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The Protective Effect of Coenzyme Q10 against Doxorubicin-induced Nephrotoxicity in Albino Rats

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Abstract

Despite the fact that doxorubicin (Dox) is effective anticancer chemotherapy, it has a number of adverse effects, including nephrotoxicity, which limits its clinical value. The present study aimed to investigate the potential protective effect of coenzyme-Q10 (CoQ10) on Dox-induced nephrotoxicity. Male albino rats were pretreated with either 10 mg/kg of CoQ10 or placebo for 17 days, and on day 13 of the experiment, some of the rats were either given a single 15 mg/kg injection of Dox or normal saline into the peritoneum. Serum urea and creatinine were measured. A full histopathological examination was performed on the kidney. Dox caused significant elevation of serum urea and creatinine levels. CoQ10 was able to inhibit the elevation of these renal function tests. According to histopathological inspection, the control and CoQ10 groups exhibited normal renal glomeruli, Bowman's space, and renal tubule architecture. However, Dox-treatment caused glomerular atrophy, dilated Bowman's space, renal cyst, hemorrhage, blood vessel congestion, infiltration of inflammatory cells, and significant degeneration and necrosis of renal tubules. Pretreatment with CoQ10 resulted in considerable inhibition of the histological nephrotoxic effects of Dox. It is concluded that pre-treatment with CoQ10 can have a protective role against Dox-induced nephrotoxicity via, at least partially, preserving the normal histological architecture of the kidney.Supplementation with CoQ10 is important for Dox-treated individuals.

Keywords: CoQ10, doxorubicin, nephrotoxicity.

Introduction

Doxorubicin (Dox) is an anthracycline antibiotic and effective anticancer drug derived from the natural substance daunomycin, which was formerly known as adriamycin. Dox is made by several wild Streptomyces strains, and it is often used to treat solid and liquid cancerous tumors, including lymphoma, leukemia, and malignancies of the bladder, breast, ovary, and stomach. (Ganash, Mujallid, Al-Robai, & Bazzaz, 2014; Gonçalves, Mignani, Rodrigues, & Tomás, 2020)

Dox exerts pharmacological effects by destroying DNA and inhibiting macromolecule production (Swarnakar, Thanki, & Jain, 2014) and has many negative side effects, including renal damage. Glomerular and tubular damage are the causes of Dox-mediated nephropathy (Lee & Harris, 2011; Rafiee, Moaiedi, Gorji, & Mansouri, 2020). Even though the mechanism behind Dox-induced multi-organ toxicity is still unknown, the most likely reasons are oxidative stress, apoptosis, and the start of an inflammatory process (El-Moselhy & El-Sheikh, 2014).

Coenzyme Q10 (CoQ10), also known as ubiquinone, is a kind of natural antioxidant that may be produced in the body or obtained from the diet. The best dietary sources of CoQ10 include meat, fish, nuts, and some oils. Although CoQ10 is found in the cell membrane (Gutierrez-Mariscal, Yubero-Serrano, Villalba, & Lopez-Miranda, 2019) and different cellular organelle

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membranes including lysosomes and peroxisomes, it is mostly found in the inner membrane of mitochondria as a portion of the electron transport system, which is essential for ATP production (da Silva Machado, Mendonça, de Paula Venancio, Bianchi, & Antunes, 2013; Pravst, Žmitek, & Žmitek, 2010). CoQ10 is a powerful lipophilic antioxidant that acts as a free radical scavenger due to its essential role in the mitochondrial respiratory chain, thereby avoiding damage associated with oxidative stress (Jiménez-Santos et al., 2014)(Cervellati & Greco, 2016)**.** In addition to CoQ10's effect in limiting the synthesis of lipid peroxidation products and reactive oxygen species (ROS), it also prevents excessive nitric oxide (NO) generation and protects tissues from nitrative stress (Sohet et al., 2009). In addition, CoQ10 also has anti-inflammatory characteristics since it inhibits the production of proinflammatory cytokines after inflammatory damage (Salama & El-Baz, 2013).

The nephroprotective properties of CoQ10 are currently being debated. On one hand, animal studies have indicated that CoQ10 can protect the kidneys (Fouad, Al-Sultan, Refaie, & Yacoubi, 2010; Persson et al., 2012). On the other hand, other animal research found no evidence of kidney protection. Despite the obvious antioxidant impact of CoQ10, kidney function, which is measured by creatinine level, was not improved in a trial of renal transplant recipients (Długosz et al., 2004; Sutken et al., 2007).

