ACTA FACULTATIS
MEDICAE NAISSENSIS

UDC: 633.88:542.943
DOI:10.5937/afmnai2003252O

Original article

Annona Muricata Protects against Cadmium-Mediated Oxidative Damage in the Brain and Liver of Rats

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SUMMARY

This present research work was designed to investigate the potential chemopreventive effects of *Annona Muricata* on cadmium-induced hepatotoxicity and oxidative neuronal damage in Wistar albino rats. In this study, twenty-eight (28) Wistar albino rats were randomized into four groups, with seven rats each. Group A served as the control and provided distilled water orally. Groups B, C and D were exposed to 5 mg/kg body weight cadmium chloride orally, while in Groups C and D 200 and 500 mg/kg body weight of ethanolic seed extract of *Annona Muricata* were administered, respectively, via oral administration, while group B was left untreated for 14 days. Cadmium induced hepatic damage with significant ($p < 0.05$) elevation of serum total bilirubin, total protein, AST and ALT. Cadmium also caused oxidative neuronal and hepatic damage in rats with significant decrease in ascorbic acid level, GSH, GPx, CAT and SOD activities in the tissues. Lipid peroxidation (MDA level) was significantly increased in rats treated with cadmium alone. Histological findings reveal distortion in brain architecture with intense inflammatory cells especially seen between the grey and white matter. Liver histology reveal chronic inflammation and infiltration of the hepatic cells. However, administration of ethanolic seed extract of *Annona Muricata* significantly reverse all the toxic effects of cadmium in the brain and liver, suggesting its hepatoprotective effects and therapeutic importance in neurodegenerative disorders.

Key words: **hepatotoxicity, neurotoxicity, cadmium, *Annona Muricata*, chemoprevention**

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INTRODUCTION

Cadmium is an industrial heavy metal with many toxicological effects on health such as hepatorenal degeneration, neuropathies, pneumoconies, and cancers (1, 2). Toxicitiy of cadmium has been associated with oxidative stress via its high affinity to sulfhydryl groups such as that of cysteine residues richly present in glutathione (GSH) and metallothionein (MT) which then result in alteration of the intracellular redox status, thus stimulating deleterious effects on essential biochemical processes (3). The mechanism of cadmium-mediated hepatotoxicity include activation of protein kinase C (PKC) via alteration of calcium homeostasis which drives the harmful effects of reactive oxygen species (ROS), exasperating oxidative damage of cellular components. This further leads to cell death (apoptosis) and release of inflammatory mediators such as cytokine and ROS that induce inflammation, generating infiltration and activation of phagocytic cells (4).

The liver is the major site of metabolic activities in the body and is being continually assaulted when there is exposure to xenobiotics such as heavy metals, chemicals, toxins or physical agents, including radiations. Histological studies on rats treated with cadmium alone reported that cadmium cause some pathological alterations which include cellular degeneration and necrosis, cytoplasmic vacuolization, loss of architecture of the parenchymatous tissue, and severe glycogen depletion (5). Brain is also vulnerable to attacks of foreign chemicals, especially free radicals in the body due to its low content of antioxidant and other cellular protective mechanisms; therefore, neurological conditions have also been associated with exposure to cadmium (1).

Annona muricata (*A. muricata*) is a medicinal plant with various types of phytochemicals and other natural products which have been widely employed traditionally in the treatment of many medical conditions. It is used as traditional medicine in the treatment of arthritic pain, dysentery, fever, malaria, neuralgia, arthritis, diarrhea, parasites, rheumatism, skin rushes and worms, and it is also eaten to elevate mother's milk after childbirth, while its leaves are employed to treat cystitis, diabetes, headaches and insomnia (6, 7, 8). The crushed seeds are believed to have anti-helmintic activities against external and internal worms and parasites. In South America and tropical Africa, including Nigeria, leaves of *A. muricata* are deployed as an ethnomedicine against tumors and cancer (9). Anti-inflammatory, hypoglycemic, sedative, smooth muscle relaxant, hypotensive and antispasmodic properties have also been attributed to the leaves, barks and roots of *A. muricata*, (6). Studies on the hepato- and neuroprotective effects of *A. muricata* on cadmium-mediated oxidative stress in animal models are scarce in literature, therefore, this study was designed to investigate the chemopreventive effects of *A. muricata* against cadmium-mediated hepatotoxicity and oxidative neuronal damage in rats.

