

ORIGINAL ARTICLE

Protective effect of avenanthramides against cisplatin induced nephrotoxicity in rats

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ABSTRACT

Objective: The aim of this study is to inspect the ameliorative effect of avenanthramides (AVA) on CP nephrotoxicity in Sprague-Dawley rats.

Materials and Methods: Blood samples were collected for the determination of hematological parameters. Creatinine, blood urea nitrogen (BUN), and tumor necrosis factor- α (TNF- α) were measured in serum. Specimens from both kidneys were taken for histopathological examinations.

Results: Administration of AVA resulted in significant decrease in the level of creatinine and TNF- α when compared with CP group. Histopathologically, CP-induced vacuolar degeneration and necrosis of the kidney tubules. Administration of AVA ameliorates the histopathological alterations induced by CP.

Conclusion: AVA can be considered as a protective agent for kidneys during administration of CP. The protective effect of AVA may be related to the reduction of TNF- α which implicated in the pathogenesis of CP nephrotoxicity.

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Introduction

Cisplatin (CP) is an anti-tumor drug used as chemotherapy [1]. It is effective against various types of cancers. CP-induced nephrotoxicity, hepatotoxicity, ototoxicity, hypersensitivity, gastrointestinal tract toxicity, ocular toxicity, and cardiotoxicity [2–7]. Kidney injury with increased risk of renal failure was demonstrated in many studies [8,9]. Morphologically, administration of CP-induced degeneration of renal tubules, vacuolization, and hyaline cast formation [10,11]. Acute kidney injury develop in 25%–30% of patients following single injection of CP [12]. The damage in renal tubular epithelium was associated with elevation in serum creatinine and blood urea nitrogen (BUN) levels with proteinuria, glucosuria, and phosphaturia [13].

CP forms covalent adduct with purine DNA bases [14]. It accumulates in kidney more than other organs. CP concentration in the renal tubular epithelium is about

five times the concentration in the serum [15]. It was demonstrated that CP increased lipid peroxidation and decreased the antioxidant enzymes [13]. It was also found that tumor necrosis factor- α (TNF- α) is responsible for CP nephrotoxicity [16].

Avena sativa in Latin means “wild oats”. *Avena sativa* contains vitamins, minerals, essential fatty acids, fibers, phytochemicals, and avenanthramides (AVAs) [17]. AVAs are a group of phenolic alkaloids [18]. It is known that AVAs have both antioxidant and anti-inflammatory effects [19]. Treatment of cells with AVA-induced inhibition of TNF- α and a decrease of interleukin-8 (IL-8) [20]. Hassanein and El-Amir [21] found that AVAs significantly decreased DNA damage. AVAs can also decrease the oxidative stress and improve the histopathological changes induced by CP in testes [22]. This study was performed to investigate the ameliorative effect of AVA on CP nephrotoxicity in rats.

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Materials and Methods

Ethical approval

All experimental procedures were ethically approved by Standing Committee for Scientific Research Ethics, Jazan University, Jazan, KSA (REC40/1-045).

Experimental animals

Twenty male adult Sprague Dawley rats (200–250 gm) were purchased from animal house, Medical Research Center, Jazan University, KSA.

Chemicals

CP (0.5 mg/ml) was obtained from EBEWE Pharma GmbH. Nfg. KG, A-4866 Unterach, Australia. The AVA-enriched extract of oats was obtained from Shannix, China.

Experimental design

Twenty adult male Sprague Dawley were divided randomly and equally into four groups with five rats in each group (Fig. 1). The first group is used as control group, rats administered 1% saline daily by oral gavage for one week followed by injection of saline. The second group (CP group) was received intraperitoneal injection of CP (7 mg/kg b.wt.). The third group (CP+AVA group) was administered AVA (20 mg/kg b.wt.) daily for one week followed by injection of CP (7 mg/kg b.wt.). The fourth group (AVA group) was administered only AVA (20 mg/kg b.wt.) daily for the whole experimental period. After 72 h of CP inoculation, the body weights of all rats were measured, and then they were euthanized by anesthesia. Blood samples were

collected from the descending aorta. The relative weight of kidneys was evaluated using the following formula:

$$\text{Relative weight of kidneys} = \frac{\text{Weight of kidneys (gm)}}{\text{weight of the body (gm)}} \times 100$$

Hematological parameters

Blood samples with anticoagulant were collected for the estimation of erythrocyte count, hemoglobin level, platelets count, and total and differential leucocytic count by Full Auto Hematology Analyzer device.

