

(RESEARCH ARTICLE)



Nutraceutical from *Moringa oleifera* Protect against Cadmium Chloride-Induced Hypertension in Albino Rats

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Abstract

Moringa oleifera like many other plants possess antioxidant and free radical scavenging property, which could be helpful in reducing the oxidative stress caused by cadmium chloride, maintaining the antioxidant potential and significantly reducing elevated electrolytes and serum biomarker values in the rats. This study was designed to evaluate the nutraceuticals from *Moringa oleifera* and its protective ability against cadmium chloride-induced hypertension in albino rats. Rats were induced with cadmium chloride to elicit hypertension. The study was a total number of 50 rats grouped in five different groups of 10 per group; the Control Group, Hypertensive Group, Standard group, methanol group and n-hexane group. Biochemical analysis was done on renal function and liver biomarkers by spectrophotometry method of analysis. Standard methods were used to estimate the serum Urea and Creatinine, Electrolyte and Calcium. Aspartate Transaminase (AST), Alanine Aminotransferase (ALT) and Alanine Phosphatase (ALP), total and conjugated bilirubin. One way ANOVA was used for analysis of the collected data and was expressed as Mean \pm SEM. The result of Hypertensive group showed significant increase in sodium level ($p < 0.05$) and chloridr when compared with Control and other test groups. There was significant decrease in Sodium level of Standard drug, methanol *Moringa* and n-hexane *Moringa oleifera* groups when compared with the hypertensive Control. *Moringa oleifera* study groups exhibited significant decrease in Total bilirubin and Conjugated Bilirubin values. The liver and kidney tissues showed distorted patchy necrotic areas on the Hypertensive groups while Standard and Test groups showed normal histological cells or. The cardiac tissue did not show any sign, may suggest that cadmium is mainly accumulated in kidneys and liver, not in the heart or cardiac tissues or cells.

The study findings suggest that *Moringa oleifera* possesses some nutraceuticals capable of protection against hypertension.

Keywords: *Moringa oleifera*; Cadmium chloride; Hypertension; Nutraceutical; Rats

1. Introduction

Abundant polyphenols from natural compound possess intense antioxidant effects and can reduce oxidative damage in tissues by removing free radical [1; 2; 3; 4]. *Moringa oleifera* has antioxidant activity due to its abundant content of high bioactive polyphenols [5; 6]. There are strong antioxidant activities in *Moringa oleifera* extracts from tender to mature leaves against free radicals which prevent oxidative damage due to the enrichment of polyphenols [5]. A recent study reported that *Moringa oleifera* decreased vascular oxidation in spontaneously hypertensive rats. *Moringa oleifera* is a rich source of various natural bioactive compounds that is known to assist in maintenance of human health and

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wellbeing and acquire nutraceutical potential [6]. Four pure compounds, niacinin A, niacinin B, niacinin A + B and niachimicin isolated from ethanol extract of *Moringa oleifera* leaves showed a blood pressure lowering effect in rats which is as a result of calcium antagonist effect [7; 8]. *Moringa*, nutrient-packed super food that comes from the *Moringa oleifera* tree in India, has been used for centuries in Eastern cultures and now in Nigeria to alleviate headaches, ease constipation, stimulate the immune system, promote weight loss, and increase libido. The leaf extract contains β -carotene, flavonoids, lycopene, polyphenols, and exhibit hydrogen peroxide 2, 2-diphenyl-1-picrylhydrazyl, and hydroxyl radical scavenging activities [9] while in another study it was shown that *Moringa oleifera* have hypotensive effects due to extracts like thiocarbamate glycosides which it possesses [10].

Hypertension and dyslipidemia are the two major factors of cardiovascular disease found in the pathogenesis and progression of cardiovascular diseases [11]. Epidemiologic importance of negative correlation between cardiovascular events and renal function in potassium, sodium, bicarbonate, chloride and other electrolyte handling are important in hypertension and extracellular volume expansion.

