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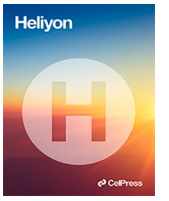

Research article

Coenzyme Q10 ameliorates carbofuran induced hepatotoxicity and nephrotoxicity in wister rats

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ABSTRACT

Carbofuran is a widely used poisonous pesticide around the world that helps to control insects during farming. Upon oral ingestion to humans, it exaggerates oxidative stress in various organs like the liver, brain, kidney, and heart. Several studies reported that oxidative stress in the liver initiates and propagates hepatic cell necrosis, ultimately resulting in hepatotoxicity. It also reported that coenzyme Q10 (CoQ10) can neutralize oxidative stress due to its antioxidant properties. However, the hepatoprotective and nephroprotective role of CoQ10 against carbofuran toxicity has not been investigated. Therefore, the present study aimed to evaluate the hepatoprotective and nephroprotective role of CoQ10 in carbofuran-induced hepatotoxicity and nephrotoxicity in a mouse model for the first time. We determined the blood serum diagnostic markers, oxidative stress parameters, antioxidant system, and histopathological characteristics of liver and kidney tissues. The administration of 100 mg/kg of CoQ10 in carbofuran-treated rats significantly attenuated AST, ALT, ALP, serum creatinine, and BUN levels. Moreover, CoQ10 (100 mg/kg) remarkably altered the level of NO, MDA, AOPP, GSH, SOD, and CAT in both the liver and kidney. The histopathological data also unveiled that CoQ10 treatment prevented inflammatory cell infiltration in carbofuran-exposed rats. Therefore, our findings infer that CoQ10 may effectively protect liver and kidney tissues against carbofuran-induced oxidative hepatotoxicity and nephrotoxicity.

1. Introduction

The liver, is an accessory organ in vertebrates, synthesizes, stores, and metabolizes diverse biomolecules, including plasma proteins, enzymes, hormones, vitamins, and cholesterol [1–4]. It also helps in the detoxification of xenobiotics through a complex hepatic enzymatic process [5]. However, the liver also accumulates reactive metabolites such as reactive oxygen species (ROS), and reactive nitrogen species (RNS) capable of inducing cellular stress [6]. Then, oxidative stress initiates and propagates hepatic injury through

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aggravating inflammation and apoptosis [6]. On the other hand, the kidney filters the blood from the whole body, and the nephrons are exposed to ROS and RNS during this filtration process. Besides, various xenobiotics can directly accumulate in the nephron, producing oxidative stress in the kidney and ultimately resulting in renal damage [7].

Carbofuran, a highly toxic carbamate, is used in insecticides, nematicides, and acaracide in crops and fruits farming. Humans can be exposed to this systemic insecticide by consuming or contacting carbofuran-treated plants and animals. Carbofuran is metabolized in the liver and converted into 3-hydroxycarbofuran and 3-ketocarbofuran through oxidation reaction and three minor phenolic carbamate metabolites (3-keto-7-phenol, 3-hydroxy-7-phenol, and 7-phenol) through hydrolysis reaction and all of these metabolites are excreted in urine [8,9]. Carbofuran irreversibly inhibits acetylcholinesterase (AChE) and may result in cholinergic toxicity [10]. Hepatic metabolism of carbofuran generates ROS and RNS, which then causes concentration-dependent changes in oxidative stress biomarkers, ensuing toxicities in various organs [11]. Several studies reported that carbofuran is capable of producing oxidative stress in the mammalian brain [11], rat heart [12], rat brain [13], rat liver [14], rat kidney [15], and mice liver [16].

Coenzyme Q10 (CoQ10) has a role in the mitochondrial electron transport chain and is a critical regulator of cellular ATP production as an essential cofactor. Besides, CoQ10 catalyzes various biochemical processes, including free radical sequestration, reduction of the α–tocopheryl radical to α-tocopherol, stabilization of the calcium channels [17,18], and photosynthesis and membrane stabilization in plants [19]. CoQ10 is a lipophilic antioxidant biosynthesized in three steps: aromatic quinine head group formation, isoprene tail production, and condensation of isoprene units to the aromatic head group [19]. CoQ10 is also taken as a supplement to treat heart failure, migraine, diabetes, age-related infertility, and cancer. It neutralizes ROS, RNS, and oxidative stress in preventing DNA damage and lipid peroxidation [20,21]. CoQ10's anti-inflammatory and antiapoptotic effects have been implicated in many experimental conditions such as acetaminophen-induced acute hepatotoxicity [22,23], alloxan-induced type 1 diabetes [24], doxorubicin-induced nephrotoxicity [25], and acute cisplatin nephrotoxicity [26]. In the present study, our objective is to assess the hepatoprotection and nephroprotection by CoQ10 in a carbofuran-induced hepatotoxicity rat model.

