Cell. Mol. Biol. (ISSN: 1165-158X)

Journal Homepage: www.cellmolbiol.org

Cellular and Molecular Biology

Original Article

Coenzyme Q10 and its liposomal form prevent copper cardiotoxicity by attenuating oxidative stress, TLR-4/NF-κB signaling and necroptosis in rats

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Article Info

Article history:

Received: October 24, 2024
Accepted: December 19, 2024
Published: January 31, 2025

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Abstract

Copper (Cu) is an essential element involved in numerous biochemical, metabolic and cellular processes. Excessive exposure to the pesticide copper sulfate (CuSO4) was associated with toxic effects. This study aims to evaluate the efficacy of Coenzyme Q10 (CoQ10) and its liposomal form (L-CoQ10) against myocardial injury induced by CuSO4, pinpointing the involvement of redox imbalance, TLR-4/NF-κB signaling and apoptosis. Cardiac injury in rats was induced by daily oral doses of CuSO4 for 7 days, the rats were treated orally with either CoQ10 or L-CoQ10 concurrently with CuSO4 for 7 days. Elevated serum cTnI, CK-MB and LDH were observed in CuSO4-intoxicated animals. Additionally, cellular antioxidant biomarkers were decreased and the expression levels of cardiac MDA, TLR-4, NF-κB, IL-6, IL-1β, and TNF-α were upregulated. CoQ10 and L-CoQ10 prevented myocardial injury and decreased the levels of both MDA and pro-inflammatory cytokines. CoQ10 and L-CoQ10 enhanced antioxidant capacity and Bcl-2, and downregulated caspase-3, Bax, p53, RIP3, MLKL, caspase-8 and TLR-4/NF-κB signaling. In conclusion, CoQ10 and L-CoQ10 effectively prevent CuSO4 cardiotoxicity in rats. Attenuation of redox imbalance, TLR-4/NF-κB signaling, pro-inflammatory response, and necroptosis along with enhancement of antioxidant response mediated their cardioprotective efficacy. CoQ10 could be valuable in protecting people vulnerable to Cu toxicity.

Keywords: Cardiotoxicity, Coenzyme Q10, Inflammation, Oxidative stress.

1. Introduction

Copper (Cu), an essential metal present in various tissues, is involved in numerous biochemical, metabolic and cellular processes [1]. It is redox-active and serves as a crucial cofactor for proteins involved in redox regulation. Cu homeostasis is tightly regulated by mechanisms that manage its absorption, excretion, and circulating levels to maintain normal concentrations [2, 3]. Copper sulfate (CuSO4) is a widely known pesticide used to deter pests that reduce agricultural crop yields [4]. Owing to its fungicidal and bactericidal properties, it is also commonly applied in cell culture incubators to reduce the risk of contamination. CuSO4 poisoning, either accidental or intentional, can lead to multiorgan failure, which may be fatal [4]. Cu can enter the body through absorption via skin, lungs and intestine and the clinical signs of its toxicity are numerous and include seizures, kidney injury, liver damage, arrhythmia, gastropathy, and hemolysis, arrhythmia, rhabdomyolysis, and [5]. Animal studies have shown that chronic oral administration of CuSO4 leads to liver and kidney damage due to the accumulation of Cu in these organs [6].

The negative impact of Cu on the cardiovascular system has been reported with cardiotoxicity representing the most prominent effect. Cardiotoxicity refers to heart dysfunction or injury that can be triggered by various agents, including Cu [7-9]. In zebrafish, exposure to Cu has been linked to cardiotoxicity, showing signs such as cellular stress, tissue necrosis, and loss of heartbeat [9, 10]. Research has also found a correlation between elevated Cu levels and increased risk of cardiovascular diseases (CVDs) and heart failure (HF) [11-13]. Despite that the precise mechanisms of Cu-induced toxicity remain unclear, oxidative stress (OS) induced by excessive production of reactive oxygen species (ROS), and hormonal imbalances are thought to play key roles [14-16]. ROS are highly reactive molecules that can harm vital cell molecules, such as proteins, lipids, and DNA, leading to cell death [17, 18]. Accordingly, we have previously demonstrated oxidative injury in the reproductive organs, brain and heart of rats following exposure to CuSO4 [19-21]. In the same context, studies have revealed OS in the frontal cortex and hippocampus of rats exposed to CuSO4 [22], with memory and learning deficits linked to OS in rats

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Doi: http://dx.doi.org/10.14715/cmb/2025.70.1.13

treated with copper chloride [23].

