2 received 100 mg/kg of Cadmium (Cd). Cd (100 mg/kg), donepezil (2.5 mg/kg), AO (200 mg/kg), MS (200 mg/kg), and 200 mg/kg of AO and MS were administered to groups 3, 4, 5, and 6 respectively. All groups received oral treatment once a day for 21 days. One hour after 21 days of treatment, the animals were assessed for cognitive and olfactory function using the radial maze and buried food tests. After the behavioural test, the animals were sacrificed by cervical dislocation on day 22, and biochemical evaluations of Superoxide Dismutase (SOD), Acetylcholinesterase Enzyme (AChE), Malondialdehyde (MDA), and histological analysis were conducted. In comparison to groups 2, 4, and 5, the neurobehavioural investigation's findings showed a significant ($p<0.05$) improvement in spatial and reference memory and olfactory responses, as well as elevated SOD levels and a significant ($p<0.05$) decrease in AChE and MDA activities after co-treatment with AO and MS. Furthermore, a section of the hippocampus showed moderate regeneration in groups co-treated with AO and MS. Conclusively, co-treatment with AO and MS exhibited a beneficial antioxidant and neuroprotective potential in mitigating Cd-induced brain insult.

Keywords:Antioxidant, *Anacardium occidentale, Musa sapientum*, Dementia

Introduction

Dementia, a neurodegenerative disease, is the gradual reduction of cognitive abilities that impacts language, memory, and daily functioning. As the world's population ages, dementia is on the rise, which is a significant public health problem. Numerous pharmaceutical interventions and therapy modalities have been studied to reduce the cognitive deterioration caused by this menacing disorder.[1]The most prevalent type of dementia is AD and accounts for between 60 and 70 percent of cases. Dementia negatively affects cognitive abilities [2,3,4], which involves the mind's capacity for thought and memory.[5,6]Odu *et al.*[7] found that the loss of structure and function in the brain of AD sufferers is primarily linked to cognitive impairment.

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Cognitive function is hampered by dementia in several ways, commonly involving memory loss, trouble picking up new knowledge, language difficulties, confusion and disorientation, poor judgment, personality, and behavioural changes.[8]According to certain studies, olfactory impairment may be among the first signs of AD. Additionally, the entorhinal cortex is initially involved in the pathophysiology of typical AD. Unlike auditory and visual abnormalities frequently detected by clinicians, olfactory malfunction in AD mainly manifests as decreased olfactory recognition. It is linked to pathogenic protein alterations within the olfactory projection and bulb area. Acetylcholine and glutamate are abundant in the olfactory system, and a lack of certain neurotransmitters, especially acetylcholine, is thought to be a primary contributor to memory loss and other cognitive disorders. [9,10]Plants have been investigated for their potency in managing dementia, especially those with antioxidant properties. One such plant is *Anacardium occidentale*, reportedly indigenous to Brazil and introduced to Africa and Asia around the sixteenth century.[11]
Anacardium occidentale (AO), a member of the Anacardiaceae family, is well-known for its nutritional and medicinal qualities and is a rich source of natural antioxidants.[12,13] Due to their high concentration of polyphenols, flavonoids, and tannins, cashew leaves have drawn interest for their possible medicinal benefits.[14] Numerous studies conducted in laboratories and animals have revealed that these bioactive substances have neuroprotective, anti-inflammatory, and antioxidant qualities.[1] Usually, cashew leaves contain various volatile chemicals

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that give them their distinct scent.[15] The fruit contains other biological substances like carotenoids, vitamins C and A, and flavonoids. These phytochemical substances comprise a substantial portion of the content that may be connected to crucial biological functions.

