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Organo-protective Potentials of *Momordica balsamina* aqueous plant extract against

cadmium-induced stress in wistar rats

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Abstract

This study investigated the protective potentials of *Momordica balsamina* aqueous plant extract against cadmiuminduced stress in wistar rats. Forty-five albino rats weighing 150-200g were used in the study. The rats were randomly divided into 5 groups of 9 rats each; Group A which served as negative control received normal rat feeds and distilled water only while Group B (positive control) received normal rat feeds, distilled water and Cadmium Chloride (CdCl₂) with no plant extract administered. Groups C, D and E received 1500, 1000 and 500mg/kg b.w. respectively of aqueous extract of *M. balsamina* orally for 6 weeks. Following administration of *M. balsamina* aqueous extract, experimental rats in groups B, C, D and E were intraperitorally administered 2.5mg/kg b.w of CdCl² for 24h before sacrificing them. Animals were sacrificed at weeks 2, 4 & 6; blood samples were collected for biochemical analysis while the liver and kidney were harvested for histological investigations. There were significant (P<0.05) increases in plasma levels of ALP, AST, and ALT in the CdCl2-treated group recording 575.00±6.17, 101.51±3.78 and 96.76±3.78IU/Lrespectively at week 2, as compared to the negative control group which recorded 216.00±15.20, 64.00±4.27 and 36.76±3.78 IU/L at week 2. The CdCl2 group showed significant (P<0.05) increases in plasma levels of K-, Na+ and Urea as compared with the negative control. *M. balsamina* treated rats showed significant (P<0.05) increase in serum levels of LDH, MDA and SOD. Photomicrographs obtained showed histologically distorted liver and kidney tissues in the CdCl₂ group at weeks 2, 4 and 6. Overall, the architecture of the liver was preserved by the administered aqueous leaf extract of *M. balsamina.* This study suggests that *M. balsamina* leaves exhibit promising hepatoprotective and antioxidant potency against CdCl2 induced stress and organ damage in wistar rats.

Keywords: Cadmium Chloride; Stress; *Momordica balsamina*; Plant extract; Protective effects

1 Introduction

Heavy metal toxicity is a major threat with several associated health risks [1]. Multiple applications of these metals have led to their widespread distribution in the environment [2]. Various sources of heavy metals include soil erosion, natural weathering of the earth's crust, mining, industrial effluents, urban runoff, sewage discharge, insect or disease control agents applied to crops, and many others [3]. Heavy metals also enter the surroundings by natural means. Their toxicity depends on several factors including the dose, route of exposure, and chemical species, as well as the age, nutritional status, genetics, and gender of exposed individuals [2]. Reactive oxygen species (ROS) production and oxidative stress play a key role in the toxicity and carcinogenicity of heavy metals. Systemic heavy metal toxicants such as lead [4], chromium [5, 6], arsenic [7, 8], mercury [9] and cadmium [10] are known to induce multiple organ damage, even at lower levels of exposure.

Cadmium is a by-product of zinc production which humans or animals may get exposed to at work or in the environment. The adverse effect of Cadmium on human health is further exacerbated by its toxicity at low dosage, long

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biologic half-life and low rate of excretion from the body. The general human population is exposed to cadmium by contaminants found in different foods, cereals, grains, root crops, and leafy green vegetables, drinking water, and cigarette smoke [11]. Once this metal gets absorbed by humans, it will accumulate inside the body throughout life [1]. Cadmium absorption through the lungs is more efficient than through the gut. More than 50% of Cd is inhaled through cigarette smoke [11]. Cadmium binds to cysteine-rich protein such as metallothionein. In the liver, the cysteinemetallothionein complex causes hepatotoxicity and then, circulates to the kidney and gets accumulated in the renal tissue causing nephrotoxicity. Cadmium has the capability to bind with cysteine, glutamate, histidine and aspartate ligands and can lead to the deficiency of iron [12]. Cadmium and zinc have the same oxidation states and hence cadmium can replace zinc present in metallothionein, thereby inhibiting it from acting as a free radical scavenger within the cell [1].

