



Cardio-Protective Effect of Coenzyme Q10 Against Nitrofurantoin-induced Cardiotoxicity in Rabbits

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Abstract | Nitrofurantoin-induced cardiotoxicity presents a significant concern in clinical practices, necessitating exploration of potential protective therapeutic agents against cardiotoxicity. This study investigates the cardioprotective efficacy of Coenzyme Q10 (CoQ10) against nitrofurantoin-induced cardiac damage. For this purpose, rabbits were categorized into four groups: control group was mock-treated with distal water only (G1), another group was treated with nitrofurantoin alone (G2), a third group with CoQ10 alone (G3), and a fourth group was treated with nitrofurantoin plus CoQ10 (G4). Serum levels of oxidative stress markers (e.g. MDA), cardiac injury markers (CPK and troponin), inflammation markers (e.g. CRP), and thyroid function (e.g. TSH) were assessed. Additionally, histological examination was performed post-H and E staining to for pathological lesions. The group G2 exhibited elevated levels of MDA (4.22 ± 0.16 mmol/L), CPK (317.40 ± 0.24 U/L), and troponin (1.19 ± 0.004 mg/dL), which collectively indicated oxidative stress and cardiac injury. In response to treatment with CoQ10, especially in groups G3 and G4, histopathological alterations in cardiac tissue were decreased significantly, including areas of necrosis and vacuolation. More specifically, light microscopy demonstrated a trend toward reduction in necrosis and vacuolation in liver tissue in animals in group G3 and G4 compared to animals in G2. Respectively, in conjunction with the results for groups with no differences in serum CRP levels (0.24 ± 0.003 mg/dL), the animals in G4 showed aortic subintimal vacuolation points towards a modulatory effect also observed with CoQ10. These results clearly conclude that CoQ10 can ameliorate all the drug-induced side effects in the cardiac muscles and also points the directions for the future research on the potential benefits of CoQ10 in clinical settings.

Keywords | Coenzyme Q10, Cardiotoxicity, Nitrofurantoin, Cardiac protection, Antioxidant therapy

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Nitrofurantoin is one of the widely used antibiotics that is being applied for the treatment and prophylaxis of urinary tract infections (UTI). The usage of nitrofurantoin is considered efficient for the management of UTI, however, it has reportedly caused cardiotoxicity, which ranges from arrhythmias, myocardial damage to heart failure (Hoang and Salbu, 2016). The cardiotoxic effect of nitrofurantoin is derived from free radicals which induce oxidative stress and cause cell damage and impaired function of the cardiac muscles (Ramirez-Hincapie *et al.*, 2023). These adverse properties indicate that developing an understanding of the cardiotoxicity of these agents and means by which this can be minimized is important to the resolution of the clinical problems faced by patients.

Coenzyme Q10 (CoQ10) is an essential component of the mitochondria. Biochemically, CoQ10 is a lipid soluble quinone which has the principal and active roles in the process of generating energy. Owing to carry characteristics of eliminating free radicals and preventing the oxidation of lipids and proteins CoQ10 has antioxidant activity (Samimi, 2017). It is synthesized in the body and exists in two bioactive forms: ubiquinone (oxidized form) and ubiquinol (reduced form). Both forms are critical for maintaining the cellular homeostasis, especially in tissues that have a high rate of metabolism, for instance, the heart, kidneys, liver, and muscles (Mantle and Dybring, 2020).

Recent several studies have highlighted that CoQ10 deficiency is linked to numerous diseases, including cardiovascular diseases, hypertension, liver diseases, and reduced immunity (Samimi, 2017). Also, it has been proposed that CoQ10 may carry therapeutic effects in cardiovascular disorder, metabolic syndrome, kidney function, inflammation, and neurodegenerative diseases (Samimi, 2017). In last few decades, CoQ10 has been approved for use to treat CVD and HF, and cross-sectional studies showing a negative relationship between serum and tissue concentrations of CoQ10 and severity of heart failure (HF) symptoms (Sue-Ling, 2022).

Based on the determination of CoQ10 as a non-enzymatic endogenous antioxidant that safeguard cell membranes from oxidative stress, its impact in mitigating nitrofurantoin induced cardiotoxicity is of great interest. Hormetic effect assertiveness of CoQ10 plasma concentrations and the ubiquinone–ubiquinol ratio are used as indicators of oxidative stress to ensure the antioxidant's function of shielding heart, kidney, and other high-energy tissues (Oleck and Ventura, 2016).