ROS can also provoke inflammation through the activation of several mediators and signaling proteins, such as toll-like receptor (TRL)-4 and subsequently NF-κB, resulting in the release of pro-inflammatory mediators [24-26]. Excess production of ROS is implicated in the development of CVDs like atherosclerosis, hypertension, and heart failure [27]. It impairs the function of endothelial cells, which form the inner lining of blood vessels, thereby contributing to disease progression. Additionally, excess ROS can deteriorate mitochondrial function, leading to reduced energy production and weakened cardiac performance. This oxidative damage also affects DNA, potentially triggering genetic alterations that contribute to the onset of CVDs [28]. This body of research highlights the crucial involvement of OS in Cu toxicity. Therefore, reducing OS and inflammation may offer protection against Cu cardiotoxicity and other harmful effects. The treatment of Cu intoxication involves the use of chelating agents which can cause several side effects on the cardiovascular, respiratory, gastrointestinal, and nervous systems [29, 30], highlighting the need for safer alternatives.

Coenzyme Q10 (CoQ10) is a key cofactor in ATP synthesis, playing a vital role in energy production and the function of mitochondria, which contributes to its protective effects against CVDs [31]. CoQ10 supports energy metabolism across and participates in mitochondrial redox reactions, and protects cell membranes and lipoproteins from oxidative injury [32]. In its reduced form, ubiquinol, CoQ10 acts as a free radical scavenger, preventing the initiation and propagation of oxidative chain reactions [33]. Additionally, CoQ10 activates key molecules within the cell, exerts antioxidant effects in skeletal muscle, and aids in regenerating the active states of antioxidant vitamins [33]. The antioxidant efficacies of CoQ10 include further enhancement of catalase (CAT) and superoxide dismutase (SOD) antioxidant activities [33]. The ability of CoQ10 to attenuate OS induced by different agents in the heart, blood vessels and other organs has been reported. A recent study revealed that CoQ10 can protect the murine heart against cadmium toxicity by mitigating OS and inflammation [34]. The therapeutic doses of CoQ10 suppressed lipid peroxidation (LPO) within atherosclerotic lesions, potentially limiting the progression of these lesions in the aorta [35]. Moreover, CoQ10 demonstrated protective effects mediated via suppression of OS and NF-κB in the heart and liver of animals challenged with chemotherapy [36]. In fibromyalgia patients, CoQ10 exerted anti-inflammatory properties as observed in a clinical trial by Cordero et al [37]. Despite the established beneficial effects of CoQ10, its potential to protect the heart against Cu toxicity hasn't been explored. This study investigated the role of CoQ10 and its liposomal form (L-CoQ10) in mitigating OS, inflammation and cell death induced by Cu in the heart of rats.

2. Materials and methods

2.1. Animals and treatments

The experiment included thirty Wistar rats (180–200 g) maintained under controlled standard conditions of temperature (22±1 °C) and humidity (50-60%) on a 12h dark-light cycle with free access to food and water. The experiment was conducted according to the guidelines of the National Institutes of Health (NIH publication No. 85–23, revised 2011) and was approved by the Research Ethics Committee at King Saud University (Ref. NO: KSU-SE-24-4). The rats were allocated into 5 groups as follows:

Group I: received the vehicle.
Group II: received CuSO4 (100 mg/kg) (Sigma, USA).
Group III: received deferoxamine (DFO) (23 mg/kg) and CuSO4 (100 mg/kg).
Group IV: received CoQ10 (10 mg/kg) and CuSO4 (100 mg/kg).
Group IV: received L-CoQ10 (10 mg/kg) and CuSO4 (100 mg/kg).