2. Materials and methods

2.1. Chemicals

Carbofuran, coenzyme Q10 (CoQ10), and thiobarbituric acid (TBA) were obtained from Sigma-Aldrich (USA); 3,5-dithionitrobenzoic acid (DTNB), reduced glutathione (GSH) and trichloroacetic acid (TCA) from J.I. Baker (USA); sodium hydroxide from Merck (Germany) and a biochemical test kit from Fortress diagnostics (UK). Analytical grade chemicals and reagents were used in this study.

2.2. Experimental animals

This study was performed using thirty 8-week old male Wistar rats (*Rattus norvegicus*) weighing 130–175 g. We collected all the rats from the Animal House at the Department of Pharmaceutical Sciences, North South University, Dhaka-1229, Bangladesh. Animals were reared in individual cages containing softwood shavings in an air-conditioned room having standard room conditions including 25 ± 3 °C room temperature, 55–65% relative humidity, and 12 h (7 a.m.–7 p.m. artificial laboratory light period, and 7 p.m.–7 a.m. dark period) dark-light cycle. Rats had access to standard laboratory feed as food pellets (about 150 g) and pure drinking water (about 200 ml) daily. We recorded the body weight and consumption of food and water of all animals daily during the study period. 3 Rs (reduction, refinement, replacement) of animal care and study protocol of the Ethical Committee of Department of Pharmaceutical Sciences, North South University for animal care and experimentation were followed throughout the study process (AEC-0023-2018).

2.3. Preparation of samples

Olive oil was used to dissolve carbofuran to make a 1 mg/ml concentration. We prepared the 100 mg/ml and 50 mg/ml concentration of CoQ10 dissolving with olive oil.

2.4. Experimental design

The study was done using the following groups (six rats per group):

i) Control: The animals were orally administered olive oil.
ii) Carbofuran: Animals received orally at 1 mg/kg dose of carbofuran.
iii) Silymarin: Animals received orally carbofuran (1 mg/kg) together with silymarin (100 mg/kg).
iv) CoQ10 (50 mg/kg): Animals received orally carbofuran (1 mg/kg) together with CoQ10 (50 mg/kg).
v) CoQ10 (100 mg/kg): Animals received orally carbofuran (1 mg/kg) together with CoQ10 (100 mg/kg).

Silymarin or CoQ10 were administered at an interval of 24 h for 22 consecutive days. After completion of treatment, all the animals were anesthetized by administering ketamine at a 3 ml/kg dose intraperitoneally and then sacrificed.

2.5. Evaluation of plasma biochemical markers

The blood sample was collected using a syringe containing citrate buffer solution. Plasma was collected from the supernatant in Eppendorf tubes after centrifuging the sample at 8000 rpm for 15 min at 4 °C temperature and finally, the serum was stored at 4 °C. We determined the level of the liver biochemical markers such as aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase (ALP) by using Fortress diagnostic kit (UK) according to the user manual. We also evaluated kidney biochemical markers such as the Blood Urea Nitrogen (BUN) and serum creatinine by using LiquiUV diagnostic kits (HUMAN GmbH, Germany) and a biochemistry analyzer (Erba Chem v3).

2.6. Preparation of both liver and kidney tissue homogenates

Livers and kidneys tissue samples were collected from the rats surgically, perfused with ice-cold saline (0.9% NaCl, w/v), blotted, weighed, and stored at −20 °C. To prepare rat liver or kidney homogenates, 0.1 g tissue samples from each rat were taken in 400 μl phosphate buffer saline (PBS) and then centrifuged at 8000 rpm for 15 min at 4 °C. The supernatants were collected in ice-cold Eppendorf tubes for enzymatic studies.

2.7. Assay of oxidative stress markers

2.7.1. Evaluation of nitric oxide (NO) level

We determined the nitric oxide scavenging activity of the homogenized sample by using the GriessIllosvoy reaction following the Tracey et al. (1996) method [27]. We modified the GriessIllosvoy reaction with 0.1% of naphthyl ethylenediamine dihydrochloride instead of 5% 1-naphthyl amine. We determined the NO level using the standard curve, and the result was expressed as nmol/gm of tissue.

2.7.2. Evaluation of lipid peroxidation

We determined the lipid peroxidation of tissue samples according to the method of Niehaus and Samuelsson (1968) [28]. We detected the lipid oxidation of split product malonaldehyde (MDA) using a thiobarbituric acid reactive substance (TBARS) assay. We measured the absorbance of each sample against the reference blank at 535 nm, and the results were expressed as nmol/mg.

2.8. Evaluation of advanced oxidation protein products (AOPP)

We determined the AOPP levels using Witko-Sarsat et al., 1996 [29] methods with some modifications. We diluted samples with phosphate-buffered saline (PBS) and added 1.16 M potassium iodide (KI) to each tube. After 2 min, acetic acid was added. A blank containing PBS with KI and acetic acid was used to measure the absorbance of the reaction mixture at 340 nm. The final result was expressed as μmol/mg.