Although it is known that nitrofurantoin is toxic to the heart and CoQ10 has cardioprotective properties, there

are few scientific evidence that CoQ10 can prevent nitrofurantoin-induced cardiotoxicity. Therefore, in this research we seek to address this gap by assessing the effects of CoQ10 on rabbits subjected to ischemic-reperfusion injury, with regards to changes in oxidative stress indices and histopathological changes of the posterior cardiac tissues. We aim to evaluate whether CoQ10 supplementation can mitigate the cardiotoxic effects of nitrofurantoin, thereby providing insights into potential therapeutic strategies for patients undergoing nitrofurantoin treatment.

MATERIALS AND METHODS

STUDY PERIOD AND ANIMAL MODEL

This study was conducted from September 2023 to January 2024 using twenty adult Swiss albino rabbits aged between 9–11 weeks.

EXPERIMENTAL DESIGN

The animals were randomly allocated into four groups with five rabbits in each group. The control group (G1) received distilled water. The G2 group received Coenzyme Q10 (CoQ10) only at a dose of 10 mg/kg body weight (B.wt) orally (Mohammed and Ismail, 2021). The G3 group

- received Nitrofurantoin only at a dose of 200 mg/kg B.wt orally (Al-Azawi and Asker, 2016).
- The fourth group (G4) received both CoQ10 at 10 mg/kg B.wt and Nitrofurantoin at 200 mg/kg B.wt orally.

ADMINISTRATION PROTOCOL: Each group underwent daily oral administration for a duration of 60 days, as outlined in Figure 1.

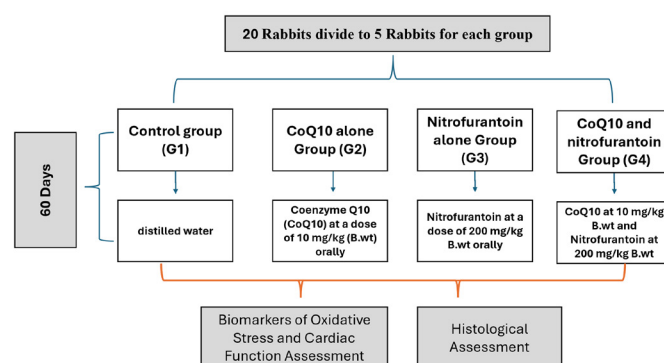


Figure 1: Experimental design used in this study.

ANIMAL HOUSING AND HANDLING

All animals were housed individually in standard cages under normal laboratory conditions carrying light-and-dark cycle, 40–60% humidity, and 20–22°C temperature. During the trial, rabbits received standard rabbit diet and water and had free access to both during the experimental period. In each stage of the process, it was ensured that all necessary precautions that deal with correct handling

Table 1: The protective role of CoQ10 administration on oxidative stress marker (MDA) and some biological cardiac markers (CPK, CRP, Troponin) and TSH of the heart in rabbits administered with Nitrofurantoin.

Group	Serum MDA (mmol/L)	Serum CPK (U/L)	Serum CRP (mg/dL)	Serum Troponin level (ng/M)	Serum TSH (mlu/L)
G1 (Control)	2.08 ± 0.02 d	412.60 ± 3.52 a	2.71 ± 0.005 a	1.92 ± 0.008 a	2.7 ± 0.05 A
G2 (Nitrofurantoin)	4.22 ± 0.16 b	317.40 ± 0.24 b	1.19 ± 0.004 b	0.45 ± 0.002 b	2.2 ± 0.05 B
G3 (CoQ10)	1.09 ± 0.02 e	270.60 ± 3.62 c	0.66 ± 0.007 c	0.91 ± 0.005 c	2.3 ± 0.07 B
G4 (Nitrofurantoin + CoQ10)	2.16 ± 0.03 d	228.00 ± 1.09 d	0.24 ± 0.003 d	0.25 ± 0.005 d	2.7 ± 0.07 A
LSD	0.3741	0.25	0.0188	0.008	0.12

*Statistical significance between groups is indicated by different letters. Lowercase letters (a, b, c, d, e) show significant differences at $p < 0.05$ by ANOVA with Tukey's post-hoc test, and uppercase letters (A, B) denote significance for other parameters at the same threshold.

were implemented so that stress is kept to a minimum.

