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Microscopic evaluation of cadmium-induced nephrotoxicity and the protective role of date palm fruit extract

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ABSTRACT

Chronic cadmium exposure is known to be a major health concern due to its nephrotoxic effects. Consequently, this study aimed to assess the potential protective effects of date palm fruit extract (DPFE) against cadmium-induced renal toxicity in male albino rats. A total of 48 rats were divided equally into four groups and subjected to specific treatments. Group I (control given 1 ml distal water orally daily), group II (200 mg DPFE /kg b.wt. orally daily), Group III (5 mg $CdCl_2$/kg b.wt. orally, twice a week), and VI (DPFE and $CdCl_2$). Serum samples were collected after 4 and 8 weeks for biochemical analysis, and kidney tissue specimens were obtained for histopathological examination. The administration of cadmium chloride for 4 and 8 weeks resulted in a significant ($p<0.05$) increase in the serum creatinine, urea, and uric acid levels, indicating kidney dysfunction. Histopathological changes, including vascular lesions, hemorrhage, edema, periglomerular, perivascular and interstitial fibrosis, mononuclear leucocytic cellular infiltration and excessive glomerular and tubular degeneration and necrosis which further confirmed the nephrotoxic effects of cadmium. However, pre-treatment with DPFE exhibited a substantial ameliorative effect against cadmium-induced nephrotoxicity. DPFE supplementation led to a significant reduction in kidney biochemical parameters toward normal levels and improved renal tissue architecture. Our findings indicate that date palm fruit extract has a time-dependant protective effect on kidney function indices and histopathological alterations induced by cadmium, highlighting its potential as a natural medication to mitigate renal damage caused by chronic cadmium exposure.

Introduction

The kidney plays the most important role in the elimination of xenobiotics, including drugs and toxic environmental agents (Reyes *et al*., 2013). However, this crucial function can be compromised by nephrotoxicity, a condition characterized by a rapid deterioration in kidney function caused by the toxic effects of medications, chemicals, and heavy metals (Al-Naimi *et al*., 2019). Understanding the different mechanisms leading to nephrotoxicity is critical, including renal tubular toxicity, inflammation, glomerular damage, crystal nephropathy, and thrombotic microangiopathy (Al-Naimi *et al*., 2019).

Among the various nephrotoxic agents, cadmium (Cd) has emerged as a significant hazard, capable of inducing kidney damage even at low concentrations (Hernández-Cruz *et al*., 2022). Chronic exposure to Cd can result in severe kidney damage, making the kidneys a prime target for Cd accumulation after oral administration (Kim *et al*., 2018). The pathophysiological processes underlying Cd-induced kidney injury are complex and not fully understood (Jayasumana *et al*., 2015). However, apoptosis has been identified as a primary contributor to Cd-induced cell death, underscoring its role in nephrotoxicity (Wang *et al*., 2011).

Interestingly, multiple polyphenols have emerged as potential nephroprotective agents, as they can effectively maintain oxidative homeostasis and activate cytoprotective signaling in vivo (Ashkar *et al*., 2022). Given their antioxidative effects, dietary antioxidants could offer a protective role against Cd toxicity (Dua *et al*., 2015).

Date palm (*Phoenix dactylifera*) is recognized for its numerous health benefits, which can be attributed to its rich content of antioxidant, anti-apoptotic, and anti-inflammatory compounds. The presence of total phenolic content, flavonoids, and essential vitamins such as C, A, E, and β-carotene contributes to its powerful antioxidant effect (El-Far *et al*., 2016). Additionally, date palm possesses a wide range of medicinal properties, including antihyperlipidemic, anticancer, gastroprotective, hepatoprotective, and nephroprotective activities (Tang *et al*., 2013). The antioxidant and anti-inflammatory properties of date palm fruit extract (DPFE) may explain its renoprotective efficacy (Abdeen *et al*., 2021). As a result, DPFE has emerged as a promising alternative therapy for various diseases, offering potential therapeutic benefits (Ahmad Mohd Zain *et al*., 2022). Consequently, this study aimed to explore the ameliorative effects of DPFE in the context of cadmium-induced nephrotoxicity, with the hope of uncovering a promising therapeutic intervention against renal damage caused by Cd exposure.