The aim of this study is to investigate the nephroprotective impact of CoQ10 on kidney damage induced by Dox treatment.

Methodology

Thirty-one adult male albino rats weighing 250 ± 50 g and aged 10–12 weeks were obtained from the Veterinary Medicine's animal house at the University of Mosul. The rats were kept in a controlled environment of temperature (25°C ± 2°C), humidity (45 ± 50%), and lighting (12-h light, 12-h dark cycle, lights on at 08:00 h), as well as given a normal quantity of water and food for one week before the experiment. Dox (Saba-Turkey) and CoQ10 (21st Century®-USA) were administered to the rats. A 1% aqueous solution of Tween 80 (SCHLAU-SPAN) was used to dissolve CoQ10.

Experimental Design

Rats were distributed into four groups. Group A has given a 1% aqueous Tween 80 solution and acted as a control. Group B was given CoQ10 (10 mg/kg) for 17 days. Group C received a single dose of Dox (15 mg/kg) intraperitoneally on day 13th and acted as a positive control. Group D was administered both CoQ10 (10 mg/kg) for 17 days, and Dox (15 mg/kg, single dose) on day 13th of the experiment.

Euthanasia, sample preparation

After 24 hours of fasting, all of the rats were slaughtered under euthanasia. The animals had been euthanized through cervical spine dislocation. This procedure was carried out in compliance with animal euthanasia rules. Blood samples were taken from the retro-orbital venous plexus prior to sacrifice. These samples were stored at room temperature for 30 minutes before being centrifuged for 15 minutes at 3000 rpm. After the experiment, serum

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samples were divided up and stored in a freezer at -20C° for biochemical tests. A 10 % neutral buffered formalin solution was used to preserve kidney specimens.

Biochemical analyses

Serum samples were taken after blood collection and utilized to measure serum urea and creatinine by spectrophotometer using the corresponding colorimetric kits supplied by "Biosystems URE/BUN–COLOR UREASE/SALICYLATE kit" (Spain) for urea, and "BIOLABO CREATININE Kinetic method" kit (France) for creatinine.

Physiological and Histopathological examination

Kidney samples were embedded in paraffin after being fixed in 10% neutral buffered formalin. Hematoxylin and eosin staining were used on all tissue samples. A colour USB 2.0 digital image (HDMC) camera with image processing software was used to evaluate two slides for each specimen (Scope Image 9.0-China). The Olympus-CX21 light microscope's camera software was calibrated to work with all of the lenses. The sections were examined for different forms of nephrotoxicity, including glomerular atrophy, Bowman's space dilatation, renal cyst, degeneration, necrosis of epithelial cells lining the renal tubules, hemorrhage, and infiltration of inflammatory cells.

Statistical Analysis

The data were analyzed using the GraphPad Prism program (version 9.3.1). The results were expressed as Mean ± SD. A one-way Analysis of Variance (ANOVA) was used to compare various groups, using Tukey's multiple comparison test as a post-hoc analysis. The significance level was accepted at a P-value of < 0.05.

Results

Biochemical Markers

Serum urea levels were significantly higher in Dox-treated rats than in control rats, (control: 49.51 ± 3.34 vs. Dox: 57.52 ± 2.82). Furthermore, pre-treatment with CoQ10 inhibited significantly the elevation of s urea Dox-treated rats, (50.456 ± 5.383). (Figure 1).

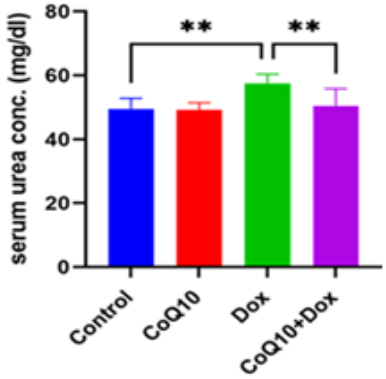

Figure 1. Prophylactic role of CoQ10 against Dox effects on serum urea in albino rats. Serum urea levels are evaluated following a single dosage of Dox (15mg/kg) or placebo, as well as with or without pre-treatment with CoQ10 (10mg/kg orally daily). The data are presented as mean ± S.D. * indicates $P < 0.05$, ** indicates $P < 0.01$. A one-way ANOVA followed by Tukey's post hoc test vs. control values was used.