CLINICAL OBSERVATION AND SAMPLING

At the end of the treatment period, general health check-up was done, the rabbits were weighed and subsequently sacrificed. Blood samples were collected, cardiac puncture analysis and biochemical analysis was performed.

TISSUE COLLECTION AND HISTOLOGICAL ANALYSIS

The heart and aorta were excised, weighed, and fixed in 10% formalin for preservation. For histological analysis, and sections were stained using Hematoxylin and Eosin (H andE) staining according to the method described by (Luna, 1993).

STATISTICAL ANALYSIS

Data were analyzed using one-way analysis of variance (ANOVA) followed by LSD post-hoc test for multiple comparisons among the groups. Assumptions of ANOVA, including data normality, were assessed using Shapiro-Wilk test. Results were expressed as mean ± standard deviation (SD). Differences were considered statistically significant at $p < 0.05$. All statistical analyses were conducted using SPSS software (Version 26.0, IBM Corp.).

ETHICAL CONSIDERATIONS

All procedures performed in studies involving animals were in accordance with the ethical standards of the institution at which the studies were conducted. This study was approved by the institutional animal care and use committee of Baghdad, University of Veterinary Medicine and the committee of animal care (ACUC), also the Minutes of the Scientific Subcommittee at Al-Mustansiriya University No. 312 at 8/28/2023.

RESULTS AND DISCUSSION

BIOMARKERS OF OXIDATIVE STRESS AND CARDIAC FUNCTION

The protective effects of Coenzyme Q10 (CoQ10) on ox-

idative stress and cardiac function markers in rabbits subjected to nitrofurantoin-induced cardiotoxicity were investigated. As detailed in Table 1, significant differences were observed across groups for several biomarkers. Serum malondialdehyde (MDA) which is a marker of oxidative stress showed elevated levels in the nitrofurantoin group (G2), which were significantly reduced in the group treated with CoQ10 (G3), and remained moderated when CoQ10 was combined with nitrofurantoin (G4) ($p < 0.05$). Likewise, cardiac enzymes such as Creatine Phosphokinase (CPK) and Troponin were significantly elevated in G2, indicating cardiac injury, which was notably mitigated in the CoQ10 treated groups (G3 and G4) ($p < 0.05$). The findings also showed improved biomarkers on CoQ10 treatment, which decreased the CRP levels denoting the anti-inflammatory role of CoQ10 ($p < 0.05$).

These results support the current literature on the need to explore further CoQ10 as a treatment intervention for reducing drug-associated cardiac adverse effects. Oxidative stress, characterized by increased levels of MDA were also presented in rabbits that received nitrofurantoin alone as showed earlier (Hoang and Salbu, 2016). This discovery corresponds with previous finding that highlight nitrofurantoin as a source of ROS and their destructive effects on heart muscle (Ramirez-Hincapie *et al.*, 2023). Yet, CoQ10 support the toxicity in animals treated with nitrofurantoin alone and CoQ10 and nitrofurantoin combined therapy in reducing MDA levels. These findings pointed out protective roles CoQ10 against nitrofurantoin led oxidative stress (Samimi *et al.*, 2017). This is also in support of other studies showing that CoQ10 possesses antioxidant potential in decreasing oxidative stress in different disease settings (Raygan *et al.*, 2015; Martelli *et al.*, 2020).

Abnormal changes in CPK enzymes and troponin levels show that myocardial nitrofurantoin was increased in the group (G3) as compared to the previous study conducted by Hoang and Salbu (2016). These enzymes are released into the blood each time there is myocardial tissues damage and is therefore very relevant especially when one