Measurement of serum creatinine and BUN

Blood samples without anticoagulant were centrifuged at 2,000 rpm for 10 min for serum separation. The levels of BUN and creatinine were estimated using fully automated chemistry analyzer (Humastar 200, Human GmbH, Max-Planck-Ring 2, 65205 Wiesbaden, Germany).

Estimation of serum TNF- α

The levels of TNF- α were estimated using vitrog enzyme-linked immunosorbent assay kits (catalog number KRC3014; Invitrogen, Carlsbad, CA).

Histopathological technique

Kidney specimens were fixed in neutral buffered formalin, followed by dehydration, clearing, and paraffin impregnation. The paraffin blocks were sectioned at 5 μm and then were stained with hematoxyline and eosin (H&E) according to Bancroft et al. [23].

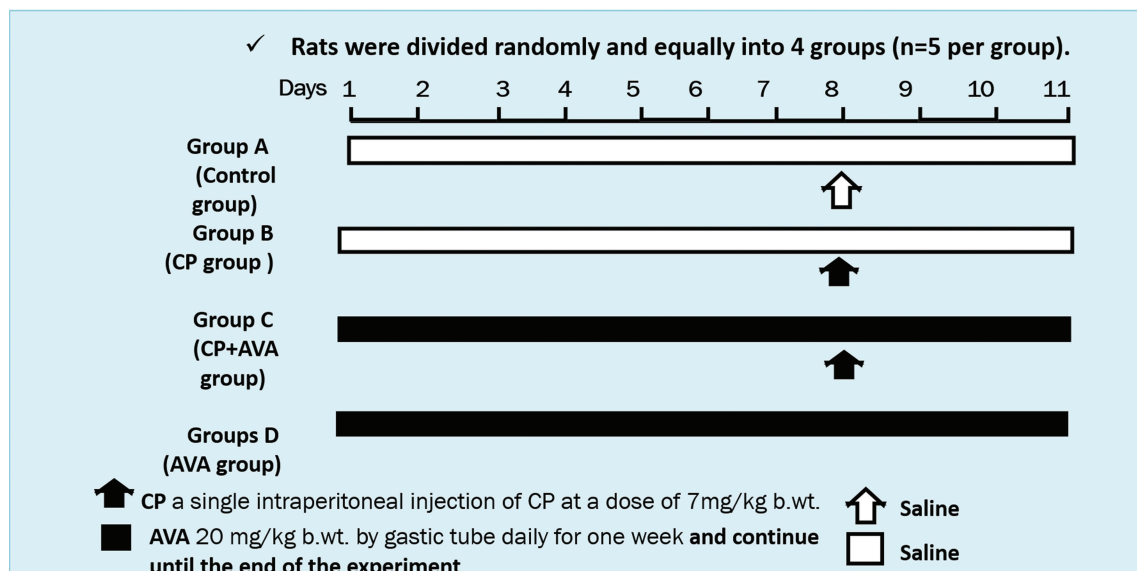


Figure 1. Summary of the experimental design.

Statistical analysis

Data were expressed as the mean \pm SE. The analysis of data was done using program of GraphPad Prism data analysis. A one-way analysis of variance test was done, followed by post hoc Tukey's multiple comparison test. $p < 0.05$ was considered as statistically significant.

Results

Effect on body weight, kidney weight, and relative weight of kidneys

No significant effect on body weight and kidney weight was observed in groups that received CP or AVA compared to control animals. There was a significant increase in the relative weight of kidneys in the CP group and CP + AVA group comparing with the control group (Table 1).

Effect on serum level of creatinine, BUN, and TNF- α

CP induced a significant increase in serum level of creatinine and TNF- α in CP and CP+AVA when compared to control groups. AVA administration resulted in a significant decrease in the level of creatinine and TNF- α when compared with the CP group. No significant effect of CP on the level of BUN was observed when compared to the control group (Table 2).

Effect on blood parameter

The effect of CP on the blood parameter was presented in Table 3. Administration of CP significantly decreased

Table 1. Effect of CP and AVA treatment on body weight, kidney weight, and relative weight of kidney of rats.

Relative weight of kidneys (%)	Kidney weight (gm)	Body weight (gm)	Groups
0.39 \pm 0.017	0.92 \pm 0.06	234.6 \pm 8.26	Control group
0.83 \pm 0.05 ^a	0.98 \pm 0.07	229.6 \pm 5.92	CP group
0.85 \pm 0.046 ^a	0.97 \pm 0.06	225.8 \pm 3.14	CP + AVA group
0.45 \pm 0.028	1.03 \pm 0.07	217.6 \pm 5.45	AVA

Values are presented as mean \pm SE.

^aStatistical significance when compared with the control group ($p < 0.05$).

