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Renal Histopathology and Serum Biochemistry of Cadmium-exposed Rabbit Bucks Administered Methanolic Extract of *Phoenix dactylifera* Fruit

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Abstract

Cadmium (Cd), a prevalent heavy metal pollutant, is known for its harmful effects on physiological functions within the biological system. In this study, the effects of Cd exposure on some kidney related biochemical and histopathological parameters in rabbits were investigated, alongside exploring the potential protective role of methanolic extract from *Phoenix dactylifera* (MEPD) on the kidney. The study included 45 male rabbits, aged 24-28 weeks and weighing approximately 1.41-1.43 kg were assigned into five (5) treatment groups (control, Cd-only, Cd + 300 mg MEPD, Cd + 600 mg MEPD and Cd + 900 mg MEPD) in a completely randomized design. The rabbits received a 7-day dose of 3 mg $CdCl_2$/kg feed, followed by MEPD every 72 hours for 28 days. Results revealed higher significant ($P<0.05$) differences in serum glucose, urea and creatinine in Cd-only treated group when compared with the control group. MEPD treatment significantly ($P<0.05$) lowered serum glucose levels in Cd-exposed rabbits, indicating a potential glycemic modulating activity, but had no significant ($P>0.05$) effect on urea and creatinine concentrations. High density lipoprotein (HDL), low-density lipoprotein (LDL) and cholesterol ratios were not significantly different but showed marginal improvement in the Cd+MEPD groups compared to the Cd-only group. The findings also revealed significant differences in both absolute and relative kidney weights between the group treated with Cd alone and the control group, indicating potential renal injury induced by Cd. Histopathological examination revealed kidney damage in Cd-exposed rabbits, with observed changes such as disruption of Bowman's capsule, glomerular shrinkage, degeneration of renal tubules and haemorrhage. The administration of MEPD did not ameliorate the observed histopathological alterations. In conclusion, this study suggests that Cd exposure may induce hyperglycemia and kidney injury in rabbits. MEPD treatment demonstrated some protective effects against Cd-induced hyperglycemia but did not significantly mitigate kidney damage.

Keywords: Blood, cadmium, date, nephrotoxicity, phytochemistry.

INTRODUCTION

There have been growing concerns in industrial activities and human interventions which have caused a surge in environmental pollution, significantly threatening ecosystems and organisms (Özkara and Akyıl, 2019; Bashir et al., 2020; Siddiqua et al., 2022). Among these pollutants, heavy metals like cadmium have emerged as potent nephrotoxic agents, causing detrimental effects on renal function in exposed organisms (Genchi et al., 2020). The kidneys, being primary sites of cadmium accumulation, are highly susceptible to its detrimental impact, leading to oxidative stress, inflammation, and impaired serum biochemistry (Satarug, 2018).

Cadmium toxicity is a multifaceted issue, and understanding the intricate biochemical responses is imperative for developing effective interventions. The quest for novel, safe, and natural compounds has led to the exploration of plant-based remedies. *Phoenix dactylifera*, commonly known as date palm, has emerged as a potential candidate due to its rich composition of bioactive compounds with antioxidant properties (Al-Alawi et al., 2017). The methanolic extract derived from the fruits of *Phoenix dactylifera* has demonstrated significant antioxidant and cytoprotective effects, making it a subject of interest (Ferdosh et al., 2023).

This study seeks to bridge the gap between environmental toxicology and natural interventions by investigating the kidney and serum biochemistry response of cadmium-exposed rabbit bucks administered with the methanolic extract of *Phoenix dactylifera* fruit. The intricate interplay between cadmium-induced renal damage and the potential protective effects of the date palm extract will be explored to provide valuable insights into the therapeutic strategies against heavy metal toxicity.