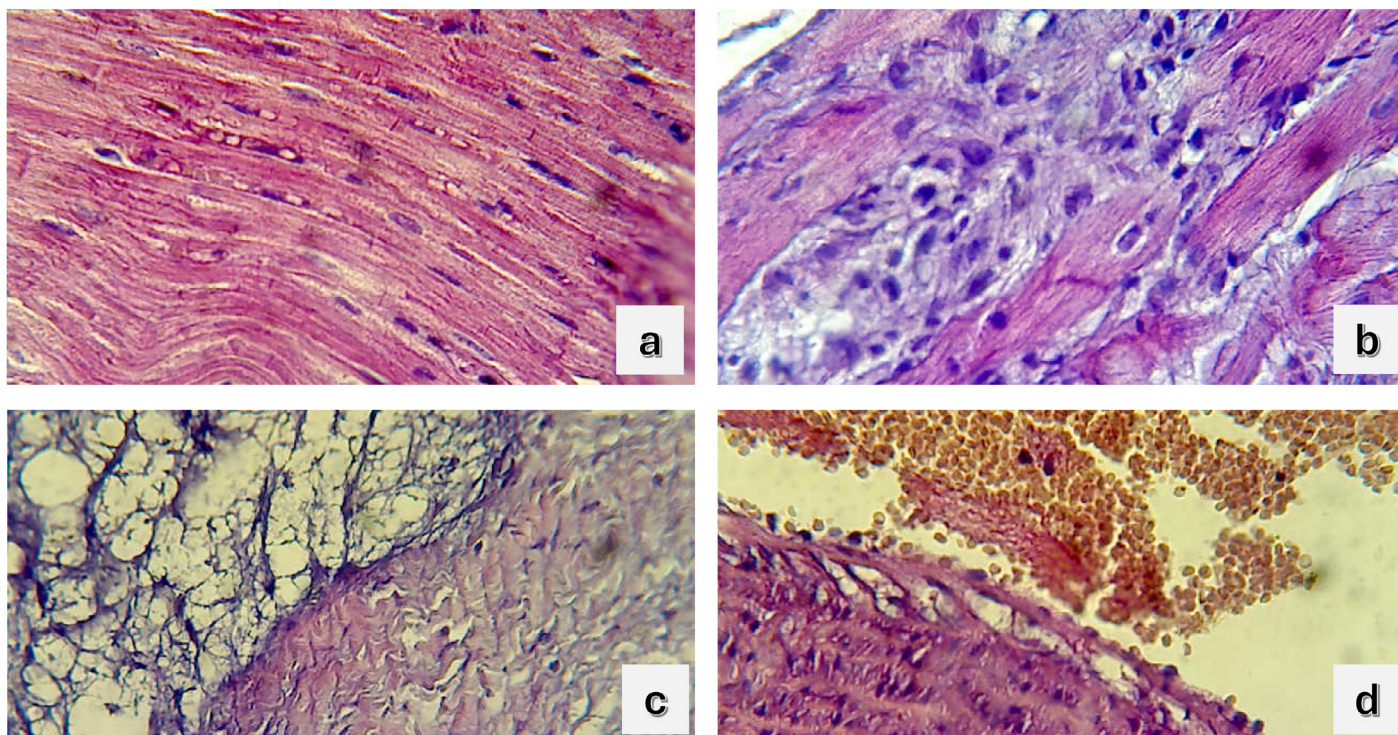


Figure 2A: Section in normal cardiac muscle architecture in control group (G1); **2B:** Section in the heart of group 2 shows no mononuclear cells infiltration between cardiac muscle; **2C:** Section in the heart of group 2 shows necrotic cardiac muscle with vacuole of fatty droplets; **2D:** Section in the aorta of G4 group shows vacuolation in subintima (H andE stain 400X).

is assessing cardiac dysfunction (Connell *et al.*, 2017). Thus, the reduction of the number in CoQ10 supplementation in nitrofurantoin alone Group and CoQ10 and nitrofurantoin combined group indicates the co-treatment pattern observed in rabbits. This is partly in agreement with the finding of (Ramirez-Hincapie *et al.*, 2023). It was aligned with prior studies assuming that CoQ10 has the potential of offering cardiac protection across all the severities of cardiac dyscrasia (Gutiérrez-Mariscal *et al.*, 2021).

These results demonstrate that consuming CoQ10 lowered C-reactive protein, a marker of inflammation in the nitrofurantoin only group (G3) as observed by (Ramirez-Hincapie *et al.*, 2023) and similar observations were also recorded in nitrofurantoin alone group and the CoQ10 and nitrofurantoin combined group. This means that there is an element of CoQ10 contributing to the fight against inflammations that in one way or the other offer an explanation of how the compound protects the heart (Samimi *et al.*, 2017). The ability of CoQ10 to suppress the aforementioned inflammatory biomarkers is in parallel with previous studies highlighting that CoQ10 has anti-inflammatory effects in various diseases (Raygan *et al.*, 2015).