The banana (*Musa sapientum*) plant is a popular tropical fruit from the Southwestern Pacific. It arrived in India and spread throughout the earth's tropical regions around 600 BC.[16] The Efiks call it 'Mboro,' the Igbos call it 'Unele,' and the Yorubas call it 'Ogede'.[17]Inwang*et al.*[18] reported that *Musa sapientum* is a Musaceae family member with significant antiulcer, antidiabetic, and antioxidant characteristics. Chabuck*et al.*[19] reported that *Musa sapientum* is an excellent source of vital nutrients, including antioxidants, vitamins, and minerals. Bioactive substances, such as flavonoids, carotenoids, and polyphenols, are found in the ripe peels *of Musa sapientum.*[20]It is thought that the antioxidants in bananas help protect cells from oxidative damage.[21]

Headache and vertigo, olfactory dysfunction, Parkinson's symptoms, declining vasomotor performance, neuropathy, diminished equilibrium, cognitive deficit, and memory impairment are only a few of the symptoms of exposure to cadmium (Cd), which has a significant negative impact on nervous system function.[23] Thus, it is essential to investigate how ripe fruit peels of *Musa sapientum* (MS) and ethanol leaf extract of *Anacardium occidentale* (AO) affect cognitive and olfactory functioning in female Wistar rats with Cd-induced dementia. Assessing how *Anacardium occidentale* and *Musa sapientum* affect cognitive functions is crucial. Most people in underdeveloped nations, such as Nigeria, take herbal medicines without proper awareness of their pharmacologic actions and side effects. The study considered female animals because approximately two-thirds of AD patients are females, and studies have shown that women are more likely than men to have AD.[24, 25,26]

Materials and Methods

Drugs

Donepezil and Cadmium were obtained from Sigma-Aldrich Cooperation, USA. Cadmium and Donepezil were given orally using an oral cannula after being dissolved in normal saline (0.9% NaCl). All reagents used in the study were of analytical quality.

Animals

Thirty healthy female Wistar rats, about 6 months and weighing between 75-154 g, were obtained from the animal house of Alex Ekwueme Federal University, Ndufu Alike, Ebonyi State, Nigeria (AE-FUNAI). The rats were housed in a normal environment, acclimated for 2 weeks, and then randomly divided into six groups. The animals were kept at ambient temperature, 50 ± 5% relative humidity, and a 12-hour cycle of light and dark. The animals had unlimited access to feed (raw chow, Vital Feeds Nigeria Ltd., Jos) and water. The ethical approval committee of the AE-FUNAI, Faculty of Basic Medical Sciences committee, provided the experiment with ethical permission number AEFUNAI 2024/00127. The animals were managed following the recommendations of the Committee on Care and Use of Laboratory Animals. [27]

Extraction of plant material

Leaves of *Anacardiumoccidentale* were gathered from a few cashew trees at the Faculty of Agriculture, AE-FUNAI, Ebonyi State, on January 16, 2024. Similarly, unripe bananas were purchased from Nwakpu market, Ebonyi State, Nigeria, on January 17, 2024, and stored until they ripened. A taxonomist at the University of Uyo's Department of Botany and Ecological Studies identified and verified *Anacardiumoccidentale* and *Musa sapientum* plants. The voucher specimen was deposited in the department with the herbarium numbers UUPH51(b) and UUPH3(a), respectively. The banana peels were cut into bits and allowed to dry before extraction. For around 14 days, the plant components were adequately cleaned and allowed to dry in the shade. The dried plants were ground into powder using an electric blender. A 1 kg powdered sample of each plant part was macerated in 2 x 2.5 L of absolute ethanol for 72 hours in a glass jar with intermittent steering and filtered. The filtrates were concentrated separately at 40 °C in a rotary evaporator and stored at -4 °C until use.

Experimental Design

The extract's antitoxicity activity for dose selection was determined following a previously reported method.[28]The study's design and categorization are displayed as follows in Table 1:

Table 1: Experimental Grouping For Dosages Administration

Treatment Group (n=5)	Dosage	Duration
Control	1 mL of distilled H_2O	3 weeks
Cadmium	100 mg/kg	3 weeks
Donepezil+ Cd	2.5 mg/kg BW donepezil + 100 mg/kg BW Cd	3 weeks
AO+ Cd	200 mg/kg BW AO +100 mg/kg BW Cd	3 weeks
MS+ Cd	200 mg/kg MS BW+100 mg/kg BW Cd	3 weeks
AO and MS + Cd	200 mg/kg BW AO+200 mg/kg BW MS+100 mg/kg BW Cd	3 weeks

Key: AO =*Anacardium occidentale*, MS =*Musa sapeintum*, Cd= Cadmium, BW=Body weight

Note: Group 6 received a combined treatment of AO (200 mg/kg BW) and MS (200 mg/kg BW) + Cd (100 mg/kg) each for three weeks. Doses were given once daily via the oral route for all groups.

