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Research Article

Nephroprotective Effect of *Ipomoea Cairica* Leaf Extract against Cadmium-Induced Renal Damage

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ABSTRACT

Cadmium is a toxic heavy metal whose presence has been reported in both children and adults. Accumulation of cadmium in the body can lead to kidney failure. *Ipomoea cairica* is one of the most underutilized medicinal plants in Nigeria, despite its numerous health benefits. This research investigated the nephroprotective effect of *I. cairica* leaf 80% methanolic extract against cadmium-induced renal damage. Twenty-eight male Wistar rats were divided into four groups of seven animals per group. Group I- control; group II- single intraperitoneal administration 35 mg/kg of cadmium chloride ($CdCl_2$); III- orally administered 100 mg/kg *I. cairica* extract (ICE) for five days + 35 mg/kg $CdCl_2$; IV- orally administered 250 mg/kg ICE + $CdCl_2$. The results show that cadmium caused a significant increase in serum concentration of urea, creatinine, and uric acid, compared to the control. Furthermore, cadmium-induced oxidative stress was evident in the kidney tissue, with significant increase in MDA concentration, decrease in glutathione concentration, catalase, superoxide dismutase, and glutathione transferase activity. In conclusion, the results revealed that *I. cairica* is a good medicinal plant that can be used in maintaining renal function against oxidative stress-induced toxicants as treatment with ICE protected the kidney against cadmium intoxication.

Keywords: *Renal injury; Heavy metals; Phytochemicals; Cadmium; Ipomoea cairica; Antioxidant*

INTRODUCTION

The incidence of kidney disease is on the rise globally (Wu *et al*., 2018). Acute or chronic kidney diseases have been reported to be a risk factor in cardiovascular diseases, coupled with the high cost of managing kidney problems and loss of lives associated with kidney damage (Wu *et al*., 2018). It was estimated that more than 1,234,900 deaths in 2010 were a result of kidney diseases (Wu *et al*., 2018). The industrial revolution has further increased the proliferation of various toxic compounds into the environment which accumulate in the air, soil, and water, where they are taken up by plants and animals, later finding their way into the human body through the food chain (Sirot *et al*., 2008; Winiarska-Mieczan, 2015; Kim *et al*., 2018; Satarug, 2019 Shi *et al*., 2020). The World Health Organization reported that more than 12.6 million deaths were as a result of avoidable environmental risk, while more than 1.7 million children below the age of 5 are lost annually due to living in a polluted environment (Xu, 2018).

Cadmium (Cd) is a heavy metal that is soft with a silver-white color, it is naturally found in the environment in combination with oxygen, sulfur, and carbonates (Casado *et al*., 2008). Cd is an environmental pollutant to all forms of living organisms, be it microorganisms, plants, or animals. The non-biodegradable nature prolongs its lifespan in the environment as compared to other heavy metals. Industrial activities such as mining of zinc, lead, and copper production, further increased its level in the environment

(Lokhande *et al*., 2004; Karunakaran and Dhanalakshmi, 2009). While Cd is toxic to most organs in the body (Dua *et al*., 2015; Joardar *et al*., 2019), the kidney is the most susceptible organ to Cd poisoning (Satarug, 2018). Cd reportedly disrupts the role of the kidney in blood purification, filtration, and reabsorption of protein often resulting in proteinuria (Wu *et al*., 2016). Nephrotoxicity of Cd can be chronic or acute depending on the duration and magnitude of exposure (Joardar *et al*., 2019). More than 50% of Cd is deposited in the kidney, making it prone to renal injury due to Cd poisoning (Kim *et al*., 2018).