Cadmium is a very well-known heavy metal which is found in the environment, it has been reported to cause serious occupational and environmental hazard to human [12; 13]. Exposure to toxic metals has become an increasingly recognized source of illness worldwide [14; 15]. Cadmium has been shown to be possible factor in arteriosclerotic heart disease and hypertension.[16] Cadmium chloride induces lipid peroxidation by stimulating the production of superoxide anions and inhibits antioxidants such as superoxide dismutase and glutathione peroxidase, it also causes accumulation of free radicals that damage the cells and produce chronic disease [17]. *Moringa oleifera* is reported to possess a wide range of therapeutic and medicinal properties through executing its potent anti-inflammatory activity, inhibiting the activation of NF- κ B and PI3K/Akt pathways, enhancing neuroprotective roles and mitigating oxidative stress by scavenging free radicals [18]. In addition, *Moringa oleifera* can reduce the risk of cancer and regulate blood glucose, although the underlying mechanisms remain to be further explored. Therefore, *Moringa oleifera* provides the potential for the prevention or treatment of a series of chronic diseases [18]. Thus changes of hypertension and dyslipidemia associated parameters with nutraceutical could be useful in the control and treatment of cardiovascular disease. *Moringa oleifera* possess free radicals and antioxidant scavenging property, which could reduce the oxidative stress caused by cadmium, thereby maintained the antioxidant potential, reduced the reactive oxygen species (ROS) production and significantly reduced increased serum biomarker levels in the body [19]. Evidences of efficacy of *Moringa oleifera* against cadmium chloride-induced cardio protective and hepatoprotective effects of some liver, kidney and heart parameters in hypertensive albino rats were scanty, hence this study was designed for such investigation.

2. Material and methods

2.1. Identification and Preparation of Plant Materials

Fresh leaves of *Moringa oleifera* was purchased by researcher and was identified by Dr. Chimezie Ekeke of the Department of Plant Science and Biotechnology University of Port Harcourt, with a Herbarium number UPH/P/105. *Moringa* leaves were selected, washed, completely drained and allowed for some days to air-dried at room temperature. They were shuffled as we monitored them daily to avoid decay. At the end of the three weeks, 2 kilogram of completely dried leaves were grinded into powdered form using electrical blender.

2.2. Extraction of the blended leaves of *Moringa oleifera*

Rotary Vane Extraction process was done on the blended leaves of *Moringa oleifera* solvents methanol and n-hexane extraction into two stages – first stage involved crude extraction with ethanol and the second stage was further extraction with Whatman No 1 filter paper. Within 5 days, ethanol were evaporated to semi-solid state at 80°C. The aqueous filtration was also evaporated to semi-solid state using rotary evaporator. Each 500g of blended forms was refluxed in two (2) liter volume of methanol solvent (1:4) [20].

Basic phytochemical screening was done to detect the presence of alkaloids, flavonoids, tannins, anthraquinone, (Bontragers test), triterpenoid/steroids, fixed oils, carbohydrates, cardenolide, cyanogenic glycosides and saponins in the plants methanol and n-hexane, extracts in accordance with [21] established procedures.

2.3. Animal experiment

A total number of 50 albino rats (30 males, 20 females) were used for the study. The animals were breed in the Animal House of the Department of Human Physiology, Nnamdi Azikiwe University Okofia Campus. The animals were acclimatized for 14 days, their blood pressure were measured with UgoBasil tail-cuff pressure measurement (to enable the animals also acclimatized with the equipment to avoid unnecessary agitation at the first time) before the inducement

and treatment which lasted for another 35 days. The albino rats were housed in rat cage of room temperature of 12 hour lightened 12 hour darkness cycle and well ventilated. Feed were purchased from Pfizer Nigeria limited feeds, Benin throughout the study and water was provided. The albino rats were used in accordance with NIH Guide for the care and use of laboratory animals and Standard Operation Procedures (SOPs) were applied, while biochemical parameters and histological study of the heart, kidney and liver were analyzed following standard methods.

