



Research Paper

Nephroprotective Effects of Fisetin and Coenzyme Q10 Against Cyclophosphamide-Induced Renal Injury in Rats

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ABSTRACT

Background: This study investigated the potential protective effects of fisetin and coenzyme Q10 (CoQ10), administered individually or in combination, against cyclophosphamide (CP)-associated renal injury in rats.

Methods: Forty rats were allocated into five groups: Group 1 received the corresponding vehicles (1% DMSO and 0.5 mL of corn oil) and intraperitoneal (IP) normal saline; Group 2 received the corresponding vehicles plus CP via a single IP injection at 150 mg/kg; Group 3 received CoQ10 (100 mg/kg) dissolved in corn oil, together with 1% DMSO as a separate vehicle, and CP. Group 4 received fisetin (20 mg/kg) prepared in 1% DMSO/glycerin, together with corn oil administered separately as a vehicle, and CP. Group 5 received CoQ10 (100 mg/kg), fisetin (20 mg/kg), and CP. Treatments were administered orally once daily for 21 consecutive days. On day 17, the designated oral treatment was administered before a single IP injection of CP (150 mg/kg), and oral treatments were continued daily for the remaining four days (days 18–21).

Results: Exposure to a toxic dose of CP significantly increased serum β 2-microglobulin levels (ng/mL). Caspase-3 (ng/mL) and urea (mg/dL) levels increased, whereas creatinine (mg/dL)

levels did not change significantly; TAC (U/mL) significantly decreased; and histopathological alterations occurred. Treatment with CoQ10 or fisetin alone improved several biochemical parameters and histopathological alterations, whereas the combination provided less protection than either individual treatment.

Conclusion: CoQ10 and fisetin individually showed nephroprotective effects against CP-induced renal injury, whereas their combination provided less protection under the conditions tested.

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Introduction

Nephrotoxicity refers to kidney injury or impaired renal function resulting from exposure to drugs or toxic chemicals [1]. Cyclophosphamide (CP) is an established cytotoxic chemotherapeutic drug. Following administration, CP undergoes extensive hepatic biotransformation, primarily mediated by cytochrome P450 enzymes, generating several active and inactive metabolites. Through this metabolic activation, CP is converted to its active metabolite, 4-hydroxycyclophosphamide (4-OHCP). This subsequently produces phosphoramidate mustard and acrolein. Acrolein can promote the generation of reactive oxygen species (ROS) and nitric oxide (NO), thereby contributing to oxidative stress, cellular injury, and tissue damage [2].

Coenzyme Q10 (CoQ10) is a naturally occurring, vitamin-like compound characterized by antioxidant, anti-inflammatory, and anti-apoptotic effects. It modulates reactive oxygen species (ROS) production. The benzoquinone structure of CoQ10 facilitates its involvement in mitochondrial respiratory chain electron transfer, which in turn supports ATP generation and normal cellular energy metabolism [3].

Fisetin is a naturally derived flavonoid associated with pronounced antioxidant, anti-inflammatory, and anti-apoptotic effects [4]. Fisetin's antioxidant activity is associated with its ability to scavenge reactive oxygen species (ROS) and enhance endogenous antioxidant defense mechanisms, as reported in previous studies [5]. Moreover, its anti-apoptotic activity has been linked to suppression of caspase-3 and Bax expression, accompanied by an increase in Bcl-2 expression [5]. To evaluate the nephroprotective effects of fisetin and CoQ10, alone or in combination, against cyclophosphamide-induced renal injury in rats.

Materials and Methods

Experimental Animals

Male Wistar albino rats weighing 180–220 g and aged 2–3 months were used. All experimental procedures were conducted at the College of Pharmacy, University of Basrah, Basrah, Iraq. The experiment was conducted in accordance with the approved study protocol (Approval No. EC 88; ethical approval was obtained on 7 October 2025). The room temperature was maintained at $20 \pm 5^{\circ}\text{C}$, with relative humidity maintained at 40–70% and a 12-h light/12-h dark cycle. Wood shavings were provided as bedding. Animals had unrestricted access to standard pellet feed and tap water

throughout the experimental period. Animals were monitored daily, and a two-week acclimatization period was allowed before the experimental procedures began.

