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Ameliorative role of diets fortified with *Artocarpus altilis* in a *Drosophila melanogaster* model of aluminum chloride-induced neurotoxicity

Jamiyu Ayodeji Saliu[1*], Ayobami Matthew Olajuyin[2*] and Samuel Faith Olowolayemo[1]

Abstract

Backgrounds: *Artocarpus altilis* (breadfruit) belongs to the family Moraceae. *Artocarpus altilis* possesses antioxidative, anti-inflammatory, and anti-proliferative properties. Aluminum (Al) is extensively utilized for consumer products, cooking utensils, pharmaceuticals, and industries. Indication for the neurotoxicity of Al is investigated in various studies, notwithstanding the precise mechanisms of Al toxicity are yet to be fully elucidated, and, which requires novel therapy. In this study, we determined the ameliorative role of *Artocarpus altilis* on aluminum chloride-induced neurotoxicity in *Drosophila melanogaster*.

Methods Varying concentration of the extract were used to formulate diets for 6 groups of flies. Group 1 contained basal diet, group 2 contained basal diet and aluminium chloride ($AlCl_3$), group 3 contained basal diet + 0.1% unseeded breadfruit (UBF), group 4 contained basal diet + 1% unseeded breadfruit, group 5 and 6 contained basal diet + AlCl3 + 0.1% and 1% unseeded breadfruit. Assays such as acetylcholinesterase activity, malondialdehyde (MDA) concentration level, catalase activity, and superoxide dismutase (SOD) activity were carried out after 7 days of exposure respectively.

Results The results showed low activity of acetylcholinesterase activity and MDA level and high catalase and SOD activity in the pretreated and post-treated flies with *Artocarpus altilis* compared to the normal and negative control respectively.

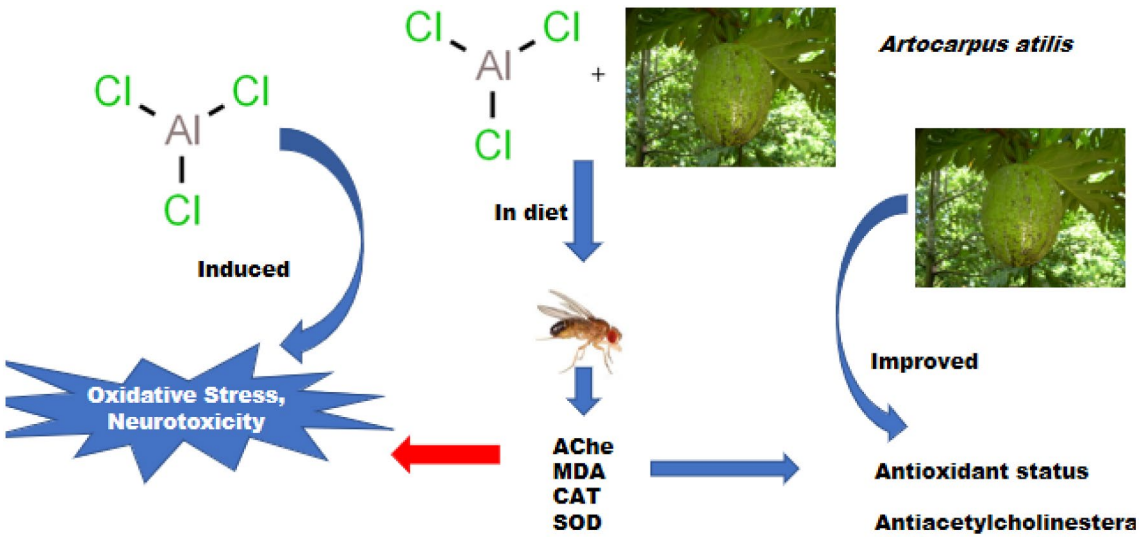
Conclusions Taken together, *Artocarpus altilis* is a promising prophylactic, antiacetylcholinesterase, and antioxidant plant in the prevention, management and treatment of neurodegenerative diseases.