Materials and methods

Materials

Cadmium chloride ($CdCl_2$) Monohydrate 98% was obtained from LOBA CHEME PVT.LTD, India, while date palm fruits (*Phoenix dactylifera* L.) at the Tamr phase were obtained from Haye*et al* Madina Company, Al Madinah Al Munawara, Saudi Arabia.

Date palm fruit extract preparation

The date palm fruits were subjected to botanical identification and authentication by the Department of Horticulture, Faculty of Agriculture, Benha University. After washing and removing the seeds, the fruits were

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chopped into small pieces. The fully dried date palm powder was then macerated with 70% ethyl-alcohol twice for three days with daily stirring. The resulting alcoholic extract was filtered and evaporated under vacuum until dryness, yielding the hydroalcoholic extract. The dried extract was dissolved in 2% tween 80 in distilled water using a sonicator and stored at 4°C until use (Stephen *et al*., 2018).

Experimental animals and experimental procedures

The experimental animals, with an average weight of 250 grams, were procured from the Nile Pharmaceutical Company, Al-Sawah Street, Al-Amiriya, Cairo, Egypt. The rats were housed in stainless steel wire cages under controlled environmental conditions, maintaining a temperature of 22-23°C and relative humidity of approximately 60%. They followed a 12-hour light-dark cycle and had unrestricted access to standard rat ration and water throughout the entire experiment. The research adhered to ethical guidelines, receiving approval from the Ethical Committee of the Faculty of Veterinary Medicine, Benha University, under ethical approval number BUFVTM 20-10-22.

After an acclimatization period of one week, forty-eight rats were included in the study and randomly divided into four equal groups, each containing 12 rats. Group I (control) received a daily oral gavage of 1ml distilled water as a vehicle. In Group II (DPFE group), rats were given DPFE orally at a dose of 200 mg/kg bw every day (Alhaider *et al*., 2017). Group III ($CdCl_2$) received intragastric administration of $CdCl_2$ at a dose of 5 mg/kg BW, twice a week (Sadek *et al*., 2017). In Group IV (DPFE + $CdCl_2$), rats were treated orally with DPFE (200 mg/kg bw) daily, followed by oral administration of $CdCl_2$ at a dose of 5 mg/kg bw twice a week. Samples were collected after 4 and 8 weeks of treatment. During the experimental period, all rats were monitored daily to assess any clinical signs and mortality rate. This study focused on renal parameters, serum biochemical assays and performed histopathological examinations.

Body and kidney weight assessment

Throughout the study, the body weight of the experimental rats was accurately recorded using an electronic balance. These measurements were taken both at the beginning of the experiment and the end of each treatment period. In addition, at the end of the treatment period, the kidney weight of each animal was measured (Bharathiraja *et al*., 2013).

Serum biochemical assays

To assess the renoprotective effect of DPFE, blood samples were collected from the retro-orbital venous plexus of the eye puncture after 4 and 8 weeks of treatment. Under diethyl ether anesthesia, blood was carefully drawn without anti-coagulants, and the serum was subsequently obtained through centrifugation at 2000 g for 10 minutes. The collected serum samples were then stored at -20°C until further analysis. To evaluate kidney function, serum levels of urea, uric acid, and creatinine were measured using established methods (Coulombe and Favreau, 1963; Caraway, 1955; Larsen, 1972).

Histopathological examination

Kidney specimens were carefully collected from rats in all groups. After collection, the specimens were immediately fixed in 10% neutral buffered formalin. To prepare the tissue for microscopic evaluation, the fixed specimens underwent a precise process involving dehydration in ascending grades of ethyl alcohol, clearing in xylene, and embedding in paraffin wax. Subsequently, 5 µm tissue paraffin sections were skillfully prepared and stained using hematoxylin and eosin (H&E) for general microscopical evaluation of tissue structure and Van Gieson stain for an accurate assessment of renal fibrosis (Bancroft and Layton, 2019a,b). For the quantitative study, five nonoverlapping fields in slides of four selected tissue paraffin sections from each group were evaluated for morphometric determination of the area percentage of the Van Gieson reaction at 400X magnification. The area of positive collagen or elastic fibres was determined and compared to the overall area of the tissue section. The histopathological slides were evaluated using a Nikon Eclipse E800 microscope fitted with a digital camera and analyzed using ImageJ software (ImageJ 1.54g, National Institutes of Health, USA).