This investigation holds significance not only in advancing our understanding of the potential therapeutic applications of *Phoenix dactylifera* in combating heavy metal toxicity but also in contributing valuable data to environmental toxicology. The findings may lead to the development of novel strategies to prevent or alleviate the detrimental effects of cadmium exposure on renal health, benefiting both animal and human populations exposed to environmental pollutants.

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MATERIALS AND METHODS

Ethical consideration

This experiment was approved and conducted according to the provisions of the Ethical Committee on the use of animals for biomedical research at the University of Benin, Benin City, Nigeria.

Location of study

The study was conducted at the Rabbitary Unit within the Teaching and Research Farm of the University of Benin, Benin City, Edo State, Nigeria.

Acquisition of Phoenix dactylifera fruits

Dates from *Phoenix dactylifera* were obtained from the Nigerian Institute for Oil Palm Research (NIFOR) in Benin City, Edo State, Nigeria. A botanist authenticated the acquired fruits, which were then split, air-dried, finely ground using an electric blender, and stored in an airtight container.

Preparation of fruit extracts

A quantity of 0.5 kg of ground *Phoenix dactylifera* fruits was measured and subjected to extraction using 99 % methanol in a soxhlet apparatus. The resulting extract underwent concentration through the recovery of methanol using a rotary vacuum evaporator, and the concentrated extract was then stored in an airtight container.

Acute toxicity evaluation

Acute toxicity of MEPD fruit was studied using the method outlined by Lorke (1983). Twenty five (20) matured albino rats of both sexes with body weight range of 25 to 30 g were randomized into five groups of four rats per group. Each group received a single dose of NBL extract at 0, 500, 1000, 2000 and 3000 mg/kg body weight, respectively, through oral routes, while the control group received normal saline at 10 ml/kg body weight. The rats were closely observed for signs of toxicity for 72 hours.

Experimental materials and management

In this study, a total of forty-five (45) composite rabbit bucks, aged 24 to 28 weeks and weighing between 1.41-1.43 kg, were used. The rabbits were individually housed in cages measuring 50×55×40 cm, each equipped with a feeder and a drinker. Before the commencement of the experiment, the rabbits underwent a two-week quarantine period during which they received Ivomec® injections to control haemoparasites, internal, and external parasites. Throughout the study, the rabbits were provided with *ad libitum* access to both water and a commercial growers' diet (15% crude protein; 2700 kcal/kg metabolisable energy).

Experimental design

The treatment procedures involved the randomization of rabbit bucks into five groups: group 1 (control), group 2 (3 mg of $CdCl_2$/kg feed/day for 7 days), group 3 ($CdCl_2$/kg feed/day for 7 days + 300 mg/kg body weight of MEPD fruits for 28 days), group 4 ($CdCl_2$/kg feed/day for 7 days + 600 mg/kg body weight of MEPD fruits for 28 days), and group 5 ($CdCl_2$/kg feed/day for 7 days + 900 mg/kg body weight of MEPD fruits for 28 days). Each treatment group was replicated three times, with three bucks per replicate in a completely randomized design.

Blood collection

At the end of the 28-day experiment, a 5 ml blood sample was collected from the rabbit bucks via the ear vein using a needle and syringe between 0600-0900 hours. The drawn blood was transferred into plain sample bottles for serum biochemical analysis.

Determination of serum biochemical

Serum contents of glucose, creatinine and urea were measured spectrophotometrically (Photometer 5010®-Boehringer Mannheim) following the procedures defined in the commercial test kits (Biolabo, France), while serum Na^+, K^+, HCO_3^-, and Cl^- were analysed on an ion selective device (ISE®-Medica). Serum triglycerides, total cholesterol, high density lipoprotein (HDL), and low density lipoprotein (LDL) were determined by using the diagnostic kit (Pars Azmoon Kit, IRI) on an automatic analyser (Abbot, model Alcyon 300, USA).

Evaluation of kidney weight

Following the blood sample collection, the experimental rabbit bucks were humanely sacrificed by stunning using a captive bolt, immediately followed by exsanguination. The kidneys were harvested and weighed using an electronic scale.