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Serum creatinine levels were significantly higher after Dox therapy compared to controls (control, 0.557 ± 0.053 vs. Dox, 1.11 ± 0.153). Furthermore, pretreatment with CoQ10 substantially decreased the rise in serum creatinine produced by Dox (0.693 ± 0.146). (Figure 2).

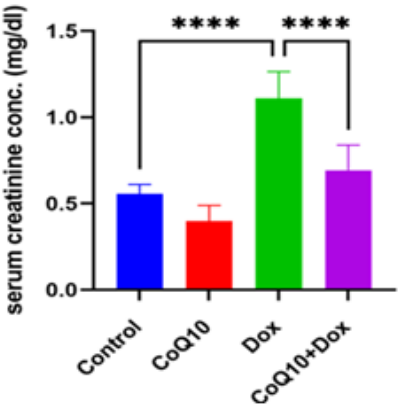

Figure 2. Prophylactic role of CoQ10 against Dox effects on serum creatinine in albino rats. Serum creatinine levels were determined in albino rats following a single dosage of Dox (15mg/kg) or placebo, as well as with or without pretreatment with CoQ10 (10mg/kg orally daily). The data are presented as a mean ± SD. **** indicates P-value < 0.0001. A one-way ANOVA followed by Tukey's post hoc test vs. control values was used.

Histological Results

The histological finding of the control group

According to a light microscopic examination of the control groups, renal tissue of rats had normal Bowman's space (4.8 ± 0.5), glomeruli (87.1 ± 15.4), proximal renal tubules (10.2 ± 2.6), and distal renal tubules (24.4 ± 7.3) (Figures 3 and 7) (Table 1).

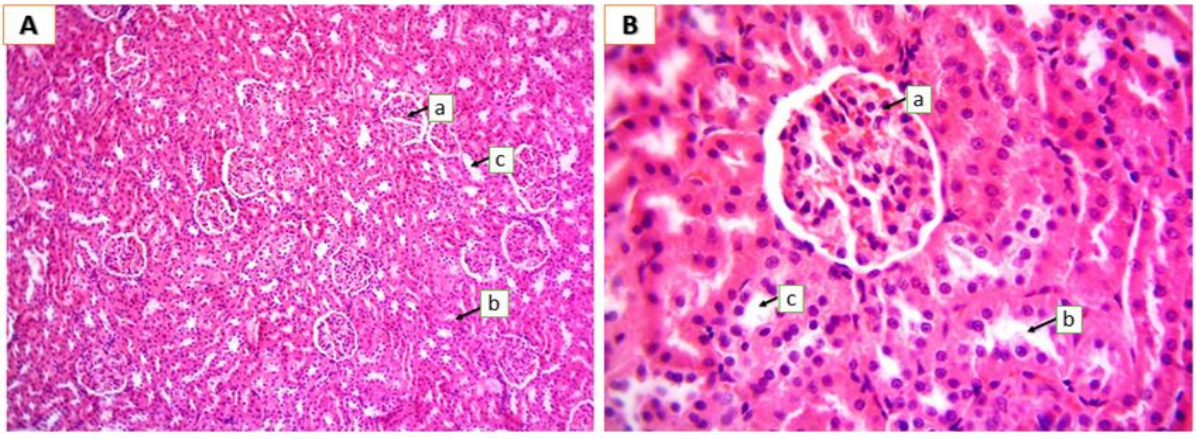

Figure 3. Photomicrographs of renal tissue from the control group. Images showed normal glomeruli (a), proximal renal tubules (b), and distal renal tubules (c) of the rat kidney; A (100X), B (400X). H and E stains.

The effect of CoQ10 on histology of the kidneys

After treatment with CoQ10, renal tissues of rats also have normal glomeruli (91.4 ± 9.2), proximal renal tubules (10.9±2.2), distal renal tubules (20.7±2.1), and blood vessels (Figure 4 and 7) (Table 1).