2.9. Evaluation of glutathione (GSH)

Reduced glutathione was measured according to the method decribed by Jollow et al. [30]. First, the sample was precipitated with sulfosalicylic acid (4%). The samples were then incubated at 4 °C for 1 h and spun at 1200×*g* for 20 min at 4 °C. The total volume of the assay mixture consisted of filtered aliquot, phosphate buffer (0.1 M, pH7.4), and DTNB (5,5-dithiobis-2-nitrobenzoicacid) (100 mM). Finally, the mixture developed a yellow color, and we measured absorbance immediately at 412 nm on a Smart Spec TMplus spectrophotometer.

2.10. Evaluation of superoxide dismutase (SOD)

We determined the activity of superoxide dismutase (SOD) according to the described method of Marklund and Marklund [31]. We measured the spectrophotometric absorption at 412 nm of the colored complex involving pyrogallol auto-oxidation with or without the enzyme protein.

2.11. Evaluation of catalase (CAT)

We determined the catalase activity according to the modified method of Chance and Maehly [32]. We measured the absorbance (240 nm) at 30-sec intervals for 3 min.

2.12. Histopathological examination of liver and kidney

We performed the histopathological examinations for the liver and kidney according to the protocol reported by Quaresma et al. [33]. Liver tissues were embedded in paraffin after fixation with formalin. Later, 5-μm microtome sections were stained with hematoxylin. Eosin staining (an acidic dye that binds with the basic components of cells) was also used to evaluate the inflammation process and necrosis in the liver and kidney. Finally, liver and kidney tissue stained sections were photographed under a light

microscope at a magnification of × 40.

2.13. Statistical analysis

We performed to analyze and compared the result of the coenzymeQ10 with or without the carbofuran treated group by using the One-way ANOVA test. The result was compared the means of different groups with the help of Tukey's multiple comparison test. We have performed an analysis of the result by using Graph pad prism (version 7.0) software. The difference was considered when the p-value was less than 0.05.

3. Results

3.1. Effect of CoQ10 on rat liver and kidney weight

We have measured both the liver and kidney weight that was significantly ($P < 0.05$) reduced compared to the carbofuran-treated group. However, CoQ10 (100 mg/kg)-treated group significantly reversed the body weight against carbofuran. Table 1 shows the effect of carbofuran and CoQ10 on liver and kidney weights.

3.2. Effect of CoQ_{10} on biochemical parameters

The carbofuran-treated group exhibited significant hepatic damage and elevated level of AST, ALT, and ALP in plasma compared to control rats (Fig. 1A and B). Low dose CoQ10 (50 mg/kg) exhibited a slight reduction in plasma levels of the hepatic markers of ALP, AST and ALT compared to the carbofuran-treated rats (Fig. 1A–C). Intriguingly, high dose CoQ10 (100 mg/kg) noticeably attenuated carbofuran-induced rise in AST, ALP, and ALT levels (Fig. 1A–C). Following administration of the standard hepatoprotective agent silymarin, similar results were obtained, suggesting comparable hepatoprotective effects of silymarin and CoQ10 in the carbofuran-induced liver toxicity model (Fig. 1A–C). This data suggests that both CoQ_{10} and silymarin can alter the liver marker against carbofuran-induced hepatotoxicity.

We next analyzed the renoprotective potentials of CoQ10 administration in carbofuran-treated rat. Carbofuran sharply elevated the kidney disease markers BUN and serum creatinine whereas both silymarin (100 mg/kg) and CoQ10 (100 mg/kg) reversed the BUN and serum creatinine levels (Fig. 2A and B). However, these markers were almost unaltered after low-dose CoQ10 (50 mg/kg) treatment.

3.3. Effect of CoQ10 on oxidative stress parameters in the liver

The carbofuran-treated group showed elevated NO, MDA and AOPP in the rat liver compared to the control group (Fig. 3A–C). CoQ10 (100 mg/kg) administration in the carbofuran-treated rats significantly reduced liver NO, MDA, and AOPP levels compared to the carbofuran group (Fig. 3A–C). However, CoQ10 (50 mg/kg) did not alter the NO, MDA, and AOPP levels (Fig. 3A–C). As expected, the 100 mg/kg silymarin administration significantly reversed the oxidative stress parameters in the rat liver.

Next, we analyzed the endogenous antioxidant levels in the rat liver. Carbofuran treatment significantly ($P < 0.05$) diminished the levels of GSH, SOD, and CAT (Fig. 3D–F). Interestingly, 100 mg/kg of CoQ10 in carbofuran-treated rats significantly ($p < 0.05$) increased the GSH, SOD, and CAT activities compared to the carbofuran group. However, 50 mg/kg of CoQ10 did not show any noticeable change in the antioxidant levels. Silymarin (100 mg/kg) also reversed the antioxidant enzyme activities compared to the carbofuran-treated group (Fig. 3D–F). This data suggests that both silymarin (100 mg/kg) and CoQ10 (100 g/kg) treatment prevented the development of oxidative stress conditions in the carbofuran-treated rat liver.