- **Group 1:** Control group, these were normal rats that was not induced nor treated with any extract but were fed with animal feed and water on daily basis throughout the study period.
- **Group 2:** Hypertensive control group were induced with Cadmium chloride, confirmed hypertensive and were not treated throughout the study. They received animal feed and water only.
- **Group 3:** Standard drug group were induced with cadmium chloride and were treated with Nifedipine (a known hypertensive drug) and were fed.
- **Group 4:** Cadmium Chloride induced hypertensive group treated with methanol *Moringa oleifera* leaf extract and were fed with food and water.
- **Group 5:** Cadmium Chloride induced hypertensive group treated with n-Hexane *Moringa oleifera* leaf extract, fed with fed and water.

Treatment lasted for 4 weeks, thereafter animals were sacrificed. Blood were collected by cardiac puncture into sodium fluoride and ethylene diamine tetra acetic acid sample bottles for biochemical analysis. The animals were sacrificed, organs (kidney, heart and liver) of each animal in each group were harvested into a plane sample bottle for histopathology analysis.

2.4. Measurement of biochemical parameters

The biochemical analysis carried out were kidney function test and endocrine test on serum electrolyte test (sodium, potassium, bicarbonate, chloride), urea and creatinine; liver enzymes on serum aspartate aminotransferase (AST), alanine phosphatase (ALP), alkaline transaminase (ALT), metabolic system test and total protein, albumin, total bilirubin, conjugate bilirubin was analysed using spectrophotometry method of analysis [2]

2.5. Histological study: (hematoxylin and eosin (H&E) staining techniques)

Harvested liver, heart and kidney tissues were fixed in 10% formalin solution, embedded in melted paraffin wax. Hematoxylin & Eosin (H&E) histological techniques was implored, an Olympus light microscope were used for photomicrography on the mounted slide and was captured with Kodak digital camera.

2.6. Statistical analysis

Data were analyzed using SPSS 20.0. Student t test was used to observe the significance of difference. Data was presented as Mean \pm SD. P value less than 0.05 was considered significant.

3. Results and discussion

3.1. Effects of Serum Electrolyte, Urea and Creatinine level

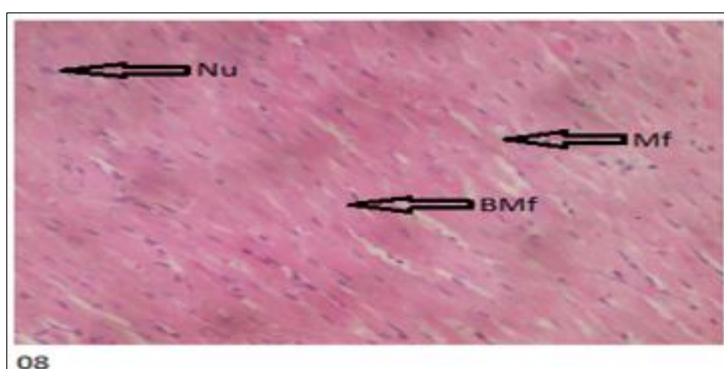


Figure 1 Photomicrograph of Cardiac muscle (x400), H/E stain for group 1 – Control

Table 1 Electrolyte values in Control Group compare to Other Groups

	Sodium (mEq\L) Mean±SEM	P-VALUE	Potassium (mEq\L) Mean±SEM	P-VALUE	Bicarbonate	P-VALUE	Chloride (mEq\L)	P-VALUE	Urea (mEq\L)	P-VALUE	Creatinine (μmol\L)	P-VALUE
1	236.33±47.55		8.52±2.17		38.83±2.28		101.29±10.67		5.28±0.35		184.84±99.05	
2	443.96±34.95	0.01*	21.80±1.44	0.00*	30.72±4.56	0.10	216.63±55.48	0.02*	4.26±0.63	0.20	212.42±47.52	0.73
3	293.73±67.95	0.46	21.36±2.73	0.01*	42.73±2.44	0.45	127.86±18.86	0.60	4.62±0.63	0.41	81.55±5.04	0.22
4	220.49±55.57	0.84	16.74±2.99	0.03*	32.94±4.49	0.25	133.22±26.40	0.53	5.55±0.47	0.73	62.97±4.88	0.15
5	189.69±53.12	0.54	18.11±2.23	0.00*	26.23±1.20	0.01*	120.19±80.64	0.70	5.63±0.24	0.70	90.93±5.52	0.25