Table 2. Effect of CP and AVA treatment on creatinine, BUN, and TNF- α .

Groups	Creatinine (mg/dl)	BUN (mg/dl)	TNF- α (pg/ml)
Control group	0.36 \pm 0.02	50.3 \pm 0.0.3	74.60 \pm 1.72
CP group	1.69 \pm 0.35 ^a	51.2 \pm 0.5	256.67 \pm 8.82 ^a
CP+AVA group	0.76 \pm 0.064 ^{a,b}	50.1 \pm 0.4	166.6 \pm 12.01 ^{a,b}
AVA group	0.33 \pm 0.01	47.8 \pm 1.6	77.83 \pm 1.36

Values are presented as mean \pm SE.

^aStatistical significance when compared with the control group ($p < 0.05$).

^bIndicates statistical significance when compared with the CP group ($p < 0.05$).

the number of white blood cells (WBCs), lymphocytes, and granulocytes when compared to the control group. However, AVA could not reverse the effect of CP on these parameters.

Histopathological results

Lesions score was summarized in Table 4. The lesions were in the form of congestion, hemorrhage, edema, vacuolation of renal tubular epithelium, coagulative necrosis, and hyaline casts formation. These changes were prominent in the CP group. All these changes were reduced in the CP+AVA group. Examination of the control kidney revealed normal renal corpuscles and renal tubules (Fig. 2A). Administration of CP-induced vascular and cellular alterations in kidneys. The vascular changes were in the form of congestion and hemorrhage (Fig. 2B–C). The cellular changes the alteration manifested by vacuolar degeneration and coagulative necrosis of the renal tubular epithelium. The coagulative necrosis characterized by increased eosinophilia of cytoplasm and pyknosis of the nucleus (Fig. 2D). Some renal tubules contain only cellular debris (Fig. 2E). Hyaline casts were also constant manifestations (Fig. 2F). Administration of AVA reduced the histopathological change, and the changes were in the form of

Table 3. Effect of CP and AVA treatment on body weight, kidney weight, and relative weight of kidney (in gm) of rats.

Blood parameters	Control group	CP group	CP + AVA group	AVA
WBCs ($10^9/l$)	11.76 \pm 0.02	2.37 \pm 0.4 ^a	2.65 \pm 0.4 ^a	11.06 \pm 0.3
Lymphocytes ($10^9/l$)	8.2 \pm 0.3	1.6 \pm 0.9 ^a	1.1 \pm 0.2 ^a	7.6 \pm 0.16
Granulocyte ($10^9/l$)	2.37 \pm 0.05	0.4 \pm 0.02 ^a	0.69 \pm 0.28 ^a	2.1 \pm 0.2
RBCs ($10^{12}/l$)	8.19 \pm 0.3	6.4 \pm 1.3	7.45 \pm 0.15	7.7 \pm 0.1
Hb (g/dl)	17.3 \pm 0.04	13.9 \pm 2.0	14.4 \pm 0.27	17.2 \pm 0.19
PLT ($10^9/l$)	434 \pm 18.0	191.5 \pm 67.5	291.7 \pm 88.47	394.5 \pm 28.5

Values are presented as mean \pm SE.

^aStatistical significance when compared with the control group ($p < 0.05$).

WBCs = white blood cells; RBC = red blood cells; HB = hemoglobin, PLT = platelets.

Table 4. Summary of lesions score.

Lesions	Control group	CP group	CP+AVA group	AVA group
Vascular changes:				
Congestion	–	+++	+	–
Hemorrhage	–	+++	+	–
Edema		++	++	
Vacuolation of renal tubular epithelium	–	+++	+	–
Coagulative necrosis	–	+++	+	–
Hyaline casts	–	+++	+	–

– (0 rat), + (1–2 rats), ++ (3–4 rats), +++ (5 rats)