3.4. Effect of CoQ10 on oxidative stress parameters in the kidney

Similarly, we also determined the oxidative stress markers in the rat kidneys. The carbofuran-treated group exhibited a significant elevation of NO, MDA, and AOPP levels in the kidney compared to the control group. Interestingly, both silymarin (100 mg/kg) and CoQ10 (100 mg/kg) reversed the level of NO. MDA and AOPP in the rat kidney (Fig. 4A–C).

In addition, the carbofuran-treated group exhibited a significant reduction of the antioxidant enzymes such as GSH, SOD, and CAT

Table 1
Effect of CoQ10 on rat liver and kidney weight.

SL. No.	Name of Groups	Initial BW (g)	Final BW (g)	Liver weight (g)	Kidney weight (g)
1	Control	145.5 ± 5.6	178.8 ± 6.2	11.06 ± 0.35	2.52 ± 0.15
2	Carbofuran (1 mg/kg)	150.3 ± 3.4	169.5 ± 3.9	9.16 ± 0.23**	2.08 ± 0.01**
3	Carbofuran + Silymarin (100 mg/kg)	150.5 ± 5.1	182.0 ± 5.8	10.74 ± 0.27*	2.42 ± 0.03*
4	Carbofuran + CoQ10 (50 mg/kg)	147.0 ± 5.2	172.3 ± 5.354	9.76 ± 0.53	2.46 ± 0.09*
5	Carbofuran + CoQ10 (100 mg/kg)	147 ± 5.5	178.8 ± 6.0	11.45 ± 0.31**	2.55 ± 0.09**

The values were expressed as Mean ± SD; n = 6, where n is the number of determinations. Significant difference is reported when *$P < 0.05$, **$P < 0.01$ vs. Control; *$P < 0.05$, **$P < 0.01$ vs. Carbofuran was observed.

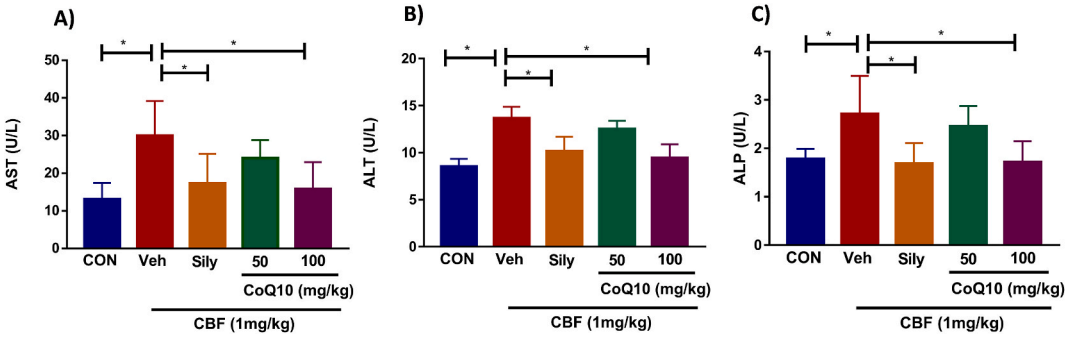

Fig. 1. Effect of CoQ10 on hepatic markers in the rat liver: (A) Aspartate Amino Transferase (AST), (B) Alanine aminotransferase (ALT) and (C) Alkaline Phosphatase (ALP) levels. The data were expressed as Mean ± SEM; n = 6, where n is the number of determinations. Significant difference is reported when *P < 0.05, **P < 0.01 vs. Control group; *P < 0.05, **P < 0.01 vs. Carbofuran group was observed. CON = Control, CBF = Carbofuran, CoQ10 = ConenzymeQ10, Sily = Silymarin.

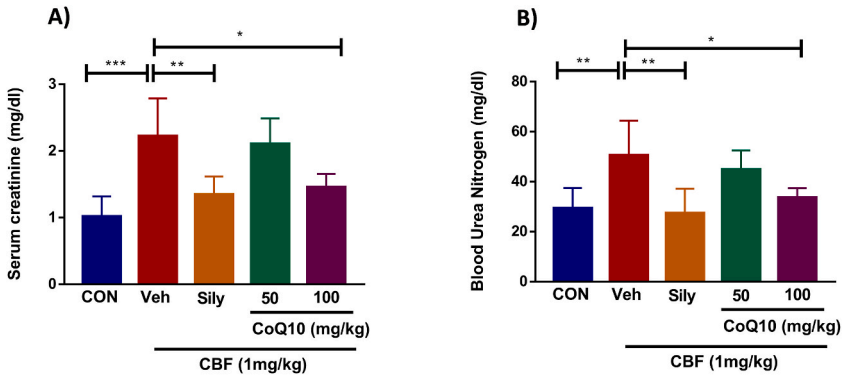

Fig. 2. Effect of CoQ10 on kidney markers in the rat kidney: (A) Serum creatinine, (B) BUN levels. The data were expressed as Mean ± SEM; n = 6, where n is the number of determinations. Significant difference is reported when *P < 0.05, **P < 0.01 vs. Control group; *P < 0.05, **P < 0.01 vs. Carbofuran group was observed. CON = Control, CBF = Carbofuran, CoQ10 = ConenzymeQ10, Sily = Silymarin.

in the kidney compared to the control group. However, CoQ10 (100 mg/kg) treatment in the carbofuran-treated rat reversed the antioxidant activity (Fig. 4D–F). In the case of the standard drug silymarin, we obtained a very similar result. This result suggests that both silymarin and CoQ10 ameliorated the carbofuran-induced oxidative stress in the rat kidney.