HISTOLOGICAL ASSESSMENT:

Nitrofurantoin and CoQ10 treatment-regulated changes in cardiac tissue histology were assessed using histopathological approaches. The samples of heart sections were stained

by using H andE stain at 400X and the finding are shown in Figure 2. The heart section from the control group (G1) exhibiting normal cardiac muscle architecture with no discernible pathological lesions, indicating the baseline health of the tissue (Figure 2A). In contrast, analysis of animals in Group 2 (treated only with nitrofurantoin) displays mononuclear cell infiltration, typically indicative of an inflammatory response and tissue damage (Figure 2B). However, quantitative analysis reveals a mild degree of infiltration, suggesting a moderate inflammatory reaction. More pronounced changes were observed in animals from Group 2, where clear evidence of necrosis in the cardiac muscle was observed, along with the presence of vacuoles filled with fatty droplets (Figure 2C). Quantitative assessment of necrotic areas confirms significant tissue damage, characterized by extensive necrosis affecting approximately 30% of the myocardium. Analysis of the aorta of rabbits from Group 4 (nitrofurantoin combined with CoQ10 treatment), revealing vacuolation in the subintimal layers (Figure 2D). Collectively, quantitative analysis of vacuolation indicates mild to moderate changes, suggesting potential protective or modulatory effects of CoQ10.

Histological assessment revealed notable pathological changes in the cardiac tissues following nitrofurantoin administration, including mononuclear cell infiltration and necrosis in line with Hoang and Salbu, 2016. However, CoQ10 treatment attenuated these pathological changes.

es, as evidenced by reduced inflammation and necrosis in CoQ10 supplementation with nitrofurantoin alone Group and CoQ10 and nitrofurantoin combined Group as observed by (Ramirez-Hincapie *et al.*, 2023). This suggests a protective role of CoQ10 against nitrofurantoin-induced cardiac damage, potentially through its antioxidant and anti-inflammatory properties (Hernández-Camacho *et al.*, 2018).

The observed protective effects of CoQ10 against nitrofurantoin-induced cardiotoxicity are consistent with findings from other studies investigating the cardioprotective properties of CoQ10 in various experimental models (Singh *et al.*, 2018). For instance, the study (Al-Shimaysawee *et al.*, 2024) also demonstrated a similar level of decrease in oxidative stress, and cardiac biomarkers were observed with CoQ10 in doxorubicin intoxicated rats. In a meta-analysis conducted by (Akbari *et al.*, 2020), it was shown that CoQ10 supplementation enhance the heart function and lower inflammatory and oxidative levels in patients with heart failure (Akbari *et al.*, 2020).

CONCLUSIONS AND RECOMMENDATIONS

The research focuses on the finding of how CoQ10 can facilitate prevention of rabbit hearts from toxicological impact of nitrofurantoin induced cardiac toxicity. Our findings reported herein suggest that supplementation with CoQ10 offer valuable therapeutic strategy to reduce post-treatment nitrofurantoin-induced heart injury. More research is needed to fully understand the mechanisms which CoQ10 uses to alleviate the impact of toxicity in clinical settings.

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NOVELTY STATEMENT

This study constitutes a novel and groundbreaking investigation of the cardioprotective activity of Coenzyme Q10 (CoQ10) against the cardiotoxicity caused by nitrofurantoin, a commonly used antibiotic for the treatment of urinary tract infections. Even though the nitrofurantoin medicine is widely known to have cardiovascular risks and the CoQ10 supplement is also recognized for its antioxidant properties, no prior studies have examined the efficacy of CoQ10 to mitigate these specific effects. Our conducted

study would uniquely fill this gap since it is beneficial to identify biochemical markers which ameliorate cardiac injury, oxidative stress and histopathological changes in cardiac tissues..

AUTHOR'S CONTRIBUTION

Equally contributed to each of these authors.

CONFLICT OF INTEREST

The authors have declared no conflict of interest.

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