Renal histopathological study

The kidneys obtained from the assessment of kidney weight were transversely cut and immersed in Bouin's fluid for 24 hours. The tissues were washed in ascending ethanol concentrations (50%, 75%, and 100%) and were then cleared with xylene. Following embedment in paraffin wax, the tissues were sectioned using a microtome at a thickness of 4-5 µ. Dewaxed sections were stained with Hematoxylin and Eosin (H&E). DPX mountant (Distyrene, Plasticizer, and Xylene) was applied to enhance the refractive index of the stained preparation, and cover slips were added to prevent scratches. Examination of all sections was conducted under a light microscope at ×40 magnification. Olympus photomicroscope was utilized for capturing photomicrographs of the renal tissues to observe and document histopathology.

Statistical analysis

Obtained data were subjected to statistical analysis using the Analysis of Variance (ANOVA) procedure in GenStat 12th edition at a 5% probability level. Significant mean differences were identified through the application of the Duncan Multiple Range Test (DMRT) within the same statistical software.

RESULTS

Table 1 presents the mean values of glucose, electrolyte, urea, creatinine and lipid profile of cadmium exposed rabbit bucks treated with methanolic extract of *Phoenix dactylifera* fruit.

The result presented in Table 1 indicates significant differences ($P<0.05$) in serum levels of glucose, urea and creatinine. The serum glucose level in the Cd-only group was significantly higher than that in the control group. Additionally, the control group exhibited significantly lower levels of serum urea and creatinine ($P<0.05$) compared to the Cd-exposed groups. Nevertheless, treatment with MEPD significantly ($P<0.05$) decreased the serum glucose level, although no significant reduction was observed in urea and creatinine concentrations compared

to the control group. Notwithstanding that the mean values of the lipid panel, including HDL, LDL, and cholesterol ratios (TC/HDL and LDL/HDL) were not significantly (P>0.05) different in the Cd+extract treated groups, they showed marginal improvement in their respective ratios when compared to the Cd-only exposed rabbits.

The results of performance, absolute and relative kidney weight of rabbit bucks studied in this finding are presented in Table 2.

Table 1. Glucose, electrolytes, urea, creatinine, and lipid profile of cadmium exposed rabbits administered MEPD

Parameters	Control	Cd	Cd + 300 MEPD	Cd + 600 MEPD	Cd + 900 MEPD	SEM
Glucose (mg/dl)	113.30^{b}	139.00^{a}	110.70^{b}	116.70^{b}	101.70^{b}	7.28
Urea (mg/dl)	20.67^{c}	25.33^{b}	27.33^{b}	30.00^{a}	26.67^{b}	2.80
Na^{+}(mmol/L)	144.00	143.30	150.00	144.70	147.70	2.32
K^{+} (mmol/L)	6.37	5.63	6.57	5.63	5.40	0.38
Cl^{-} (mmol/L)	105.00	103.00	104.33	102.67	102.00	1.80
HCO (mmol/L)	19.33	19.33	18.33	19.00	19.33	1.42
Creatinine (mg/dl)	0.67^{b}	0.94^{a}	0.91^{a}	0.80^{a}	0.80^{a}	0.09
Total cholesterol (mg/dl)	49.33	55.00	55.67	51.67	54.67	7.28
HDL (mg/dl)	30.00	30.67	40.00	35.00	33.67	3.90
LDL (mg/dl)	14.40	13.67	11.73	9.00	12.90	4.83
TC/HDL	1.63	1.87	1.38	1.49	1.65	0.17
LDL/HDL	0.50	0.46	0.28	0.27	0.39	0.13

^{a,b,c} Means bearing different letters of superscript within the same row differ significantly (P < 0.05). HDL- High density lipoprotein; LDL- Low density lipoprotein; TC- Total cholesterol.