Data analysis and statistical evaluation

All collected data were subjected to comprehensive statistical analysis using the Prism GraphPad software version 9.0 (San Diego, California, USA). A one-way analysis of variance (ANOVA) was employed to rigorously compare the groups, and post hoc analysis using the Tukey-Kramer test was conducted for multiple comparisons. The results were expressed as the mean ± SD, and statistical significance was considered at P-values 0.05.

Results

Effect of DPFE on body and kidney weight

There were no significant decreases in the body and kidney weights of rats exposed to $CdCl_2$ treatment for 4 weeks when compared with the corresponding control group and DPFE group. On the other hand, after 8 weeks there was a significant demination in body and kidney weight among this group. Meanwhile, oral administration of DPFE in the Cd-intoxicated group for 8 weeks markedly increased ($p<0.05$) the body and kidney weights compared with those of the cadmium-treated group only (Table 1).

Effect of DPFE on kidney function tests

Figure 1 revealed no significant differences were noticed in the levels of serum urea, uric acid and creatinine of rats administrated DPFE only in comparison to the control group after 4 and 8 weeks. Although high levels of serum urea, uric acid and creatinine were detected in rats intoxicated with cadmium for 4 and 8 weeks. However, after the 4th and 8th week of daily treatment with DPFE in $CdCl_2$ group. There was a marked reduction in these parameters and restored almost to near-normal levels when compared to groups intoxicated with $CdCl_2$ only.

Table 1. The effect of DPFE and $CdCl_2$ on the final body and kidney weights after 4 and 8 weeks of treatment.

	Body weight		Kidney weight	
	4 weeks	8 weeks	4 weeks	8 weeks
Control group	274.8±31.78	314.0±14.67 [a]	1.683± 0.06504	1.989±0.1044 [a]
DPFE group	287.5±11.41	332.5±22.13 [a]	1.792±0.1855	2.051±0.1666 [a]
$CdCl_2$ group	261.3±6.455	268.3±23.26 [c]	1.541±0.01396	1.490±0.1469 [c]
DPFE+$CdCl_2$ group	270.2±7.095	309.8±14.31 [b]	1.623±0.05085	1.890±0.05890 [b]

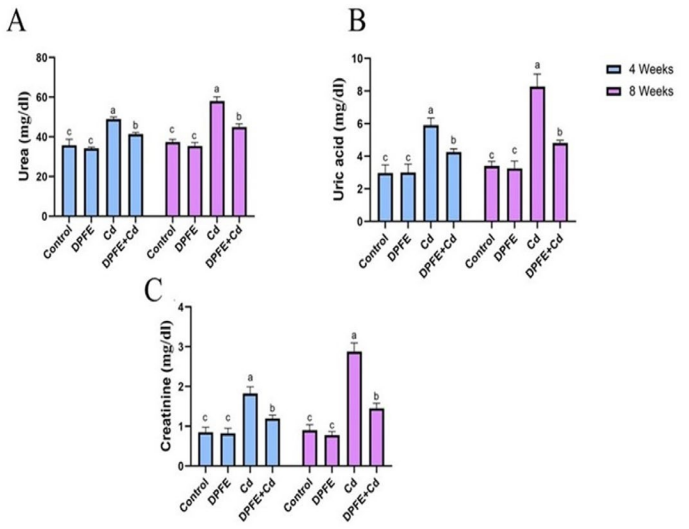

Fig. 1. The levels of urea (A), uric acid (B) and creatinine (C) in serum from Control, DPFE, and DPFE plus Cd groups after 4 and 8 weeks from the experiment. Data are expressed as the mean ± SD. Differences were considered statistically significant at P values < 0.05. a significant change at $p < 0.05$ from the control group. b Significant change at $P < 0.05$ from the $CdCl_2$ group.

Histopathological examination

The tissue sections of the kidneys from the control group and rats treated only with DPFE displayed a normal histological structure in the renal glomeruli and tubules after the 4th (Fig. 2A) and 8th weeks of the study (Fig. 4A).

