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## SYNERGISTIC EFFECT OF ETHANOL EXTRACT OF *ANACARDIUM OCCIDENTALE* LEAVES AND *MUSA SAPEINTUM* PEELS ON FINE MOTOR FUNCTION AGAINST CADMIUM-INDUCED NEUROTOXICITY IN RATS

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### Keywords:

*Anacardium occidentale*, *Musa sapientum*, Neurotoxicity, Interleukin-6, cadmium, Donepezil

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**ABSTRACT:** Cadmium (Cd) is the seventh most toxic heavy metal; a potentially hazardous metal found that has a substantial impact on the peripheral (PNS) and central nervous systems (CNS). This study is aimed at investigating the concomitant administration of ethanol leaf extract of *Anacardium occidentale* (AO) and ripe *Musa sapientum* (MS) peels on fine motor functions in Cd-induced neurotoxicity in female wistar rats through. 30 adult female wistar rats (75 - 154 g) were used for this study. They were divided randomly into six groups (n=5). Group 1 (Control) received 1mL of distilled water. Group 2, 3,4 and 5 were treated with 100 mg/kg of Cd, 2.5 mg/kg of Donepezil, 200 mg/kg AO and 200 mg/kg MS respectively. Group 6 was co-treated with 200 mg/kg of AO and 200 mg/kg of MS for 21 days. Animals were then subjected to Neurobehavioural experiment using wire hang test for assessment of muscular strength. Biochemical assay for the assessment of Interleukin-6 (IL-6) and histological analysis of the cerebellum was done. The result of the neurobehavioural investigation revealed a significant (P<0.05) enhancement in muscular strength, as well as decreased expression of IL-6 proinflammatory cytokines in the treated group. Furthermore, moderate healing with well outlined active purkinge cells and mild degeneration of the granular cells in histological section of the treated groups was observed. In conclusion, the combine treatment of AO and MS enhanced fine motor functions, and had a beneficial anti-inflammatory and ameliorative potential on the neurotoxic effect of Cd.

**INTRODUCTION:** According to the Agency for Toxic Substance and Disease Registry's (ATDSR)<sup>1</sup> ranking, cadmium (Cd) is the seventh most toxic heavy metal. It is found widely in both natural and man-made sources, making it potentially hazardous for both humans and animals to come into contact with.

Working in mines and ground water, commercial products, industrial wastes, automobile emissions, batteries, fertilizers, paints, and contaminated foods can all expose one to Cd. There are several ways that cadmium can get into the human body. Primary olfactory neurons carry cadmium particles which accumulate in the olfactory bulb into the brain<sup>21, 29</sup>.

Also, after inhalation, Cd builds up in the lungs and enters the circulatory system through the alveolar cells<sup>16, 30</sup>. The other mechanism of cadmium intake is through food or water consumption that contains cadmium. Cadmium can enter neurons through voltage-gated calcium channels<sup>22, 31</sup>.

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In fact, a substantial amount of *in-vitro* and *in-vivo* research demonstrated that exposure to Cd has a substantial impact on the peripheral (PNS) and central nervous systems (CNS)<sup>14, 13, 32</sup>. This has been connected to a variety of clinical symptoms, including learning disabilities, peripheral neuropathy, neurological disturbances, mental retardation, and impairment of motor activity in both adult and pediatric patients<sup>23, 33, 42</sup>.