Plants have long been used for medicinal purposes, both as supplement for body maintenance and as therapy for illnesses [13]. *Mormodica balsamina (MB)*, our plant of interest, is common and widespread in Southern Africa and is closely related to *M. charantia* [14]. *M. charantia* has been shown to improve renal function by normalising oxidative status [15] while *M. balsamina* has been shown to have hypoglycaemic activity [16]. However, the organoprotective effects of *M. balsamina* have not yet been established. We envisage that measuring hepatotoxic biomarkers, nephrotoxicity and status of the antioxidant defense system will reveal the protective potentials of *M. balsamina* plant.

The aim of the study therefore is to investigate the protective effects of *M. balsamina* plant extract on CdCl2-induced organ damage in wistar rats.

2 Material and methods

2.1 Experimental Animals

Forty-five wistar rats weighing 150-200g were obtained from the Animal House of the Department of Biochemistry, University of Port Harcourt, Nigeria. The animals were housed in standard iron cages within the laboratory animal facility. The rats were acclimatized under controlled temperature (25 ± 2 $^{\circ}$ C), 12 hours of light and 12 hours of darkness for 14 days before the experiment. After acclimatization, the wistar rats were separated into five groups of five rats each and given ad libitum access to standard feed and water.

2.2 Collection and Preparation of aqueous plant extract of *Mormodica balsamina*

Fresh whole plants of *Momordica balsamina* were obtained from Aluu and Rumuolumeni Communities in Obio/Akpor LGA of Rivers State, Nigeria. The plants were identified and authenticated by a Plant Technologist in the Department of Plant Science and Biotechnology (PSB), University of Port Harcourt, Nigeria and deposited in herbarium with voucher number: 78472. The whole plant samples were thoroughly washed with tap water and then, distilled water. The whole plant was dried under room temperature and atmospheric pressure, shredded into pieces, ground and pulverized into coarse powder form using a hammer mill. *M*. *balsamina* aqueous extract was prepared according to a previously reported method [17]. The dry powder (687g) was placed in a Soxhlet extractor with 300 ml distilled water and continuously heated at 40°C for 48hours and the mixture was vacuum-filtered through Whatman No 1 filter paper. The water extract was then concentrated under reduced pressure at 40°C in a rotary evaporator and the solid material residue (97g) stored in sealed dark glass bottles under free moisture conditions in a deep freezer until use.

2.3 Experimental Design

Forty-five rats were randomly divided evenly into five groups as follows:

- Group 1: Normal rats; received standard feed and water (Negative Control).
- Group 2: Received standard feed and water $+ 2.5$ mg/kg b. w. of CdCl₂ (24 h before sacrificing). (Positive Control).
- Group 3: Received standard feed and water + 1500mg/kg of *M*. *balsamina* (42days) + 2.5mg/kg b. w. of CdCl² (24 h before sacrificing).
- Group 4: Received standard feed and water + 1000mg/kg of *M*. *balsamina* (42days) + 2.5mg/kg b. w. of CdCl² (24 h before sacrificing).
- Group 5: Received standard feed and water + 500mg/kg of *M*. *balsamina* (42days) + 2.5mg/kg b. w. of CdCl² (24 h before sacrificing).

The experiment lasted for 42 days. At days 14, 28 and 42, the rats received 2.5mg/kg b. w. CdCl₂ for 24 h prior to sampling and then mildly anesthetized with chloroform and sacrificed. Blood samples were collected for biochemical analysis. The serum was separated by centrifugation at 3,000 g for 5 min and kept at −20°C until use for biochemical assay. The kidney and liver were excised and placed in a formalin bottle to preserve the tissue for histology analysis.

2.4 Biochemical Analytical Methods

2.4.1 Hepatic biomarkers

Plasma L - alanine aminotransferase (ALT) and L - aspartate aminotransferase (AST) activities were determined using the method described by Reitman and Frankel [18] while Alkaline phosphatase (ALP) activity was measured using the colorimetric method using phenolphthalein monophosphate as substrate [19].

2.4.2 Renal biomarkers

Creatinine estimation was carried out by colorimetric method [20]. Urea concentration was determined using the Berthelot's reaction [21]. Plasma sodium determination followed the precipitation method [22]. Serum Potassium ion concentration was measured using the Tetraphenylborate method [23].

2.4.3 Antioxidant assays

Determination of malondialdehyde concentration was carried out using lipid peroxide assay method [24]. Superoxide dismutase (SOD) and Lactate Dehydrogenase activities were investigated using the Randox commercial kit [25].