Keywords *Artocarpus altilis*, Aluminium chloride, *Drosophila melanogaster*, Neurotoxicity, Antioxidant

*Correspondence:
Jamiyu Ayodeji Saliu
jamiyu.saliu@aaua.edu.ng
Ayobami Matthew Olajuyin
doctorayobami@gmail.com; ayobami.olajuyin@aun.edu.ng

Full list of author information is available at the end of the article

Graphical Abstract



Background

Aluminium (Al) has been known for its ability to activate different types of disorders such as neurological, haematological, neurodegenerative, and skeletal diseases [1, 2]. It is a possible neurotoxic element that results in different health complications in humans [3–6]. There are some various factors that contribute to the exposure of humans to aluminium which includes, polluted drinking water, cooking utensils, environment, medications and diets, antiperspirants, adjuvant for vaccination, desensitization procedures, anthropogenic activities such as mining and industrial processes [6–12]. Previous investigations discovered that the consumption of aluminium from different parts of the world ranges between 3 and 12 mg/day [13, 14]. Improvement of some vaccine utilized aluminium oxyhydroxide against certain bacterial and viral diseases (Jankovic) [15–17]. Excessive aluminium has some dangerous and toxic effects which disrupt a lot of biological reactions [18, 19]. Some of the mechanisms of aluminium-induced toxicity include oxidative damage and free radical production [20]. When reactive oxygen species are in excess, it can affect the enzymatic and non-enzymatic reactions which can be a result of aluminium [21, 22]. Previous investigations have been conducted in mammals to show that aluminium has numerous toxicological effects [14, 23–25]. Al is known to affect numerous physiological and molecular processes and leads to disruptions of the mammalian central nervous system (CNS). The following processes, gene expression, protein degradation, inflammatory processes, synaptic transmission, axonal transportation, dephosphorylation or phosphorylation, epigenetic regulation, circadian rhythms are been altered as a result of Al toxicity [26–28].

The excessive accumulation of aluminum may lead to neurological and neurodegenerative diseases such as parkinson's disease, tauopathies, alzheimer's disease, and amyotrophic lateral sclerosis etc. [29–31]. It disrupts and causes dysfunction of the central nervous system (CNS). Alzheimer's disease (AD) is predominantly found in older people of about 85 years or older in the United States [32–35]. Meanwhile, parkinson affects 1–3% of the population over 60 years old [36, 37]. Therefore, there is a need for investigations in degenerative diseases caused by aluminium toxicity and using natural products to be able to combat the disease [38–41].

Artocarpus altilis (breadfruit) belongs to the family Moraceae [42]. The Artocarpus genus has different secondary metabolites such as flavonoids, flavones, stilbenoids and arylbenzofurons. There are many compounds which have been identified from *Artocarpus altilis* derived from the phenylpropanoid pathway. They have different biological activities such as inhibition of platelet aggregation [43], antiproliferative effects of leukemia cells [44, 45], anti-bacterial activity, anti-tumor agent and anti-fungal properties etc. [44]. The following nutritional compositions are found in the seeds which includes vitamin C, iron, phosphorous, water, protein, fat, thiamine, niacin and carbohydrate etc. [46, 47]. Furthermore, the important effects of *Artocarpus altilis* have been investigated in some diseases [48–50] but the research on alzheimer's disease and parkinson diseases in *Drosophila melanogaster* have not been fully elucidated.

This study investigated the role of *Artocarpus altilis* in aluminum chloride-induced neurotoxicity in *Drosophila melanogaster*. Hence, we conducted an investigation

using diets fortified with *Artocarpus altilis* to ameliorate the different effects of aluminum-induced neurotoxicity.

Methods

Apparatus

Spatula, Beaker, Measuring cylinder, Gas cooker, Funnel, Foil paper, Whatman filter paper, Glass jar, Cotton wool, Teas tubes, Cuvette, Micro pipette, eppendorf tube, Unviversal bottle, Aluminium foil, Conical flask, Volumetric flask, Blender, Syringe, Stove, Pot. Dried unseeded Bread fruit (*Artocarpus altilis).*

Equipment

Spectrophotometer, Uniscope Laboratory Centrifuge, Electrical Weighing balance, Refrigerator, Freeze drying machine, water bath, Blender, PCR machine and electrophoresis.

