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Effect of *Allium cepa* (Onion) Extract on Cadmium-induced Nephrotoxicity in Rats

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ABSTRACT

This study aims at investigating the effect of pre-treatment, co-treatment and post-treatment with *Allium cepa* extract, AcE, on cadmium-induced renal toxicity and confirming possible mechanisms by which *Allium cepa* extract reduce/restore cadmium induces nephrotoxicity. Thirty male Sprague Dawley rats were used. They were divided into 5 groups (n = 6). Group 1 was used as control. Group 2 was intraperitoneally administered 1.5 mL kg⁻¹ BW of 0.3 mg L⁻¹ of cadmium sulphate for 3 days. Group 3 was pretreated with 1.0 mL kg⁻¹ BW of AcE for 8 weeks followed by intraperitoneal administration of 1.5 mL kg⁻¹ b.wt. of 0.3 mg L⁻¹ of cadmium sulphate. Group 4 was co-treated with 1.5 mL kg⁻¹ BW of 0.3 mg L⁻¹ of cadmium sulphate for 3 days and 1.0 mL kg⁻¹ BW of AcE for 8 weeks simultaneously. Group 5 was post-treated with 1.0 mL kg⁻¹ BW of cadmium sulphate for 8 weeks following a 3 day course of 1.5 mL kg⁻¹ BW of 0.3 mg L⁻¹ of cadmium sulphate intraperitoneal administration. All groups were allowed free access to standard rat chow and water throughout the period of experiment. After the experiment period, rats were sacrificed by cervical dislocation and blood sample were obtained via cardiac puncture. The kidneys were also excised. Changes in body and kidney weights were determined. Renal weight index, 24 h urine volume, renal clearance and lipid peroxidation status were also determined. There was no significant change in body and kidney weight and renal weight index in all groups. Renal clearance and 24 h urine volume were significantly reduced in group 2 rats when compared to all groups. Renal clearance was also reduced in group 3 and 5, though this decrease was only significant when compared with the control group. Plasma and tissue SOD activities were significantly increased in group 2. Plasma and tissue MDA levels were significantly increased in group 2, 3 and 5. This study shows that cadmium induces nephrotoxicity by impairing renal functions and stimulating lipid peroxidation. Pre-treatment and post-treatment of AcE in cadmium-treated rats produced mild protective potentials. However, co-treatment with AcE during cadmium administration showed significant antioxidative potentials in preventing cadmium-induced nephrotoxicity.

Key words: *Allium cepa*, cadmium, kidney, lipid peroxidation, antioxidant

INTRODUCTION

Cadmium is a common nephrotoxic agent in food and tobacco. Other major sources of cadmium are include cereals, vegetables and shellfish (Akesson *et al.*, 2005). Cadmium mainly accumulates in the kidneys and liver (Nogue *et al.*, 2004). Cadmium accumulates in the renal cortex and induces tubular toxicity (Barbier *et al.*, 2005).

Clinical and experimental studies have shown that cadmium stimulates lipid peroxidation, LPO (Sarkar *et al.*, 1995; Bagchi *et al.*, 1996; Casalino *et al.*, 1997; Shaikh *et al.*, 1999; Manca *et al.*, 1991; Hussain *et al.*, 1987; Ige *et al.*, 2009) with consequent glomerular damage (Barrouillet *et al.*, 1999) and impaired glomerular function (Kido *et al.*, 1990; Uriu *et al.*, 1993; Jarup *et al.*, 1995; Barrouillet *et al.*, 1999; Roels *et al.*, 1981; Ige *et al.*, 2009). This is associated with altered activities of antioxidant enzymes (Sarkar *et al.*, 1995; Hussain *et al.*, 1987; Ige *et al.*, 2009).

On the other hand, *Allium cepa*, popularly known as onion, has been reported to have protective properties such as reduction of the risk of rectal carcinoma (Dorant *et al.*, 1996), antiplatelet activity (Cavagnaro *et al.*, 2007) and antioxidant properties (De Whalley *et al.*, 1990; Helen *et al.*, 2000; Prakash and Singh, 2007; Ige *et al.*, 2009).

Though our previous study (Ige *et al.*, 2009) has showed that pre-treatment with AcE prevents cadmium-induced renal dysfunction, no report has been documented on the effect of co-treatment and post-treatment of AcE with cadmium. This study therefore aims at investigating the effect of pre-treatment, co-treatment and post-treatment with AcE on cadmium-induced renal toxicity and confirming possible mechanisms by which *Allium cepa* extract alleviates cadmium-induced nephrotoxicity.

MATERIALS AND METHODS

Experimental animals: The experiment was conducted in the Animal House of the Ladoko Akintola University of Technology, Ogbomoso, Nigeria from 2008 to 2009. Thirty male Sprague Dawley rats weighing 150-200 g were used. They were divided into 5 groups each group consisting of six rats. They were all housed in standard rat cages and allowed free access to standard rat chow and water. The animals were allowed to acclimatize for two weeks.