Table 2. Performance, absolute and relative kidney weight of cadmium exposed rabbits administered MEPD

Parameters	Control	Cd	Cd + 300 MEPD	Cd + 600 MEPD	Cd + 900 MEPD	SEM
Initial weight (kg)	1.43	1.42	1.43	1.41	1.42	0.08
Final weight (kg)	1.67	1.53	1.57	1.62	1.62	0.07
Weight gain (kg)	0.23	0.12	0.13	0.18	0.20	0.04
Feed intake (g/day)	89.30	73.00	82.3	85.3	92.0	6.68
Mortality	0.00	1.00	0.33	1.00	0.67	0.42
Kidney (g)	7.60^{b}	8.83^{a}	9.10^{a}	9.23^{a}	8.63^{a}	0.31
Relative kidney weight (expressed as percentage of body weight)						
Kidney	0.46^{b}	0.59^{a}	0.55^{ab}	0.56^{ab}	0.54^{ab}	0.04

^{a,b} Means bearing different letters of superscript within the same row differ significantly (P<0.05).

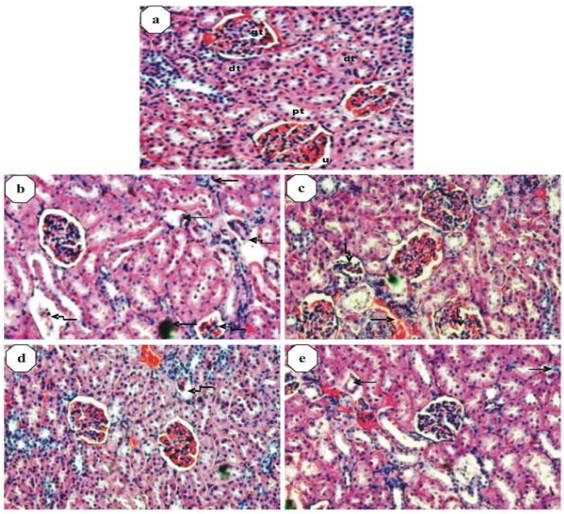

Figure 1. A photomicrograph of the kidney of cadmium exposed rabbits administered MEPD fruit stained with H&E.

(a) Renal tissue of the control group demonstrating normal appearance of glomerular tuft (gt), urinary space (U), Bowman's capsule, proximal tubule (pt), distal tubule (dt) with their nuclei. (b) Renal tissue of Cd-only treated rabbit showing; Disruption of Bowman's capsule, shrinking and degeneration of some glomeruli (elbow arrow), degenerated cytoplasm of some cells of the renal tubules (thin arrow). (c – e): Renal tissues of rabbit treated with Cd+300, 600 and 900 mg/kg MEPD showing. (c) Shrinking and degeneration of some glomeruli (elbow arrow), haemorrhage (thin arrow) (d) shrinking and degeneration of some glomeruli (elbow arrow) (e) degenerated cytoplasm of some cells of the renal tubules (thin arrow).

The results of performance, absolute and relative kidney weight of rabbit bucks in Table 2 revealed that significant ($P<0.05$) differences existed in absolute and relative kidney weight between Cd-only treated and the control rabbit groups. The administration of MEPD did not significantly ($P>0.05$) moderate the higher mean values of absolute and relative kidney weights recorded in the Cd-treated groups.

The result of histopathological study of kidney is presented in Figure 1.

DISCUSSION AND CONCLUSION

The assessment of acute oral toxicity in this study revealed that the MEPD fruit caused neither mortality nor observable health concerns in the test rats, even when given at the highest dose of 3000 mg/kg over the 72-hour monitoring period. The rats exhibited typical behaviour, retained their regular feeding patterns, and showed no variation in the consistency of their droppings compared to the control group.