2.4.4 Histological studies

Liver and kidney tissues were fixed in 10% formalin, routinely processed for dehydration, and embedded in paraffin wax. Section cuts were stained with hematoxylin and eosin for light microscopic examination [26]. The histological sections were examined as the slides were mounted using Canada balsam and examined using \times 400 objective lens.

2.5 Statistical analysis

All values were expressed as mean ± SD and then subjected to analysis of variance (ANOVA) using the Statistical Package for Social Sciences (SPSS) version 17.0 (SPSS Inc., Chicago Illinois). Statistical significance was considered at P=0.05.

3 Results and discussion

3.1 Effects of *M***.** *balsamina* **Aqueous plant Extract on Hepatotoxic Biomarkers**

Table 1 show the effect of *M. Balsamina* aqueous leaf extract on the activity of liver enzymes [Plasma L - aspartate aminotransferase (AST), L - alanine aminotransferase (ALT) and Alkaline phosphatase (ALP)], as a result of cadmiuminduced damage in wistar rats. There was significant increase (P<0.05) in plasma levels of ALP in group D, recording 365.00±0.00, 376.00±5.65 and 367.50±3.53 IU/L at weeks 2, 4 and 6 respectively. There were no changes in plasma AST, ALT and ALP in groups A and B at weeks 2, 4 and 6.

3.2 Effect of *M***.** *balsamina* **Aqueous plant Extract on Nephrotoxic Biomarkers**

Table 2 show the effect of *M. Balsamina* aqueous leaf extract on kidney function parameters. The negative control group recorded 66.70 \pm 1.27 umol/L and 12.50 \pm 0.70 umol/L for Creatinine and plasma Na+ levels at Week 2. With the administration of *M. Balsamina* aqueous plant extract, groups C, D and E recorded 141.00±1.41, 144.00±1.41, 130.50±0.70, mmol/L for Na+, 4.85±0.70, 2.70±0.14, 3.00±0.42mmol/L for Urea, 91.15 ±1.34, 58.90 ±1.27, 117.75 ±0.27 mmol/L for Creatinine, all at week 6, an indication of improvement in the levels of these nephrotoxic biomarkers.

3.3 Effect of *M***.** *balsamina* **Aqueous plant Extract on Antioxidant Enzymes**

Effects of *M*. *balsamina* aqueous leaf extract on antioxidant enzyme activity are shown in Table 3. Group E (500mg Extract +Cadmium) showed a significant $(P < 0.05)$ reduction in LDH in the CdCl₂ only group.

3.4 Results for Histological Studies

3.4.1 Liver Photomicrographs

Plates A – K are defined as follows: Light microscope photographs of liver paraffin sections, stained with hematoxylin and eosin, obtained from negative control at week 2 (A), positive control at week 2 (B), 1500 mg/kg *M*. *balsamina* group at weeks 2, 4 & 6 (C, D, E), 1000 mg/kg *M*. *balsamina* group at weeks 2, 4 & 6 (F, G, H) and 500 mg/kg *M*. *balsamina* group at weeks 2, 4 & 6 (I, J, K) .

3.4.2 Kidney Photomicrographs

Plates L – V are defined as follows: Light microscope photographs of kidney paraffin sections, stained with hematoxylin and eosin, obtained from negative control at week 2 (L), positive control at week 2 (M), 1500 mg/kg *M*. *balsamina* group at weeks 2, 4 & 6 (N, O, P), 1000 mg/kg *M*. *balsamina* group at weeks 2, 4 & 6 (Q, R, S) and 500 mg/kg *M*. *balsamina* group at weeks 2, 4 & 6 (T, U, V).

3.4.3 Cardiac Photomicrographs

Plates K – T are defined as follows: Light microscope photographs of liver paraffin sections, stained with hematoxylin and eosin, obtained from negative control at day 14 & 28 (K, P), H2O2 group at day 14 & 28 (L, Q), 100 mg/kg A. godseffiana group at day 14 & 28 (M, R), 200 mg/kg A. godseffiana group at day 14 & 28 (N, S), 400 mg/kg A. godseffiana group at day 14 & 28 (O, T).

Values are reported as Mean \pm Standard Deviation, (n = 3). Treatment with same or similar superscripts "a,b,c" are not statistical significantly difference (P≤ 0.05) from one another while treatments with different superscript are statistically significantly different from one another.