In contrast, rats exposed to cadmium for four weeks exhibited notable vascular alterations such as congestion, dilation of renal blood vessels and mild endothelial cell proliferation in association with extensive vacuolation of the blood vessel wall with perivascular edema admixed with few leucocytic infiltration (Fig. 2B). Additionally, the glomerular tuft showed significant vacuolation of their endothelial cells and segmentation as well as necrosis and atrophy with a widening of Bowman's space in some glomeruli (Fig. 2C). In most renal tubules marked degenerative changes in the form of cloudy swelling and hydropic degeneration were noticed. Accidentally, necrosis of the lining epithelium of renal tubules with pyknotic nuclei was also observed (Fig. 2D). Interestingly, focal proliferation of the interstitial tissue was also seen (Fig. 2E). Meanwhile, the renal sections from rats that orally received DPFE plus $CdCl_2$ for four weeks showed mild congestion of renal blood vessels and slight vacuolation of their muscular layer with mild perivascular edema. Mild congestion of the glomerular capillaries with mild degeneration and segmentation of the glomerular tuft in association with mild degeneration of the renal tubular epithelium was observed in some examined sections (Fig. 2F).

In control groups, Van Gieson staining of kidney sections revealed thin strands of pink-stained collagen fibers around glomeruli and renal tubules (Fig. 3A). In CdCl2 intoxicated rats after 4 weeks, marked fibrous connective tissue proliferation was confirmed by Van Gieson stain that stained deep pink around the wall of renal blood vessels (Fig. 3B), Bowman's capsules, renal tubules and in the interstitium (Fig. 3C). DPFE co-treatment in the CdCl2- intoxicated group showed attenuation in the severity of fibrous connective tissue proliferation where few periglomerular and peritubular pink stained collagen fiber were detected (Fig. 3D). However, in some examined sections focal tubulointerstial fibrosis was confirmed by Van Gieson stain (Fig. 3E). The morphometric determination of the Van Gieson reaction revealed that the area percentage of Van Gieson-stained collagen fibres was significantly increased in the cadmium intoxicated group compared to the control group. Contrary, in the cadmium DPFE-cotreated group the area percentage of Van Gieson-stained collagen fibres was significantly decreased compared to cadmium intoxicated group (Fig. 3F) After 8 weeks of Cd intoxication, significant histopathological changes were observed in the renal tissue as marked endothelial cell proliferation and vesiculation in the tunica media of renal blood vessels, along with perivascular hemorrhage and fibrosis (Fig. 4B). Additionally, there was hypercellularity in the endothelial lining the glomerular tuft and its adhesion with Bowman's capsule. Marked glomerular tuft shrinkage and widening of the Bowman's capsule with its distention by eosinophilic proteinaceous material (Fig. 4C). Severe thickening of the