The preference for natural products and their supplements as against synthetic drugs by humans is on the rise. This can be attributed to the perceived safety, abundance, and reduced cost (Gabr *et al*., 2019). Medicinal plants and their bioactive components have been reported against the various models of Cd toxicity (Gabr*et al*., 2019). Some medicinal plants have been investigated and discovered to be effective against cadmium toxicity. These includes green tea, Buthusoccitanus, while antioxidant compounds, isolated from these plants include curcumin, selenium, Vit. E, Co enQ10, naringenin (El-Sharaky *et al*., 2007; Ognjanovi *et al*., 2010; Renugadevi and Prabu 2010; Bekheet *et al*., 2011; Deevika *et al*., 2012). The efficacy of most plants against cadmium poisoning is due to the presence of antioxidant-rich phytochemicals with pharmacological activities (Ognjanovi *et al*., 2010 and Deevika, *et al*., 2012). *Ipomoea cairica* is a plant that is often classified as a weed due to its invasive nature and natural habitat, which include dumpsites and abandoned areas (Weber, 2003; Deepa and Shukla, 2015*)*. Its origin is unknown, however, it is found in various parts of the world such as Asia and Africa (John *et al*., 2021). In Nigeria, it is consumed as fruits in the south-south region (John *et al*., 2021). It is locally used in the management of jaundice, liver disorders, and aphrodisiac (Singh, 1988; Ashraf *et al*., 2020). Several reports have confirmed the antioxidant, anti-inflammatory, cardioprotective, neuroprotective activities of the plant (Ralte, 2014; Lin *et al*., 2008; Yanchun *et al*., 2021). Some active compounds isolated from the plant includes matairesinol, vanillic acid, and lignin (Lin *et al*., 2008). So far, there is no published data on the nephroprotective effect of *I. cairica* on renal injury induced by $CdCl_2$. Based on the limited scientific literature, the protective effect of *I. cairica* against Cd-induced nephrotoxicity in male Wistar rats was investigated.

MATERIALS AND METHODS

Study design and location

A health Cadmium Chloride, Reduced glutathione, thiobarbituric acid (TBA), trichloroacetic acid (TCA), Chloro dinitrobenzene (CDNB), nicotinamide adenine dinucleotide (NADH) (Sigma-Aldrich, Germany). Creatinine kit, Urea kit, and Uric acid kit were obtained from Randox laboratories Ltd. All chemicals used in this study were of analytical grades.

Extraction of Plant Materials

Ipomoea leaves were harvested from Nembe town, Bayelsa State, Nigeria, and identified by a botanist and assigned a voucher number- UBH-1561. The leaves were air-dried and ground into powdered form. The powdered sample was weighed and soaked in 2.5 liters of 80 % methanol with regular stirring for even distribution for 48 h. The extracts were filtered using a Whatman filter paper. The filtrate was concentrated and lyophilized to obtain a pure sample free of methanol and water. The lyophilized sample was stored at 4 °C before the experiment.

Experimental Design

Twenty-eight (28) adult male Wistar rats weighing 170±10 g were purchased from the Central Animal House, University of Benin, Edo State, Nigeria were used for this experiment. The animals were housed in well-ventilated cages and provided water and food *ad libitum*. Animals were randomly divided into four groups equally. Group I served as the control and administered vehicle (distilled water), group II was intraperitoneally administered 35 mg/kg of cadmium chloride ($CdCl_2$) once, group III were orally administered 100 mg/kg of ICE for five consecutive days before administering $CdCl_2$, and group IV was administered 250 mg/kg of ICE for five consecutive days prior to $CdCl_2$ administration.

Group I: administered vehicle (distilled water)

Group II: administered cadmium chloride ($CdCl_2$: 35 mg/kg) intraperitoneally

Group III: administered 100 mg/kg of ICE before intraperitoneal administration of $CdCl_2$

Group IV: administered 250 mg/kg of ICE before intraperitoneal administration of $CdCl_2$

Preparation of serum

Blood was collected from the heart by cardiac puncture technique into sample tubes. The blood samples were centrifuged at 3,000g for 10 min in a MSC bench centrifuge to obtain serum which was later used for renal function test (urea, creatinine, and uric acid).

Renal function Biomarkers

Serum concentrations of urea, creatinine, and uric acid were determined following the instruction from the kit manual.