Furthermore, amyotrophic lateral sclerosis, multiple sclerosis, Alzheimer's disease (AD), Parkinson's disease (PD), and amyotrophic lateral sclerosis<sup>20, 34</sup> have all been linked to Cd-dependent neurotoxicity. An increasing number of studies are focusing on the investigation of natural products that might possess antioxidant properties. The nutritional and medicinal properties of the tropical cashew tree, *Anacardium occidentale*, are widely recognized. Moreover, it has high antioxidant content<sup>12, 35, 18, 41</sup>. Cashew leaves have generated interest due to their potential medical benefits because of their high concentration of polyphenols, flavonoids, and tannins<sup>7, 36</sup>. Numerous *in-vitro* and *in-vivo* studies have shown that these bioactive substances have neuroprotective, anti-inflammatory, and antioxidant qualities<sup>2, 37</sup>. *Musa sapientum* is a great source of important nutrients, including vitamins, minerals, dietary fiber, and antioxidants, according to Chabuck et al.<sup>5</sup>. *Musa sapientum* contains bioactive compounds including flavonoids, carotenoids, and polyphenols that have anti-inflammatory and antioxidant properties<sup>3</sup>. Consequently, it is imperative to examine the impact of the concomitant administration of ethanol leaf extract of *Anacardium occidentale* (AO) and ripe *Musa sapientum* (MS) peels on fine motor functions in Cd-induced neurotoxicity in female Wistar rats through an anti-inflammatory mechanism. The study considered female animals because approximately two-thirds of AD patients are females and studies have shown that women have higher prevalence of AD<sup>24, 25, 43, 44</sup>.

## MATERIALS AND METHODS:

**Experimental Animals:** About 6 months old healthy female wistar rats numbering 42 and weighing between 75-154 g were obtained from the animal house of Alex Ekwueme Federal University Ndufu Alike, Ebonyi State, Nigeria. The rats were given two weeks to acclimatize, and then divided

into six groups at random. The rats were kept in standard laboratory conditions with a 12 h light/dark cycle, relative humidity of  $50 \pm 5\%$ , and room temperature ( $23 \pm 2$  °C). The rats had unrestricted access to food (raw chow, Vital feeds Nigeria Ltd., Jos) and water *ad libitum*. The National Institutes of Health's rules for the care and use of laboratory animals were carefully followed when handling the animals<sup>14, 38</sup>. The ethical approval number Aefunai 2024/00127 for this experiment was acquired from Alex Ekwueme Federal University Ndufu-Alike, Ebonyi State, Faculty of Basic Medical Sciences Ethical Approval Committee.

**Drug Preparation:** Cadmium was gotten from the Laboratory of Physiology Department, Alex Ekwueme Federal University, Ndufu Alike, Nigeria. The chemical was weighed using an electric weighing in h balance in Physiology Laboratory using a beaker. 1 g of Cd was dissolved in 10 mL of distilled water to get the stock concentration. Donepezil obtained from Sigma-Aldrich Cooperation, USA. Donepezil were given orally using oral cannula after 2.5 mg/kg was dissolved in 10 mL of distilled water. All the reagents used in the investigation were of analytical grade.

**Extraction of Plant Material:** *Anacardium occidentale* leaves were collected from some Cashew trees at the Faculty of Agriculture, Alex Ekwueme Federal University, Ndufu Alike, Ebonyi State and unripe Banana were bought from Nwakpu market, Ebonyi State, Nigeria and kept until they got ripe. The Banana peels were removed and dried for the purpose of extraction. *Anacardium occidentale* and *Musa sapientum* plants were identified and authenticated by a Taxonomist in the Department of Botany and Ecological studies, University of Uyo, the voucher specimen was deposited in the department with the herbarium number: UUPH51(b) and UUPH3(a) respectively. The plants were thoroughly washed and shade-dried for about 14 days. Using an electric blender, the dried plants were then ground into powder in the appropriate amounts. 1 kg powdered sample of the plants were immersed in 2 x 2.5L of absolute ethanol respectively for a duration of 72 hours in a glass jar. The liquid filtrate were then concentrated, dried in a rotary

evaporator at 40 °C, and then stored at -4 °C until they were needed.

**Experimental Design:** The extracts antitoxicity activity for dose selection was done due to the

method described previously by Inwang et al.,<sup>35</sup>. The grouping and the design of this study is as follows:

**TABLE 1: EXPERIMENTAL GROUPING WITH RESPECT TO DOSAGES ADMINISTRATION**

Treatment Group	Dosage	Duration
Control	1 mL of distilled H <sub>2</sub> O	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 sapientum*, Cd= Cadmium, BW=Body weight. **Note:** Group 6 received a combine treatment of AO (200 mg/kg BW) and MS (200 mg/kg BW) + Cd (100 mg/kg) each for three weeks.