Neurobehavioral Test

Radial Arm Maze (RAM) Test

In neurobehavioral research, the RAM test is a behavioural assessment tool used to study rodents' spatial learning and memory, particularly in rats and mice. The training procedure was the same as previously described.[29]This experiment was done an hour after the last dose on day 21. It was carried out from 8 am to 10 am. The maze has a platform at the centre (32 cm in diameter) with several arms extending outward (48 x 3x 12 cm). The number of arms was 8, and 4 contained food rewards at the end. Before the test started, the animals were habituated to the testing facility. Reducing stress was necessary for precise behavioural evaluation. The animals were briefly deprived of food to spur them to explore and finish the task. The animals underwent a training phase in which they were taught the food locations and the maze's spatial arrangement. The animal was trained to link certain arms with rewards by baiting some arms with food. The Maze was arranged with some arms (4 arms) holding food rewards and others being empty during the testing phase. The animal was supposed to use its prior training to help it recall and select the arms that held rewards. The animal must learn to visit every arm without returning to an arm already visited during that session. The animal's decisions, right ones (visiting arms with reward) and wrong ones (visiting arms without rewards), were observed by the researcher and noted. The number of right choices and mistakes were recorded.

Olfactory Response Test (Buried Feed Test)

The olfactory test is a sensory experiment that assesses a rat's olfactory ability, level of social curiosity, and perception of social novelty. This experiment was done an hour after the previous experiment. It was carried out from 11 am to 1 pm. The rat was kept in a sterile polypropylene cage and given a feeding restriction for eight hours. A tiny quantity of feed was added to one of the cage's edges where the bedding had been spread out and used to cover the feed. A stopwatch recorded the rat's time to sniff the feed. [30]

Biochemical Analysis

The animals were sacrificed by cervical dislocation on day 22 following behavioural tests. The sacrifice was carried out from 9 am to 10 am. The

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entire brain was carefully extracted from the skull, weighed, and placed in a glass homogenizer. Subsequently, the tissue homogenate was prepared in 0.1M phosphate buffer (pH 7.4) and stored at -2 to 8 °C. The mixtures were centrifuged for 10 minutes at 3000 revolutions per minute, yielding a cloudy liquid supernatant for biochemical examination.

Acetylcholinesterase (AChE) Activity
This was carried out according to the method of Ellman*et al.* [31]

Superoxide Dismutase (SOD) Activity
Pyrogallol oxidation was used to measure the activity of superoxide dismutase. The rate of pyrogallol oxidation was assessed using the increase in absorbance at 420 nm. [32, 33]

Malondialdehyde (MDA) Activity
This was done according to the method of Ohkawa*et al.* [34]

Histopathological Studies
Following behavioural and biochemical analyses, 4% paraformaldehyde in a 0.1 M phosphate buffer solution was used to perfusion-fix the brains of several groups. After being removed, the brain was post-fixed in the same fixative for an entire night at 48 °C. Hematoxylin-Eosin staining was applied after the brains were submerged in paraffin. At 400 magnifications, the lesions were evaluated under a microscope. Because the hippocampus is an essential part of the brain for many types of learning and memory, its histology was considered. [35]

Statistical Analysis
One-way ANOVA and Turkey's multiple comparison tests were used to examine the data, reported as mean ± SEM. P values ($p<0.05$) were statistically significant. The Graph Pad Prism 8.0 program was used to do the statistical analysis.