Processing the Kidneys

24-hr after the last administration, animals were sacrificed by cervical dislocation and the kidney were excised, rinsed, and homogenized in phosphate buffer saline (0.1M, pH 7.4). The homogenate was centrifuged at 15000 rpm for 10 min at 4^{o}C to obtain a clear supernatant that was used for biochemical assays (malonedialdehyde, reduced glutathione, catalase, superoxide dismutase, glutathione transferase.

Biochemical assay

Estimation of oxidants in kidney tissues

The level of oxidative stress was determined by measuring the amount of malonedialdehyde (MDA) formed from lipid peroxidation (LPO) in the kidney tissue according to the method of Varshney and Kale, 1990.

Estimation of antioxidants in kidney tissues

The concentration of glutathione (GSH) was measured according to the method described by Jollow *et al*., (1973). Catalase (CAT) activity was determined according to the method described by Aebi (1974). The activity of Superoxide dismutase (SOD) was measured according to the method described by Misra and Fridovich, (1972).

Glutathione transferase (GST) Assay

The activity of GST was assessed as according to the method described by Habig *et al*., (1974).

Statistical analysis

Results were analyzed statistically using GraphPad Prism, 6.01 software. One-way ANOVA was used to compare values between groups while Duncan's multiple range test was used as descriptive. All values were expressed as the mean ±standard deviation of five animals per group. P<0.05 was considered statistically significant.

RESULTS AND DISCUSSION

Table 1. Serum Urea, Uric Acid and Creatinine Levels in Control and in All Experimental Groups.

GROUPS	UREA (mg/dL)	URIC ACID (mg/dL)	CREATININE (mg/dL)
Control	5.2 ± 0.91	40.0 ± 3.70	15.4±1.73
$CdCl_2$ (35 mg/kg)	11.7 ± 1.35***	77.2 ± 8.51***	89.9±6.57***
ICE (100 mg/kg) + $CdCl_2$	8.7 ± 1.15$^{\#\#}$	49.0 ± 3.01$^{\#\#}$	65.0±6.57$^{\#\#}$
ICE (250 mg/kg) + $CdCl_2$	6.1 ± 0.35$^{\#\#\#}$	37.5 ± 14.27$^{\#\#\#}$	41.8±4.26$^{\#\#\#}$

ICE (*Ipomoea cairica* leaf extract); **$CdCl_2$** (cadmium chloride) Results are expressed as mean ± standard deviation (SD) for 7 animals. Statistically significant differences: *** P<0.0001=Control group vs Cd; $^{\#\#}$ P<0.05= Cd vs 100 mg/kg ICE; $^{\#\#\#}$P<0.001=Cd vs 250 mg/kg

Effect of ICE and $CdCl_2$ on serum markers of renal damage.

Table 1 summarizes the effect of ICE and $CdCl_2$ on serum urea, creatinine and uric acid levels. Exposure of the rats to the $CdCl_2$ causes a significantly increase in the serum level of urea, creatinine and uric acid as compared to the control (P<0.05). Pretreatment of the rats with 100 and 250 mg/kg of ICE significantly inhibited $CdCl_2$ induced renal damage as observed in the significant decrease in the serum level of urea, creatinine and uric acid as compared to the control. (P<0.05). The table also showed that the protective effect of ICE against $CdCl_2$ nephrotoxicity was dose-dependent as 250 mg/kg was more effective than 100 mg/kg of ICE.

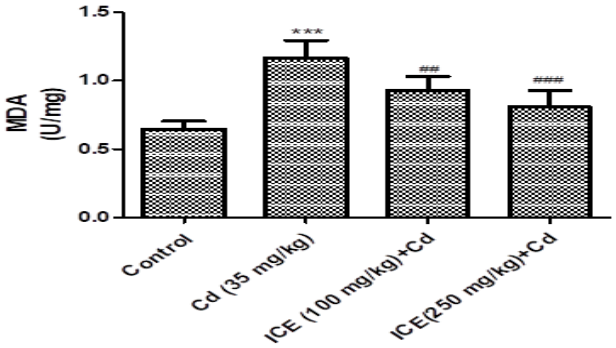

Figure 1. The concentration of lipid peroxides product - malondialdehyde (MDA), in the kidney of male Wistar rats after pretreatment with *Ipomoea cairica* leaf extract (ICE) and exposure to cadmium chloride (35 mg/kg) via intraperitoneal administration.