Reagents

Chemical reagents such as semicarbazide, sodium acetate, acetylthiocholine iodide, Trichloroacetic acid (TCA) ferrous sulphate, sulphanilamide, n-n-diethyl-para-phenylenediamine (DEPPD), reduced glutathione were procured from Sigma Al-drich Co. (St Louis, Missouri, USA). Ferric chloride, Iron (II) sulphate, Hydrogen peroxide, sodium dodecyl sulphate, methanol, potassium acetate, Ascorbic acid, aluminium chloride, hydrochloric acid, starch, acetic acid, potassium ferrycyanide and were sourced from BDH Chemicals Ltd., (Poole, England).

Sample collection and preparation

A sample of (*Artocarpus altilis*) was collected from from Ilara-mokin, Ondo state. The sample was identified and confirmed in the Department of Plant Science at Adekunle Ajasin University, Akungba Akoko, Ondo State. *Artocarpus altilis* fruit was washed, diced into smaller pieces, dried, and then blended into semiliquid form. The ground plant material was soaked in cold distilled water for 24 h placed in an orbital shaker. The mixture was then filtered through Whatman No. 1 filter paper and the filtrate was centrifuged at 805 ×g for 10 min. The clear supernatant collected was freeze-dried, labeled, and stored in a small, airtight container and stored at a low temperature (4 ∘C) in the refrigerator. This was later reconstituted in water for subsequent analysis.

D. Melanogaster stock culture

The investigation was performed using Wild type *D. melanogaster* (Harwich strain) stock culture obtained from Federal University of Technology Akure Faculty of Science, Department of Biochemistry, Drosophila research laboratory, Functional Food and Nutraceutical Unit, Nigeria. It was fed corn meal medium containing 0.08% v/w nipagin and 1% w/v brewer's yeast under 12 h dark/light cycle conditions at a constant humidity of 60% and a constant temperature of 25 °C.

Corn meal preparation

Using a measuring cylinder, 700 ml of distilled water was measured and poured into pot, place on a gas cooker. In distilled water, yeast was added in a concentration of 5 g and nutrient agar in a concentration of 7.9 g. 150 ml of distilled water diluted with 52 g of corn meal and poured into the pot. Nepagin (1 g) that has been dissolved in 3 ml of absolute ethanol to the solution on fire. The solution was stirred occasionally to prevent lumps in the mixture. The mixture was removed from the source of heat and allowed to solidify for 10 min.

Determination of ferric reducing antioxidant property (FRAP)

Previous investigation on the reducing antioxidant property was conducted on the extracts to elucidate its capability to reduce FeCl3 described by Oyaizu et al. [51]. 0.20 ml of the extracts was used for the experiments. The following was also used respectively 0.25 ml of 1% potassium ferricyanide and 0.25 ml of 200 mM sodium phosphate buffer (pH 6.6). Hence, it was incubated at 50 °C for 20 min and then 0.25 ml of 10% trichloroacetic acid was added. 1 ml of water and 0.20 ml of 0.1% ferric chloride. Measurement of the absorbance was taken at 700 nm and ferric reducing power was calculated using ascorbic acid equivalent.

Tissue homogenate preparation

Firstly, we anesthetized the flies on ice and we used Teflon homogenizer with 0.1 M phosphate buffer, pH 7.4. for homogenization. It was centrifuged at 10,000 X g, 4 °C for 10 min. Lipid perioxidation, AChE inhibition and other biochemical assays were conducted using the supernatant.

Determination of superoxide dismutase (SOD) activity

Alia et al. method described Superoxide dismutase (SOD) activity was used in this investigation [52]). Tissue homogenate (0.05 ml) was mixed with 0.05 mL of adrenaline (0.06 mg/mL) and 0.1 mL of 50 mM carbonate buffer (pH 10.2). The measurement of the absorbance was done with spectrophotometer using 480 nm for 2 min at 15 s intervals. The unit for the SOD was expression in mmol/min//mg protein.