Results and Discussion

Dementia is a neurological disease that causes mental disabilities, particularly memory loss and impairment of cognitive functions.[36]It results in a gradual loss of cognitive functions that makes daily activities difficult and is a major contributor to dependency, incapacity, and death. [37] In this study, the effect of concomitant administration of *Anacardium occidentale and Musa sapientum* on cognitive function and olfactory responses in cadmium-induced dementia was investigated.
Following the extract administration and observation period, spatial and reference memory are evaluated using the Radial Maze, which also lowers the percentage of right answers, a sign of impairment in spatial working memory. [38] Figure 1 reports the Radial maze's number of correct choices.

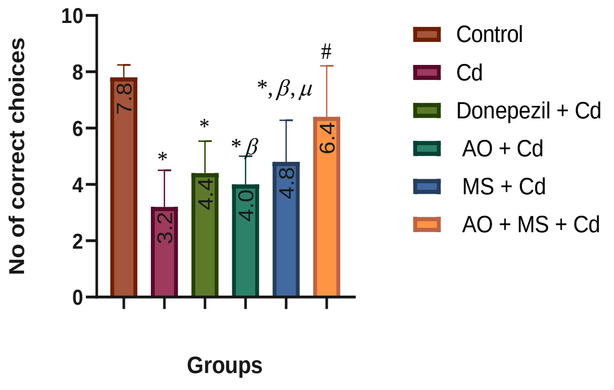

Figure 1: Bar chart showing the number of correct choices in the Radial maze task. Data presented as mean ± SEM; (n=5); *control, #Cd; βAO & MS; μ MS ($p<0.05$).

The results showed that the number of correct choices was significantly ($p<0.05$) lower in the cadmium-induced group than in the control group. Additionally, it was discovered that the co-treated group (AO + MS) had significantly more correct choices ($p<0.05$) than the cadmium-induced group, the AO and MS groups had significantly ($p<0.05$) fewer correct choices than the co-treated group (AO + MS), respectively. In addition, Figure 2 shows the total number of errors in the Radial maze. Comparing the cadmium-induced group to the control group, the results showed a significant ($p<0.05$) increase in the number of wrong choices. Furthermore, compared to the co-treated group (AO + MS), the MS group had a significant ($p<0.05$) reduction in the number of accurate choices. Comparing the co-treated group to the cadmium-induced group in this study, the former demonstrated a significant ($p<0.05$) increase in the number of correct choices and a significant (p<0.05) decrease in the number of errors, suggesting that the combined treatment of *Anacardium occidentale* and *Musa sapientum* significantly improved reference and spatial memory. Also, compared to the AO group, the co-treated group had a significant ($p<0.05$) increase in the number of accurate selections. Similarly, it was discovered that the co-treated group significantly ($p<0.05$) outperformed the MS group regarding the number of correct choices. This suggests that the simultaneous administration of *Musa sapientum* and *Anacardium occidentale* was more effective than the MS and AO groups at improving spatial and reference memory.

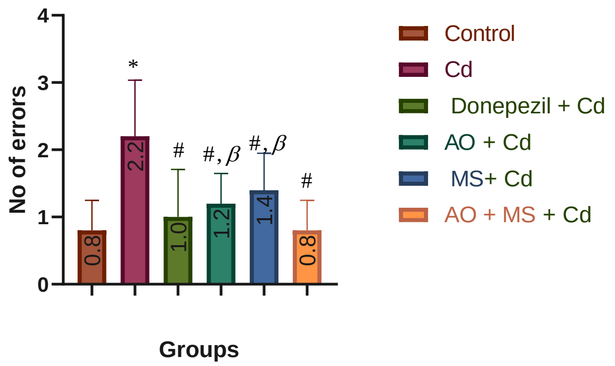

Figure 2: Bar chart showing the number of errors in the Radial maze task. Data presented as mean ± SEM; (n=5); *control, #Cd; βAO & MS ($p<0.05$).

In the olfactory response test, Figure 3 shows the rats' olfactory reaction to the olfactory response test. Comparing the cadmium-induced group to the control group, the results show a significant ($p<0.05$) increase in olfactory response time. AO's olfactory reaction time was significantly ($p<0.05$) lower than that of the co-treated group (AO + MS).