MATERIALS AND METHODS

Chemicals/ Reagents

AST and ALT kits are products of Randox, Glacial acetic acid, Ferric Chloride, Conc. H_2SO_4, Ethyl Acetate, Ammonia solution, HCl, Chloroform, Acetic anhydride and other reagents are of analytic grade.

Collection of plant material and preparation of extract

A. muricata seeds were collected at Osogbo Osun State, Nigeria. The seeds were air-dried to a constant weight at room temperature. The dried seeds were grinded into powdery form with Diki blender machine. The powdered seeds were stored in an air-tight polythene bag until use. 500 g of the powdered sample was dissolved in 3.0 l (1: 6 w/v) of 98% absolute ethanol to extract the phytochemical present in the seed sample. Soaking lashed 72 h after which the extract was filtered. The mixture was concentrated using rotary evaporator at 80°C. Concentrated extract was obtained by the total removal of ethanol in the water bath. The obtained crude extract was weighed and used to prepare the stock solution for administration.

Experimental animals

Twenty-eight (28) Wistar rats used for this study were obtained and raised at the Central Animal House, Osun State University, Osogbo, Nigeria. The rats' weights ranged from 140g to 150 g. Rats were kept under laboratory conditions (25 ± 2 °C and relative humidity of 50 ± 15%) in cages cleaned of metabolic waste twice daily and were allowed to acclimatize for two weeks. They were

exposed to 12 hours daylight and darkness, fed with rat pellet and water ad libitum. The experiment was carried out in accordance with the current rules and guidelines that have been established for the care of the laboratory animals (10). The rats were acclimatized for two weeks before the treatment commenced.

Animal grouping and administration

The rats were randomized into four groups containing seven (7) animals each. The mean weight for each group was determined and recorded. 5 mg/kg bw of cadmium chloride was used in this study based on previous method of Oyewole, et al. (11). Ethanolic seed extract of *A. muricata* (EEAM) were administered every 24 h and cadmium was administered every 72 h over 14 days of administration.

- Group A rats received no administration, serving as normal control.
- Group B rats received 5 mg/kg body weight of cadmium chloride orally serving as cadmium control.
- Group C rats received 5 mg/kg bw of cadmium chloride + 200 mg/kg b/w of EEAM.
- Group D rats received 5mg/kg bw of cadmium chloride + 500 mg/kg bw of EEAM.

Preparation of serum

The experimental rats were sacrificed 24 h after the last administration by cervical dislocation and blood samples were collected into clean, dry centrifuge tube. The blood was left for 10 min at room temperature to clot after which it was centrifuged at 4,000 rpm in an MSC (Essex, UK) bench centrifuge. The clear supernatant (serum) was aspirated using a Pasteur pipette into clean, dry sample bottles and then stored at 4°C for biochemical analyses.

Preparation of tissue homogenates

The liver and brain were immediately removed from the rat and placed on a blotting paper to remove blood stains. It was then rinsed in 1.15% KCl to remove haemoglobin, followed by homogenization in 4 volumes of ice-cold 0.01 M potassium phosphate buffer, (pH 7.4) using Teflon homogenizer. The homogenate was centrifuged at 12,500 g for 20 min at 4^0C to obtain supernatants (post-mitochondrial fractions) which was stored till required for assay.

Determination of Biochemical parameters

The Superoxide dismutase (SOD) activity levels in brains and livers were determined by the method of Mistra and Fridovich, (12). Catalase activities were measured according to the method of Sinha (13). The method described by Jollow et al. (14) was employed in estimating the level of reduced glutathione (GSH). Glutathione peroxidase (GPx) activities were determined according to the method of Rotruck et al. (15). Lipid peroxidation (malondialdehyde {MDA}) level was determined by using the method of Vashney and Kale (16). Ascorbic acid concentration was assayed according to procedure of Jagota and Dani (17). Serum AST and ALT were determined colometrically by the method described by kit manufacturer.