Determination of catalase (CAT) activity

Determination of the Catalase activity was conducted [53]. 2 M H_2O_2 (0.1 ml) with 0.25 ml 0.01 M phosphate buffer (pH 7.0) was added to the homogenate (0.05 ml). The reaction was stopped using 0.4 ml dichromate acetic acid. Absorbance of 620 nm was recorded using

spectrophotometer. 1.0 ml 0.01 M sodium phosphate buffer (pH 7.0) was used in the preparation of the standard curve. The unit of the catalase activity was expressed µmol H_2O_2 consumed/mg protein.

Nitric oxide scavenging activity

The extracts in various concentration was mixed with of 5mM sodium nitroprusside (0.3 mL) and incubated for 1 h 30 min at 25^0C. of Griess reagent (0.5 mL) was added to the solution and the absorbance was done at 546 nm [54].

Determination of tissue malondialdehyde (MDA) content

In brief, of tissue homogenate (0.05 ml) was mixed with 8.1% Sodium dodecyl sulfate (SDS) (0.15 ml) then, acetic acid or hydrochloric acid (pH=3.4) (0.25 ml), and Thiobarbituric acid (TBA) 0.25 ml were in the solution incubated for 1 h at 100^0C. The thiobarbituric acid reactive species (TBARS) was measured at 532 nm in a spectrophotometer and the MDA equivalent was determined.

Determination of total protein

Here in, we used the method Coomassie blue according to Bradford using bovine serum albumin (BSA) as standard the of Total Protein content of fly homogenates were determined.

Experimental design

Flies Male and Female with age range of 3–6 days was used for the experiments. Each group contained 20 flies per vial.

Groups	Treatment
I	Basal Diet
II	Basal Diet + Aluminium chloride
IV	Basal Diet + 1% powdery unseeded bread fruit
V	Basal Diet + Aluminium chloride + 0.1% powdery unseeded bread fruit
VI	Basal Diet + Aluminium chloride + 1% powdery unseeded bread fruit

Data analysis

We used the software called Graph pad PRISM (V.5.0). One-way Analysis of Variance (ANOVA) was used followed by Turkey's post hoc test, with levels of significance accepted at $p<0.05$, $p<0.01$ and $p<0.00$. Mean ± standard deviation (S.D) was used for the calculation of the replicate data.

Results

Catalase activity in Drosophila melanogaster

There was significant rise in catalase activity of the flies treated with 0.1% and 1% UBF compare to the control at ($p \leq 0.05$) and also there was significant rise in the catalase activity of the flies induced with $AlCl_3$ and treated 0.1% and 1% UBF compared to the negative control at ($p \leq 0.05$).

SOD activity of Artocarpus altilis in Drosophila melanogaster

There was significant rise in SOD activity of the flies treated with 0.1% and 1% UBF compare to the control at ($p \leq 0.05$) and also there was significant rise in the SOD activity of the flies induced with $AlCl_3$ and treated 0.1% and 1% UBF compared to the negative control at ($p \leq 0.05$).

Acetylcholinesterase activity in *Drosophila melanogaster*

In the acetylcholinesterase activity in *Drosophila melanogaster*, no significant different in the acetylcholinesterase activity of the flies treated with 0.1% UBF compared to the control but there was significant low acetylcholinesterase activity of the flies treated with 1% UBF compared to the control at ($P \leq 0.05$), there is a significant low acetylcholinesterase activity of the flies induced with $AlCl_3$ and treated with 0.1% & 1% UBF compared to the negative control at ($P \leq 0.05$).

MDA level in Drosophila melanogaster

There was a significantly low MDA level in the flies treated with 0.1% & 1% UBF compared to the control at ($P \leq 0.05$), there was a significantly low MDA level in the flies induced with $AlCl_3$ and treated with 0.1% and 1% UBF compared to the negative control at ($P \leq 0.05$).

Discussions

Drosophila melanogaster may be utilized to investigate chemicals and pharmacological analogues for their potential capability to ameliorate or aggravate diseases, which can unveil novel therapeutics in biomedical research and neurodegenerative diseases [55–57]. Aging individuals are mostly affected with the disease of neurodegenerative which causes a lot of psychological effects. Investigations are currently done on the pharmacological activities of *Artocarpus altilis* which may be a potential therapy for neurodegenerative diseases [58, 59]. It is, therefore, crucial to determine the main effect of *Artocarpus altilis* on the acetylcholinesterase activity, MDA (malondialdehyde) level, catalase and SOD (superoxide dismutase) activity on *Drosophila melanogaster*. *Artocarpus altilis*, is mostly investigated due to its antioxidant properties which makes it potential therapeutics.