 $4 \qquad 84.95 \pm 2.05$ b&c 4.50 ± 0.41 a 141.00 ± 1.41 a 10.00 ± 0.00 a 6 $\vert 91.15 \pm 1.34$ b&c $\vert 4.85 \pm 0.70$ a 141.00 ± 1.41 a 9.50 ± 0.70 a

2 66.70 ±1.27^a 3.55±0.07^a 148.00±7.07^a 12.50±0.70^a 4 $\vert 64.05 \pm 0.21 \vert$ $\vert 3.40 \pm 0.00 \vert$ $\vert 148.50 \pm 0.70 \vert$ $\vert 13.10 \pm 0.14 \vert$ 6 \vert 58.90 ±1.27c \vert 2.70 ± 0.14a \vert 144.00 ± 1.41a \vert 11.90 ± 0.84a

2 111.50 ± 0.70^b 3.50 ± 0.70^a 140.00 ± 2.82^a 09.15 ± 0.12^a 4 116.90 ± 2.16 ^{c&c} 3.60 ± 0.56 ^a 138.00 ± 1.41 ^a 11.90 ± 0.14 ^a 6 117.75 \pm 0.27a 3.00 ± 0.42 a 130.50 \pm 0.70a 13.05 \pm 0.07a

+Cadmium)

+Cadmium)

+Cadmium)

Group D (1000mg Extract

Group E (500mg Extract

Table 2 Effect of Momordica basalmina Aqueous plant Extract on some kidney parameters in cadmium chloride induced Renal Toxicity.

Values are reported as Mean \pm Standard Deviation, (n =3). Treatment with same or similar superscripts "a,b,c" are not statistical significantly difference (P≤ 0.05) from one another while treatments with different superscript are statistically significantly different from one another

Table 3 Effect of *Momordica Basalmina* (MB) Aqueous plant Extract on some oxidative stress markers in cadmium chloride-induced toxicity (IU/L)

Values are reported as Mean \pm Standard Deviation, (n =3). Treatment with same or similar superscripts "a,b,c" are not statistical significantly difference (P≤ 0.05) from one another while treatments with different superscript are statistically significantly different from one another.

Figure 1a Plates A-K. Light microscope photographs of liver paraffin sections (H & E stained), (Mag *400)

Figure 1b Plates L-V. Light microscope photographs of kidney paraffin sections (H & E stained), (Mag *400)

Results obtained in the present study showed that toxicity induced with Cadmium Chloride (CdCl2) showed elevated plasma AST, ALT and ALP activity. This finding corroborates previous studies that demonstrated rise in plasma AST and ALT activities, indicating hepatic damage [27, 28]. Anokwuru et al. (2019) [29] also reported elevated plasma AST and ALT activities in the untreated group in a study on the chemoprotective activity of aqueous leaf extract of *Acalypha wilkesiana* against cyclophosphamide-induced toxicity in rats. The elevated levels of these hepatic enzymes in the Cadmium Chloride are indicative of alteration in hepatocellular integrity. Experimental groups treated with aqueous plant extract of *M. balsamina* recorded reduced plasma AST and ALT activities when compared with CdCl₂ alone treated group. This finding corroborates a report by Abubakar *et al*. (2024) where they showed that *Momordica balsamina* extract significantly (*P*< 0.05) decreased the level of serum AST, ALT, ALP, TB and DB positively by inhibiting their increase in activity, in a dose-dependent manner compared to the negative control [30]. Also, the reduced liver enzymes activities were in agreement with the results of other researchers that demonstrated hepatoprotective effects of Momordica charantia [31, 32]. It can be inferred that *M*. *balsamina* leaf extract possesses antioxidant and hepatoprotective properties which may be due to the presence of bioactive compounds such as phenols, flavonoids, proanthocyanidins, steroids, terpenoids and alkaloids [33, 34]. Flavonoids are rich in antioxidants, providing our body with natural immune protections from daily environmental and endogenous toxins [35].

Results from this study showed significant (P<0.05) decrease in urea in the treated groups, compared to the positive control group. This suggests that systemic toxicity may have been initiated in the urea cycle, resulting in reduction in the production of urea, reduction in excretion of waste and resultant in-balance in body fluid and electrolytes [36, 37].