CoQ10 (California Gold Nutrition, USA), L-CoQ10 (LipoLife, UK), and DFO were suspended in 1% CMC whereas CuSO4 was dissolved in water, and all were administered orally for 7 days. The doses of CuSO4, CoQ10 and DFO were selected according to our previous studies [19, 21, 34]. Twenty-four h after the last treatment, blood was collected under ketamine/xylazine anesthesia to prepare serum, and the rats were immediately dissected. The heart was removed, rinsed with cold phosphate-buffered saline (PBS), and samples were homogenized (10% w/v) in ice-cold PBS, while others were collected on RIPA buffer and stored at -80°C.

2.2. Biochemical assays

CK-MB and LDH activities were determined in serum using Spinreact (Spain) kits, and serum cTnI was measured using MyBiosource (USA) kit. The levels of Malondialdehyde (MDA), GSH, SOD and catalase were determined in the heart homogenate using Bio-Diagnostic kits (Giza, Egypt). Levels of Bcl-2, Bax, caspase-3, p53, NF-κB, IL-6, IL-1β, and TNF-α were assayed in the heart homogenate using ELISA kits (MyBioSource, USA). All assays were conducted strictly following the manufacturers' instructions.

2.3. Western blotting

Heart samples in in RIPA buffer were homogenized, centrifuged and the supernatant was separated for protein assay using Bradford reagent. Forty µg protein was subjected to SDS-PAGE followed by protein transfer onto PVDF membranes. After blocking with 5% BSA, the membranes were probed with anti-TLR-4, anti-RIP3, anti-MLKL, anti-caspase-8, and anti-β-actin (Biospess, China) overnight at 4°C. Following washing and incubation with secondary antibodies for 1 h at room temperature, the bands were developed, and the band intensity was determined using ImageJ (NIH, USA).

2.4. Statistical analysis

All the data were expressed as the mean ± SEM. Statistics were performed using GraphPad Prism 8 software. The comparisons between the different groups were performed by one-way ANOVA, followed by the post hoc Tukey's test. P values less than 0.05 were considered statistically significant.

3. Results

3.1. CoQ10 and L-CoQ10 ameliorate Cu-induced myocardial injury

Biochemical findings represented in Fig. 1A-C showed significant elevation in serum cTnI, CK-MB and LDH in CuSO4-treated rats ($P<0.001$). Both CoQ10 and L-CoQ10 as well as DFO ameliorated serum levels of the measured

cardiac function markers in Cu-administered rats. The ameliorating effect of L-CoQ10 on LDH was more potent than other treatments, whereas cTnI and CK-MB showed non-significant differences between treatments.

3.2. CoQ10 and L-CoQ10 attenuate Cu-induced cardiac OS

The results represented in Fig. 2A reveal a significant elevation in cardiac MDA levels following treatment with CuSO4 (P<0.001). The levels of cardiac GSH (Fig. 2B), SOD (Fig. 2C), and catalase (Fig. 2D) were significantly declined following the administration of CuSO4 (P< 0.001). CoQ10 and its liposomal form as well as DFO markedly decreased cardiac MDA and enhanced antioxidant capacity in CuSO4-intoxicated rats. L-CoQ10 was more effective in ameliorating MDA and antioxidant enzymes when compared to CoQ10.