Hydrogen peroxide is due to the presence of the enzyme called catalase. It is an antioxidant enzyme which has important roles in the protection of the cells. It has two major steps for the catalase reactions. Firstly, the oxyferryl is formed due to the oxidation of the heme. Secondly, a porphyrin ring and iron is formed due to

porphyrination [60]. A resting state enzyme is formed by the second hydrogen peroxide molecule acts as a reducing agent. As indicated in Fig. 1 the catalase activity of the flies treated with 0.1% and 1% UBF increased significantly compared to the control and also there was significant increase in the catalase activity of the flies induced with $AlCl_3$ and treated 0.1% and 1% UBF compared to the negative control. Previous investigations revealed that harms are done to biomolecules in the nervous system by Al toxicity [61, 62]. Hence, due to the antioxidant properties of *Artocarpus altilis* enhance higher catalase activity in the pretreated and posttreated flies with *Artocarpus altilis.* Therefore, *Artocarpus altilis*, ameolirate the aluminium chloride-induced inhibition of catalase activity and H_2O_2 accumulation which indicates that it has free radical scavenging properties and antioxidative.

Various researchers have confirmed that the production of H_2O_2 is produced as a result of SOD which influence the activation of natural antioxidant defense mechanisms [63]. As presented in Fig. 2 there was significant increase in the SOD activity of the flies treated with 0.1% and 1% UBF and that of the $AlCl_3$ induced respectively.

In the clinical and basic research, acetylcholinesterase inhibitors are of great importance. Alzheimer's disease, digestive process, as well as in disorders such as myasthenia gravis, glaucoma have some significant linkages with acetylcholinesterase [64]. The inhibitory effect of *Artocarpus altilis* in acetylcholinesterase activity in *D. melanogaster* was determined as presented in Fig. 3 there was no significant difference in the acetylcholinesterase activity of the flies treated with 0.1% UBF compared to the control but there was low significant difference in the acetylcholinesterase activity of the flies. Partial inhibition of AChE activity in the brain has been shown to be therapeutically beneficial. AChE inhibitors that penetrate the blood–brain barrier elevate the levels of endogenous acetylcholine and are useful in the symptomatic treatment of Alzheimer's disease [65, 66]. With the lower acetylcholinesterase in the flies treated with *Artocarpus altilis* given the therapeutic potential in the management of aluminium induced neurodegeneration.

End product of lipid peroxidation may be mutagenic and accumulation may result to neuronal cell death leading to neurodegenerative diseases [67]. As presented in Fig. 4 there was low significance difference in the MDA level in the flies treated with 0.1% & 1% UBF and induced with $AlCl_3$ respectively. Showing the therapeutic potential of *Artocarpus altilis* in preventing and managing neurodegeneration, the unique structure of phenolic compounds present in the *Artocarpus altilis* facilitates their role as free radical scavengers due to resonance stabilization of the captured electron [68, 69] and activating the activity of some antioxidant enzymes. Free radical scavenging occurs by hydrogen donation to lipid radicals competing with the chain propagation reaction [70]. With the activity of catalase, SOD, acetylcholinesterase inhibition and the level of MDA in the pre-treated and post treated flies showing a great potential of *Artocarpus*