3.5. Histopathological examination on rat liver and kidney

We performed a microscopic examination of liver and kidney tissues using hematoxylin and eosin staining. Carbofuran-treated rats had inflammatory cell migration into the central vein area, though the control group showed a regular arrangement of hepatocytes (Fig. 5A and B). Coadministration of carbofuran-treated rats with CoQ10 (100 mg/kg) exhibited a significant reduction in penetration of inflammatory cells compared to the carbofuran-treated group (Fig. 5E). Nevertheless, CoQ10 (50 mg/kg) treated rats slightly reduced inflammatory cell penetration in the rat liver compared to carbofuran treated rats, as shown in Fig. 5D. As depicted in Fig. 5C, administration of silymarin (100 mg/kg) in carbofuran-treated rats reversed the cellular disarrangement. This result also suggests that a 100mg/kg dose of CoQ10 treatment prevents inflammatory cell infiltration in the hepatocyte.

Similarly, we performed the histopathological examination of the kidney tissue. The carbofuran-treated rats showed higher inflammatory cell migration in the kidney tissues (Fig. 6A and B). However, both the silymarin and CoQ10-100 treated rats showed a significant reduction of the inflammatory cell migration in the rat kidney tissue (Fig. 6C–E).

4. Discussion

Exposure to different chemicals or toxicants induces swelling, degeneration, and apoptosis of the hepatic cells [34–36]. Several studies reported that carbofuran exposure in different animals exhibited liver damage with alteration of the liver function markers such as ASL, ALT, and ALP in the blood and oxidative stress parameters in the liver [37,38]. Recently, CoQ10 has been reported to improve the effects against carbon tetrachloride-mediated liver toxicity [39]. No previous study evaluated the hepatoprotective and nephroprotective roles of CoQ10 against carbofuran. We have studied both the hepatoprotective and nephroprotective roles of CoQ10 in

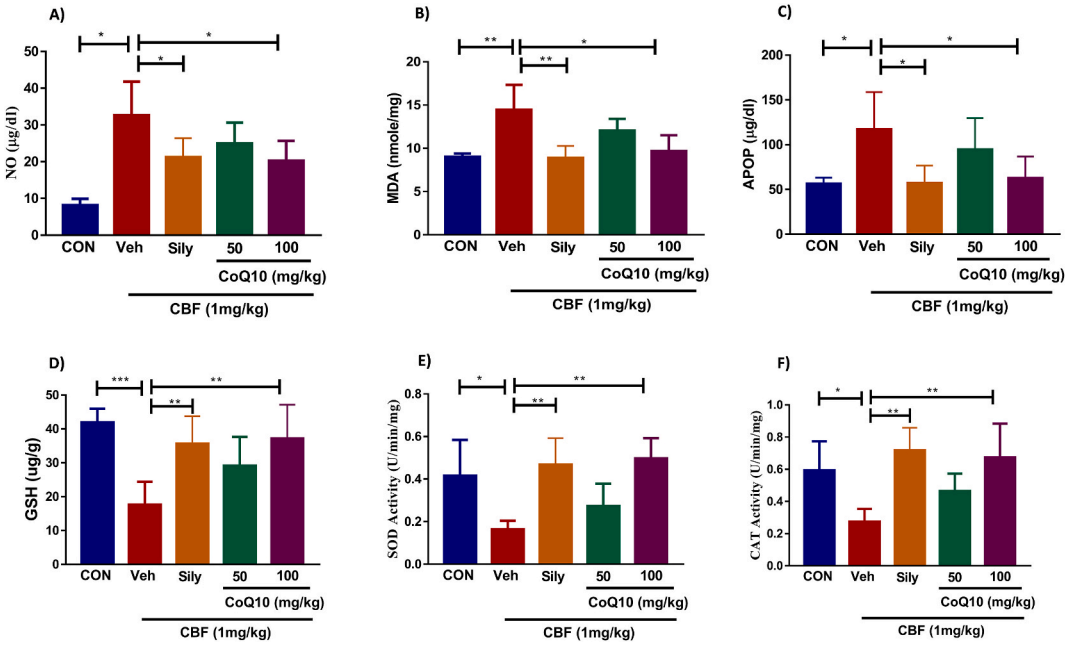

Fig. 3. Effect of CoQ10 on oxidative stress parameters in the liver: (A) NO level (B) MDA level (C) AOPP level (D) GSH level and (E) SOD level and (F) CAT level in rats exposed to carbofuran induced hepatotoxicity. The values were expressed as Mean ± SD; n = 6, where n is the number of determinations. Significant difference is reported when *P < 0.05, **P < 0.01 vs. Control group; *P < 0.05, **P < 0.01 vs. Carbofuran group was observed. CON = Control, CBF = Carbofuran, CoQ10 = ConenzymeQ10, Sily = Silymarin.