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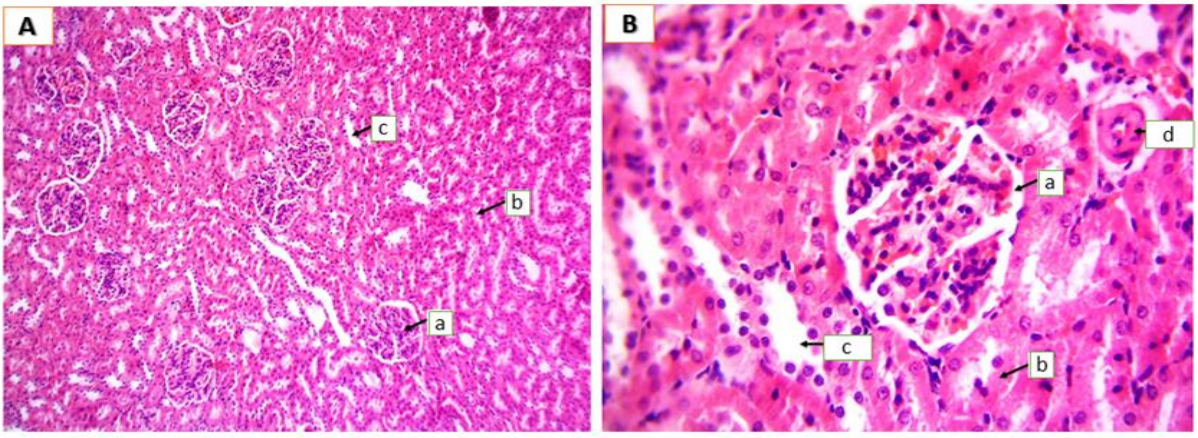

Figure 4. Photomicrographs of renal tissue from CoQ10-pretreated rats. Images showed normal glomeruli (a), proximal renal tubules (b), distal renal tubules (c), and blood vessels (d); A (100X), B (400X). H & E staining.

The effect of Dox on histology of the kidneys

Treatment with Dox causes nephrotoxicity which has been shown histologically as glomerular atrophy (56.4±6.9), Bowman's space dilatation (23.1±1.8), renal cyst, hemorrhage, blood vessel congestion, and infiltration of inflammatory cells. Further inspection at (400X) reveals evidence of degeneration and necrosis (Figures 5 and 7) (Table 1).

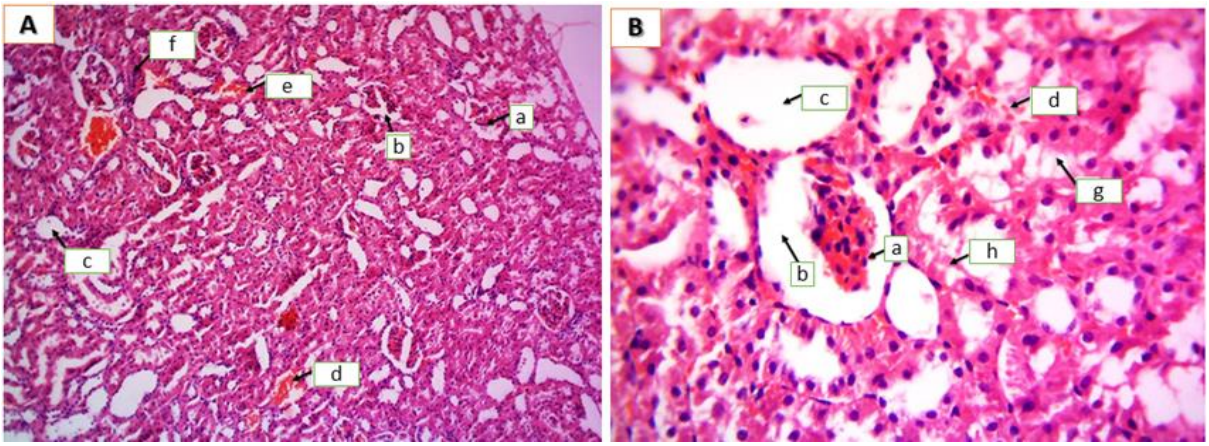

Figure 5. Photomicrographs of renal tissue from Dox-treated rats. Images showed several signs of nephrotoxicity, including glomerular atrophy (a), Bowman's space dilatation (b), renal cyst (c), hemorrhage (d), blood vessel congestion (e), infiltration of inflammatory cells (f), signs of degeneration (g), and necrosis (h); A (100X), B (400X). H & E staining.