Histological examination

The liver and brain were fixed in 10% formalin and embedded in paraffin wax. Thin sections (7 – 9 mm thickness) of the tissues were cut and dewaxed in xylene, hydrated in decreasing percentage of alcohol and stained with hematoxylin. They were then dehydrated in increasing percentage of alcohols till 70% and stained with 1% alcoholic eosin. They were differentiated in 90% alcohol and cleared in xylene. These stained sections were observed under the microscope for histopathological analysis.

Statistical analysis

Data of results were expressed as mean ± SD. Comparison was done using one-way analysis of variance (ANOVA) between the control and treatment groups. P values < 0.05 were considered statistically significant.

RESULTS

Results revealed that cadmium caused significant increase in the level and activities of the selected hepatic markers when compared with the control indicating hepatic damage. However, treatment with EEAM at 200 and 500 mg/kg body weight significantly modulated these observations (Table 1).

Table 1. *Effects of administration of cadmium and ethanolic seed extract of Annona Muricata on selected serum hepatic markers in rats*

	CONTROL	Cd alone	Cd + EEAM 1	Cd + EEAM 2
Bilirubin	31.65 ± 5.24	42.83 ± 4.77[a]	39.91 ± 5.00[ab]	35.66 ± 4.72[ab]
Total protein	50.03 ± 4.28	58.74 ± 5.31[a]	54.22 ± 4.63[ab]	52.09 ± 4.04[b]
AST (IU/L)	45.03 ± 3.83	58.60 ± 3.72[a]	50.70 ± 4.11[ab]	48.35 ± 3.50[b]
ALT	31.75 ± 4.92	52.55 ± 5.02[a]	45.80 ± 4.79[ab]	43.21 ± 5.14[ab]

Values are means ± SD.: [a] indicates that value is significantly different from the control value at $p < 0.05$, while
[b] indicates significant difference from Cd alone administered in the rat group at $p < 0.05$

Table 2. *Hepatic redox status of rats treated with Cadmium and ethanolic seed extract of Annona Muricata*

	CONTROL	Cd alone	Cd + EEAM 1	Cd + EEAM 2
MDA (nmol/mgprotein)	5.48 ± 0.66	12.05 ± 0.45[a]	8.82 ± 0.50[ab]	7.02 ± 0.53[b]
Reduced GSH (umol/mgprotein)	15.27 ± 2.01	7.37 ± 1.24[a]	10.97 ± 2.12[ab]	13.04 ± 1.81[ab]
Ascorbic acid (umol/mgprotein)	40.62 ± 4.36	31.91 ± 3.94[a]	35.33 ± 4.04[ab]	37.12 ± 3.89[b]
CAT (u/mgprotein)	48.55 ± 5.09	37.86 ± 4.83[a]	42.72 ± 4.86[ab]	44.26 ± 5.10[b]
SOD (u/mgprotein)	31.02 ± 3.88	24.15 ± 3.03[a]	28.73 ± 3.29[ab]	30.04 ± 4.03[b]
GPx (u/mgprotein)	44.82 ± 4.79	32.65 ± 4.30[a]	39.50 ± 4.20[ab]	41.26 ± 5.08[ab]

Values are means ± SD.: [a] indicates that value is significantly different from the control value at $p < 0.05$ while
[b] indicates significant difference from Cd alone administered to the rat group at $p < 0.05$.

Effects of EEAM on hepatic redox status of rats treated with cadmium

Cadmium caused significant increase in MDA level, while the levels and activities of antioxidant molecules were significantly decreased in the liver when compared with the control; co-administration with EEAM at 200 and 500 mg/kg body weight resulted in significant moderation of these molecules in a dose-dependent manner (Table 2).

Effects of administration of cadmium and ethanolic seed extract of *A. muricata* on redox status of the brain of experimental rats

Exposure of rats to cadmium caused significant increase in MDA level, while the levels and activities of antioxidant molecules were significantly lowered in the brain when compared with the control; co-administration with EEAM at 200 and 500 mg/kg body weight was able to abrogate these conditions significantly in a dose-dependent manner (Table 3).