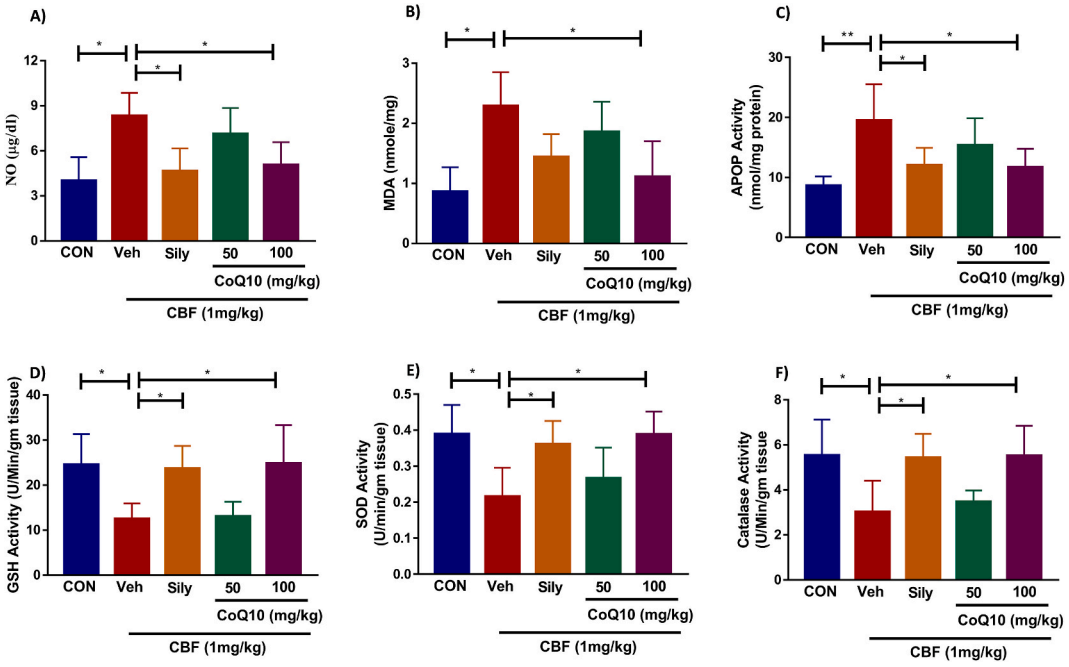

Fig. 4. Effect of CoQ10 on oxidative stress parameters in the kidney: (A) NO level (B) MDA level (C) AOPP level (D) GSH level and (E) SOD level and (F) CAT level in rats exposed to carbofuran induced hepatotoxicity. The data were expressed as Mean ± SEM; n = 6, where n is the number of determinations. The significant difference is reported when *P < 0.05, **P < 0.01 vs. Control group; *P < 0.05, **P < 0.01 vs. Carbofuran group was observed. CON = Control, CBF = Carbofuran, CoQ10 = ConenzymeQ10, Sily = Silymarin.