Preparation of drugs

A fresh fisetin solution was prepared daily. Briefly, 250 mg of fisetin was dissolved in 0.4 mL of dimethyl sulfoxide (DMSO) and subsequently diluted with glycerin to a final volume of 40 mL. The resulting preparation contained fisetin at a concentration of 6.25 mg/mL in 1% DMSO [2]. The preparation was administered orally by gavage at 20 mg/kg, with the administration volume individually adjusted according to each animal's body weight. Groups not receiving fisetin received the corresponding vehicle (1% DMSO in glycerin) separately.

Coenzyme Q10 (CoQ10) was freshly prepared each day by dissolving the contents of two 200 mg soft gelatin capsules (400 mg total) in 5 mL of corn oil, yielding a final concentration of 80 mg/mL [6]. A 20 mg/mL CP solution was prepared by reconstituting a 500-mg vial with 25 mL of normal saline [7]. The preparation was administered orally by gavage at 100 mg/kg, with the administration volume individually adjusted according to each animal's body weight. Groups not receiving CoQ10 received the corresponding vehicle (corn oil) separately.

Experimental Design

Forty male rats were allocated to five experimental groups ($n = 8$ per group) based on body weight, with each group comprising animals weighing 180–220 g. Each group included eight animals to account for potential animal loss or mortality during the experimental period. No mortality occurred during the study; therefore, all animals completed the experimental protocol and were included in the statistical analysis. Group 1 (control): The control animals received 1% DMSO and 0.5 mL of corn oil orally each day throughout the 21-day experimental period. On day 17, normal saline was administered intraperitoneally. Group 2 (CP-treated): Animals in this group received 1% DMSO and 0.5 mL corn oil orally once daily for 21 days. On day 17, CP was administered intraperitoneally at 150 mg/kg [8]. Group 3 (CoQ10 + CP): CoQ10 was administered orally in corn oil at 100 mg/kg once daily for 21 days, and 1% DMSO/glycerin was administered separately as the vehicle. [9]. On day 17, CP was administered intraperitoneally at 150 mg/kg. Group 4 (fisetin + CP): Fisetin was administered orally at 20 mg/kg in 1% DMSO/glycerin once daily for 21 days, and corn oil was administered separately as the vehicle [4]. On day 17, CP was

administered intraperitoneally at 150 mg/kg. Group 5 (fisetin + CoQ10 + CP): Animals received fisetin (20 mg/kg, prepared in 1% DMSO/glycerin) and CoQ10 (100 mg/kg, prepared in corn oil) orally once daily for 21 days. On day 17, CP was administered intraperitoneally at 150 mg/kg.

On experimental day 22, corresponding to five days after CP administration, the rats were anesthetized with chloroform and subsequently euthanized in accordance with the approved study protocol. After blood collection from the inferior vena cava, the samples were placed in gel-based serum-separation tubes. The tubes were centrifuged at 5000 rpm for 10 min. After centrifugation, the separated serum was carefully removed, aliquoted into Eppendorf tubes, and stored for subsequent biochemical analyses.

ELISA was used to determine serum β 2-microglobulin (Cat. No. E-EL-R1085; sensitivity: 0.10 ng/mL) and caspase-3 (Cat. No. E-EL-R0160; sensitivity: 0.10 ng/mL) concentrations using kits supplied by Elabsience (Wuhan, China). Serum TAC was determined using a colorimetric assay kit from Elabsience (Wuhan, China; Cat. No. E-BC-K136-S; detection range: 0.62–145.2 U/mL), according to the manufacturer's instructions. Colorimetric methods were used to measure serum urea and creatinine.

Histopathological examination of rat kidneys

The kidneys were immediately immersed in 10% neutral buffered formalin and fixed overnight. The specimens were subsequently subjected to routine histological processing and embedded in paraffin wax. Paraffin blocks were sectioned to obtain 5- μ m-thick tissue sections, which were stained with hematoxylin and eosin (H&E). A pathologist blinded to the experimental groups examined the sections using a light microscope at 20 $\times$ magnification [10].