There was significant increase of the sodium value in the group 2; There was significant increase in the potassium values of groups 2, 3, 4 and 5; Significant increase in bicarbonate value of group 5

Table 2 Electrolyte values of Hypertensive Group compared to other Groups

	Sodium (mEq\L) Mean±SEM	P-Value	Potassium (mEq\L) Mean±SEM		Bicarbonate							
						P-Value	Chloride (mEq\L)	P-Value	Urea	P-Value	Creatinine (μmol\L)	P-Value
2	443.96±34.95		21.80±1.44		30.72±4.56		216.63±55.48		4.62±0.63		81.55±5.04	
3	293.73±67.95	0.05*	21.36±2.73	0.89	42.73±2.44	0.01*	127.86±18.86	0.08	5.42±0.32	0.99	77.09±1.01	0.11
4	220.49±55.57	0.00*	16.74±2.99	0.16	32.94±4.49	0.66	133.22±26.40	0.09	5.75±0.25	0.99	283.34±129.80	0.07
5	189.69±53.12	0.00*	18.11±2.23	0.29	26.23±1.20	0.35	120.19±80.64	0.04*	5.63±0.24	0.99	91.02±4.56	0.13

The result showed significant decrease in the sodium values of groups 3, 4 and 5; significant decrease in bicarbonate value of group 3 and significant decrease in chloride value of group 5

Table 3 Electrolyte values in the Standard Drug Group compared to other Test Groups

	Sodium (mEq\L) Mean± SEM	P-VALUE	Potassium (mEq\L) Mean± SEM	P-VALUE	Bicarbonate							
						P-VALUE	Chloride (mEq\L)	P-VALUE	Urea		Creatinine (μmol\L)	P-VALUE
3	280.44±38.90		21.36±2.73		42.73±2.44		127.86±18.86		5.42±0.32		77.09±1.01	
4	260.70±50.31	0.35	16.74±2.99	0.21	32.94±4.49	0.06	133.22±26.40	1.00	5.75±0.25	0.99	283.34±129.80	0.825
5	364.20±69.62	0.17	18.11±2.23	0.36	26.23±1.20	0.00*	120.19±80.64	1.00	5.63±0.24	0.99	91.02±4.56	0.90

Significant decrease in bicarbonate value of group 5

Table 4 Comparison of Markers between Control Group and other Test Groups

	ALT	AST	ALK.PHOS (U/L)	TOTAL PROTEIN	ALBUMIN	TOTAL BILIRUBIN	CONJ Bilirubin
1	53.56±11.17	64.00±10.09	48.97±0.27	21.05±1.93	5.45±0.16	0.62±0.15	0.45±0.09
2	83.00±4.41	76.20±8.70	48.83±0.24	21.69±2.16	5.24±0.31	0.88±0.15	0.36±0.11
3	72.44±7.83	64.22±8.03	49.21±0.20	22.57±1.99	5.60±0.26	1.09±0.13	0.30±0.03
4	85.33±8.54	72.11±7.88	49.01±0.22	24.12±0.92	6.15±0.02	0.25±0.05	0.29±0.04
5	87.60±4.27	58.80±7.12	48.58±0.31	20.45±2.05	5.75±0.17	0.76±0.14	0.62±0.06

Table 5 Comparison of Markers Values between Hypertensive Group and other Test Groups

	ALT	AST	ALK.PHOS (U/L)	TOTAL PROTEIN	ALBUMIN	TOTAL BILIRUBIN	CONJ Bilirubin
2	83.00±4.41	76.20±8.70	48.83±0.24	21.69±2.16	5.24±0.31	0.88±0.15	0.36±0.11
3	72.44±7.83	64.22±8.03	49.21±0.20	22.57±1.99	5.60±0.26	1.09±0.13	0.30±0.03
4	85.33±8.54	72.11±7.88	49.01±0.22	24.12±0.92	6.15±0.02	0.25±0.05*	0.29±0.04*
5	87.60±4.27	58.80±7.12	48.58±0.31	20.45±2.05	5.75±0.17	0.76±0.14	0.62±0.06

