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Evaluate the Effect of Coenzyme Q10 on the Prevention of Doxorubicin-Induced Acute Cardiotoxicity in Rats

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Abstract

Objective: This study will evaluate the potential protective effects of coenzyme Q10 on DOX-induced cardiotoxicity in female rats, manifested by changes in biochemical parameters in tissue and serum samples histopathological differences, and compare their changes.

Methods: 24 female rats were divided into three groups based on weight. The first group received saline, the second group received a cumulative dose of 15 mg/kg of DOX via IP injection, and the third group was pre-treated with CoQ10 before receiving DOX. The data were analysed using a one-way ANOVA test with a Bonferroni post hoc test to compare the markers and histopathological changes in different groups. The GraphPad Prism version 8.1 was used to do the statistical analysis.

Results: As indicated by a statistically significant increase ($P < 0.0001$) in TNFα and ICAM-1 level, doxorubicin-induced cardiotoxicity. Additionally, the level of GSH, SOD, and caspase-3 did not differ significantly between the DOX + CoQ10 group and the control group. Furthermore, lesions and histological alterations were induced by the substance. Significant reductions in cardiotoxicity were observed with the administration of coenzyme Q10, as indicated by notable increases ($P < 0.0001$) in SOD, GSH, and TNFα and significant decreases ($P < 0.0001$) in caspase 3 when compared to the DOX group. Also, the CMYO score and lesions exhibited a substantial improvement.

Conclusion: In this investigation, coenzyme Q10 exhibited cardioprotective effects against DOX-induced damage to the mouse heart. This phenomenon potentially pertains to inhibiting and safeguarding against oxidative stress, the pathway of apoptosis, and the inflammatory response.

Keywords: Cardiotoxicity, inflammatory markers, oxidative-stress, apoptosis, coenzyme Q10, doxorubicin

Introduction

An undesirable consequence is that a chemotherapy agent may destroy the function and organisation of healthy cells within and surrounding the heart. In addition to cell death, cardiomyopathy, congestive heart failure, pericarditis, myocarditis, acute coronary syndromes, and additional complications may also occur as a result of chemotherapy-induced cardiac damage. Chemotherapy-induced cardiac dysfunction is a significant reason for patient mortality and morbidity.[1,2] Cardiac toxicity is a growing problem associated with implementing different groups of chemotherapeutic agents because of the detrimental impact it has on prognosis and quality of life.[3] Preventing complications requires intervention at the earliest asymptomatic stage, as opposed to waiting for issues to develop. Therefore, further research and development are crucial for the limited clinical application of cardioprotective adjuvants.

Cardiotoxicity includes short- and long-term toxic effects on the heart, ranging from structural and functional myocardial abnormalities to severe cardiomyopathy and heart failure, which may result in cardiac transplantation or death.[4] Different theories suggest that reactive oxygen species (ROS) generation may lead to lipid peroxidation and mitochondrial malfunction; topoisomerase 2-beta in myocytes can be targeted, as calcium homeostasis can be impaired.[5] The primary cardiotoxic effects of drugs will be classified as left ventricular dysfunction, rhythm abnormalities, and ischemia.[6] DOX-induced cardiotoxicity can lead to arrhythmias, ischemia, systolic dysfunction, and heart failure. Cardiac cell death and necrosis are common causes. The severity of heart failure depends on the dose and time of use, and its prevalence increases after chronic exposure.[7]

Doxorubicin, an anthracycline compound, is a multipurpose anticancer drug. However, its use is significantly limited due to the risk of cardiotoxicity, which can lead to cardiomyopathy and heart failure (HF).[8] DOX is structurally similar to daunorubicin, which was found to cause heart damage in studies dating back to the 1970s. In humans, topoisomerase IIα and IIβ are ATP-dependent enzymes that relieve torsional stress during DNA processes by separating and moving the strands of DNA duplexes.[9] Ultimately, the outcomes of the above interactions include breaking DNA strands, inhibiting DNA and RNA replication, and preventing protein synthesis.[10,11] The recommended dose of Doxorubicin HCl varies based on tumour stage, chemotherapy, and patient health. The typical dose is 60–75 mg/m^2 every 21 days, with adjustments required for hepatic dysfunction, elderly patients, children, cardiac disease, and obesity.[12] This cancer treatment can cause cardiovascular changes, including vascular disorders, cardiac structural concerns, and heart failure. Various treatments, such as anthracycline, antiangiogenic therapy, trastuzumab, radiation therapy, and restrictive cardiomyopathy, can cause these changes.[13]

Cardiotoxicity induced by doxorubicin commences with myocardial cell damage and progresses to dysfunction of the left ventricle. Pathways of oxidative stress, inflammatory cytokines, myocyte membrane injuries, intracellular Ca^{2+} overload, iron-free radical production, and DNA are all crucial components of its pathophysiology.[14] Reactive oxygen species (ROS) are of significant importance in the mechanisms underlying DOX-induced cardiotoxicity. Hearts exposed to DOX also lack the anti-oxidant enzyme required in order to eliminate ROS produced by oxidative stress. Numerous free radicals accumulate in the myocardium, causing the endoplasmic reticulum (ER) to undergo destruction, an essential

organelle responsible for regulating Ca^{2+} levels, membrane proteins, translocation, and apoptosis.[15]