Statistical analysis

Statistical analyses were conducted using IBM SPSS Statistics v25 (IBM Corp., Armonk, NY, USA). Data were expressed as mean $\pm$ SD. Normality was assessed with the Shapiro–Wilk test, and homogeneity of variance was assessed with Levene's test. Differences among experimental groups were evaluated with one-way ANOVA, followed by Tukey's post hoc multiple-comparison procedure. A P value < 0.05 was considered statistically significant.

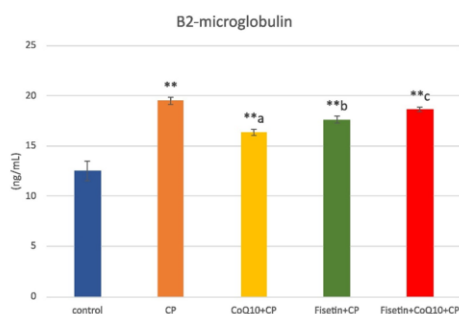
Results

As shown in Table 1 and Figures 1 and 2, serum β 2-microglobulin and caspase-3 concentrations were

Table 1. Performance metrics of emotional intelligence dataset.

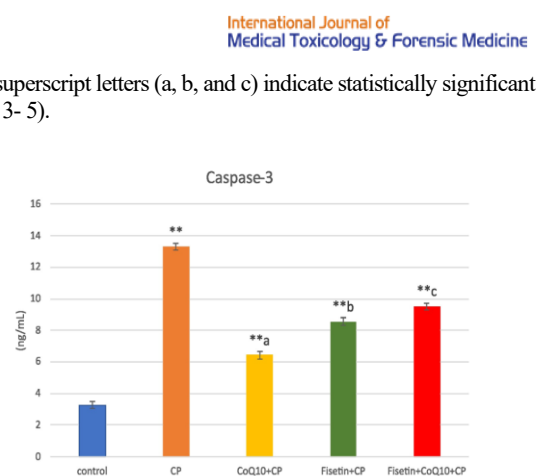
Groups	β 2-microglobulin (Mean $\pm$ SD) (ng/mL)	caspase-3 (Mean $\pm$ SD) (ng/mL)
Group 1	12.4715 $\pm$ 0.9635	3.2613 $\pm$ 0.2011
Group 2	19.5125 $\pm$ 0.3522**	13.2875 $\pm$ 0.2100**
Group 3	16.3500 $\pm$ 0.2828**a	6.4375 $\pm$ 0.2445**a
Group 4	17.6125 $\pm$ 0.3642**b	8.5625 $\pm$ 0.2560**b
Group 5	18.6250 $\pm$ 0.2314**c	9.5125 $\pm$ 0.2232**c

Double asterisks (**) indicate $P < 0.0001$ compared with Group 1. Different superscript letters (a, b, and c) indicate statistically significant differences compared with Group 2 and among the treatment groups (Groups 3–5).



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Figure 1. Serum β 2-microglobulin concentrations following administration of cyclophosphamide, fisetin, and CoQ10. Double asterisks (**) indicate $P < 0.0001$ compared with Group 1. Different superscript letters (a, b, and c) indicate statistically significant differences compared with Group 2 and among the treatment groups (Groups 3–5).



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Figure 2. Changes in caspase-3 levels following treatment with cyclophosphamide, fisetin, and CoQ10. Double asterisks (**) indicate $P < 0.0001$ compared with Group 1. Different superscript letters (a, b, and c) indicate statistically significant differences compared with Group 2 and among the treatment groups (Groups 3–5).

significantly higher in Groups 2–5 than in the control group (Group 1; $P < 0.0001$ for all comparisons). Relative to the CP-treated group (Group 2), β 2-microglobulin concentrations were lower after CoQ10 treatment (Group 3; $P < 0.0001$), fisetin treatment (Group 4; $P < 0.001$), and combined treatment (Group 5; $P < 0.05$), while caspase-3 concentrations were lower in all three treatment groups ($P < 0.0001$ for each comparison). Among the treatment groups, both markers were higher in Groups 4 and 5 than in Group 3 (β 2-microglobulin, $P < 0.001$; caspase-3, $P < 0.0001$). Both markers were also higher in Group 5 than in Group 4 (β 2-microglobulin, $P < 0.01$; caspase-3, $P < 0.001$).