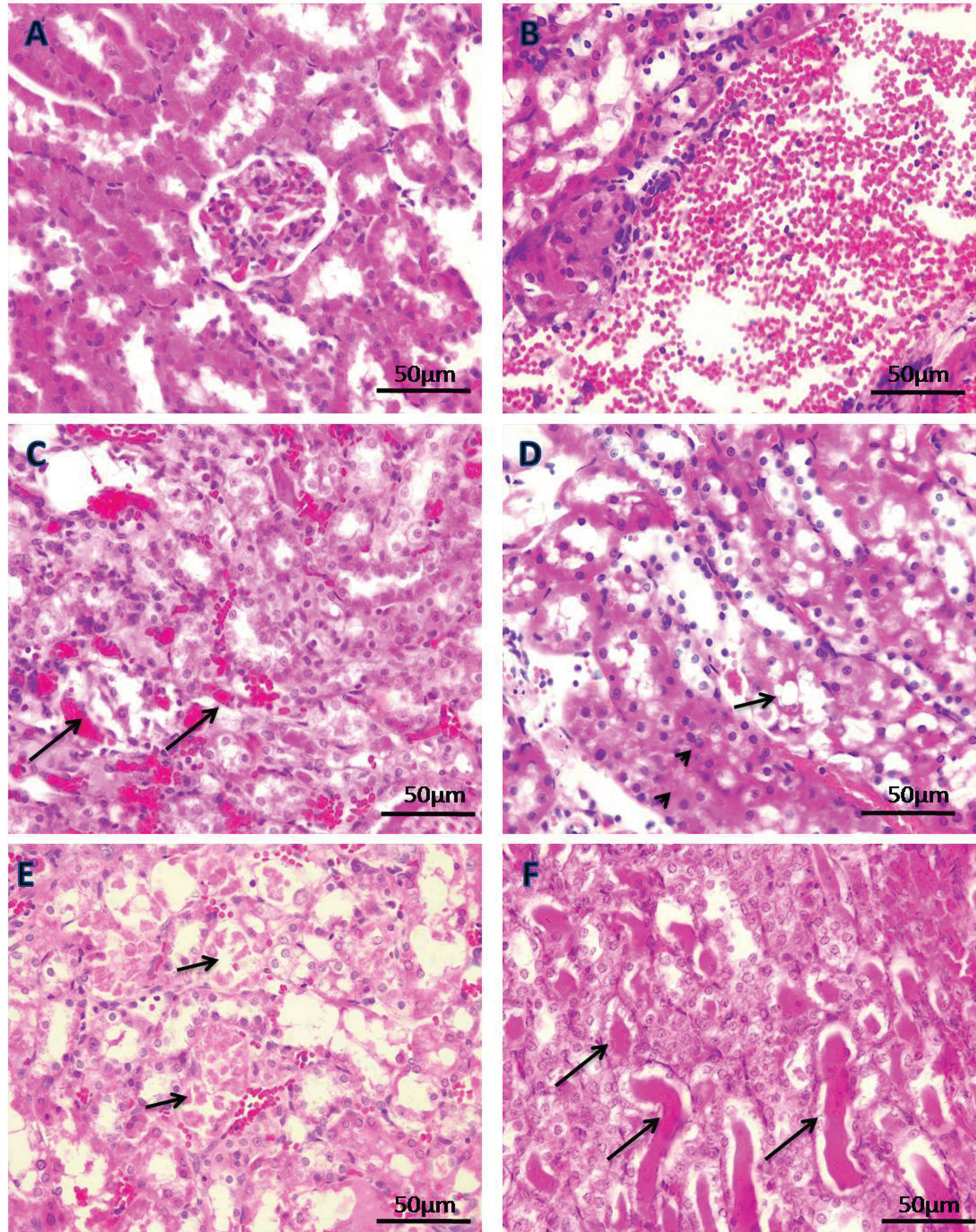


Figure 2. Kidneys of control and CP groups. (A) Control kidney showing normal renal corpuscles and renal tubules. (B)–(F) CP treated group B Congestion C Hemorrhage (arrows). (D) Vacuolation of renal tubular epithelium (arrow) and coagulative necrosis of epithelium in which there is increased eosinophilia of cytoplasm and pyknosis of nucleus (arrow heads). (E) Necrosis of renal tubules with debris in the lumen (arrows). (F) Hyaline casts (arrows). Hematoxylin and Eosin (H&E) stain.

vacuolar degeneration of some renal tubular epithelium (Fig. 3A). No histopathological lesion can be detected in the AVA-treated group (Fig. 3B).

Discussion

CP is useful in the treatment of many neoplasms, but it induced many side effects including nephrotoxicity. In this

study, CP increased relative kidney weight. The increase in relative kidney weight referred to the damage of kidneys in CP-treated rats. CP induced severe histopathological alterations in kidneys, including congestion, hemorrhage, coagulative necrosis, and hyaline casts formation. These results were in agreement with the previous investigations [24,25]. The administration of CP also increased the level of blood creatinine. It is well known that CP accumulated in renal