The effect of CoQ10 pre-treatment on histology of the kidneys of Dox-treated rats

A light microscopic examination of the renal tissue of rats pre-treated with CoQ10 and then treated with Dox revealed several improvements in the histological architecture in the rat kidney in comparison with only Dox-treated rats, including intact glomeruli (88.5 ± 3.6) and intact proximal (16.7 ± 3) and distal (30.2 ± 5.4) renal tubules, and modest inflammatory cell infiltration. Further inspection at (400X) reveals intact glomeruli with modest Bowman's space dilatation (13.3 ± 1.4), and moderate epithelial cell degradation lining renal tubules. However, hemorrhage was still seen in the photomicrographs (Figures 6 and 7) (Table 1).

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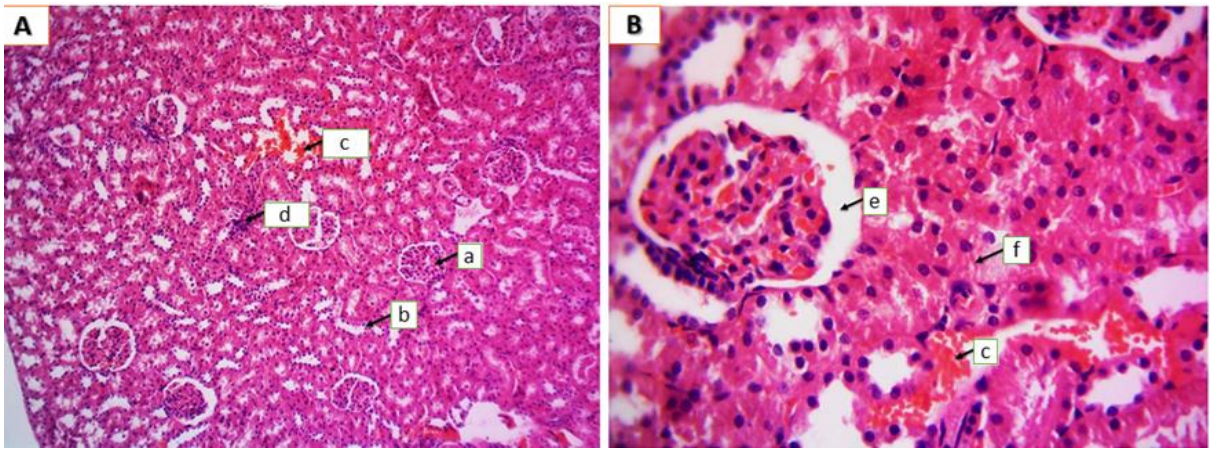

Figure 6. Photomicrographs of renal tissue from CoQ10 and Dox-treated rats. Images showed intact glomeruli (a) and renal tubules (b), with hemorrhage (c) and mild infiltration of inflammatory cells (d), slight dilatation of Bowman's space (e), and slight degeneration of epithelial cells lining renal tubules (f); A (100X), B (400X). H & E staining.

Table 1. The role of CoQ10 in protection against the effects of Dox on histological architecture in the rat kidney.

Groups / Lesion H&E stain	Control	CoQ10	Dox	Dox+CoQ10
Atrophy of glomeruli	0	0	++	0
Dilatation of Bowman's space	0	0	++	+
Degeneration	0	0	+	+
Necrosis of epithelial cells lining renal tubules	0	0	+	0
Infiltration of inflammatory cells	0	0	+	0
Congestion blood vessels	0	0	+	+
Hemorrhage	0	0	+	+
Renal cysts formation	0	0	+	0

A comparison of the histological features of the kidney tissue for all studied groups is performed and summarized in (Figure 10). This figure shows a considerable deleterious effect of Dox on the normal histology of the kidney as well as significant protection provoked by CoQ10 against this Dox-nephrotoxic effect.