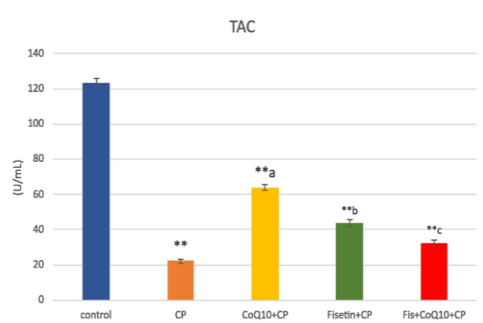
As shown in Table 2 and Figure 3, serum TAC levels were significantly lower ($P < 0.0001$) in Groups 2, 3, 4, and 5 than in the control group (Group 1). Compared with Group 2, serum TAC levels were significantly higher in Groups 3 (CoQ10 + CP), 4 (fisetin + CP), and 5 (fisetin + CoQ10 + CP) ($P < 0.0001$). In contrast, serum TAC levels were significantly lower in Groups 4 and 5 than in Group 3 ($P < 0.0001$). Moreover, serum TAC levels were significantly lower in Group 5 than in Group 4 ($P < 0.0001$).

Table 2. Serum total antioxidant capacity in the different experimental groups.

Groups	TAC (Mean $\pm$ SD) (U/mL)
Group 1	123.6250 $\pm$ 2.326
Group 2	22.0000 $\pm$ 0.9258**
Group 3	63.8750 $\pm$ 1.8077**a
Group 4	43.6250 $\pm$ 1.9226**b
Group 5	32.3750 $\pm$ 1.5979**c

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Double asterisks (**) indicate $P < 0.0001$ compared with Group 1. Different superscript letters (a, b, and c) indicate statistically significant differences compared with Group 2 and among the treatment groups (Groups 3–5).



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Figure 3. Serum TAC levels following treatment with cyclophosphamide, fisetin, and CoQ10. Double asterisks (**) indicate $P < 0.0001$ compared with Group 1. Different superscript letters (a, b, and c) indicate statistically significant differences compared with Group 2 and among the treatment groups (Groups 3–5).

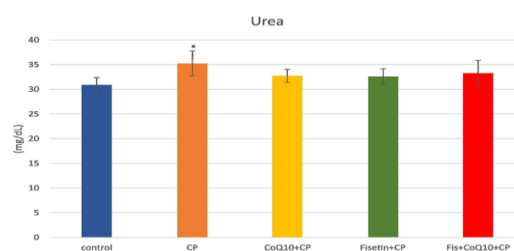
As shown in Table 3 and Figures 4 and 5, serum urea concentrations were significantly higher in the CP-treated group (Group 2) than in the control group (Group 1; $P < 0.05$). However, urea concentrations did not differ significantly between Group 2 and any treatment group (Groups 3–5), or among the treatment groups (all $P > 0.05$). Serum creatinine concentrations did not differ significantly across the experimental groups ($P > 0.05$). Although Group 2 showed a slight increase in creatinine relative to Group 1, the difference was not statistically significant; likewise, none of the treatment groups differed significantly from Group 2, Group 1, or one another (all $P > 0.05$).

Table 3. Serum urea and creatinine concentrations across the experimental groups.