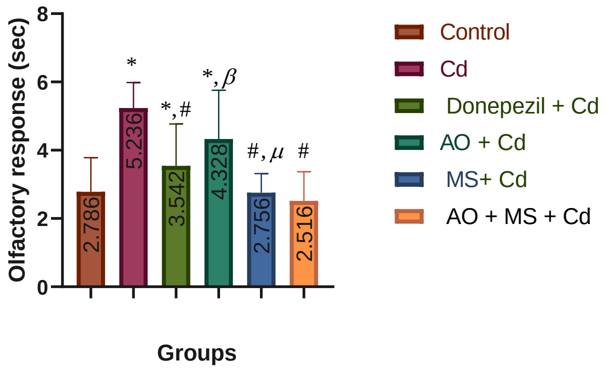

Figure 3: Bar chart showing olfactory response in all groups. Data presented as mean ± SEM; (n=5); *control, #Cd; βAO & MS; μ MS ($p<0.05$).

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By inhibiting voltage-sensitive calcium channels or by entering neurons through L- or T-type calcium channels, all of which are found in the olfactory ORNs, cadmium has been shown in studies to impair a person's sense of smell [39] and may result in olfactory illness. The decrease in olfactory response time latency in the *Musa sapientum* (MS) and co-administered groups (AO + MS) in assessing food or perception of social novelty indicates an enhancement in olfaction.

Also, the effect of the co-administration of *Anacardium occidentale* and *Musa sapientum* on Acetylcholinesterase Enzyme Activity was evaluated. The results of this study show how the co-administration of *Anacardium occidentale* and *Musa sapientum* affects the activity of the acetylcholinesterase enzyme (Figure 4).

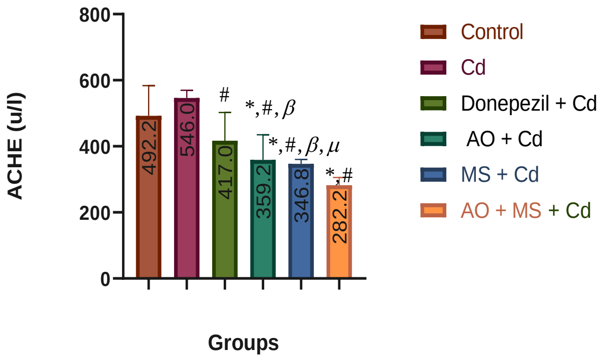

Figure 4: Bar chart showing the effect of the co-administration of *Anacardium occidentale* and *Musa sapientum* on Acetylcholinesterase enzyme Activity. Data presented as mean ± SEM; (n=5); (n=5); *control, #Cd; βAO & MS; μ MS (p<0.05).

Acetylcholinesterase enzyme activity was shown to be significantly (p<0.05) lower in the AO, MS, and co-administered (AO + MS) groups than in the control group. Additionally, in comparison to the co-treated group (AO + MS), AO and MS exhibited a significant (p<0.05) increase in acetylcholinesterase enzyme activity. It was found that both extracts alone and in combination (AO and MS) decreased AChE activities, with the co-administration of AO and MS showing greater effectiveness in this regard. Due to excessive AChE activity, the breakdown of ACh causes the brain's Ach reserves to be depleted. The somatic nervous system neurotransmitter acetylcholine is also used at neuromuscular junctions, where it triggers motor neuron firing and affects voluntary movements.[40] Acetylcholinesterase (AChE), an enzyme present in the nervous system, is involved in controlling the actions of acetylcholine (ACh). By dissolving ACh into its inert components, choline, AChE disrupts the ACh signal and stops prolonged muscle contraction. A study reported that Cadmium exposure reduced spontaneous alternation in female Wistar rats.[41] This would most likely be the consequence of a drop in acetylcholine in the nervous system due to a decrease in cholinergic transmission brought on by an increase in acetylcholinesterase activity.[42]

The effect of the Co-administration of *Anacardium occidentale* and *Musa sapientum* on Malondialdehyde (MDA) activity was also investigated. The study's results (Figure 5) revealed that the co-administration of *Musa sapientum* and *Anacardium occidentale* reduces MDA activity. According to the results, the MDA activity in the cadmium-induced group was significantly higher (p<0.05) than in the control group. Additionally, in comparison to the cadmium-induced group, MDA activity was significantly (p<0.05) lower in the AO, MS, and co-administered (AO + MS) groups. Despite its modest size, Cordiano *et al.*[43] found that malondialdehyde (MDA) is a highly reactive indicator of oxidative stress. Lipid peroxidation is known to produce MDA as a by-product. MDA levels were seen to drop in MS and AO groups when MS and AO were administered together.