Treatments: After the acclimatization period, group I animals were used as control and received distilled water orally throughout the period of the experiment. Group 2 animals received 1.5 mL kg⁻¹ BW of 0.3 mg L⁻¹ of cadmium sulphate (3CdSO₄.8H₂O_{aq}) intraperitoneally to induce nephrotoxicity three days to the end of the experiment. Group 3 animals were pre-treated with 1.0 mL kg⁻¹ BW of AcE for 8 weeks after which they were intraperitoneally administered with 1.5 mL kg⁻¹ BW of 0.3 mg L⁻¹ of cadmium sulphate. Group 4 animals were simultaneously administered with 1.5 mL kg⁻¹ BW of 0.3 mg L⁻¹ of cadmium sulphate intraperitoneally with 1.5 mL kg⁻¹ for three days and 1.0 mL kg⁻¹ BW of AcE. Group 5 animals were injected intraperitoneally with 1.5 mL kg⁻¹ BW of 0.3 mg L⁻¹ of cadmium sulphate for three day, after which they received 1.0 mL kg⁻¹ BW of AcE.

Preparation of AcE: AcE was prepared as reported by Azu *et al.* (2007) and Ige *et al.* (2009). Fresh *Allium cepa* bulbs were thoroughly rinsed in distilled water and air dried. 200g were then blended. The resulting paste was allowed to stand for 24 h. Juice was then filtered and squeezed out of it. The filtrate juice was prepared weekly following the same procedure and kept below 4°C to preserve its potency.

Measurements: Twenty four hours after the last intraperitoneal administration of cadmium sulphate, each animal was weighed and transferred into metabolic cage equipped with accessory for collecting urine. The 24 h urine sample was collected, the volume was determined and recorded for each rat. Urine and serum levels of creatinine and urea were determined using Alkaline Picrate Method and Diacetyl/Monoxime Method as described by Jaffe (1886) and Ceriotti and Spandro (1963) respectively. Creatinine clearance and urea clearance were then determined as reported by Guyton and Hall (2001) and Ige *et al.* (2009). Plasma and tissue superoxide dismutase (SOD) activities were determined as described by Fridovich (1986). Plasma and tissue malondialdehyde (MDA) concentrations were determined as reported by Varshney and Kale (1990). The kidneys were excised, cleaned and weighed. The renal weight index (KW/BW) was calculated by dividing the kidneys weight (KW) by the body weight (BW) for each rat.

Statistical analysis: Statistical analyses were performed using the Statistical Program for Social Sciences (SPSS) window versions 9.0. Comparison was done using one-way analysis of variance (ANOVA). Each of the test group was also compared with the control group using unpaired t-test. The significance level was set at $p < 0.05$. Data are presented as Mean \pm SEM.

RESULTS

Table 1 shows that there was no significant weight change in all the groups over the period of the experiment. Kidney weight and renal weight index were also not significantly different in all groups.

Twenty four hour urine volume was significantly reduced in groups 2, 3 and 5 when compared with the control group (group 1), but only group 2 showed significant reduction in the 24 h urine volume when compared with other groups. Urea clearance and creatinine clearance were significantly reduced in group 2, 3 and 5 when compared with the control group (group 1). However, only group 2 showed significant reductions in urea and creatinine clearance when compared with other groups (Table 2).

Plasma and tissue SOD activities were significantly reduced in group 2 when compared with all other groups. Group 3 also showed a significant reduction in plasma SOD activity when compared with group 1. Plasma and tissue MDA levels were significantly increased in groups 2, 3 and 5 (Table 3).

Table 1: Effect of AcE on cadmium-induced changes in body weight gain, kidney weight and renal weight index

Variables	Group 1	Group 2	Group 3	Group 4	Group 5
Body weight gain (g)	31.8300 \pm 1.014	30.5000 \pm 0.9916	32.5000 \pm 0.9916	33.1700 \pm 1.3800	32.8300 \pm 0.7923
Weight change (%)	21.2200	19.9600	21.5200	21.8200	21.6000
Kidney weight (g)	0.4824 \pm 0.0202	0.4978 \pm 0.0110	0.4920 \pm 0.0069	0.4487 \pm 0.0924	0.4490 \pm 0.0145
Renal Weight Index	0.0032 \pm 0.5020	0.0033 \pm 0.4809	0.0032 \pm 0.2990	0.0030 \pm 0.1202	0.0030 \pm 0.1021

Table 2: Effect of AcE on cadmium-induced changes in 24 h urine volume and renal clearance

Variables	Group 1	Group 2	Group 3	Group 4	Group 5
24 h urine volume (mL)	3.2170 \pm 0.0073	2.2830 \pm 0.0703**	3.0330 \pm 0.0882*	3.2330 \pm 0.0422	3.0170 \pm 0.0601*
Urea clearance (mL min ⁻¹)	0.3883 \pm 0.0087	0.1940 \pm 0.0047**	0.2390 \pm 0.0122*	0.4373 \pm 0.0212	0.2213 \pm 0.0073*
Creatinine clearance (mL min ⁻¹)	3.9940 \pm 0.5388	1.0470 \pm 0.1419**	2.7100 \pm 0.0763*	3.5140 \pm 0.2447	2.4750 \pm 0.2160*