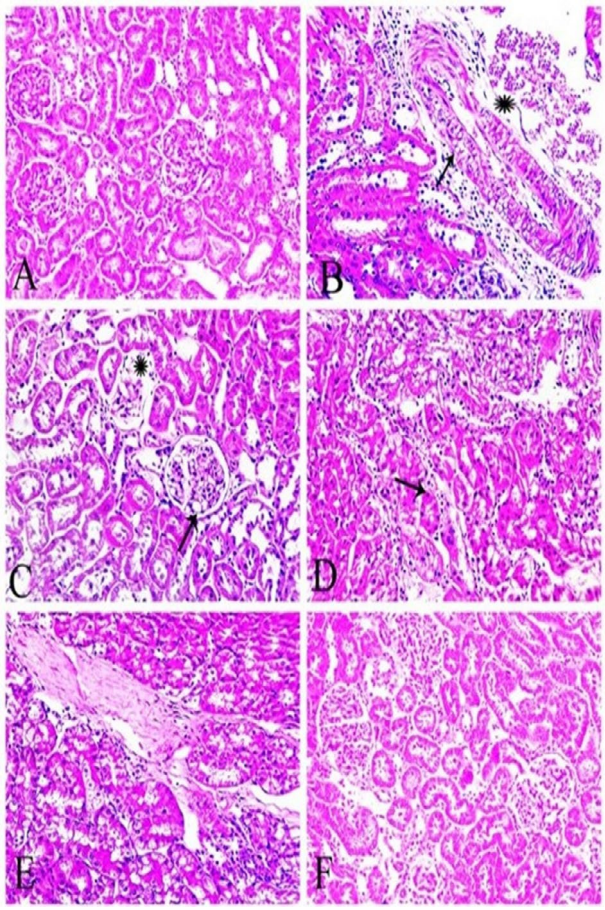

Fig. 2. Photomicrograph of renal tissue stained by H&E obtained from (A) control group revealing normal histomorphology of the kidney tissue. (B-E) $CdCl_2$ intoxicated rats for 4 weeks showing, (B) vesiculation in blood vessel wall (arrow) with perivascular edema (asterisk). (C) segmentation and vacuolation of glomerular tuft (arrow), atrophy of glomerular tuft with widening of Bowman's capsule (asterisk). (D) degeneration and necrosis of the lining epithelium of renal tubules with pyknotic nuclei (arrow). (E) interstitial fibrous connective tissue proliferation. (F) group treated with both DPFE and $CdCl_2$ revealing mild segmentation of glomerular tuft and mild degeneration in renal tubules ×200.

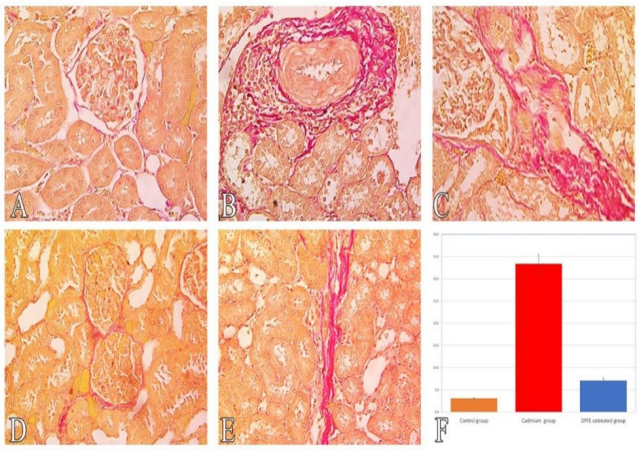

Fig. 3. Representative photomicrographs of Van Gieson-stained kidney sections after 4 weeks. (A) Control group showing thin strands of pink-stained collagen fibres surrounding the glomeruli and renal tubules. (B-C) Cd- intoxicated group showing (B) perivascular, (C) periglomerular and tubulointerstitial thick pink-stained collagen fibres. (D-E) DPFE+Cd group showing (D) a few peritubular and periglomerular pink-stained collagen fibres and (E) strands of pink-stained collagen fibres in the interstitium x200. (F) Mean area % of Van Gieson reaction in the control, cadmium-intoxicated, and DPFE-cotreated groups. Values are means ± S.E. (n = 5).

Bowman's capsule accompanied by hyperplasia and hypertrophy of the epithelial cells lining the Bowman's capsule was observed in some glomeruli (Fig. 4D). Within the renal cortex, extensive areas of degeneration and necrosis of the lining epithelium of renal tubules with their desquamation, in addition to entire fibrosis of some renal tubules were observed with multifocal inter-tubular leucocytic infiltration mainly lymphocytes (Fig. 4E). The majority of the affected renal tubules lumina, particularly the proximal ones, contained cellular cast. Extensive interstitial fibrous connective tissue proliferation admixed with mono leucocytic cellular infiltration was also seen (Fig. 4F). In contrast, rats that received oral DPFE in the $CdCl_2$ intoxicated group for 8 weeks showed a marked reduction in the severity of histopathological alterations induced by cadmium. Mild congestion of glomerular capillaries with mild degeneration in the glomerular tuft and renal tubules were the most common pathological changes detected in this group (Fig. 4G and 4H). Interestingly, mild perivascular and interstitial fibrous connective tissue proliferation was seen in some treated rats. After 8 weeks of CdCl2 intoxication, the Van Gieson stain reaction was more visible than after 4 weeks. The control group showed thin strands of pink-stained collagen fibres surrounding the glomeruli and renal tubules (Fig. 5A). The distinctive pink colour of Van Gieson stain confirmed fibrous connective tissue proliferation surrounding renal blood vessels in the Cd-intoxicated group (Fig. 5B). Thick bands of pink-stained collagen fibres in between renal tubules were frequently observed (Fig. 5C). Furthermore, there was multifocal interstitial fibrosis that stained deep pink with Van Gieson stain (Fig. 5D). Co-treatment with DPFE markedly reduced renal fibrosis induced by Cd intoxication, where only, pink-stained moderate perivascular fibrosis was detected (Fig. 3E). Rarely, pink-stained bands of collagen fiber were seen (Fig. 3F). Moreover, quantitative analysis of the Van Gieson -positive area percentage showed that, there was a significant increase in the percentage of Van Gieson-positive fibrotic areas in the cadmium intoxicated group compared to the control group. While the percentage of Van Gieson-positive fibrotic areas in the cadmium DPFE-cotreated group were significantly reduced compared to the cadmium-intoxicated group (Fig. 3F).