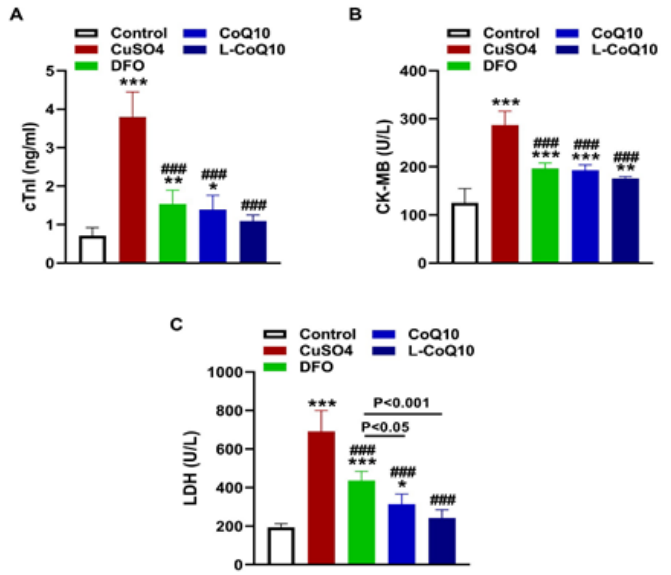

Fig. 1. CoQ10 and L-CoQ10 prevent CuSO4-induced myocardial injury. CoQ10, L-CoQ10, and DFO ameliorate serum cTnI (A), CK-MB (B) and LDH (C). Data are mean ± SEM, (n = 6). *P<0.05, **P<0.01, and ***P<0.001 vs Control, and ###P<0.001 vs CuSO4.

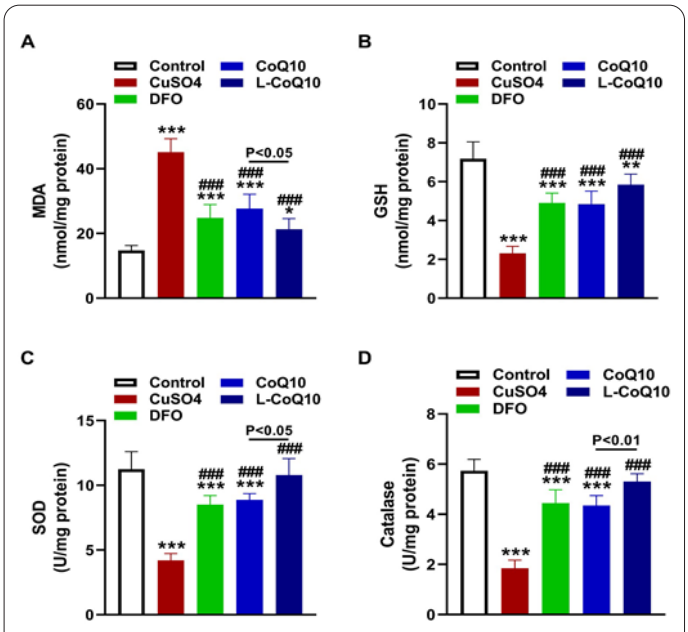

Fig. 2. CoQ10 and L-CoQ10 attenuate CuSO4-induced oxidative stress. CoQ10, L-CoQ10, and DFO decreased cardiac MDA (A), and increased GSH (B), SOD (C) and catalase (D). Data are mean ± SEM, (n = 6). *P<0.05, **P<0.01, and ***P<0.001 vs Control, and ###P.

3.3. CoQ10 and L-CoQ10 mitigate Cu-induced activation of TLR-4/NF-κB signaling and inflammatory response

The expression levels of TLR-4 and NF-κB p65 showed a significant upregulation in CuSO4-supplemented animals (P<0.001) as represented in Fig. 3A and 3B, respectively. CoQ10, L-CoQ10 and DFO suppressed cardiac TLR-4 and NF-κB p65 markedly in Cu-treated rats. The role of CuSO4 in upregulating TLR-4/NF-κB signaling was supported by the remarkable increase (P<0.001) in cardiac IL-6 (Fig. 3C), IL-1β (Fig. 3D), and TNF-α (Fig. 3E). CoQ10, L-CoQ10 and DFO decreased the levels of these cytokines in Cu-supplemented rats. The effect of L-CoQ10 on TLR-4, NF-κB p65, and IL-6 was significant when compared to the native form.

3.4. CoQ10 and L-CoQ10 prevent Cu-induced myocardial apoptosis

Changes in Bcl-2 and pro-apoptosis markers were determined to investigate the negative impact of CuSO4 on myocardial cells and the protective effect of CoQ10. CuSO4 decreased Bcl-2 (Fig. 4A) and increased Bax (Fig. 4B), caspase-3 (Fig. 4C), and p53 (Fig. 4D) (P<0.001). CoQ10, L-CoQ10 and DFO significantly ameliorated Bcl-2, Bax, caspase-3 and p53 levels, and the effect of L-CoQ10 on caspase-3 and p53 was more potent.