* $p < 0.05$ versus control, ** $p < 0.05$ versus other groups

Table 3: Effect of AcE on cadmium-induced changes in lipid peroxidation status

Variables	Group 1	Group 2	Group 3	Group 4	Group 5
Plasma SOD activity (U)	1.7430±0.0203	1.3680±0.0101**	1.6350±0.0157*	1.6980±0.0263	1.6070±0.0289
Tissue SOD activity (U)	1.6680±0.0991	1.3550±0.0293**	1.7270±0.0226	1.7430±0.0203	1.6800±0.0289
Plasma MDA concentration (µg dL ⁻¹)	1308±24.5000	1837±34.0100**	1414±26.3000**	1341±7.48700	1493±6.27600**
Tissue MDA concentration (µg g ⁻¹)	1304±24.5100	1831±33.9000**	1407±26.4600**	1335±7.8530	1487±5.8710**

*p<0.05 versus control, **p<0.05 versus other groups

DISCUSSION

Tissue damage resulting from cadmium exposure associated with oxidative stress is often observed in the kidney (Manca *et al.*, 1991; Ige *et al.*, 2009). The present study confirms the pro-oxidative properties of cadmium and evaluates the potential of AcE, a known antioxidant, in improving the renal dysfunction related to oxidative stress in cadmium-induced nephrotoxicity. In agreement with previous studies, the data generated in this current study revealed that neither cadmium nor AcE is associated with significant alteration in body weight, kidney weight and renal weight index (Compos *et al.*, 2003; Ige *et al.*, 2009). However, this is inconsistent with the previous study of Goyer and Cherian (1991), that showed significant weight alteration on chronic administration of cadmium for more than 8 weeks. The result of the present study can be associated with the low caloric and protein content of *Allium cepa* (Haimmouril and Ereifej, 1997; Zeier and Schreiber, 1998) and probably because cadmium was administered for 3 days which might not be enough duration to cause weight change compared with that administered for 8 weeks. These could also explain why there were no significant changes in kidney weight and renal weight index.

This study also showed that there was a significant reduction in the 24 h urine volume of cadmium-treated rats. This is in consonance with previous studies and confirms that cadmium administration or exposure causes renal tubular damage, declined renal function, decrease glomerular rate (GFR) and impaired renal blood flow (RBF) (Uriu *et al.*, 1993; Barrouillet *et al.*, 1999; Roels *et al.*, 1981; Asagba and Obi, 2004; Satarug *et al.*, 2004; Akesson *et al.*, 2005; Ige *et al.*, 2009). Administration of AcE alleviated cadmium-induced urine volume alteration. This could suggest that AcE improves renal function by preventing renal tubular damage and enhancement of RBF and GFR.

This study also documents the effect of cadmium and AcE on renal clearance. A significant decrease in urea and creatinine clearance was seen in rats treated with cadmium only when compared to all other groups. This is similar to previous studies (Uriu *et al.*, 1993; Akesson *et al.*, 2005; Ige *et al.*, 2009). This study suggests that the impaired renal clearance seen in cadmium exposure is due to the reduced 24 h urine volume. A significant decrease in urea and creatinine clearance was also seen in AcE-pre-treated and post-treated rats. However, this was only significant when compared to the control group, but not the other groups. Co-treatment of cadmium with AcE showed no significant impairment of renal clearance. This suggests that co-treatment of cadmium with AcE is most potent in preventing cadmium-induced renal dysfunction by improving renal clearance and 24 h urine volume than pre-treatment and post-treatment of cadmium with AcE.

In agreement with previous studies, results from this study revealed that cadmium-induced oxidative stress in the kidneys is indicated by significant decrease in plasma and tissue SOD activities as well as an increase MDA, an index of lipid peroxidation (Manca *et al.*, 1991; Sarkar *et al.*, 1995; Bagchi *et al.*, 1996; Casalino *et al.*, 1997; Shaikh *et al.*, 1999; Ige *et al.*, 2009). The decrease in the enzymatic antioxidant, SOD, activities in the plasma and kidney tissue may be responsible for the increased levels of MDA seen in plasma and kidney tissue.

Groups 3 and 5 rats which were pre-treated and post-treated with AcE respectively also showed significant increase in MDA levels of the plasma and kidney tissue. This is inconsistent with our previous study (Ige *et al.*, 2009). This could be due to the 8-week treatment with AcE in this study as to the 10-week AcE treatment in our previous study. This suggests that the antioxidative potentials of AcE could be duration-related. Co-treatment of cadmium with AcE showed no significant alteration in the lipid peroxidation status when compared with the control. This suggests that co-treatment of AcE is very potent in preventing cadmium-induced oxidative stress.

CONCLUSION

This study shows that cadmium induces nephrotoxicity by impairing renal functions and stimulating lipid peroxidation. Pre-treatment and post-treatment of AcE in cadmium-treated rats produced mild protective potentials. However, co-treatment with AcE during cadmium administration showed significant antioxidative potentials in preventing cadmium-induced nephrotoxicity.

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