Results on glucose, electrolyte, urea, creatinine and lipid profile in this study shows that serum levels of fasting blood glucose in the Cd-only treated group was significantly higher ($P<0.05$) when compared to the normal control group. The Cd-MEPD treated groups showed marked reduction in serum blood glucose and the mean values were in agreement with the normal reference value of 122±15 mg/dl reported by Hewitt et al., (1989). The outcome of this study indicates that Cd has the capability to induce hyperglycemia in rabbits, and that the detrimental effect can be mitigated through the use of date extract. Cd is believed to bring about hyperglycemia through various mechanisms. According to Shanbaky et al., (1978), Cd prompts an increase in catecholamine release, indicating an epinephrine-mediated response to carbohydrate metabolism. Epinephrine, in turn, stimulates hepatic glycogenesis and inhibits insulin release (Merali and Singhal, 1980). Additionally, Lei et al., (2007) demonstrated that Cd leads to the destruction of β-cell-rich pancreatic islets, reducing the number of functional β-cells. This supports an earlier study by Bell et al., (1990) documenting Cd-induced atrophy of islets and a decline in insulin secretory activity. Hence, it could be conceived that the increased glucose in this study following cadmium administration might be attributed to reduced insulin levels resulting from the cytotoxic effects on the pancreas caused by cadmium. Nevertheless, the co-administration of date extract after cadmium exposure resulted in a decrease in the mean glucose concentration in the experimental rabbit bucks. This suggests that date extract possesses potential glycermic modulating properties.

Results of serum urea, electrolytes (Na^+, K^+, Cl^-, HCO_3^-) and creatinine were not significantly different ($P>0.05$) and the mean values obtained conformed with the range of normal serum biochemical parameters investigated by Hewitt et al., (1989), Burnett et al., (2006) and Özkan et al., (2012) for healthy rabbits. The higher significant ($P<0.05$) concentrations of urea and creatinine in the Cd-only and Cd-extract treated groups revealed that Cd may have impaired the functional integrity of the kidney of rabbits used in this study.

Although serum lipid panel (Total cholesterol, HDL and LDL) screening in this study showed no significant ($P>0.05$) differences, however, in an attempt to optimize the predictive capacity of lipid profile with greater predictive value than isolated parameters used independently, total cholesterol/HDL cholesterol and LDL/HDL cholesterol ratios as defined by Millan et al., (2009) is here adopted. Hence, individuals with elevated total cholesterol/HDL cholesterol or LDL/HDL cholesterol ratios have an increased cardiovascular risk due to an imbalance between atherogenic and protective lipoproteins (Criqui and Golom, 1998). This imbalance may result from a rise in the atherogenic component in the numerator and a reduction in the anti-atherosclerotic trait of the denominator, or a combination of both. Despite the lipid profile mean values falling within the normal range as reported by Burnett et al., (2006), the observation of the numerical decline in the total cholesterol/HDL and LDL/HDL ratios within the Cd-extract groups, compared to the Cd-only group, suggests that MEPD might have a modulatory effect on cadmium-induced hyperlipidemia in rabbits.

Clinical observations indicated that rabbits exposed to feed contaminated with Cd exhibited a slight reduction in appetite and were docile compared to those in the control group. Within the 7 days of Cd administration, nine (9) cases of mortality were recorded, each preceded by audible gasping indicative of respiratory distress.

The kidney, being a well-perfused organ, eliminates large quantities of toxic substances from the blood through urine. Occasionally, the proximal convoluted tubule of the kidney becomes a target for exposure to toxic substances. Changes in organ weight are commonly linked to treatment-related effects. This study reveals a significant ($P<0.05$) difference in both the absolute and relative mean weight of the kidney. Comparing the results of key kidney function indices (urea and creatinine) with the kidney weight obtained, it suggests potential injury to the renal architecture of rabbits in the Cd-only and Cd+extract treated groups.