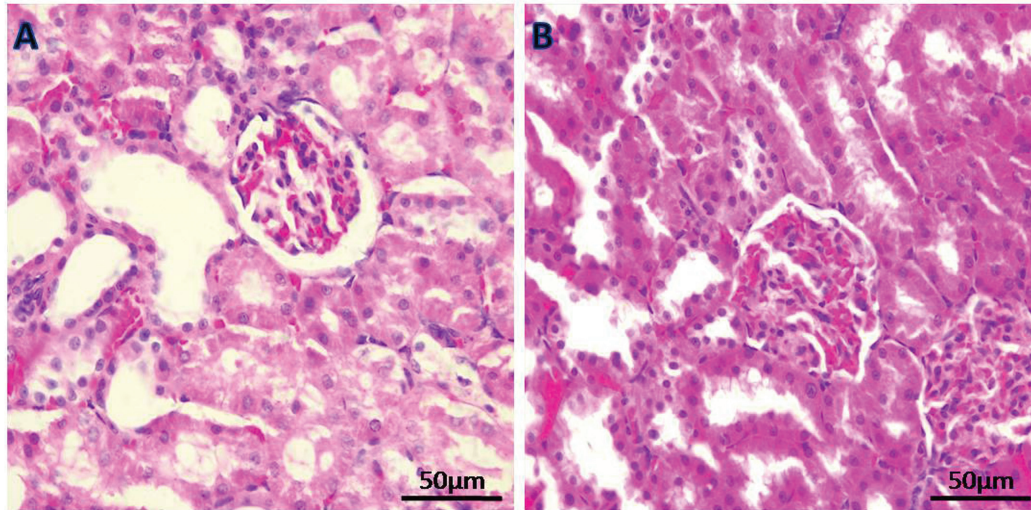


Figure 3. Kidneys of CP + AVA and AVA treated groups. (A) CP + AVA group. Vacuolation of some renal tubules and necrotic changes in renal tubular epithelium. (B) AVA group. Normal kidney architecture. Hematoxylin and Eosin (H&E) stain.

parenchymal cells increases the concentration of CP in the kidney than that in the blood [26]. The extensive renal damage leads to the failure of creatinine clearance resulting in the accumulation of creatinine in the blood [27].

It was suggested that the inflammatory mechanisms may be involved in CP nephrotoxicity. CP administration resulted in an increased level of TNF- α when compared to the control group. This is in agreement with the previous investigations [28–30]. Ma et al. [11] found that the administration of CP produced a significant increase in TNF- α and IL-6. TNF- α stimulates cytokine expression in the kidney [31]. TNF- α directly induced necrosis of the renal tubular epithelium through TNF receptor type 1 [32]. It was also found that mice deficient TNF- α were not susceptible to CP nephrotoxicity and also treatment with TNF- α inhibitor ameliorate CP-induced renal damage [33]. Sanchez-Gonzalez et al. [34] concluded that Reactive Oxygen Species (ROS) induced by CP activated the transcript factor NF- κ B, which induced the release of TNF- α .

In this study, CP administration significantly decreased the number of WBCs, lymphocytes, and granulocytes. These results were in agreement with previous investigations [35]. It was found that CP-induced depression of bone marrow [36].

Recently, Oats (*Avena sativa* L.) are concerned about their health benefits [37]. AVA is a nitrogen-containing phenolic compound found in oats. It has antioxidative and anti-inflammatory effects [21]. In this study, AVA attenuated the histopathological alterations in kidneys and significantly decreased the level of blood creatinine and TNF- α when compared to the CP group. A previous investigation found that treatment of cells with AVA induced

a significant inhibition of TNF- α and a decrease of interleukin-8 (IL-8) [20]. A recent study also found that AVA reduced the level of TNF- α in rats treated with titanium dioxide nanoparticles (TiO₂ NPs) [21]. The inhibition of TNF- α improved CP-induced renal damage [28,31]. The inhibition of inflammation induced by CP could be due to its inhibitory effect on the toll-like receptor 4/NF- κ B signaling pathway [11]. These observations suggest that the ameliorating effect of AVA may be due to the reduction of TNF- α which implicated in the pathogenesis of CP nephrotoxicity.

Conclusion

This study demonstrated the histopathological changes in kidneys induced by CP. AVAs improved the alterations of the kidneys induced by CP. AVAs can be considered as a protecting agent for kidneys during CP administration. The ameliorating effect of AVA may be due to the reduction of TNF- α which implicated in the pathogenesis of CP nephrotoxicity.

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Conflict of interest

The authors declare that they have no conflict of interest.

Authors' contribution

This study was accomplished in participation between all authors. Yasmin O. El Amir designed the study. Amani Y. Khabrani, Amani E. Jahfali, Shahd M. Alhakami, Nada M. Dobab conducted the experiment, collected the samples and analyzed the hematological and biochemical parameters. Wisam Omar prepared the histopathological sections. Yasmin O. El Amir examined the histopathological sections and wrote the article. The manuscript was approved by the authors.

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