Table 3: *Effects of administration of cadmium and ethanolic seed extract of Annona Muricata on redox status of the brain of experimental rats*

	CONTROL	Cd alone	Cd + EEAM 1	Cd + EEAM 2
MDA (nmol/mgprotein)	4.93 ± 0.50	13.55 ± 0.47^{a}	9.72 ± 0.81^{ab}	8.33 ± 0.69^{ab}
Reduced GSH (umol/mgprotein)	12.74 ± 0.95	6.48 ± 0.74^{a}	9.37 ± 0.50^{ab}	10.15 ± 0.80^{ab}
Ascorbic acid (umol/mgprotein)	20.13 ± 1.97	11.28 ± 1.41^{a}	16.00 ± 2.03^{ab}	18.26 ± 1.88^{b}
CAT (u/mgprotein)	21.50 ± 1.92	13.73 ± 2.10^{a}	18.55 ± 1.57^{ab}	19.94 ± 2.05^{b}
SOD (u/mgprotein)	16.54 ± 1.78	9.10 ± 1.36^{a}	14.04 ± 2.16^{b}	16.13 ± 2.91^{b}
GPx (u/mgprotein)	18.00 ± 2.25	11.27 ± 2.08^{a}	15.03 ± 1.96^{ab}	17.20 ± 2.08^{b}

Values are means ± SD. : ^{a} indicates value is significantly different from the control value at $p < 0.05$ while ^{b} indicates significant difference from Cd alone administered rat group at $p < 0.05$.

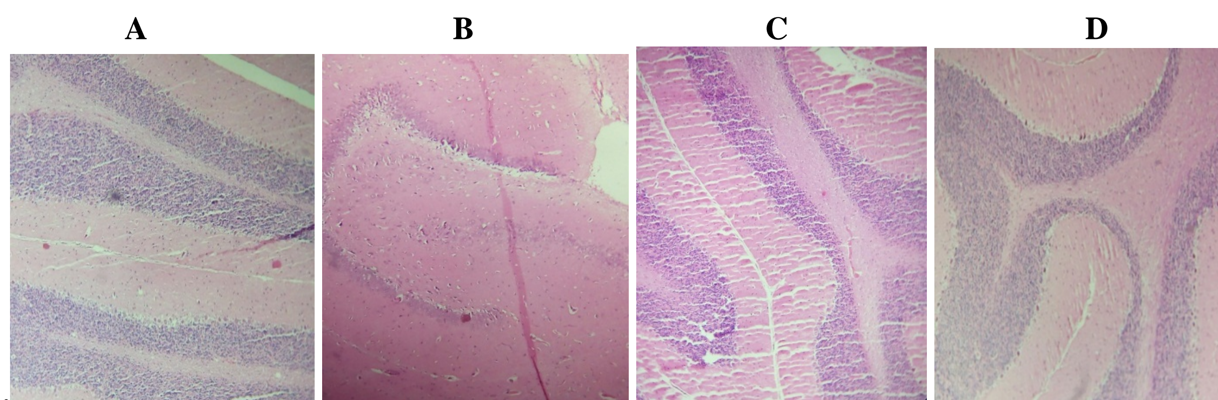

Figure 1. *Effects of administration of cadmium and ethanolic seed extract of Annona muricata on histology of the brain of experimental rats:*

A (Control): section shows neural tissue, the white and grey matters are well preserved. The neurons are morphologically and architerally well disposed. Nil area of infarction, no inflammatory cells seen. No loss of neural tissue, no hemorrhage. B (Cd alone): section shows neural tissue, with distorted architecture, there are intense inflammatory cells especially seen between the grey and white matter. C (Cd+EEAM 1): Section shows neural tissue, no cytological atypia. No inflammatory cells seen. No loss of neurons. D (Cd+EEAM 2): section shows neural tissue, no cytological atypia. No inflammatory cells seen. No loss of neurons.