**Hand Grip Test:** The Hand grip test is a simple non-invasive method designed to evaluate rodents muscle force, by taking advantage of the animal's tendency to grasp a horizontal metal grid while suspended by its tail<sup>27, 39</sup>. Mouse was carefully held from the base of the tail and forelimb was placed on the horizontal metal grid, a stop watch was started and the time taken for the forelimb of the rat to be released from the horizontal metal grid was noted<sup>28</sup>.

**Wire Hang Test:** This was previously reported by Deacon<sup>8</sup>. The rats were placed in the centre of the wire mesh screen. After positioning the rats in the centre of the wire mesh and turning on a stopclock, the screen was turned in an inverted position for two seconds, with the rats' heads lowering first. A cushioned surface was kept 40–50 cm above the screen. These steps were taken for every rat, and the moment the rat falls off was recorded.

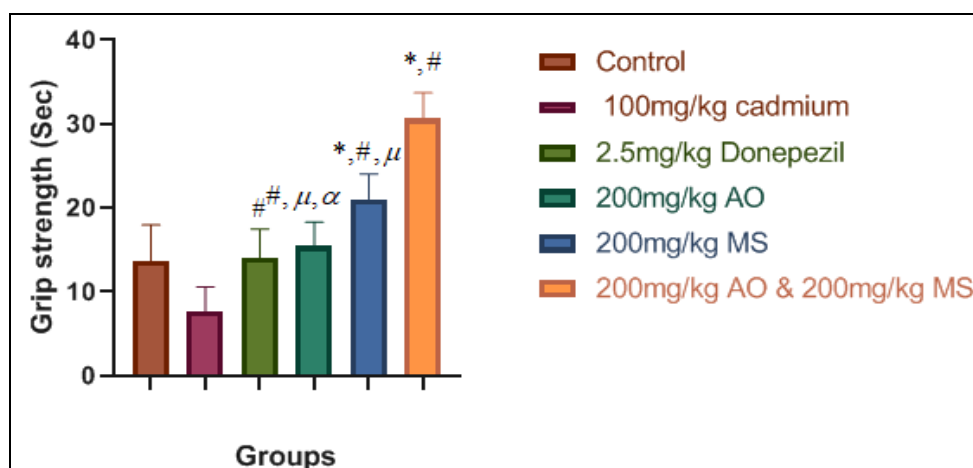
**Animal Sacrifice and Organ Collection:** The rats were anaesthetized with pentobarbital sodium (30 mg/kg i.p) and the brain was excised and the cerebellum obtained. They were homogenized with external ice-cold saline bath. The homogenates were centrifuged at 3000 rpm for 30 min at 4 °C, and the supernatant was collected and stored at -80 °C before assay. The supernatant was use to assay for Interleukin-6 activity. Interleukin-6 activity (IL-6) levels were determined by ELISA using Quantikine Immunoassay kits according to the manufacture's instruction. After behavioural and biochemical studies, the brain of different group was perfusion-fixed with 4 % paraformaldehyde in a phosphate buffer solution of 0.1 M.

The tissues were immersed in paraffin and stained with Hematoxylin-Eosin and viewed under a light microscope at 400 magnifications.

**Statistical Analysis:** The data were statistically expressed as mean ± SEM and analyzed using one-way ANOVA, followed by Tukey's multiple comparison tests. P value less than 0.05 (p<0.05) was considered to be statistically significant. The statistical analysis was done using the Graph Pad prism 8.0 software.

**Evaluation of Grip Strength Test:** The grip strength of the rats in hand grip test was reported in **Fig. 1**. The result reveals that there was a statistical significant (p<0.05) decrease in the grip strength in the cadmium-induced group when compared with the control group.