The Co-administration of *Anacardium occidentale* and *Musa sapientum* to the rats also affected superoxide dismutase (SOD) activity. The impact of simultaneous administration of *Musa sapientum* and *Anacardiumoccidentale* on SOD activity is presented in Figure 6.

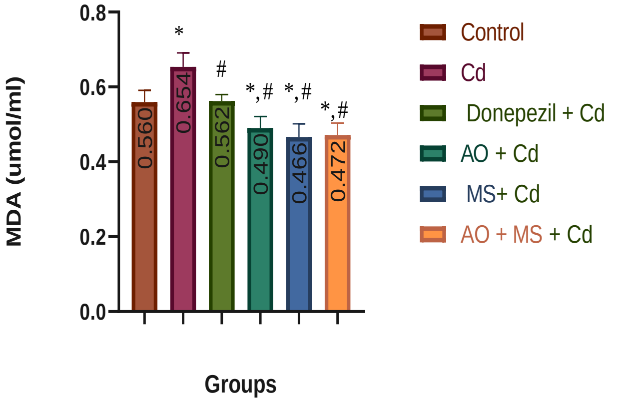

Figure 5: Bar chart showing the effect of the co-administration of *Anacardiumoccidentale* and *Musa sapientum* on Malondialdehyde (MDA) activity. Data presented as mean ± SEM; (n=5); *control, # Cd; (p<0.05).

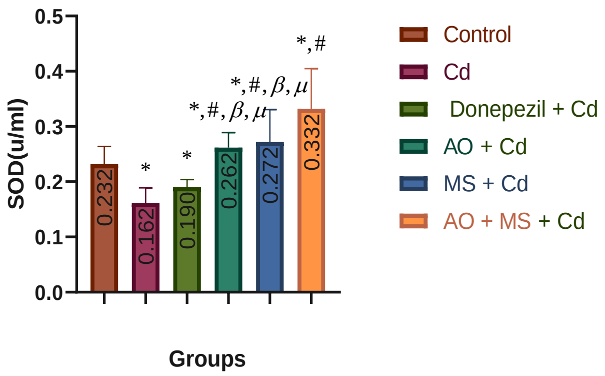

Figure 6: Bar chart showing the effect of the co-administration of *Anacardium occidentale* and *Musa sapientum* on Superoxide dismutase activity. Data presented as mean ± SEM; (n=5); *control, #Cd; βAO & MS; μ MS (p<0.05).

SOD activity was significantly (p<0.05) lower in the cadmium-induced group than in the control group. Also, it was revealed that AO significantly (p<0.05) reduced SOD activity in comparison to the co-treated group (AO and MS). Similarly, when compared to the co-treated group (AO and MS), MS and AO demonstrated a significant (p<0.05) decrease in SOD activities. A study reported that *Musa sapientum* ripe fruit peels had strong antioxidant activity.[44] Comparing the cadmium-induced group to the control group, there was a notable drop in SOD activity. The study's findings demonstrated that, in comparison to the cadmium-induced group, SOD activity was significantly higher in the AO, MS, and co-treated (AO + MS) groups. Furthermore, compared to the MS or AO groups, the co-treated (AO + MS) group exhibited a substantial increase in SOD activity, suggesting that the co-treated group's antioxidant activity was more potent than that of the AO or MS groups respectively.