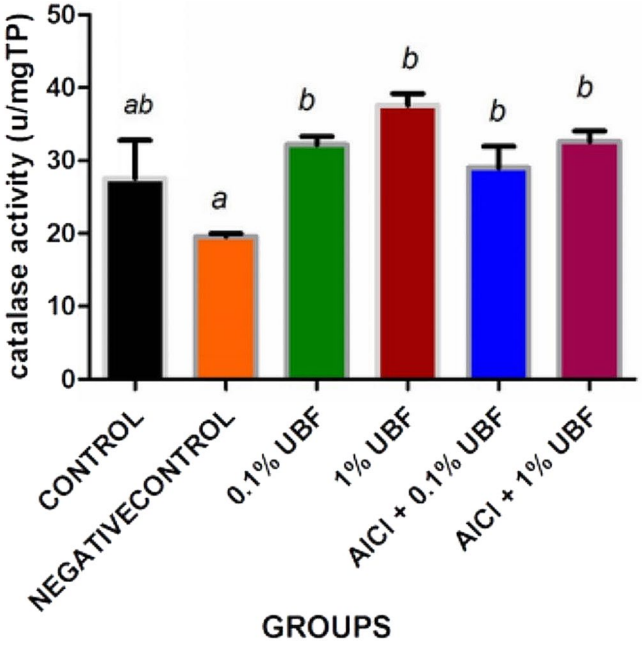


Fig. 1 Catalase activity in *Drosophila melanogaster.* In the figure above there was a significant rise in catalase activity of the flies treated with 0.1% and 1% UBF compared to the control at ($p \leq 0.05$) and also there was a significant rise in the catalase activity of the flies induced with $AlCl_3$ and treated 0.1% and 1% UBF compared to the negative control at ($p \leq 0.05$)

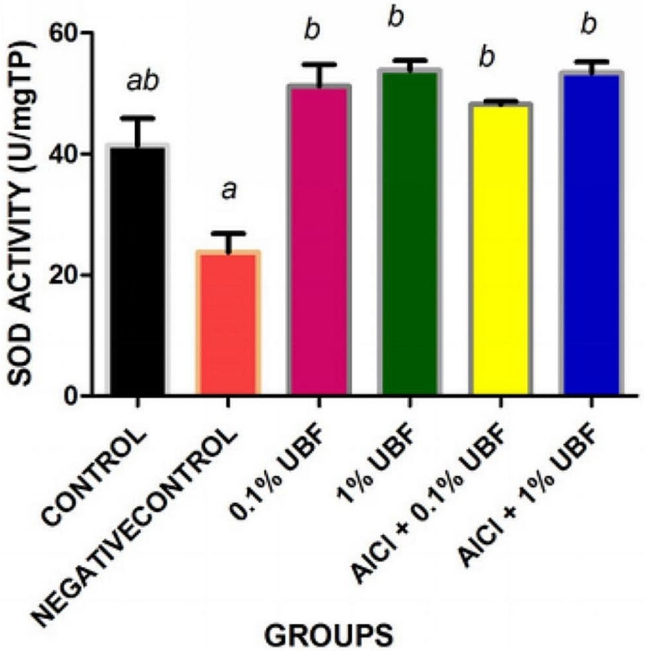


Fig. 2 SOD activity of *Artocarpus artilis* in *Drosophila melanogaster.* In the figure above there was a significant rise in the SOD activity of the flies treated with 0.1% and 1% UBF compared to the control at ($p \leq 0.05$) and also there was a significant rise in the SOD activity of the flies induced with $AlCl_3$ and treated 0.1% and 1% UBF compared to the negative control at ($p \leq 0.05$)

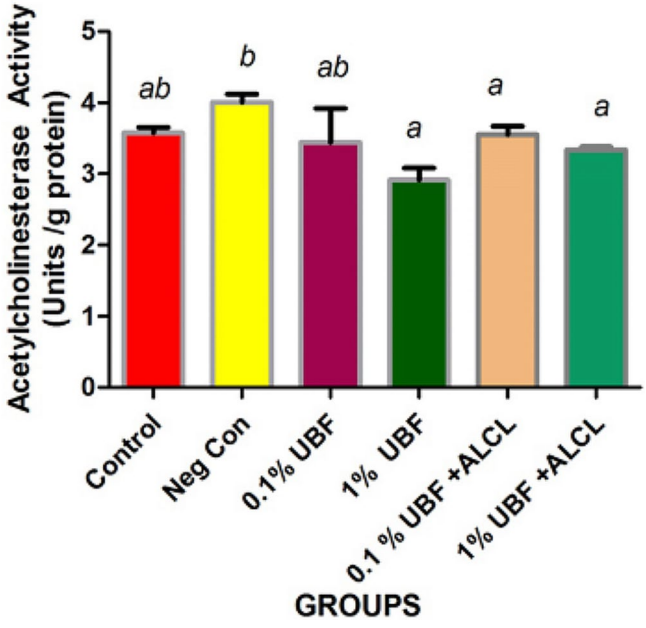


Fig. 3 Acetylcholinesterase activity in *Drosophila melanogaster*. In the figure above there was no significant different in the acetylcholinesterase activity of the flies treated with 0.1% UBF compared to the control but there was significant low acetylcholinesterase activity of the flies treated with 1% UBF compared to the control at ($P \leq 0.05$), there is a significant low acetylcholinesterase activity of the flies induced with $AlCl_3$ and treated with 0.1% & 1% UBF compared to the negative control at ($P \leq 0.05$)