3.5. CoQ10 and L-CoQ10 attenuate necroptosis in the heart of CuSO4-administered rats

CuSO4 upregulated the necroptosis mediators RIP3, MLKL and caspase-8 (P<0.001) in the heart samples as represented in Fig. 5A-D. CoQ10, L-CoQ10 and DFO

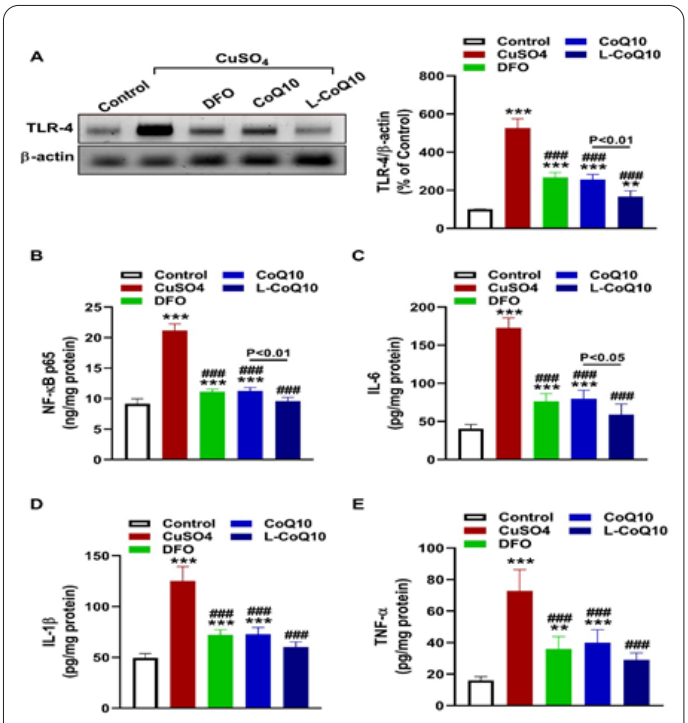

Fig. 3. CoQ10 and L-CoQ10 mitigate CuSO4-induced inflammation. CoQ10, L-CoQ10, and DFO downregulated cardiac TLR-4 (A), NF-κB p65 (B), IL-6 (C), IL-1β (D), and TNF-α (E). Data are mean ± SEM, (n = 6). **P<0.01, and ***P<0.001 vs Control, and ###P<0.00.

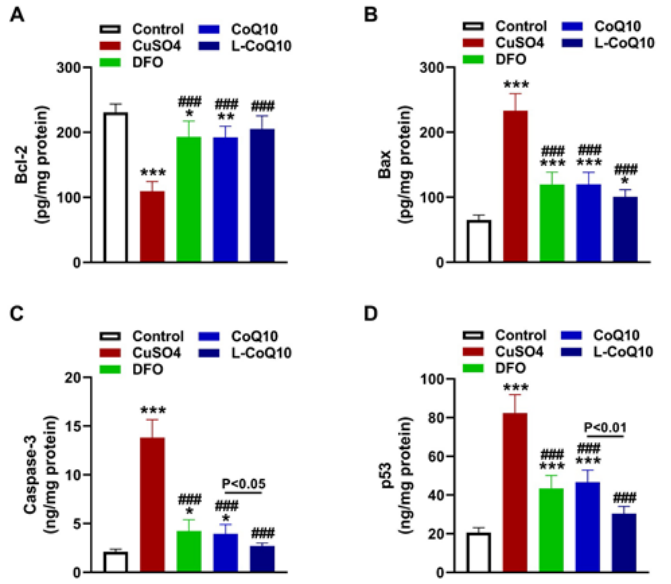

Fig. 4. CoQ10 and L-CoQ10 attenuate CuSO4-induced apoptosis. CoQ10, L-CoQ10, and DFO increased cardiac Bcl-2 (A), and decreased Bax (B), caspase-3 (C), and p53 (D). Data are mean ± SEM, (n = 6). *P<0.05, **P<0.01, and ***P<0.001 vs Control, and ###P<0.001 vs Cu.