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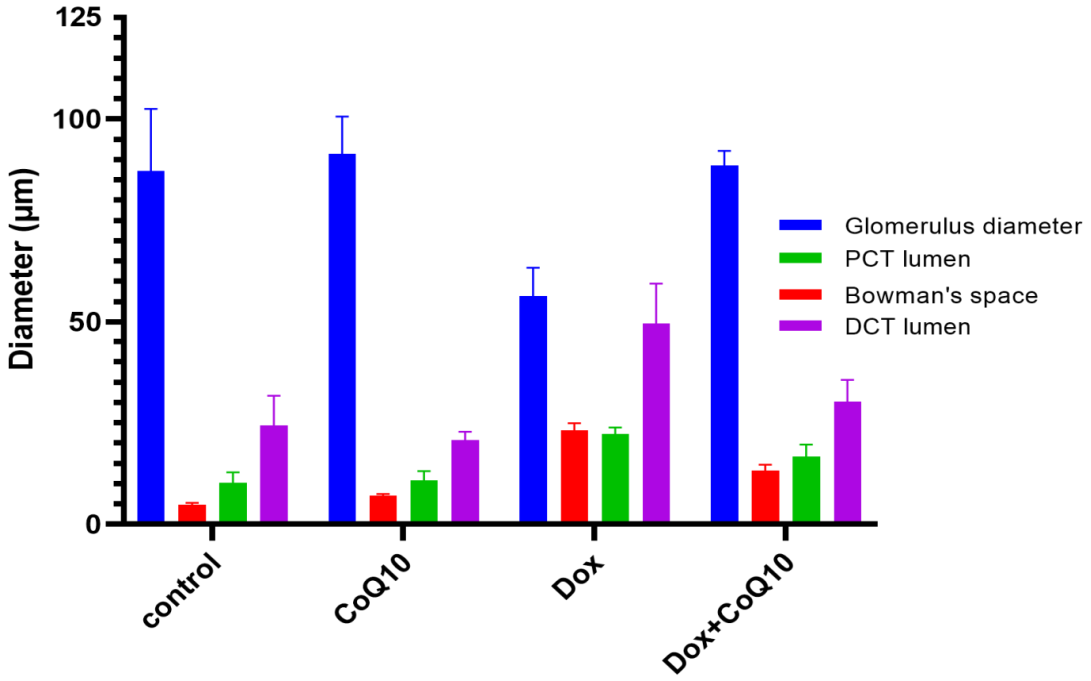

Figure 7. Comparison of the histological features in the kidney tissue of all groups. The graph shows variation in glomerulus diameter, Bowman's space size, PCT (proximal convoluted tubule) lumen, DCT (distal convoluted tubule) lumen.

Discussions

Kidney damage is a common side effect of various chemotherapy medications, as they can lead to glomerular or tubular injury, renal hypertension, and a reduction in renal endocrine function. (Adikwu, Ebinyo, & Orakpor, 2021) Despite its widespread use in a variety of cancers, doxorubicin has many adverse effects that may be lethal. Because of its renal excretion and buildup, doxorubicin can cause direct kidney injury (LEE & HARRIS, 2011). In fact, nephrotoxicity is a major side effect of Dox that is currently being debated (Sheikh et al., 2012; Ibrahim et al., 2020). The Dox's clinical usage has been seriously restricted due to its negative side effects (Khames et al., 2017) which urges the need to find an adjuvant therapy that can be used to increase therapeutic effectiveness and prevent unwanted side effects.

In the present study, Dox treatment resulted in significant increases in serum urea and creatinine levels as compared to the control group. The levels of serum urea and creatinine are two essential indicators of renal function, and a rise in these two indicators shows that the filtrating function of the kidney is compromised. Our findings are consistent with other recent researches which showed that Dox's nephrotoxic impact is marked by a decrease in glomerular filtration rate and an increase in serum urea and creatinine (Demir, Demir, & Aygun, 2020; Elsherbiny & El-Sherbiny, 2014; Wei et al., 2016). This rise in nephrotoxicity biomarkers could be caused by toxic doxorubicin metabolites building up in the nephrons and a drop in the glomerular filtration rate. Due to the ring shape of the anthracycline in Dox, which facilitates reactive oxygen species (ROS) exit from molecular oxygen via redox cycles, an imbalance between antioxidant activity and ROS formation occurs, resulting in oxidative stress, which damages the glomerular membrane, releasing serum creatinine and urea into the

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bloodstream (Asaad, Hassan, & Mostafa, 2021; Stark, 2005). This is confirmed by another study which showed that Dox-induced kidney injury can be exacerbated by oxidative stress and lipid peroxidation (Rehman et al., 2014). In addition, Dox can induce toxicity in major organs, including the liver and heart, which could disrupt blood flow to the kidneys, resulting in a reduction in renal clearance (A. A. K. El-Sheikh, Morsy, Mahmoud, Rifaai, & Abdelrahman, 2012).