Significant decrease in the total bilirubin value of groups 4; there was significant decrease in the conjugated bilirubin value of group

Table 6 Comparison of Markers Values between Standard Drug Group and other Test Groups

	ALT	AST	ALK.PHOS (U/L)	TOTAL PROTEIN	ALBUMIN	TOTAL BILIRUBIN	CONJ Bilirubin
3	72.44±7.83	64.22±8.03	49.21±0.20	22.57±1.99	5.60±0.26	1.09±0.13	0.30±0.03
4	85.33±8.54	72.11±7.88	49.01±0.22	24.12±0.92	6.15±0.02	0.25±0.05*	0.29±0.04
5	87.60±4.27	58.80±7.12	48.58±0.31	20.45±2.05	5.75±0.17	0.76±0.14	0.62±0.06*

Significant decrease in the total bilirubin value of groups 4; significant decrease in the Conjugate bilirubin value of groups 5

Figure 1 Showing histologically normal cardiac muscle [2; 22]

- Homogeneous muscle fiber (mf) diameter, with intact sarcolemma.
- Peripherally placed nuclei (Nu)
- Branching cardiac muscle fiber (Bmf).

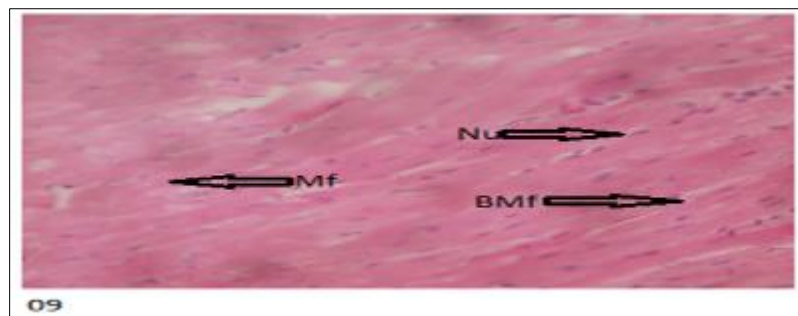


Figure 2 Photomicrograph of Cardiac muscle (x400). H/E stain for group 4 – *Moringa oleifera* methanol extract.

Showing histologically normal cardiac muscle

- Peripherally placed nuclei (Nu)
- Homogeneous muscle fiber (mf) diameter, with intact sarcolemma.
- Branching cardiac muscle fiber (Bmf).

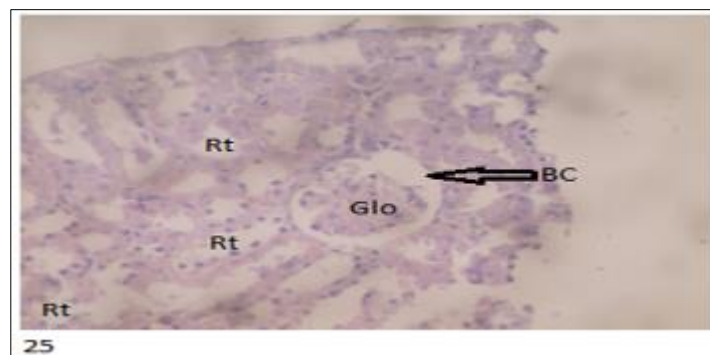


Figure 3 Photomicrograph of Kidney (x400), H & E stain for group 1 – control

Histologically normal kidney showing [2; 22]

- Bowman's capsular spaces (BC)
- Glomerular tuft (Glo) containing mesengial cells, capillaries and mesengial matrix.
- Renal tubules (Rt).