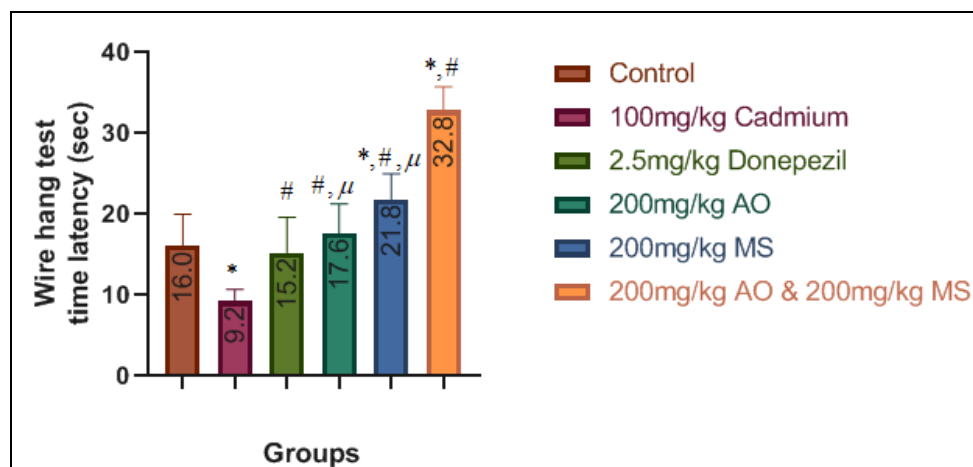
There was a statistical significant (p<0.05) increase in the grip strength in *Anarcadium occidentale* and *Musa sapientum* (MS) groups when compared with the control group. Also, there was a statistical significant (p<0.05) increase in the grip strength in Donepezil group, *Anarcadium occidentale* group, *Musa sapientum* (MS) group and the co-administered group (AO and MS) when compared to the cadmium-induced group. It was also shown that AO showed a significant (p<0.05) decrease in the grip strength when compared to the co-treated group (AO and MS). Similarly, it was also revealed that MS showed a significant (p<0.05) decrease in the grip strength when compared to the co-treated group (AO and MS). There was a significant (p<0.05) increase in the grip strength in MS group when compared with AO group.



**FIG. 1: GRIP STRENGTH IN HAND GRIP EXPERIMENT.** Data presented as mean  $\pm$  SEM; (n=5); \*control, #Cd;  $\mu$ co-treated group,  $\alpha$ MS (p<0.05).

**Assessment of Wire Hang test:** The time latency during which the rats held on to the wire mesh during the wire hang test was reported in **Fig. 2**. The results reveals that there was a statistical significant (p<0.05) decrease in time latency in the cadmium-induced group and a statistical significant (p<0.05) increase in the co-administered group (AO and MS) when compared to the control group. Also, there is a statistical significant (p<0.05) decrease in time latency in Donepezil group,

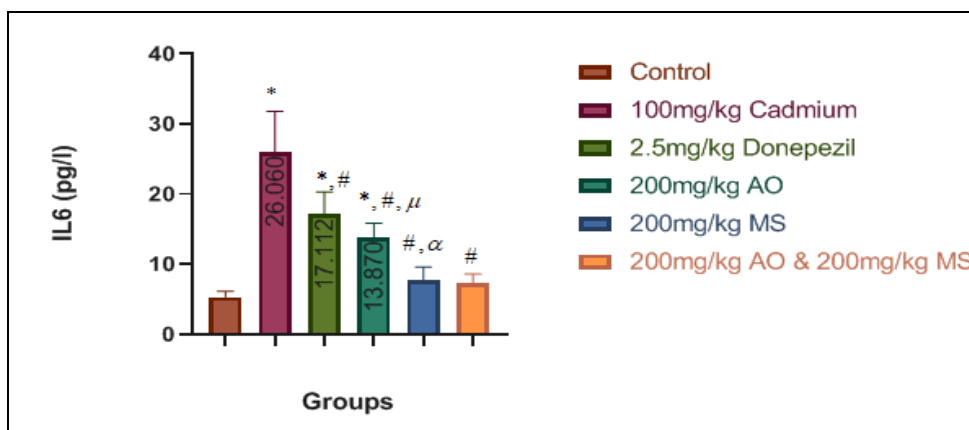
*Anacardium occidentale* group, *Musa sapientum* (MS) group and co-administered group (AO and MS) when compared to the cadmium-induced group. It was also revealed that AO showed a significant (p<0.05) decrease in the grip strength when compared to the co-treated group (AO and MS). Similarly, it was also revealed that MS showed a significant (p<0.05) decrease in the grip strength when compared to the co-treated group (AO and MS).