Discussion

Nephrotoxicants, such as cadmium, can induce renal toxicity through various mechanisms, including altered hemodynamics, direct toxic effects on renal cells, inflammation, and crystal nephropathy (Tiong *et al*., 2014). As the kidney plays a crucial role in eliminating xenobiotics and toxic substances, it is critical to counteract cadmium-induced renal toxicity. In this context, the current research aimed to investigate the protective effects of DPFE on $CdCl_2$-induced nephrotoxicity.

In the current research, the impact of $CdCl_2$ on the rat's body weight was assessed after 4 and 8 weeks of treatment. After 4 weeks, there was no significant difference in body weight between the Cd-intoxicated group and the control one, indicating that Cd did not cause retardation in the growth rate. This result aligns with previous findings of Haouem and El Hani (2013) who suggest that the low dose of Cd might not have a pronounced effect on body weight. However, 8 weeks of $CdCl_2$ treatment caused a significant diminution in body weight, possibly attributed to metabolic alterations (Liang *et al*., 2021). Interestingly, DPFE treatment resulted in a significant elevation in body weight in $CdCl_2$-intoxicated rats

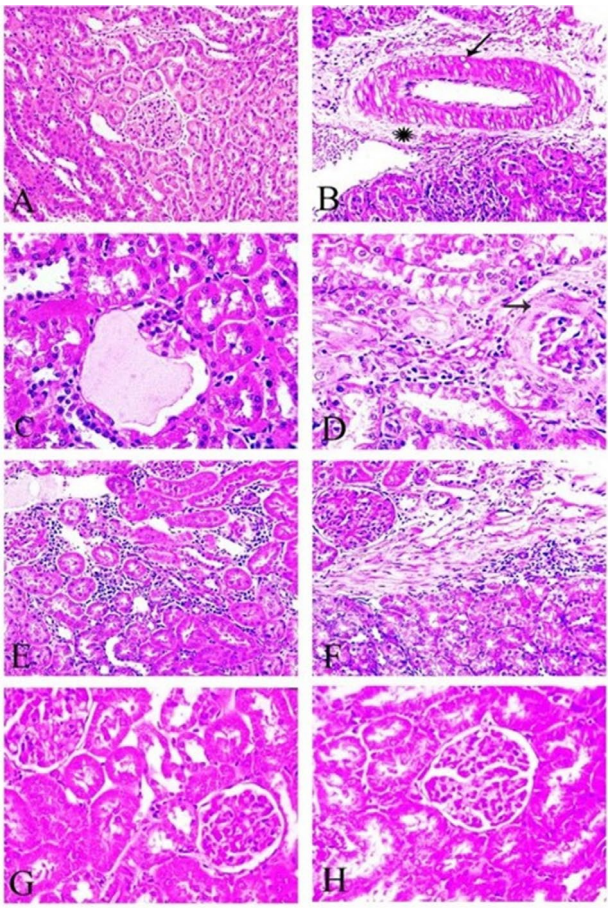

Fig. 4. Photomicrograph of renal sections stained by H&E from different experimental groups. (A) control groups revealing normal histomorphology of both glomeruli and renal tubules. (B-H) $CdCl_2$ intoxicated rats for 8 weeks showing (B) marked vesiculation in the blood vessel wall (arrow) with perivascular fibrosis (asterisk). (C) marked glomerular tuft shrinkage with eosinophilic pretentious material in thickened Bowman's capsule. (D) severe thickening and fibrosis in Bowman's capsule (arrow) with massive degeneration and necrosis of renal tubular epithelium and complete fibrosis in some renal tubules. (E) inter tubular mono leucocytic cellular infiltration. (F) diffuse interstitial fibrous connective tissue proliferation with lymphocytic infiltration. (G and H) treated with both DPFE and $CdCl_2$ showing mild congestion and segmentation of glomerular tuft and mild degeneration in renal tubules ×200.