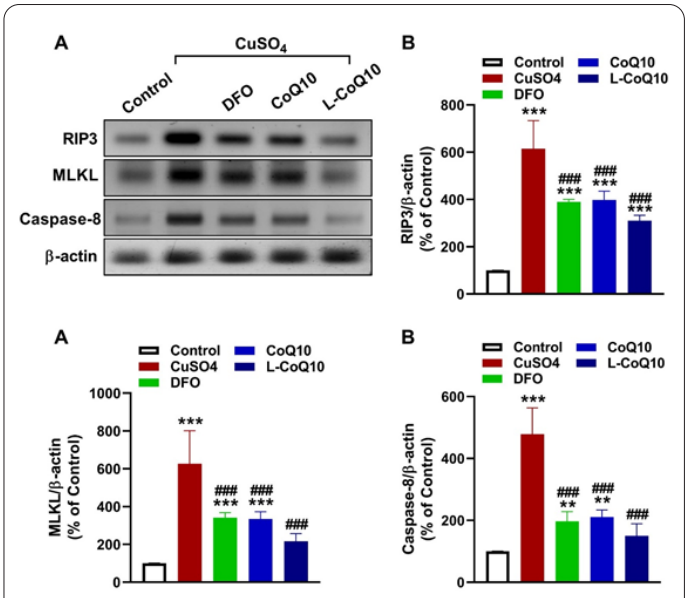

Fig. 5. CoQ10 and L-CoQ10 prevent CuSO4-induced necroptosis. CoQ10, L-CoQ10, and DFO downregulated cardiac RIP3 (A,B), MLKL (A,C), and caspase-8 (A,D). Data are mean ± SEM, (n = 6). **P<0.01, and ***P<0.001 vs Control, and ###P<0.001 vs CuSO4.

suppressed the expression of RIP3, MLKL and caspase-8 significantly in the heart tissues.

4. Discussion

Cu is a vital element involved in numerous cellular functions; however, toxicity caused by exposure to CuSO4 has been reported in different organs [11-13, 20, 21]. The high redox reactivity of Cu and its existence in reduced and oxidized and reduced forms make it a potential source of ROS and, consequently, toxic under certain conditions [14]. Disruptions in redox balance caused by Cu can induce OS and cellular damage, which are linked to various pathological conditions. CoQ10 has demonstrated potent antioxidant effects and conferred protective effects against heavy metal and chemotherapy cardiotoxicity [34, 36]. In this context, we explored the protective role of CoQ10 and L-CoQ10 against the negative impact of Cu on the heart, emphasizing the involvement of redox imbalance, TLR4/NF-κB signaling, and cell death.

Exposure to CuSO4 led to significant cardiac injury, manifested by increased circulating cTnI, CK-MB, and LDH. These findings are similar to our previous study demonstrating elevated cardiac function markers in rats challenged with CuSO4 [19]. cTnI is a valuable specific and sensitive biomarker for cardiac damage, and elevated CK-MB and LDH levels further indicate myocardial injury [38]. CuSO4, commonly used as a pesticide and disinfectant, has been linked to accidental intoxication in agricultural workers, with severe cases leading to methemoglobinemia and even death [39]. In zebrafish, Cu exposure has been associated with cardiotoxicity [9, 10], while in humans, high Cu levels have been correlated with an increased incidence of heart failure [11-13]. The cardiotoxic effects of Cu are likely mediated through OS, given its capacity to generate ROS. Our study demonstrated elevated MDA and a reduction in cellular antioxidant biomarkers (GSH, SOD and catalase), indicating OS. The redox activity of Cu contributes to the formation of reactive free radicals, while also impairing respiratory chain enzymes, thereby increasing mitochondrial ROS production [14]. ROS are potent oxidants that attack and damage cell macromolecules, ultimately leading to cell death. In accordance with the findings of this study, previous investigations have reported OS in the hippocampus following the administration of Cu compounds [22, 23], and rats that received CuSO4 exhibited an elevation in cardiac MDA and decreased antioxidants [19]. This study provides further support for the implication of redox imbalance in Cu cardiotoxicity.