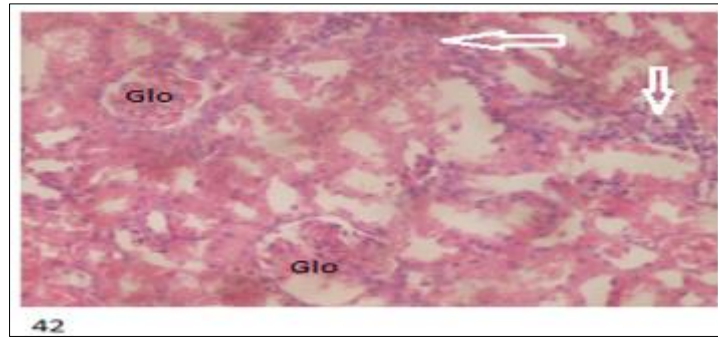


Figure 4 Photomicrograph of Kidney (x400), H & E stain for group 2 – Hypertensive group [2; 22]

Histologically distorted kidney showing

- Dilated capillaries
- Inflammatory cells

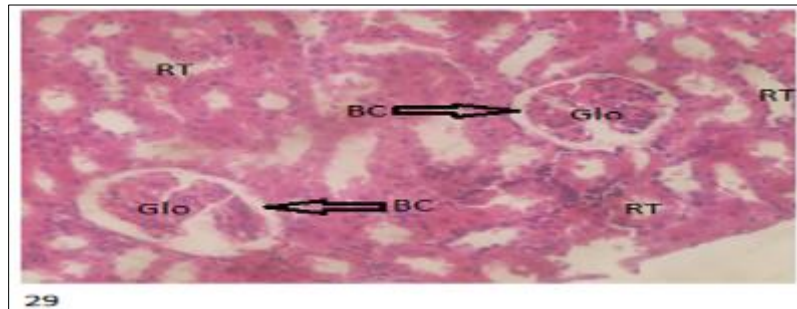


Figure 5 Photomicrograph of Kidney (x400), H & E stain for group 3 – standard drug control

Histologically normal kidney showing

- Renal tubules (Rt)
- Bowman's capsular spaces (BC)
- Glomerular tuft (Glo) containing mesengial cells, capillaries and mesengial matrix.

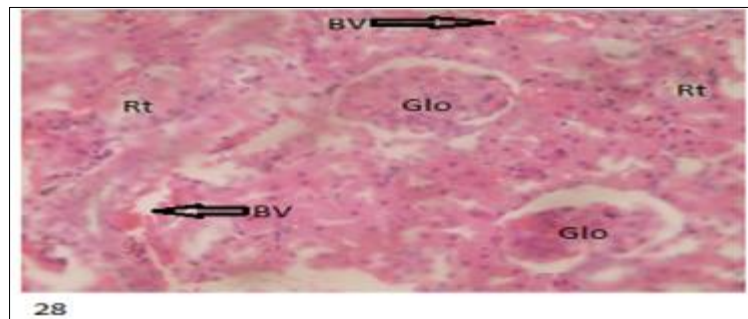


Figure 6 Photomicrograph of Kidney, (x400) H & E stain for group 4 – *Moringa oleifera* methanol

Histologically normal kidney showing

- Blood vessels (BV) arrowed.
- Renal tubules (Rt).
- Glomeruli (Glo)

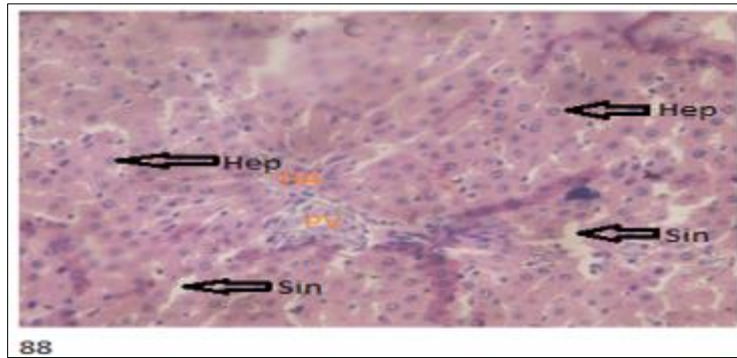


Figure 7 Photomicrograph of Liver (x400), H & E stain for group 1 - control [2; 22]

Histologically normal Liver showing

- Hepatic artery (HA) and portal vein (PV).
- Cords of normal hepatocytes (Hep)
- Sinusoids (sin) containing capillaries and Von Kupffer cells