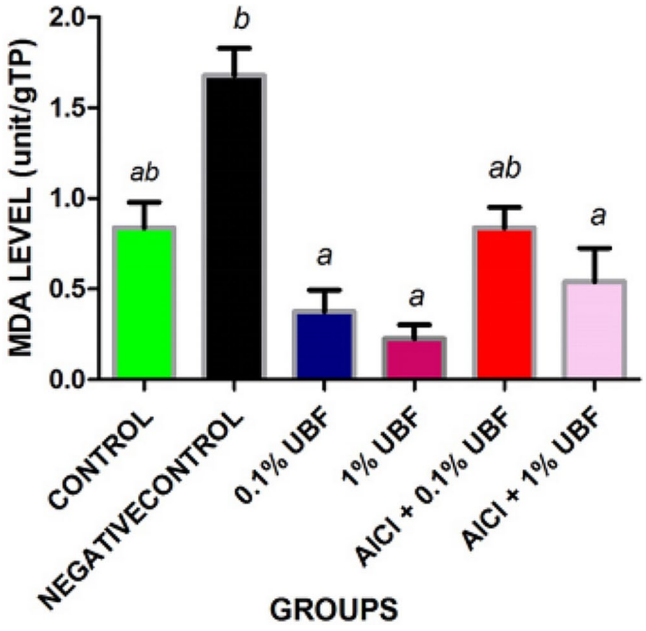


Fig. 4 MDA level in *Drosophila melanogaster*. In the figure above there was a significantly low MDA level in the flies treated with 0.1% & 1% UBF compared to the control at ($P \leq 0.05$), there was a significantly low MDA level in the flies induced with $AlCl_3$ and treated with 0.1% and 1% UBF compared to the negative control at ($P \leq 0.05$)

altilis in the prevention and management of neurodegenerative diseases.

Conclusions

This study reveals that metals such as aluminium, induce a state of neurotoxicity that significantly affect the acetylcholinesterase activity, MDA level and the antioxidant activity of catalase and SOD in *Drosophila melanogaster*. *Artocarpus altilis* significantly reduced the acetylcholinesterase activity, MDA level had a positive effect on antioxidant activity of catalase and SOD. It could be concluded that *Artocarpus altilis* is a more promising prophylactic and antioxidant plants in the ameliorative and treatment of neurodegenerative diseases.

Abbreviations

AlCl3	Aluminium Chloride
SOD	Superoxide dismutase
MDA	Malondialdehyde
Al	Aluminium
CNS	Central nervous system
AD	Alzheimer's disease
DEPPD	n-n-diethyl-para-phenylenediamine
FRAP	Determination of ferric reducing antioxidant property
CAT	Catalase
SDS	Sodium dodecyl sulfate
TBA	Thiobarbituric acid
TBARS	Thiobarbituric acid reactive species
BSA	Bovine serum albumin
ANOVA	One-way Analysis of Variance
UBF	Unseeded breadfruit

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Author contributions

JAS and AMO wrote the manuscript. JAS and OSF performed the experiments, collected and analyzed data. JAS and AMO conceived and designed the study and revised the manuscript for improved intellectual content. All authors read and approved the final manuscript.

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Data availability

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Declarations

Ethics approval and consent to participate

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Consent for publication

Not applicable.

Competing interests

The authors declare no conflict of interest.

Author details

[1]Department of Biochemistry, Adekunle Ajasin University Akungba Akoko, Ondo, Nigeria
[2]Department of Natural and Environmental Sciences, American University of Nigeria, Adamawa, Yola, Nigeria

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