Groups	Urea (Mean $\pm$ SD) (mg/dL)	Creatinine (Mean $\pm$ SD) (mg/dL)
Group 1	30.9075 $\pm$ 1.5264	0.6138 $\pm$ 0.0774
Group 2	35.2688 $\pm$ 2.474*	0.6288 $\pm$ 0.0548
Group 3	32.7513 $\pm$ 1.2698	0.5364 $\pm$ 0.06818
Group 4	32.6163 $\pm$ 1.5366	0.5925 $\pm$ 0.1058
Group 5	33.2825 $\pm$ 2.6335	0.6267 $\pm$ 0.1005

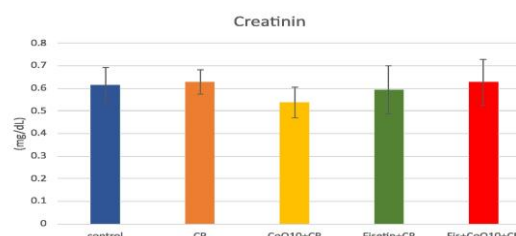
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An asterisk (*) indicates a statistically significant difference compared with the control group (Group 1) at $P < 0.05$.



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Figure 4. Changes in serum urea levels following treatment with cyclophosphamide, fisetin, and CoQ10. An asterisk (*) indicates a statistically significant difference compared with the control group (Group 1) at $P < 0.05$.



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Figure 5. Changes in serum creatinine levels following administration of cyclophosphamide, fisetin, and CoQ10.

Histopathological Findings

Histopathological examination of renal tissue from the control group showed preserved architecture, with glomeruli of regular size, shape, and distribution; intact Bowman's capsules and vascular poles; and normal proximal and distal convoluted tubules (Figure 6A). In CP-treated rats, renal architecture was relatively preserved, but glomerular alterations included enlargement, focal atrophy, possible mesangial expansion, and widening of Bowman's space. Prominent tubular dilatation with intraluminal cellular

debris, consistent with acute tubular injury, and inflammatory cell infiltration were also observed (Figure 6B).

CoQ10-treated rats exhibited normal-sized glomeruli and preserved tubules with mild inflammatory cell infiltration (Figure 6C), whereas fisetin-treated rats showed preserved glomerular and tubular architecture (Figure 6D). Rats treated with both fisetin and CoQ10 exhibited variable glomerular morphology, tubular dilatation with thickened walls and epithelial proliferation, and afferent arteriole alterations (Figure 6E).