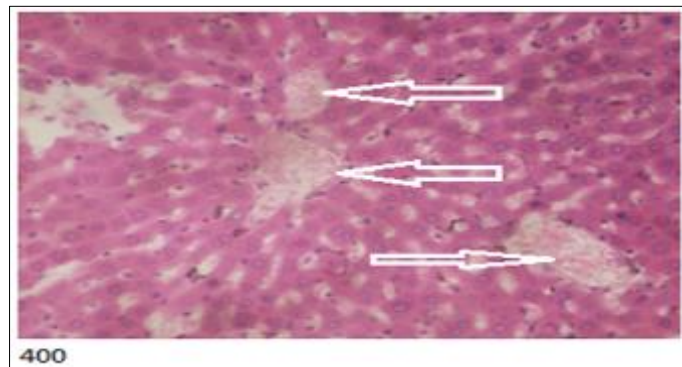


Figure 8 Photomicrograph of Liver magnification $\times 400$, H&E stain for group 2- hypertensive group [2; 22]

Histologically distorted liver showing patchy necrotic areas arrowed

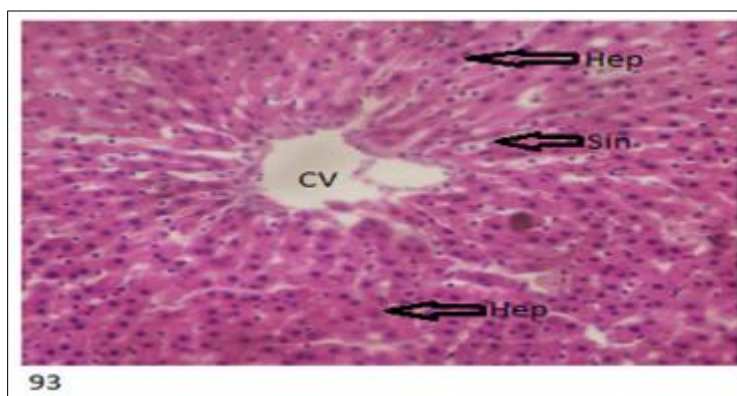


Figure 9 Photomicrograph of Liver, magnification $\times 400$ H&E stain for group 3 - standard drug [2; 22]

Histologically normal liver showing

- Normal Hepatocytes
- Patent central vein
- Sinusoid (Sin): increased inflammatory cells

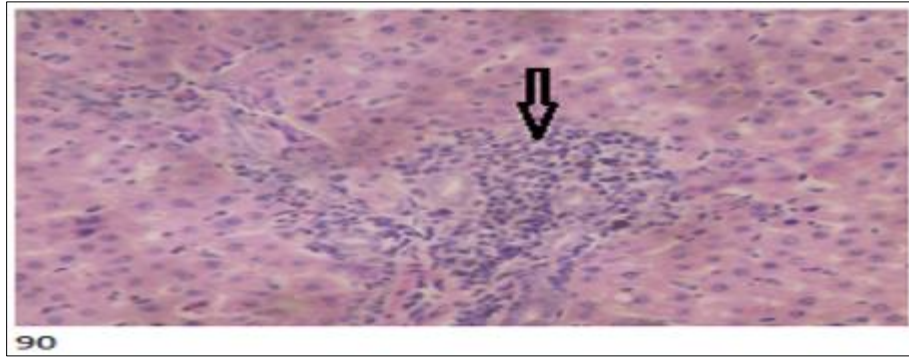


Figure 10 Photomicrograph of Liver, magnification $\times 400$ H&E stain of group 4 – *Moringa oleifera* methanol

Histologically normal liver showing

- Increased cells around vessels and sinusoids.