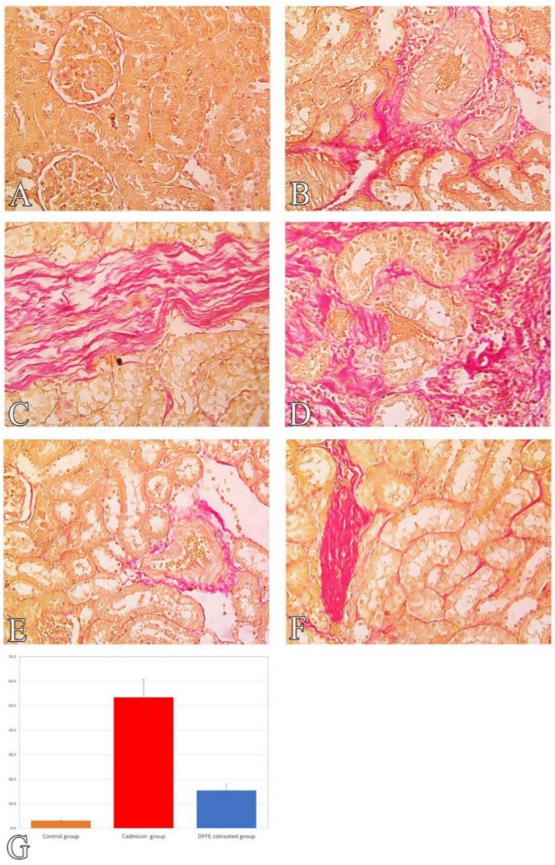

Fig. 5. Representative photomicrographs of Van Gieson-stained kidney sections after 8 weeks. (A) Control group showing thin strands of pink-stained collagen fibers around glomeruli and renal tubules. (B-D) CdCl2-intoxicated group showing (B) pink-stained perivascular fibrosis, (C) a thick band of pink-stained collagen fibers in-between renal tubules and (D) tubulointerstitial fibrosis. (E-F) DPFE+Cd group showing (E) a few pink-stained collagen fibers surrounding blood vessels, and (F) pink stained band of collagen fiber in the interstitium x200. (G) Mean area % of Van Gieson reaction in the control, cadmium-intoxicated, and DPFE-cotreated groups. Values are means ± S.E. (n = 5).

which contributed to its involvement in metabolic improvement and implications on body weight improvement.

The relative weight of the kidneys is another vital indicator of Cd-induced nephrotoxicity. Previous studies have reported conflicting results, as some studies showed atrophy of the kidney and others recorded organ enlargement (Haouem and El Hani, 2013). Meanwhile, in the current study, Cd intoxication for 4 weeks did not affect the relative weights of the kidneys, possibly due to the Cd concentration not being sufficient to produce a significant change in organ weight. This finding is consistent with the result of Satarug (2018). However, a marked reduction in the relative weights of the kidneys was observed after 8 weeks indicating renal damage. Lower body and kidney weights following Cd exposure imply severe renal impairment (Fang *et al*., 2021). These changes observed in Cd-intoxicated rats were attenuated with DPFE treatment.

In the present study, renal biomarkers for nephrotoxicity were evaluated by measuring urea, uric acid, and creatinine levels, which were found to be elevated in Cd-treated rats compared to the control group. These elevations refer to the ability of Cd to damage glomerular mesangial cells and alter the glomerular capillary network resulting in impairing glomerular ultrafiltration capacity (Chen *et al*., 2016) and consequently, a significant increase in urea, uric acid and creatinine levels was induced (Deevika *et al*., 2012). However, in the DPFE and $CdCl_2$ group, renal function showed significant improvement, indicating the renoprotective effects of DPFE. The reduction in serum creatinine and urea levels in the DPFE-treated group is in line with the DPFE protective effects as demonstrated in the work of Rahmani *et al*. (2014). Furthermore, El Arem *et al*. (2014) demonstrated that oral administration of DPFE ameliorated growth performance parameters and plasmatic renal biomarkers.