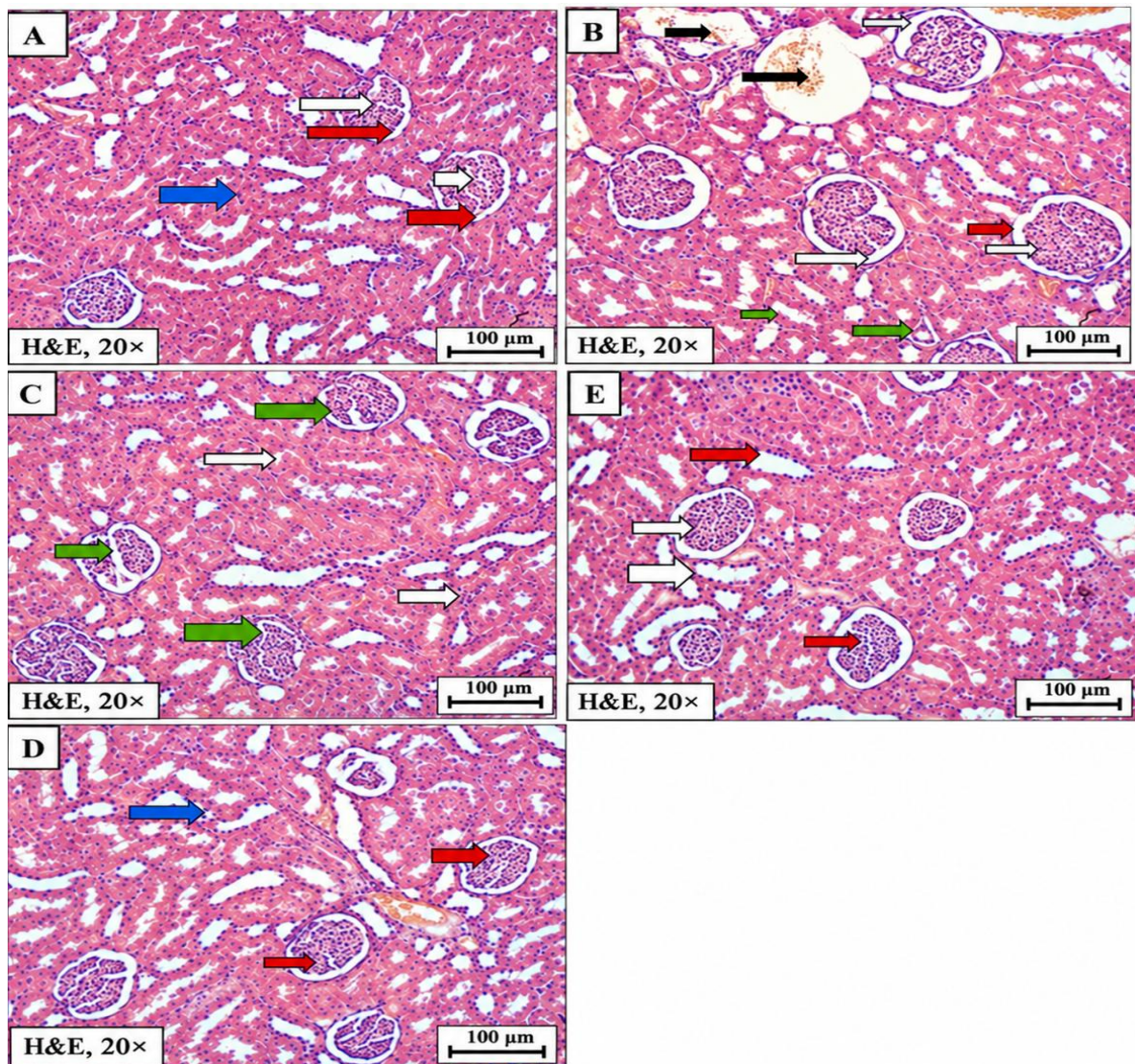


Figure 6. Photomicrographs of transverse sections of rat kidneys. H&E, 20 $\times$. (A) Control group: renal tissue showed healthy glomeruli with regular shape and size, a urinary space, a vascular pole, and a basement membrane (white arrow), surrounded by Bowman's capsule (red arrow). Normal proximal and distal convoluted tubules were observed (blue arrow). (B) CP-treated group: renal sections showed relatively enlarged glomeruli with preserved overall glomerular architecture (black arrows), with possible mesangial expansion and dilation of Bowman's spaces (white arrows). Marked tubular dilation with intraluminal debris was also observed (green arrows). (C) CoQ10 + CP group: renal architecture was relatively preserved, with normal-appearing renal tubules (white arrow) and glomeruli (green arrow). (D) Fisetin + CP group: glomerular morphology was relatively preserved (red arrow), with renal tubules also comparatively preserved (blue arrow). (E) CoQ10 + Fisetin + CP group: glomerular size varied (white arrow), with relatively preserved glomerular morphology. Tubular dilation with thickened tubular walls was also observed (red arrow).

Discussion

CP-induced nephrotoxicity promotes oxidative stress, which may result in glomerular and tubular injury and subsequently impair glomerular filtration. These results were consistent with previous studies that showed that CP induces nephrotoxicity [11].

Group 2 showed a significant increase in serum β 2-microglobulin levels compared with the control group, which is consistent with previous evidence linking elevated serum β 2-microglobulin levels with acute kidney injury [12]. Compared with Group 2, all treatment groups exhibited a pronounced decrease in serum β 2-microglobulin levels. The reduction in β 2-microglobulin observed in Group 3 may be associated with improved renal function following CoQ10 treatment, as previous studies have reported improved GFR, suggesting potential protection at both the glomerular and tubular renal levels [13]. Similarly, the reduction observed in Group 4 may be related to the previously reported anti-inflammatory properties of fisetin [4]; however, inflammatory markers were not directly assessed in the present study.