Serum creatinine is an indicator of renal health, because it is an easily measured by-product of muscle metabolism that is excreted uncharged by the kidneys. If the kidney is deficient in its filtration ability, creatinine blood level rises. This finding is in line with a previous study where creatinine levels of rats administered with aqueous extract of fresh leaves of *Ageratum conyzoides* was observed to significantly decrease (P<0.05) in the administered groups[38].

Rats administered CdCl₂ only (negative control) showed significant (P<0.05) increases in plasma levels of K- and Na+, as compared with the negative control. Electrolyte balance in the blood indicates health of the kidney and heart. Sodium level is regulated by the adrenal glands and kidneys. Sodium is the major cation of extracellular fluid. It plays a central role in the maintenance of normal distribution of water and the osmotic pressure in the various fluid compartments. Potassium is the principal cation of the intracellular fluid and it is the most important constituent of the extracellular fluid due to its influence on muscle activity [39]. Results in this study indicate that the concentrations of serum electrolytes (potassium and sodium) favorably improved in all groups administered with *M*. *balsamina* aqueous plant extract, when compared with the negative control. It can be inferred that the plant extract could aid electrolyte balance, to ensure proper maintenance of homeostasis [40].

The results of the antioxidant enzymes from this study are consistent with the known antioxidant properties of *Momordica spp* according to Semiz and Sen [41]. Baynes (1991) noted that antioxidants play important roles to protect the body against damages caused by reactive oxygen species [42]. Jacob (1995) also corroborated that endogenous antioxidant enzymes are responsible for the detoxification of deleterious oxygen radicals [43]. Decreased levels of LDH, MDA and SOD in CdCl2 group rats can be explained to be as a result of overuse of this antioxidant. The significant increase in the activities of GSH, SOD and CAT suggests a greater level of endogenous antioxidant associated with the A. godseffiana treatment resulting in an enhanced free radical scavenging activity. Plants are sources of a wide variety of compounds like flavonoids and polyphenols. *Momordica spp have* beneficial properties found to be dependent on its anti-inflammatory and antioxidant activities.[44, 45].

Photomicrographs of the normal liver showed normal hepatic architecture in rats in the negative control group. The hepatocyte, portal tract and sinusoids sinusoids containing capillaries and kupffer cells were normal at week 2 (Fig. 1a, plate A). A histologically distorted liver with hepatocytes showing microvesicular steatosis was observed in the CdCl² group at week 2 (Fig. 1a, plate B). Conversely, the same tissues were characterized by little necrosis and good recovery, fewer hepatocytes with microvesicular steatosis and fusion of nuclei in the groups treated with M. *balsamina* as shown by photomicrographs from liver section of rat administered M. *balsamina* leaf extract. Groups 3, 4 and 5 recorded mildly distorted liver with sinusoids a filled with only few inflammatory cells at weeks 2, 4 and 6 (Fig. 1a, plate C, D, E), (Fig. 1a, plate F, G, H) and (Fig. 1a, plate I, J, K) respectively. Photomicrographs of the kidney for rats in the negative control group (Fig. 1b, plate L) showed histologically normal kidney at week 2; the glomeruli, bowman's capsular space (BC) and renal tubules (RT) were observed to be normal. CdCl2 toxicity resulted in the distortion of the kidney tissues (Fig. 1b, plate M) at week 2. Groups 3, 4 and 5 recorded histologically distorted kidneys at weeks 2, 4 and 6 (Fig. 1b, plates N, O & P), (Fig. 1b, plates Q, R & S) and (Fig. 1b, plates T, U & V) respectively. Overall, the architecture of the liver and kidney was preserved by the aqueous plant extract of M. *balsamina* administered.

4 Conclusion

This study reveal that *M. balsamina* plant exhibit promising hepatoprotective and antioxidant potentials. *M*. *balsamina* has potency to serve as therapy in the management of stress caused by cadmium toxicity.

Compliance with ethical standards

Disclosure of Conflict of interest

Authors have declared that no competing interests exist.

Statement of ethical approval

All authors hereby declare that "Principles of Laboratory Animal Care" (NIH Publication no. 85- 23, revised 1985) were followed. All experiments were examined and approved by the appropriate ethics committee.

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