Data are shown as mean ± standard deviation (SD) for 7 animals. Statistically significant differences: *** P<0.0001=Control group vs Cd; $^{\#\#}$ P<0.05= Cd vs 100 mg/kg ICE; $^{\#\#\#}$P<0.001=Cd vs 250 mg/kg

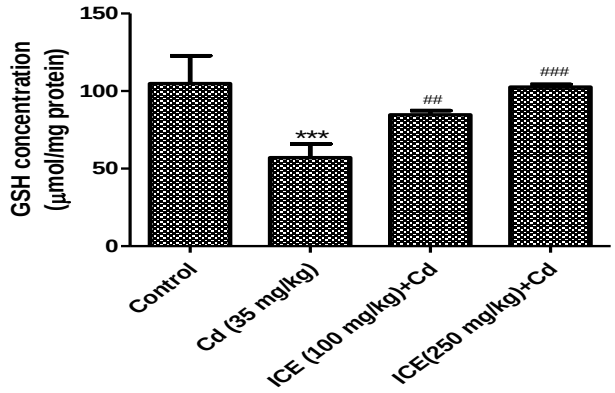

Figure 2. The concentration of non-enzymatic antioxidant- reduced glutathione (GSH) in the kidney of male rats after pretreatment with *Ipomoea cairica* leaf extract (ICE), followed by exposure to cadmium (35 mg/kg) via intraperitoneal administration.

Data are shown as mean ± standard deviation (SD) for 7 animals. Statistically significant differences: *** P<0.0001=Control group vs Cd; ## P<0.001= Cd vs 100 mg/kg ICE; ###P<0.001=Cd vs 250 mg/kg

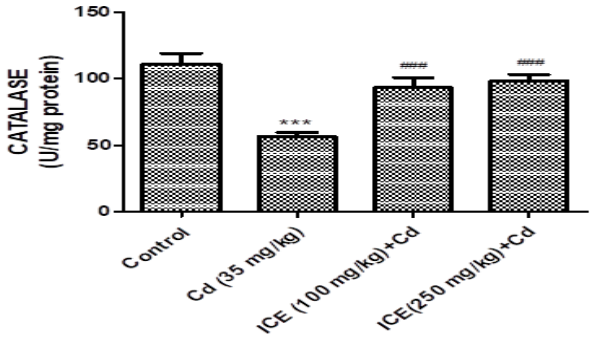

Figure 3. The catalase activity in the kidney of male rats after pretreatment with *Ipomoea cairica* leaf extract (ICE) followed by exposure to cadmium (35 mg/kg) via intraperitoneal administration.

Data are shown as mean ± standard deviation (SD) for 7 animals. Statistically significant differences: *** P<0.0001=Control group vs Cd; ###P<0.0001=Cd vs treatment group (100- and 250 mg/kg)

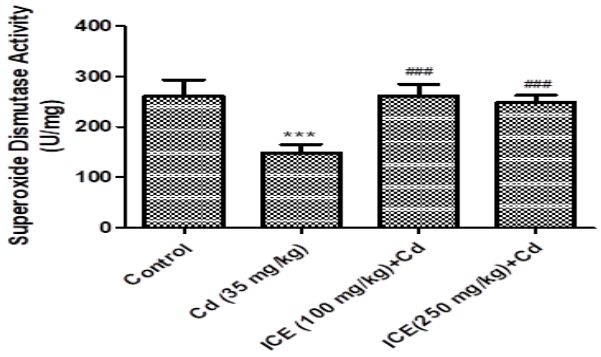

Figure 4. The superoxide dismutase activity in the kidney of male wistar rats after pretreatment with *Ipomoea cairica* leaf extract (ICE) followed by exposure to cadmium (35 mg/kg) via intraperitoneal administration.