Group 2 exhibited a significant increase in serum caspase-3 levels compared with the control group, suggesting increased involvement of apoptosis-associated processes following CP administration [14]. CoQ10 treatment reduced serum caspase-3 levels in Group 3 compared with Group 2, which may be related to apoptosis-modulating effects reported for CoQ10 [15]. Group 4 also showed a reduction in serum caspase-3 following fisetin treatment, which is consistent with the reported effects of fisetin on apoptosis-related pathways [5].

Group 2 exhibited a significant reduction in TAC compared with the control group, indicating an imbalance in antioxidant capacity following CP exposure. Previous studies have suggested that CP-induced renal injury may involve increased oxidative stress and depletion of endogenous antioxidant defenses [11]. In Group 3, the increase in TAC observed after CoQ10 treatment may be related to its reported antioxidant properties and its association with the regulation of endogenous antioxidants. Similarly, the improvement in TAC observed in Group 4 may be related to the previously reported antioxidant properties of fisetin [5].

CP exposure was associated with increased serum urea levels in Group 2, whereas serum creatinine did not change significantly across the study groups. This result may reflect CP-induced tubular injury and increased membrane permeability [16]. The lack of

significant changes in serum creatinine and urea after treatment in Groups 3, 4, and 5 suggests that these conventional renal function markers may not adequately reflect early or mild renal injury. Because both markers primarily reflect glomerular filtration, they may be less sensitive to early proximal tubular injury [17].

The lower values observed in Group 5 compared with Groups 3 and 4 across several biochemical parameters may indicate a less pronounced protective effect of the combination treatment under the tested conditions. However, the underlying mechanism remains unclear and was not directly investigated in the present study. Previous studies have suggested that CP-induced nephrotoxicity is associated with oxidative stress, apoptosis, and downregulation of the Nrf2/HO-1 signaling pathway [18]. Similarly, the antioxidant effects of CoQ10 and fisetin have been associated with Nrf2/HO-1 signaling and modulation of oxidative stress [19, 20].

In addition, both fisetin and coenzyme Q10 exhibit relatively low oral bioavailability, which may influence their systemic exposure following oral administration [21, 22]. Differences in their systemic exposure when administered concomitantly could potentially contribute to the observed findings. However, systemic bioavailability was not assessed in the present study; therefore, this explanation remains speculative.

The histopathological findings were broadly consistent with the biochemical findings. Compared with the control animals (Group 1), rats exposed to CP (Group 2) demonstrated evident renal structural abnormalities. Renal tissue architecture appeared improved in Group 3, consistent with previous reports describing the antioxidant properties of CoQ10, including its reported ability to attenuate reactive oxygen species (ROS) and preserve cellular membrane integrity [3]. In Group 4, fisetin treatment was associated with improved renal morphology, with findings approaching those of the control group. This observation is consistent with previous reports describing the antioxidant, anti-inflammatory, and anti-apoptotic properties of fisetin [17]. However, these mechanisms were not directly assessed in the present study.

Histopathological findings indicated that Group 5 experienced partial renal protection compared with Group 2. Nevertheless, the improvement was less evident than in Groups 3 and 4. This observation agrees with previous reports suggesting that the combined administration of antioxidant agents does not always provide superior protective effects compared with their individual use [23].

However, the reason for the lower observed effect of the combination treatment remains unclear and was not directly investigated in the present study.

Conclusion

The CP induced renal injury, as evidenced by alterations in selected biochemical markers and qualitative histopathological changes. Under the experimental conditions tested, CoQ10 or fisetin treatment improved selected biochemical markers, including serum β 2-microglobulin, caspase-3, and total antioxidant capacity, and was associated with qualitative improvements in renal histopathology. Among the individual treatments, CoQ10 showed a more pronounced improvement in the assessed biochemical markers than fisetin. However, neither treatment significantly improved serum urea, and serum creatinine did not differ significantly among the experimental groups. The combination of CoQ10 and fisetin showed less pronounced improvements in the assessed biochemical markers and histopathological findings than either treatment alone.

Ethical Approval

The Research Ethics Committee of the College of Pharmacy at the University of Basrah approved the study protocol (Approval No. EC 88; Approval Date: 7 October 2023).

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No external funding was received for this research.

Conflicts of Interest

The authors report no competing interests to declare.

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