**FIG. 2: BAR CHART SHOWING TIME LATENCY DURING WHICH THE RATS HELD ON TO THE WIRE MESH DURING WIRE HANG TEST.** Data presented as mean  $\pm$  SEM; (n=5); \*control, #Cd;  $\mu$ co-treated group (p<0.05).

**Effect of the Co-administration of *Anacardium occidentale* and *Musa sapientum* on Interleukin-6 Activity:** The effect of the co-administration of *Anacardium occidentale* and *Musa sapientum* on Interleukin-6 activity was reported in **Fig. 3**. The result revealed that there was a significant (p<0.05) increase in Interleukin-6 activity in cadmium-induced group, donepezil group and *Anacardium occidentale* group when compared with the control group. Also, there was a significant (p<0.05)

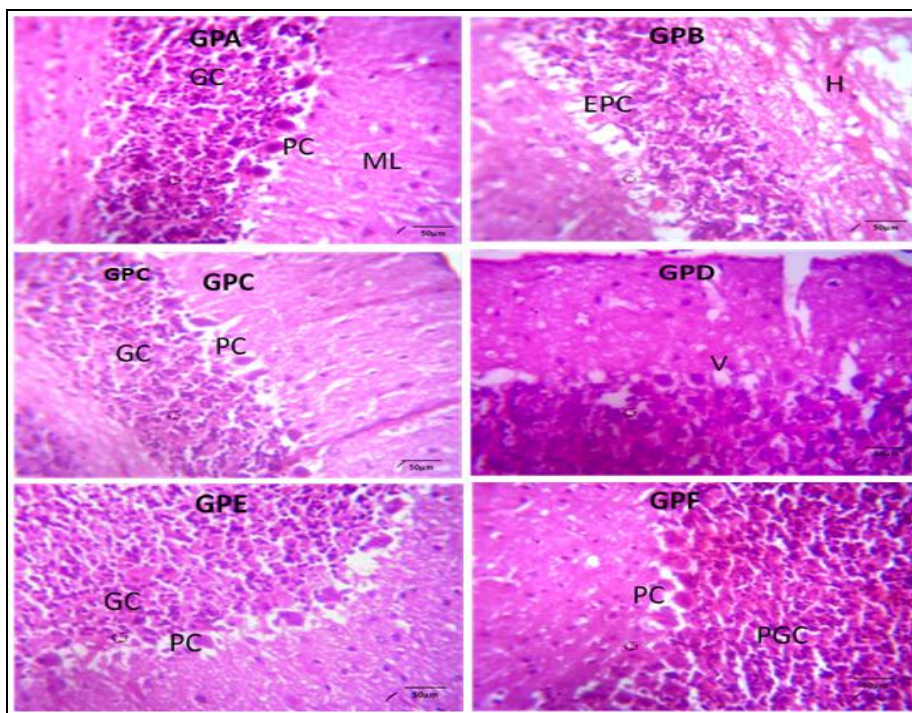
decrease on Interleukin-6 activity in donepezil group, *Anacardium occidentale* (AO) group, *Musa sapientum* (MS) group and the co-treated group (AO and MS) when compared to the cadmium-induced group. It was also shown that AO showed a significant (p<0.05) increase in interleukin-6 activity when compared to the co-treated group (AO and MS). There was a significant (p<0.05) decrease in interleukin-6 activity in MS group when compared with AO group.