Previous research by Zeng et al., (2003) and Amara et al., (2008) had shown a decrease in body weight as a primary sign of $CdCl_2$ administration in rats due to appetite loss. Also, Sajjad, (2014) documented a significant ($P<0.05$) reduction in body weight in male rabbits orally administered with 1.3 mg/kg body weight of $CdCl_2$ for 5 weeks. Similar effects were observed by Sant 'Ana et al., (2005) in Japanese quail exposed to 100 ppm $CdCl_2$ for 28 days. de Souza Predes et al., (2010) noted a temporary reduction in kidney weight after 7 days, which normalized after 56 days post-cadmium administration, suggesting that the initial weight loss in the kidney was a temporary change overcome by the natural defenses of the animal. Contrastingly, Abduljaleel and Shuhaimi-Othman, (2013) found that dietary Cd at concentrations of 5, 25, and 100 ppm did not significantly ($P>0.05$) affect the final body weight of chicks in their study. Haouem and El-Hani, (2013) reported that rats fed 1.1 mg of Cd/g of diet showed body weight gain identical to control rats. Chapatwala et al., (1982) reported a non-significant increase in total kidney weight when exposed to different doses of cadmium for four weeks. Similarly, Dwivedi, (2015) observed no significant ($P>0.05$) effects on heart, kidney, and liver weights in albino rats treated for 30 days with a dose of 2.6 mg/kg.b.wt.$CdCl_2$.

In this study, the administration of Cd to rabbit bucks resulted in nephrotoxicity, particularly evident in glomerular and tubular changes. The observed effects included the shrinking and degeneration of glomeruli, as well as pyknosis and degenerated cytoplasm in certain renal tubule cells. These findings align with the research conducted by El-Refaiy and Eissa, (2013), who noted Cd-induced impact on glomeruli, specifically affecting

glomerular capillaries, favouring Bowman's space, and leading to the atrophy of some glomeruli. Various histopathological studies have consistently shown the toxic effects of Cd on the kidney, including edema (Choi and Rhee, 2003), proximal tubular necrosis, apoptosis, and tubular degeneration (Damek-Poprawa and Sawicka-Kapusta, 2004). The nephrotoxicity induced by Cd in this study may have been mediated through the formation of the cadmium metallothionein (Cd-Mt) complex. This complex, synthesized in the liver, is released into circulation, taken up by renal proximal tubule cells, and, when insufficiently bound by metallothionein, causes injury to hepatocytes and is released into the bloodstream. Subsequently, the complex passes through the glomeruli, reaching the proximal tubule and leading to a gradual loss of kidney function (El-Refaiy and Eissa, 2013). On the other hand, the observed histopathological results may be a direct consequence of the toxic effect of Cd on the kidney. Renugadevi and Prabu, (2009) proposed that histopathological changes contributing to nephrotoxicity may result from the accumulation of free radicals due to increased lipid peroxidation caused by free Cd ions in renal tissues of Cd-treated rats.

Furthermore, the histopathological results in the kidney tissue are consistent with the elevated levels of urea and creatinine (refer to Table 1) detected in rabbits subjected to Cd exposure in this investigation. Although Al-Qarawi et al., (2008) and Hammed, (2015) reported that the administration of date extract can mitigate renal histopathological effects by reducing plasma creatinine and urea concentrations, as well as ameliorating damage to the proximal tubular regions of kidneys; the altered histomophological structures in this study remained unaffected by MEPD treatment.

The current results indicate that short term exposure to Cd could lead to kidney toxicity. There are indications that MEPD holds potential for regulating blood glucose levels, yet, may not offer kidney protection against Cd-induced dysfunction.

Conflict of Interest

The authors declare that they have no competing interests.

Authorship contributions

Research Design: A.A., Data Analysis/interpretation: A.A., Data Collection: A.A., O.A., Literature Search: A.A., O.A., Writing: A.A

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This research received no grant from any funding agency/sector.

Ethical Approval

This experiment was approved and conducted according to the provisions of the Ethical Committee on the use of animals for biomedical research at the University of Benin, Benin City, Nigeria.

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