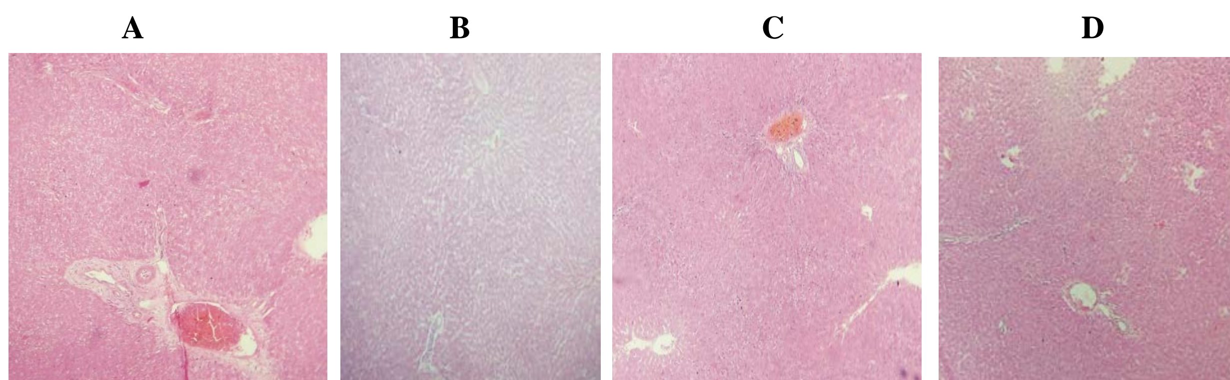

Figure 2 *shows the effects of administration of cadmium and ethanolic seed extract of Annona Muricata on histology of the liver of experimental rats:*

Group A shows normal architecture structure and no visible lesion; group B shows loss of normal architecture, small-sized cytoplasmic vacuole, cellular degeneration and necrosis; groups C and D show a mild visible lesion.

DISCUSSION

Total bilirubin and protein were significantly ($p < 0.05$) elevated in the serum of rats administered cadmium, which is an indication of liver function disruption. Bilirubin is a conventional indicator of liver diseases and its elevation in the serum has been associated with hepatocellular damage and hepatic biliary tract obstruction (18, 19). However, treatment with ethanolic seed extract of *A. muricata* significantly attenuated and reversed the elevated concentrations of bilirubin and protein in a dose-dependent manner.

Results from this study confirmed the hepatotoxic effects of cadmium as rats exposed to cadmium chloride showed a marked elevation in the serum activities of ALT and AST. Elevation of these hepatic marker enzymes might be due to their leakage out of the liver into the blood system because of destruction of hepatic membranes. This result is tandem with the previous report of Oladele et al., (20) who documented the hepatotoxicity effect of cadmium in rats. However, treatment with ethanolic seed extract of *A. muricata* significantly ameliorated these anomalies by normalizing the serum activities of the enzymes.

The observed significant increase ($p<0.05$) in the level of malondialdehyde (MDA) in the brain and liver of the rats treated with cadmium indicates lipid peroxidation (21). Oxidation of polyunsaturated fatty acids produces end-products, such as malondialdehyde, which has been implicated in the pathogenesis of neurodegenerative diseases such as Parkinson's diseases, Alzheimer's disease, etc. and is a risk factor in liver carcinogenesis. Treatment with the chosen doses of ethanolic seed extract of *A. muricata* significantly mitigate the toxic effect of cadmium and protected against the accumulation of toxic lipid peroxidation products in both the brain and liver. This protective effect of ethanolic seed extract of *A. muricata* may be due to antioxidant phytochemicals present in the extract which act as radical chain breaker and subsequently inhibits lipid peroxidation, stabilizing membrane integrity, thereby preventing the inactivation and depletion of plasma membrane enzymes.