**FIG. 3: BAR CHART SHOWING THE EFFECT OF THE CO-ADMINISTRATION OF ANACARDIUM OCCIDENTALE AND MUSA SAPIENTUM ON INTERLEUKIN-6 ACTIVITY.** Data presented as mean ± SEM; (n=5); \*control, # Cd; (p<0.05).

**Histological Staining:** Photomicrograph of the control group shows section of the cerebellum with molecular layer (ML), granular layer (GL) and well outlined active purkinje cell (PC) layer (x100 X400/(H/E) (A); Photomicrograph of the group induced with cadmium shows section of the cerebellum with severe loss of purkinje cells and focal area of hemorrhage (H) within the molecular layer (x100 X400/(H/E) (B); Photomicrograph of the group induced with cadmium and treated with donepezil shows section of the cerebellum with moderate healing with moderately outlined active purkinje (PC) and granular cell (x100 X400/(H/E) (C); Photomicrograph of the group induced with cadmium and treated *Anacardium*

*occidentale* shows section of the cerebellum with mild healing with moderate vacoulation of purkinje cell (PC) (x100 X400/(H/E) (D); Photomicrograph of the group induced with cadmium and treated *Musa sapientum* shows section of the cerebellum with moderate healing, well outlined active prymaidial cell (PC) and granular cells (GC) (x100 X400/(H/E) (E); Photomicrograph of the group induced with cadmium and co-treated with *Anacardium occidentale* and *Musa sapientum* shows section of the cerebellum with moderate healing with well outlined active purkinje cell (PC) and mild pyknotic granular cells (PGC) (x100 X400/(H/E) (F).



**FIG. 4: PHOTOMICROGRAPH OF THE HIPPOCAMPUS (X100 X400/(H/E) (F).**

**DISCUSSION:** Humans are exposed to the hazardous metal cadmium on a regular basis, and there have been several documented negative consequences on the body<sup>9</sup>. This study investigated the effect of concomitant administration of ethanol leaf extract of *Anacardium occidentale* (AO) and ripe peels of *Musa sapientum* (MS) on fine motor functions in Cd-induced neurotoxicity in female Wistar rats *via* anti-inflammatory mechanism. The wire hang test is carried out on rodents usually to assess their muscular strength and neuromuscular functions<sup>10</sup>.

The co-treated group showed a synergistic enhancement in muscular strength and neuromuscular functions which is consistent with the findings of Oyagbemi *et al.*<sup>17</sup> that revealed an enhancement in muscular strength by AO. Anti-inflammatory activity against tissue damage in the brain cerebellum was indicated by a decreased expression of IL-6 proinflammatory cytokines in the treated group with more decreased expression of IL-6 in the co-treated group. This finding is in tandem with the findings of other workers<sup>11, 40</sup>. Histological sections of the cerebellum of cadmium-induced group showed severe effect of cadmium activity with severe loss of purkinje cells and focal area of haemorrhage within the molecular layer. Bi *et al.*<sup>4</sup> shed light on the toxic effects of cadmium on cerebellum, in which cadmium was observed to initiate cerebella injury by disrupting the heat-shock response. Conversely, there was moderate healing with well outlined active purkinje cells and mild degeneration of the granular cells in histological section of the groups treated with the extracts and less vacuolation (V) was observed indicating an ameliorative potential of the extracts. These findings are consistent with the findings of other studies<sup>9,19</sup>.

**CONCLUSION:** In conclusion, the combine treatment of AO and MS enhanced fine motor functions, and had a synergistic anti-inflammatory and ameliorative potential on the neurotoxic effect of Cd.

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**Author's Contributions:** The study was conceived and designed by Uduak Anthony Inwang, Keren Chimzurum Ukaegbu and Uduak Anthony Inwang performed experiment. The original draft was written by Uduak Anthony Inwang, and Onwe Uchewa. Inwang Uduak, Keren Chimzurum Ukaegbu, Ogbonna Isaac David and Onyagu Uchechukwu analyzed and interpreted the data.

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