Data are shown as mean ± standard deviation (SD) for 7 animals. Statistically significant differences: *** P<0.0001=Control group vs Cd; ###P<0.0001=Cd vs treatment groups (100- and 250 mg/kg)

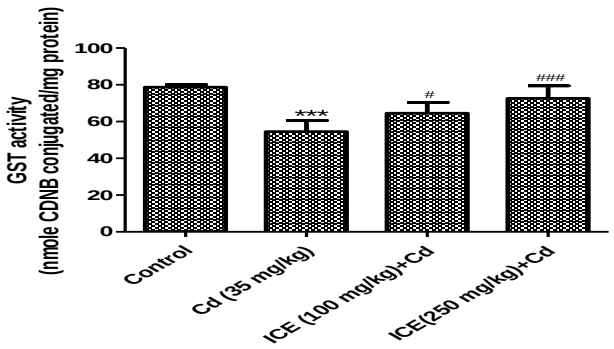

Figure 5. The glutathione-S-transferase (GST) activity in the kidney of male rats after pretreatment with *Ipomoea cairica* leaf extract (ICE) before exposure to cadmium (35 mg/kg) via intraperitoneal administration.

Data are shown as mean ± standard deviation (SD) for 7 animals. Statistically significant differences: *** P<0.0001=Control group vs Cd; # P<0.05= Cd vs 100 mg/kg ICE; ###P<0.0001=Cd vs 250 mg/kg

Effect of $CdCl_2$ and ICE on markers of oxidative stress in male Wistar rats.

Figure 1 shows that $CdCl_2$ caused significant increase in MDA level as compared to the control (P<0.05). While pretreatment with 100 and 250 mg/kg of ICE caused a significant decrease in the concentration of MDA as compared to the untreated group (P<0.05). As observed with markers of renal toxicity, 250 mg/kg of ICE was more effective in lowering the level of MDA as compared to 100 mg/kg of ICE.

Figure 2 shows the protective effect of ICE against $CdCl_2$-induced depletion of GSH. Exposure of rats to $CdCl_2$ resulted in a significant depletion of GSH concentration as compared to the control (P<0.001). Pretreatment with ICE at 100 and 250 mg/kg caused a significant increase in the level of GSH as compared to the untreated group (P<0.001). Figure 3 and 4 shows the effect of $CdCl_2$ and ICE on the activity of Catalase and SOD. $CdCl_2$ caused a significant depletion of CAT and SOD in the kidney tissue of male Wistar rat as compared to the control (P<0.001). Pretreatment with 100 and 250 mg/kg was able to prevent the inhibitory activities of CAT and SOD caused by $CdCl_2$ exposure as observed in the significant increase in the activity of CAT and SOD as compared to the untreated group. However, unlike other biochemical assays, there was no significant difference between the two doses used in the study (P>0.05).

Effect of $CdCl_2$ and ICE on GST activity in the kidney tissue of male Wistar rats

Figure 5 present the activity of GST as a result of pretreatment of rat with 100 and 250 mg/kg of ICE prior to $CdCl_2$ exposure. $CdCl_2$ caused a significant decrease in the activity of GST as compared to the control ($P<0.05$). Pretreatment with 100 and 250 mg/kg of ICE significantly increased the activity of GST as compared to the untreated group ($P<0.05$ and 0.001).