CoQ10 and L-CoQ10 were found to mitigate the cardiotoxic effects of CuSO4 by lowering serum cTnI, CK-MB, and LDH. Since OS is a central mechanism in Cu toxicity [19, 22, 23], the cardioprotective efficacy of CoQ10 can be attributed to its antioxidant and free radical-scavenging properties [32, 33]. Rats treated with CoQ10 and L-CoQ10 exhibited significant reductions in cardiac MDA and improved levels of GSH, and antioxidant enzymes. The antioxidant role of CoQ10 is well-documented in various studies involving experimental cardiotoxicity provoked by chemotherapy and cadmium [34, 36], and this study provided further evidence of the role of its antioxidant capacity in its cardioprotective mechanism. CoQ10, a hydrophobic molecule, is not only a crucial component of the electron transport chain but also a potent antioxidant [40]. As a cofactor in the electron transport chain, CoQ10 plays an important role in ATP synthesis [41]. Since the majority of ROS are generated within mitochondria, these organelles represent a key site of OS. Excessive ROS can impair electron transport, leading to reduced ATP production, metabolic dysfunction, and eventually, apoptosis [41]. Therefore, CoQ10 likely protects mitochondria from ROS-induced damage, maintaining ATP production and preventing the mitochondrial dysfunction and cell death associated with Cu exposure. Moreover, CoQ10 has been shown to improve cardiac function in the treatment of cardiomyopathy [42]. These studies along with the data of this study demonstrated the potent cardioprotective efficacy of CoQ10. Of note, both forms of CoQ10 exerted

similar effects, highlighting its potent efficacy.

The protective efficacy of CoQ10 against Cu cardiotoxicity involved suppression of inflammation and apoptosis in the heart of rats. Here, rats challenged with CuSO4 exhibited an inflammatory response evidenced by the upregulation of TLR4/NF-κB signaling and subsequent release of TNF-α, IL-1β and IL-6. These findings supported our previous research showing the involvement of inflammation promoted via TLR4/NF-κB signaling in CuSO4 cardiotoxicity [19]. Excessive ROS production and cellular damage in the hearts of CuSO4-intoxicated rats directly result in the activation of TLR4 signaling [43]. TLR4 activation is associated with various myocardial conditions, including cardiotoxicity, cardiomyopathy, and heart failure [44]. Through both MyD88-dependent and -independent mechanisms, TLR4 activates factors like NF-κB, driving the production of pro-inflammatory mediators [45]. In the MyD88-dependent pathway, MyD88 recruits and activates IRAK, which subsequently activates TRAF6, leading to TAK1 activation [46]. TAK1, in turn, phosphorylates MAPKs and IKK complex, resulting in IκB phosphorylation, NF-κB activation and nuclear translocation to provoke pro-inflammatory mediators [46]. The cytokines produced, together with ROS, contribute to cell death through a programmed necrotic process known as necroptosis [47, 48]. In this context, CuSO4 exposure led to necroptosis, evidenced by the increased expression of RIP3, MLKL, and caspase-8. Necroptosis is an inflammatory form of cell death that shares morphological characteristics with apoptosis [49]. RIP3, a serine/threonine kinase, plays a key role in necroptosis by interacting with RIP1 to form the necrosome, which subsequently recruits MLKL. This process leads to plasma membrane rupture, releasing intracellular molecules into the extracellular environment [50]. Cytokines like IL-1β and TNF-α act as necroptosis triggers, while ROS drives the process further [51, 52]. TNF-α stimulates mitochondrial ROS production, enhancing necrosome formation, and RIP1 can detect ROS via modifications to cysteine residues, facilitating RIP3 recruitment and necrosome assembly [53]. In addition to necroptosis, results of the current study revealed apoptosis marked by increased Bax and caspase-3 and diminished Bcl-2. Apoptosis is a direct result of mitochondrial damage via the concert work of pro-inflammatory cytokines and ROS. Mitochondrial membrane disruption and cytochrome c release activate caspase-3, initiating the apoptotic cascade. Therefore, mitigating OS and inflammation can effectively inhibit necroptosis and apoptosis in the hearts of rats exposed to CuSO4.