Histological staining of the hippocampus (Figure 7) photomicrograph shows a section of hippocampus with active granular cells (GC) and well perfused molecular layer (ML) (x400)(H/E)(CV) (A); Photomicrograph of the group administered cadmium shows section of hippocampus with severe degeneration, sever vacoulation (v) and severe decrease in the number of granular cell (LGC) (x400)(H/E)(CV (B); Photomicrograph of the group administered cadmium and donepezil shows section of the hippocampus with mild regeneration, vacoulation (v) and decrease in the number of granular cell (GC) (x100x400)(H/E) (C); Photomicrograph of the group administered cadmium and AOshows section of hippocampus with moderate regeneration, mild vacoulation (v) and active granular cell (GC) (x100x400)(H/E) (D); Photomicrograph of the group administered cadmium and MS shows section of the hippocampus with mild regeneration, vacoulation (v) and moderate increase in the number of granular cell (GC) (x100x400)(H/E) (E); Photomicrograph of the group administered with cadmium and treated with AO andMS shows section of the hippocampus with moderate regeneration, mild vacoulation(v) and active granular cell (GC) (x100x400)(H/E) (E). Sections of the hippocampus of the cadmium-induced group showed degeneration and severe vacuolation (V), as well as a reduction in the number of granular cells (GC).

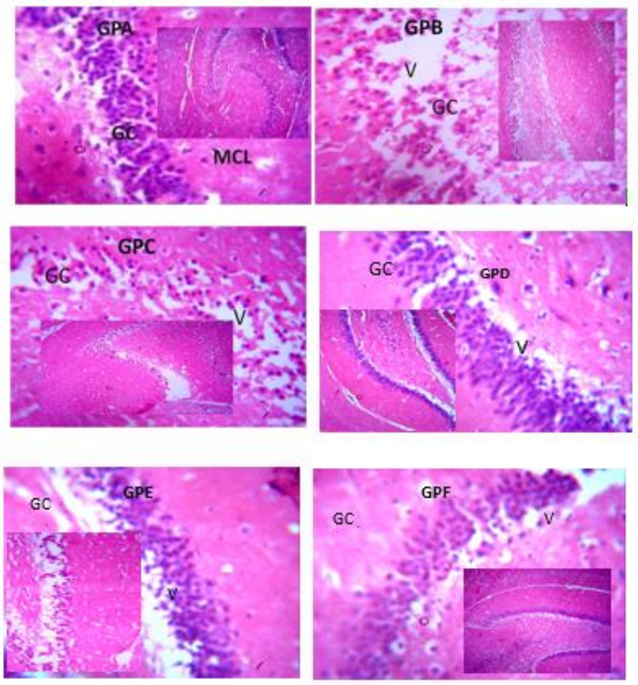

Figure 7: Histological sections of hippocampus (x100x400) H&E;Haematoxylin and eosin. V; vacoulation, GC; Granular cells; perfuse molecular layer (ML)Group1(GPA), Group2 (GPB), Group3(GPC),Group4 (GPD),Group5(GPE), Group6(GPF)

This is in line with a study done by Ritchie *et al.*[45], which reported that histotype showed microvacuolation and loss of neurons in the hippocampus and cerebella cortex of dementia patients. Histological sections of the hippocampus of the cadmium-induced and co-treated with *Anacardium occidentale* and *Musa sapientum* showed a hippocampus with moderate regeneration, mild vacuolation (V), and active granular cell (GC). Sections of the hippocampus of the cadmium-induced group showed degeneration and severe vacuolation (V), as well as a severe decrease in the number of granular cells (GC). Ritchie *et al.*[45] reported that histological sections of the hippocampus of the cadmium-induced and co-treated group (AO + MS) revealed a hippocampus with moderate regeneration, mild vacuolation (V), and active granular cell (GC). This is consistent with a study that found that dementia patients' cerebral cortex, hippocampus, basal ganglia, thalamus, and cerebella cortex all had micro vacuolation and neuron loss.

Conclusion

In conclusion, combined treatment with *Anacardium occidentale* and *Musa sapientum* demonstrated antioxidant and neuroprotective effects on fine motor performance, olfactory responses, spatial working, and reference memory. Bioactive substances that modulate antioxidative and neuroprotective potential properties include flavonoids, tannins, phenols, terpenoids, and phytosterols.

Conflict of Interest

Authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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