Moringa oleifera leaves contain a high concentration of antioxidants [23], which serves the medicinal purpose of curing disease conditions such as hypertension and cardiovascular disorders, renal and inflammatory diseases, cancer and bacterial diseases [24]. Tender and mature leaves of *Moringa oleifera* extracts exhibit strong antioxidant activity against free radicals and prevent oxidative damage due to the enrichment of polyphenols [25]. In this study, nutraceuticals from *Moringa oleifera* protect against cadmium chloride-induced hypertension in albino rats. Data obtained suggests that extract of *Moringa oleifera* has both preventive and curative functions for kidney, heart and liver tissues and also in the lowering of some electrolyte values. In table 1, there was significant increase in sodium value in the hypertensive non treated group (Group 2) when compared control group (Group 1) to other groups, whereas significant increase in potassium values was found in both standard drug (Nifedepine group) and the groups treated with *Moringa oleifera* methanol and n-hexane extract groups. There is a beneficial role played by phytosterol on electrolyte level as seen in Tables 1, 2 and 3. This implies that *Moringa oleifera* was able to clear the toxicity effect of cadmium chloride from the serum of the treated group just as was also observed in the standard drug treated group. Previous finding has demonstrated that the post-treatment of *Moringa oleifera* leaf extract for consecutive 28 days can protect from cadmium-induced hepatotoxicity in rats by suppressing the elevated alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase (ALT) and increased superoxide dismutase (SOD) level [26]. Such was not the case in this present study, rather there was slight changes in the liver markers but there is no significant difference observed in the liver enzymes serum AST, ALP and ALT, as also seen in another study [27].

There was also increase chloride level in non-treated hypertensive group in table 1 which indicates acidosis or kidney disease. This implies that cadmium chloride causes liver disease in the untreated rats, this was then corrected with *Moringa oleifera* methanol and n-hexane treated test groups. Treatment with *Moringa oleifera* also caused significant decrease in total bilirubin and conjugate bilirubin in Tables 5 and 6, which signifies healing and protective effect amongst the treated group.

Figure 1 of this histology study shows photomicrograph of cardiac muscle showing homogeneous muscle fiber (mf) diameter, with intact sarcolemma, peripherally placed nuclei (Nu) and branching cardiac muscle fiber (Bmf). There was no difference in all the cardiac muscle of all the groups in this study. Figure 2 presented us with *Moringa oleifera* cardiac muscle showing normal cells as seen in figure 1. Figures 3, 5 and 6 are all presented with photomicrograph of Kidney (x400), H & E stain for groups 1– (control), 3 (standard drug) and 4 (*Moringa oleifera*), histologically normal kidney showing Bowman’s capsular spaces (BC), glomerular tuft (Glo) containing mesangial cells, capillaries and mesangial matrix and renal tubules (Rt) [2; 22]. Figure 4 presented photomicrograph of Kidney (x400), H & E stain for group 2 (Hypertensive group) showed histologically distorted kidney showing dilated capillaries and inflammatory cells [2; 22]. This untreated kidney have again showed that cadmium chloride-induced hypertensive group can be corrected with *Moringa oleifera* leaf extract as seen in the treated groups in the previous figure. Figures 7, 9 and 10 shows photomicrograph of Liver (x400), H & E stained for groups 1 (control), 3 (standard drug) and 4 (*Moringa oleifera*) all showed histologically normal Liver showing hepatic artery (HA) and portal vein (PV), cords of normal hepatocytes (Hep) and Sinusoids (sin) containing capillaries and Yon Kupffer cells [2; 22], while figure 8 presented the photomicrograph of Liver magnification $\times 400$, H&E stained for group 2 (hypertensive untreated group) presented with histologically distorted liver showing patchy necrotic areas which are arrowed [2; 22]. The damaged showed on the hypertensive tissue without any such damage on the control and standard group is also an indication of protection and

healing effect of *Moringa oleifera* and known drug on the distorted tissues. This again have supported the study that suggested the direct target of Cadmium toxicity is in the liver and kidney since they are accumulated therein [28; 29].

4. Conclusion

Moringa oleifera possess antioxidant and free radical scavenging property, which could be helpful in reducing the oxidative stress caused by induced cadmium chloride, maintaining the antioxidant potential and significantly reducing elevated electrolytes and serum biomarker values in the rats.

The study findings suggest that *Moringa oleifera* possess some nutraceuticals capable of protection against hypertension.

Compliance with ethical standards

Acknowledgments

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Disclosure of conflict of interest

There is no conflict of interest among the authors

Statement of ethical approval

Ethical approval for the use of Animal was approved by the Ethical committee of the Unit.

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