DISCUSSION

Cadmium (Cd) is one of the heavy metals' humans are exposed to due to its presence in staple food such as rice and inhalation from smoking (Ashizawa *et al*., 2012; Arao, 2019; Horiguchi, 2019). Cd poisoning has been linked to anemia, bone degeneration, and nephrotoxicity (Bulmer *et al*., 1938; Hagino *et al*., 1960; Mona *et al*., 2018). The susceptibility of the kidney to Cd poisoning is due to Cd absorbance through the proximal tubules and glomeruli (Kim *et al*., 2018). Kidney failure from Cd poisoning is one of the common features. The global health challenge of Cd poisoning has led to the continuous search for drugs and natural products that can neutralize the toxic effect of Cd. Our study investigated the nephroprotective effect of *Ipomoea cairica* against Cd-induced kidney injury. Similar to other results from the previous investigation (Kim *et al*., 2018; Wongmekiat *et al*., 2018; Jiao *et al*., 2019), acute administration of 35 mg/kg of $CdCl_2$ caused a significant increase in serum concentrations of markers of kidney function (uric acid, creatinine, and urea). This increase might be due to Cd-induced assault on various parts of the kidney which damages the membrane integrity of the glomerular, renal cortex, and proximal tubules, causing failure in the reabsorption of the product, thus their leakage into the blood (Genchi *et al*., 2020). Report from various investigations show that oxidative stress is one of the mechanisms by which cadmium causes kidney injury (Manna *et al*., 2009; Nazima *et al*., 2015; Erboga *et al*., 2016; Luo *et al*., 2016). The results showed a significant increase in MDA concentration, decrease in GSH concentration, SOD, CAT, and GST activities. MDA is a product of lipid peroxidation, an increased level of MDA is often linked to high production of reactive oxygen species (Ansari *et al*., 2017). Although Cd does not generate ROS, its inhibition of respiratory enzymes can cause the leakage of unstable oxygen molecules from the mitochondria, thereby increasing the intracellular concentration of ROS (Matovic *et al*., 2017). ROS oxidatively damage functional biological molecules, such as lipids and proteins on the membrane. Damage to the cellular membrane leads to leakage of some cytoplasmic compounds into the intracellular matrix as observed in the increased serum level of urea, creatinine, and uric acid. GSH is an important antioxidant biomolecule involved in maintaining the redox status in the body (Matovic *et al*., 2017). Decreased concentration in GSH is connected to the production of ROS in excess of the capacity of GSH. Other antioxidants involved in neutralization of ROS includes SOD, that catalyze the conversion of superoxide anion to hydrogen peroxide and CAT that converts hydrogen peroxide to water and oxygen. Cd reportedly inhibits the activity of these enzymes by displacing the metal cofactors, such as Zn, Cu, and Mn in the enzymes (Alterio *et al*., 2015). Thus, the low activity of SOD and CAT following Cd exposure in the kidney of male Wistar rats is in support of the inhibitory effect of Cd. This is corroborated by the result of other investigators who reported similar results (Kim *et al*., 2018; Wongmekiat *et al*., 2018; Jiao *et al*., 2019).

GST is one of the metabolizing enzymes involved in drug and chemical detoxification and excretion. Its activity is often dependent on GSH availability, thus its low activity observed in the kidney of animals exposed to Cd cannot be unconnected to a low concentration of GSH (Dua *et al*., 2015). This is also similar to the results of Joardar *et al*., 2020. *I. cairica* was able to prevent the renal damage induced by $CdCl_2$ as observed in the low serum concentration of urea, creatinine, and uric acid. This can be linked to the antioxidant activities of *I. cairica* which was able to prevent the oxidative damage of Cd on the lipid and protein components of the nephrocytes. This is reflected in the low concentration of MDA, high concentration of GSH, increased activities of SOD, CAT, and GST.

CONCLUSION

In conclusion, the results indicate that pre-treatment of male Wistar rats with aqueous methanol extract of *I. cairica* leaves prevented the kidney from $CdCl_2$ toxicity. This nephroprotective effect may be attributed to the presence of antioxidant and metal chelating phytochemicals present in the plant.

AUTHORS' CONTRIBUTIONS

All authors contributed equally to the manuscript

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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ETHICAL CONSIDERATION

All the rats used for this experiment were healthy and treated according to the guidelines of the Helsinki Declaration of 1975 for the care and use of laboratory animals. The experimental design was approved by the ethical committee on animal research and treatment (ART) of the Federal University Otuoke, Nigeria. The approval code was ART2021005. In specific terms, the experiment was conducted in the animal house of the Department of Biochemistry, Faculty of Science, Federal University Otuoke from February to June, 2021.

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