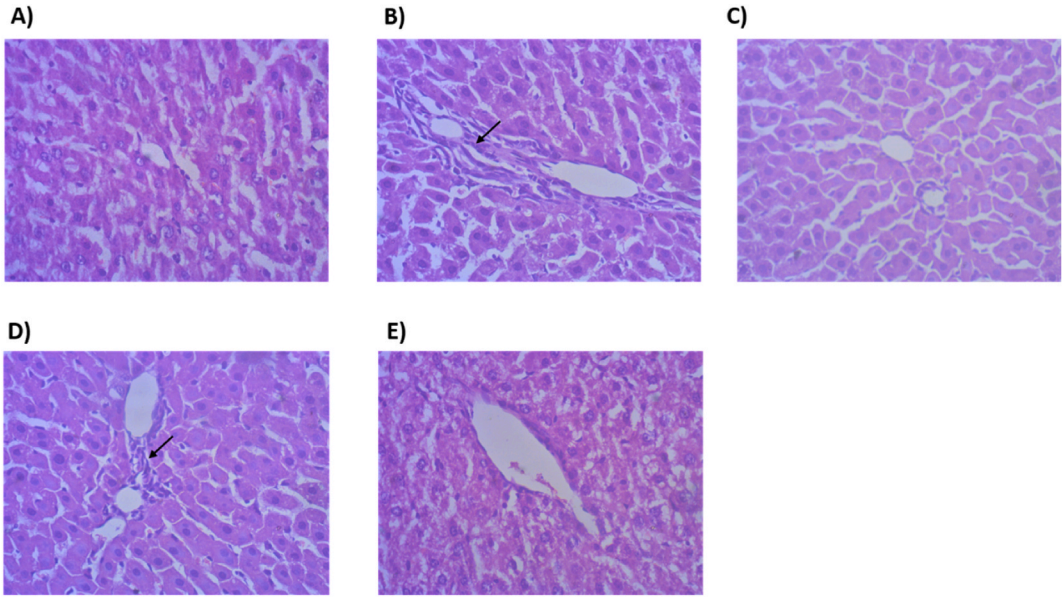

Fig. 5. Histopathological examination of CoQ10 on CBF treated liver using hematoxylin and eosin staining. (A) Control (B) Carbfuran (1 mg/kg) (C) Carbofuran (1 mg/kg) + Silymarin (100 mg/kg) (D) Carbofuran (1 mg/kg) + CoQ10 (50 mg/kg) (E) Carbofuran (1 mg/kg) + CoQ10 (100 mg/kg). All the rat livers were sectioned at 5 μm using microtome, and stained with hematoxylin. The sections were studied under light microscope at a magnification of × 40.

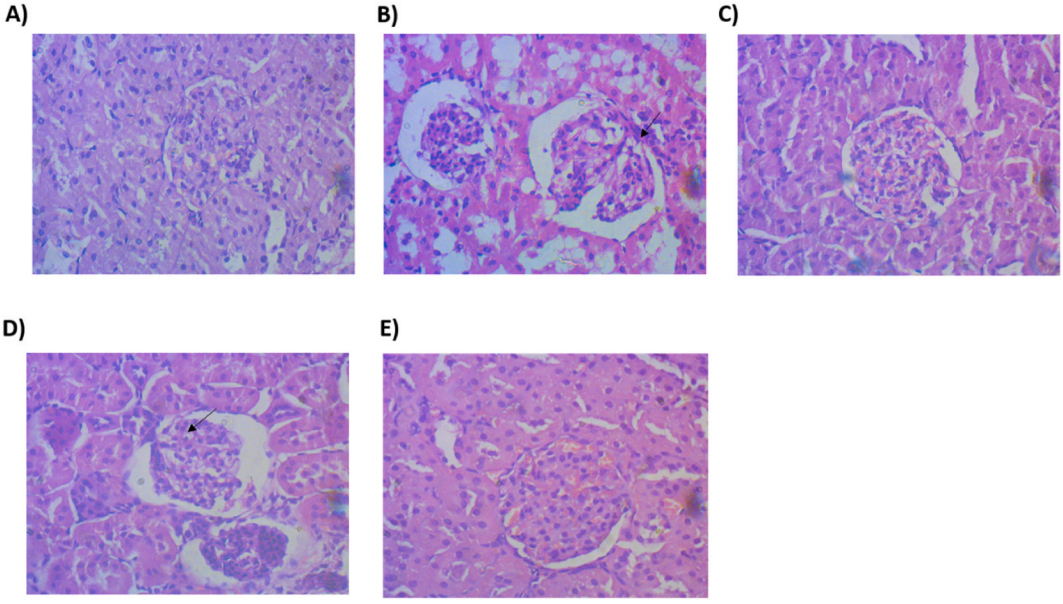

Fig. 6. Histopathological examination of effect CoQ10 on CBF treated kidney using hematoxylin and eosin staining. (A) Control (B) CBF treated (C) Carbofuran (1 mg/kg) + Silymarin (100 mg/kg) (D) Carbofuran (1 mg/kg) + CoQ10 (50 mg/kg) (E) Carbofuran (1 mg/kg) + CoQ10 (100 mg/kg). All the rat livers were sectioned at 5 μm using microtome, and stained with hematoxylin and eosin. The stained sections were studied under light microscope at a magnification of × 40.

carbofuran-induced hepatotoxicity in Wister rats.

Carbofuran is a hydrophobic pesticide showing deposition in the phospholipid bilayer of biological membranes [40]. Normally, carbofuran is deposited in highly lipid-containing areas such as the liver, kidney, ovaries, nervous systems, fat and skin [41]. Carbofuran metabolism generates free radical species (FRS), which may cause oxidative stress in liver tissues [11]. Oxidative stress is one of the primary reasons that can result in hepatotoxicity [42]. As the main purification organ, the kidney filters the whole blood. Consequently, the kidney is vulnerable to toxicities induced by ROS originating in other organs [43].

Oral administration of carbofuran in rats significantly reduced liver and kidney weight (Table .1). The rapid reduction of liver and kidney weight could indicate rapid destruction of hepatocytes and nephrocytes, a direct toxic effect of carbofuran. Nonetheless, both CoQ10 and silymarin administration in carbofuran-induced rats reversed the organ-weight reduction. Mondal and his coworker found a similar effect on liver weight in rats treated with carbofuran [44].

We also measured that carbofuran-treated rats showed a significant elevation of liver markers such as AST, ALT, and ALP levels in the serum, and this observation supported carbofuran-induced liver damage (Fig. 1). These results were consistent with a previous report assessing liver damage by a different pesticide [45]. In the present study, we observed attenuation of carbofuran toxicities following oral silymarin or CoQ10 carbofuran administration. Presumably, the hepatoprotective effects resulted from, at least partially, the antioxidant properties of CoQ10 and silymarin, as also reported earlier [46]. We also measured serum creatinine and BUN, two commonly used kidney function biomarkers (Fig. 2). Both CoQ10 and silymarin reduced the carbofuran-induced rise in serum creatinine and BUN (Fig. 2), and our results agreed with previous studies [44,47].