An investigation of the CoQ10's potential role as a nephroprotective agent against Dox-induced kidney damage has been performed in this study. Pretreatment with CoQ10 resulted in a significant reduction to elevated urea and creatinine levels as compared to Dox-treated rats. These findings support previous research that found CoQ10 to be effective in the treatment of different chemotherapy-induced nephrotoxicity such as cisplatin and carboplatin (Kabel & Elkhoely, 2017; Khalifa, Nabil Ahmed, Hashem, & Allah, 2020). After Dox treatment, the endogenous antioxidant CoQ10 seems to rise in human plasma. This is most likely due to increased CoQ10 gene expression as a cellular defense mechanism against chemotherapy, which helps cells survive and neutralize free radicals (Brea-Calvo, Rodríguez-Hernández, Fernández-Ayala, Navas, & Sánchez-Alcázar, 2006; Soliman, Ahmed, Gomaa, & Ali, 2014; Unsal, Dalkıran, Çiçek, & Kölükçü, 2020). CoQ10 lowered the levels of urea and creatinine in the blood and showed that it protects the kidneys by keeping membranes stable and intact and preventing the leakage of these nitrogenous markers into the bloodstream (Al-Megrin et al., 2020).

Our histological findings showed that Dox administration resulted in many nephrotoxic effects including glomerular atrophy, Bowman's space dilatation, renal cyst, bleeding, blood vessel congestion, infiltration of inflammatory cells, signs of degeneration, and necrosis. This result is consistent with other studies (El-Sayed, Mansour, & El-Sawy, 2017). Another study found that Dox could cause the renal function to deteriorate, which is explained by albumin loss, and characterized by glomerular atrophy and increased capillary permeability (Koçkar et al., 2010).

Pretreatment of the rats with CoQ10 caused significant improvement in the histological architecture of the kidney even after treatment with Dox compared to Dox-only-treated rats. Renal tissues of rats have been given both CoQ10 and Dox has intact glomeruli, intact proximal and distal renal tubules, and modest inflammatory cell infiltration in the renal tissue. These findings are consistent with those of El-Sheikh et al., (2012) who found that concomitant administration of CoQ10 with Dox reversed the histopathological damage caused by Dox, resulting in the regeneration of renal epithelial cells lining cortical tubules and the restoration of normal morphology to the renal cortex (A. A. K. El-Sheikh et al., 2012). However, when a high dosage of CoQ10 (100 mg/kg) was administered with Dox, it did not reverse the morphological abnormalities found in the Dox-treated rats, but it did reveal casts with exfoliated epithelial cells and severe degeneration of renal tubules, which was equivalent to that in rats treated with Dox alone. Furthermore, the high dosage without Dox therapy caused tubule epithelial lining deterioration (A. A. K. El-Sheikh et al., 2012). Other recent investigations revealed that pretreatment with CoQ10 has many improvements in the histological morphology of the rat kidney when compared to rats treated with different chemotherapy such as cisplatin and paclitaxel (Adikwu et al., 2021; Fouad et al., 2010;

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Khalifa et al., 2020). All these studies support the present study in that proper dose of CoQ10 can act as prophylaxis against Dox-induced nephrotoxicity.

Conclusion

The present study indicates that the anticancer doxorubicin can induce a substantial kidney damage which may be linked to a direct toxic effect on the direct histological architecture of the nephron. Furthermore, pre-treatment with CoQ10 can inhibit the Dox-induced nephrotoxicity, via preserving the normal histology and physiology of the kidney. Ultimately, this study recommends that supplementation with the optimal dose of CoQ10 can have potentially a beneficial effect in reducing Dox-induced renal toxicity.

Limitations and Future Studies

More parameters should be measured to get a comprehensive view about the protective effect of Coenzyme Q10 against doxorubicin-induced nephrotoxicity in albino rats.

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