CoQ10 and its liposomal form effectively mitigated myocardial inflammation and cell death provoked by exposure to CuSO4. CoQ10 significantly alleviated Cu-induced myocardial inflammation by suppressing TLR4/NF-κB signaling and attenuating the release of pro-inflammatory mediators. Since ROS are known to promote NF-κB and TLR4, the anti-inflammatory effects of CoQ10 can be attributed to its antioxidant properties. CoQ10 demonstrates its anti-inflammatory role by inhibiting the production of pro-inflammatory molecules, and previous studies have shown that CoQ10 not only suppresses OS but also protects tissues from inflammatory and nitrative damage [54, 55]. Additionally, CoQ10 reduced pro-inflammatory cytokines during inflammatory conditions. In diabetic subjects, a four-week administration of CoQ10 decreased IL-6 and TNF-α [56]. In a clinical trial with fibromyalgia patients, CoQ10 supplementation reduced serum IL-1β and IL-18 [37]. Furthermore, inhibition of ROS, NF-κB and NLRP3 inflammasome were involved in the protective effects of CoQ10 against liver ischemia/reperfusion injury [57] and cadmium cardiotoxicity [34]. The anti-inflammatory mechanism of CoQ10 in a mouse model of cadmium cardiotoxicity has been reported by Antar et al [34] who conducted both in vivo and in silico work to investigate the cardioprotective mechanism. In this study, CoQ10 effectively mitigated the inflammatory response mediated via NF-κB/NLRP3 inflammasome axis and the in silico data revealed the affinity of CoQ10 to bind with NF-κB RelA homodimer, an effect that can suppress the transcriptional activity of NF-κB [34]. In addition, CoQ10 showed binding affinity towards NLRP3 and ASC1 pyrin domains and downregulated both NF-κB and NLRP3 in cadmium-challenged mice [34]. These effects resulted in the prevention of the release of pro-inflammatory cytokines and the protection of the heart against cadmium toxicity [34]. Given the role of ROS and pro-inflammatory mediators in provoking cell death via apoptosis and necroptosis, the ability of CoQ10 to protect the heart against Cu toxicity is related to its dual anti-inflammatory and antioxidant efficacy.

5. Conclusion

These findings confer information on the protective effect of CoQ10 and its liposomal form against cardiotoxicity induced by CuSO4. CoQ10 and L-CoQ10 ameliorated cardiac tissue injury and suppressed OS, inflammation, apoptosis and necroptosis in Cu-administered rats. The beneficial role of CoQ10 was linked to suppression of TLR4/NF-κB signaling and enhancement of antioxidant activity. Both CoQ10 and its liposomal form exhibited comparable efficacy in protecting the heart against CuSo4 toxicity. Both formulations effectively prevented tissue injury, OS, and inflammation, key pathological mechanisms triggered by exposure to CuSO4. Notably, the nanoformulation of CoQ10 did not demonstrate a significant increase in the protective activity compared to the conventional form, suggesting that the high intrinsic efficacy of CoQ10 in mitigating Cu cardiotoxicity may have limited the potential for further enhancement through nanoformulation. Thus, the nanoform of CoQ10, while offering potential advantages in other contexts, does not appear to provide additional cardioprotective benefits in this model. Therefore, CoQ10 can prevent Cu cardiotoxicity, pending further investigations to delineate other involved mechanisms.

Funding

This research was funded by the researchers supporting project number (RSPD2025R622).

Conflict of interest

No conflict of interest.

Data availability

All data are included in the manuscript.

Acknowledgments

The authors would like to extend their gratitude to Researchers Supporting Project number (RSPD2025R622), King Saud University, Riyadh, Saudi Arabia for funding this work.

Author contributions

Project administration: A.M.A. L.F. and H.K.A.; Methodology: A.M.A., H.K.A., W.S.S., and I.H.H.; Validation: H.K.A., A.M.A., J.S.A., H.A.A., and W.S.S.; Formal analysis: I.H.H, and W.S.S.; Writing the original draft: J.S.A., A.S.A., N.M.A., A.A., and S.A.; All authors have read and agreed to the final version of the manuscript.

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