Nitric oxide (NO) is an outcome of normal endothelial and vascular functions [48], and NO production by the hepatocytes increases in states of inflammation [49]. Previous studies also suggest that NO may promote apoptotic cell death in various organs [50]. In this present study, carbofuran dramatically increased NO levels in both the liver and kidney, indicating oxidative stress mediating liver and kidney injury. Silymarin and CoQ10 treatment showed a significant reversal of NO levels in liver and kidney tissues, supporting the ameliorative effects of CoQ10 against carbofuran toxicity (Figs. 3A and 4A).

It is well-known that MDA overproduction accelerates cellular oxidative stress [51]. In this present study, carbofuran has significantly increased MDA levels in both liver and kidney, indicating that carbofuran has induced liver and kidney damage by oxidative stress (Figs. 3B and 4B). The subsequent treatment of CoQ_{10} restores the MDA level to normal, suggesting the protective effects of CoQ10. A very similar effect was reported for the administration of Curcuma long in carbofuran-treated rats [52].

AOPP is an oxidative stress marker, a uremic toxin produced through the reactions of plasma proteins with chlorinated oxidants [53]. In this present study, carbofuran-induced rise in APOP levels was lessened by the concomitant treatment of CoQ10 in a dose-dependent manner (Figs. 3C and 4C). The current result suggests that CoQ10 can neutralize oxidative stress and protect the liver and the kidney from carbofuran toxicities.

Enzymatic and non-enzymatic endogenous antioxidants also play pivotal roles in redox homeostasis. GSH, a tripeptide non-enzymatic antioxidant, eliminates ROS and RNS from the body [54]. In this study, liver, and kidney GSH levels were decreased by carbofuran treatment, whereas CoQ10 (100 mg/kg) and silymarin lessened the GSH reduction (Figs. 3D and 4D). Shill et al. (2021) observed the very similar activity of GSH against oxidative stress-induced liver and kidney toxicity [47].

In physiological conditions, SOD generates H_2O_2 through the dismutation of O_2. (superoxide radical). On the other hand, CAT catalyzes O_2. Degradation into H_20 and molecular oxygen. Therefore, imbalance in the enzymes mentioned above alters the body's redox system leading to oxidative stress [52,55]. In this study, we observed diminished SOD and CAT levels in the rat liver and kidney tissues indicating carbofuran-mediated redox imbalance (Figs. 3E, F and 4E, F). However, CoQ10 treatment restores the activity of these enzymes to the physiological level, supporting the antioxidative potential of CoQ10 in carbofuran-induced hepatotoxicity and nephrotoxicity.

The histopathological examination of carbofuran-induced rat liver and kidney showed increased inflammation and necrosis in hepatocytes and nephrocytes (Figs. 5B and 6B). Interestingly, CoQ10 and silymarin significantly improved the inflammatory histopathologies (Figs. 5C–E, 6C–E), which may indicate an antiapoptotic effect of CoQ10 through modulation of the mitochondrial uncoupling proteins. Our previous findings also support that CoQ10 possesses an ameliorative effect against hepatoxicity in rats [39]. It is possible that CoQ10 improved tissue structures through an Nrf2-transforming growth factor-β1 (TGF-β1) pathway [56]. Together, our results illustrated the CoQ10's protective roles against carbofuran-treated hepatoxicity and nephrotoxicity. In the future, it would be intriguing to determine the expression of proinflammatory and inflammatory genes to decipher the molecular mechanisms of CoQ10's organ-protecting effects.

5. Conclusion

This is the first report to evaluate the CoQ10's protective roles in carbofuran-induced hepatoxicity and nephrotoxicity in a rat model. Our results revealed that carbofuran treatment causes the elevation of NO, MDA, AOPP, and reduction of SOD, CAT, and GSH. On the other hand, oral CoQ10 administration normalized oxidative stress markers and different liver and kidney function biochemical markers. The current study thus advocates for using CoQ10 supplements to prevent liver and kidney damage by the carbofuran and similar pesticides.

Author contribution statement

Murad Hossain: Conceived and designed the experiments; Performed the experiments; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Tamanna Tanjim Suchi, Farzana Samiha, M. M. Monirul Islam, and Fahima Abdullah Tully: Performed experiments.

Javed Hasan, Md. Ashrafur Rahman, and Manik Chandra Shill: Conceived and designed the experiments; Analyzed and interpreted the data.

Asim Kumar Bepari: Analyzed and interpreted the data; Wrote the paper.

G.M. Sayedur Rahman: Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data.

Hasan Mahmud Reza: Conceived and designed the experiments; Contributed reagents, materials, analysis tools or data.

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Data availability statement

Data will be made available on request.

Declaration of competing interest

The authors declare that there is no conflict of interest.

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