Regarding the structural damage of the renal tissue caused by cadmium, in this study, the kidney tissue of rats intoxicated with cadmium for both 4 and 8 weeks revealed severe vascular changes as the vascular endothelium is a target for Cd toxicity, which leads to impaired endothelial function (Almenara *et al*., 2023) and could precipitate in vasculopathy (Mulher *et al*., 2023). Moreover, marked glomerular and tubular degeneration and necrosis besides perivascular, periglomerular and interstitial fibrosis which was further confirmed by van Gieson stain, were consistent with the studies of Renugadevi and Prabu (2010); Nazima *et al*. (2015); Ehimigbai and Nwosu (2022) who reported congestion of renal blood vessels, thickening of glomerular basement membrane and glomeruli degeneration, interstitial inflammation, tubular necrosis and atrophy with luminal cast formation post-$CdCl_2$ administration for 4 weeks. Meanwhile, extreme damage to the glomeruli and dilatation of Bowman's capsule with massive congestion of the veins, perivascular fibrosis and focal interstitial fibrosis with few mononuclear leucocytic infiltration were recorded by Sadek *et al*. (2017); Saleh and Awadin (2017). The present study showed extensive perivascular and interstitial leucocytic cellular infiltration. Inflammation is a risk factor for renal fibrosis (Lawson *et al*., 2015). This finding was confirmed by the results of Hassanein *et al*., (2022) who described that Cd-nephropathy is mainly associated with inflammation. In the meantime, the renal histopathological alterations induced by Cd could be attributed to the fact that cadmium poses a long half-life of more than 10 years, making it challenging to excrete from the body and the kidney is more susceptible to its toxic effects as it holds 50% of the total body of Cd. Additionally, after entering the body, Cd binds to metallothioneins and is cleared through the glomeruli and then reabsorbed by the tubules, leading to the constant release of highly toxic-free Cd. Consequently, degeneration of the renal tissue and impairment of the renal function was induced (Pizzorno, 2015).

Interestingly, examined kidney sections of rats in cadmium-intoxicated rats co-treated with DPEF after 4 and 8 weeks revealed a significant attenuation of the renal degeneration, necrosis, inflammation and fibrosis indicating the renoprotective effect of date palm fruit extract against Cd-induced nephrotoxicity. The potent anti-inflammatory properties of DPFE are related to the gallic, ferulic and caffeic acids (El Hilaly et al., 2018). This protective effect also could be attributed to the ability of DPFE to mitigate oxidative stress and cellular damage in rat kidneys by preventing excessive lipid peroxidation and renal antioxidant enzyme activities (Saafi-Ben Salah et al., 2012). The total phenolic and flavonoid content accounts for the DPFE and its antioxidant activities were evaluated in our previous research (Badawy et al., 2023). Moreover, DPFE markedly reduced the perivascular, periglomerular and interstitial fibrosis in cadmium intoxicated group. The antifibrotic mechanism of DPFE is mainly due to its ability to induce collagen degradation via lowering the expression of α-smooth muscle actin (Attia et al., 2016; Al Alawi et al., 2017). In addition, DPFE pretreatment with Cd in rats resulted in significant improvement in renal function and restoration of biochemical markers with significant improvement in histopathological alteration induced by cadmium (Ehimigbai and Nwosu, 2022). Interestingly, the renoprotective effect of DPFE was in a time-response pattern (Abdeen et al., 2021).

Conclusion

This study provides strong evidence that oral administration of cadmium for 4 and 8 weeks induces severe nephrotoxicity. However, the oral administration of DPFE demonstrates a time-dependent beneficial effect in preventing experimental nephrotoxicity induced by cadmium as DPFE administration was associated with improvements in kidney function and histological alterations. The findings support the potential use of DPFE as a natural therapeutic agent against cadmium-induced renal damage. Further investigations are needed to elucidate the underlying mechanisms of DPFE's protective effects and explore its potential clinical applications.

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Conflict of interest

The authors declare that they have no conflict of interest.

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