The significant ($p < 0.05$) decrease in GSH level, GPx, CAT, and SOD activities in the liver and brain of rats exposed to cadmium alone indicate that oxidative stress has been induced in the rats (21). Oxidative stress occurs when there is imbalance between ROS generation and antioxidants in the body which can lead to oxidative damage of macromolecules. Brain contains limited amount of antioxidant enzymes which make it vulnerable to oxidative stress. Cytoprotection in these organs (brain and liver) is provided by glutathione peroxidase (GPx), catalase, and SOD. SOD is a family of metalloenzymes that is known to accelerate the dismutation of endogenous cytotoxic superoxide radicals to H_2O_2, which are deleterious to polyunsaturated fatty acids and structural proteins of plasma membrane. GSH is conjugated with a wide variety of xenobiotics (including lipid peroxides), carcinogens and drugs to form more water-soluble bioproducts that are readily excreted from biological system.

Treatment with ethanolic seed extract of *A. muricata* significantly ($p < 0.05$) ameliorated all the markers of oxidative stress in the liver and liver of rats by significantly increasing GSH concentration, GPx, SOD and CAT activities. The protective activities of the extract can be due to its antioxidant phytochemical constituents, free radical scavenging abilities, and its ability to enhance the synthesis of these antioxidant enzymes and influence their enzymatic functions.

The histological findings of the brain of rats treated with cadmium reveal that there is distortion in brain architecture with intense inflammatory cells, especially seen between the grey and white matter (Figure 1). Liver histology reveal chronic inflammation and infiltration of the hepatic cells (Figure 2). All these histological alterations were restored following the administration of ethanolic seed extract of *A. muricata* in a dose-dependent manner which further strengthens the biochemical studies.

CONCLUSION

The present study suggests that ethanolic seed extract of *A. muricata* may exert an important function in protecting against hepatic and neurotoxins. The mechanism of the protective actions of the extract may be via its free radical scavenging and antioxidant activities, which inhibits lipid peroxidation and stabilizes membrane integrity, thereby preventing the inactivation and depletion of plasma membrane enzymes.

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Protektivna dejstva biljne vrste *Annona muricata* kod oksidativnih oštećenja izazvanih kadmijumom u mozgu i jetri pacova

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SAŽETAK

Cilj ovog istraživačkog rada bilo je ispitivanje potencijalnih hemoprotektivnih efekata biljne vrste *Annona muricata* na hepatotoksičnost izazvanu kadmijumom i oksidativna oštećenja neurona kod Vistar albino pacova. U ovoj studiji, ukupno 28 Vistar albino pacova nasumično je podeljeno u četiri grupe, a svaku grupu činilo je osam pacova. Pacovima u grupi A, koja je služila kao kontrolna grupa, data je samo destilovana voda. Pacovima iz grupa B, C i D oralno je dat kadmijum hlorid u dozi od 5 mg/kg telesne mase, nakon čega je pacovima iz grupa C i D oralno dat etanolni ekstrakt semena biljne vrste *Annona muricata* u dozi od 200 mg/kg i 500 mg/kg telesne mase; pacovi iz grupe B ostali su netretirani narednih 14 dana. Kadmijum je izazvao oštećenje jetre sa značajnim povećanjem ukupnog bilirubina u serumu ($p < 0,05$), ukupnih proteina, kao i povećanje vrednosti AST i ALT. Takođe, kadmijum je izazvao oštećenje neurona i jetre kod pacova, što je dovelo do značajnog smanjenja nivoa ascorbinske kiseline, kao i aktivnosti GSH, GPx, CAT i SOD u tkivima. Lipidna peroksidacija bila je značajno povećana kod pacova koji su tretirani samo kadmijumom. Histološki nalazi ukazali su na poremećaj arhitekture mozga sa intenzivnom inflamacijom ćelija, koje se naročito uočavaju između sive i bele mase. Histologija jetre ukazala je na hroničnu inflamaciju i infiltraciju hepatičnih ćelija. Međutim, primena etanolnog ekstrakta semena biljne vrste *Annona muricata* značajno je smanjila sve toksične efekte kadmijuma u mozgu i jetri, što ukazuje na njene hepatoprotektivne efekte i terapeutski značaj kod neurodegenerativnih poremećaja.

Ključne reči: **hepatotoksičnost, neurotoksičnost, kadmijum, *Annona muricata*, hemoprevencija**