Coenzyme Q10 (CoQ10) is an essential constituent of the membrane oxidoreductase system found in cellular organelles, such as mitochondria, lysosomes, and Golgi vesicles.[16] Natural sources include foods like red meat, fish, cereals, broccoli, and spinach, whereas synthetic sources include capsules or solutions containing varying concentrations.[17] Experimental applications of CoQ10 have demonstrated encouraging outcomes in the management of diverse intoxications and ailments, including paracetamol toxicity,[18] inflammatory diseases,[19] and heart failure.[20] Coenzyme Q, also known as ubiquinone or CoQ, is an indispensable cofactor in mitochondrial oxidative phosphorylation and a lipid-soluble, potent antioxidant.[21,22]

CoQ10 functions as a redox-active lipophilic reactive oxygen species (ROS) scavenger, engaging in extra-mitochondrial electron transport, regulating cellular permeability, inhibiting DNA membrane protein oxidation, sustaining endothelial function via tocopheryl radical-mediated vitamin E regeneration, and preventing lipid peroxidation.[17] As a result, the therapeutic application of CoQ10 in incurable ailments that confront contemporary societies, such as Alzheimer's, Huntington's, Parkinson's, and cardiovascular diseases, has garnered increased interest.[23] The mevalonate pathway consists of the following reactions: farnesyl pyrophosphate (FPP), the substrate for the biosynthesis of CoQ, cholesterol, dolichol, and isoprenylated proteins, and acetyl-coenzyme A (acetyl-CoA). The fact that the first two reactions take place in peroxisomes, the endoplasmic reticulum, and mitochondria suggest that animal cells have numerous sites of synthesis.[24] Insufficiency of CoQ10 in humans may result from either augmented utilisation by the body or diminished biosynthesis. Biosynthesis requires a minimum of 12 genes, and severe mutations can result in a deficiency of CoQ10. CoQ10 levels may also be adversely affected by mutations in mitochondrial DNA, ETFDH, APTX, FXN, and BRAF genes, among others; such conditions may result in the development of severe ailments like steroid-resistant nephrotic syndrome with sensorineural deafness.[25]

Given the efficacy of DOX as a chemotherapeutic agent and its limitation in terms of cardiotoxicity, it is critical to investigate novel prospective pharmaceuticals that can mitigate its more pronounced cytotoxic effects. Consequently, the objective of this study was to assess the potential cardioprotective properties of coenzyme Q10 in mitigating cardiac injury subsequent to the administration of DOX.

Materials and Methods

Twenty-four female Sprague Dawley rats, aged 10–12 weeks and weight (150–200g) have been used. After that, they were divided according to their weight into three groups, with eight rats in each group. The rats in the control group received normal saline 0.9%. For a duration of two weeks, 2.5 mg per kg of doxorubicin was administered intraperitoneally to each rat in the induced group.[26,27] The dapagliflozin with doxorubicin-group (induced pretreated) received DAPA at a dose of 1 mg/kg orally for three days prior to treatment and continued for two weeks; doxorubicin was also administered via the same route in the induced group.[28] The Astra-Zeneca® dapagliflozin was dissolved in a solution of normal saline.[29] Rats from all groups were sacrificed 48 hours after the final dose of doxorubicin, and the body weight of each individual was documented.[30]

Anaesthetising the animal with ketamine (90 mg/kg) and xylazine (20 mg/kg) was performed. The gathered serum was placed in deep freeze until the inflammatory parameters, which were analysed with Eliza-Kits (BT LAB®), could be determined; for histopathological analyses and the quantification of apoptotic and oxidative stress parameters, heart tissue samples were utilised.

Results

Table 1 indicates a significant increase ($P < 0.0001$) of the caspase-3 enzyme activity in the DOX group compared to the control group. In contrast, no significant differences were observed in the DOX + CoQ10 group compared to the control group. The results revealed significant decreases ($P < 0.0001$) in the DOX + CoQ10 group compared to the DOX group. The SOD level in Table 2, had a significant decrease ($P = 0.0112$) in the DOX group compared to the control group. However, there was no significant difference between the control and DOX + CoQ10 groups. In contrast, the DOX + CoQ10 group showed a significant increase in SOD level compared to the DOX group ($P < 0.0004$). The data in the same table shows that the DOX-treated group had significantly lower GSH levels ($P > 0.0001$) than the control group. However, there was no significant difference between the control and DOX + CoQ10 groups. While the DOX + CoQ10 group showed significantly increased GSH levels ($P < 0.0001$) than the DOX group. As appeared in Table 3, there was a significant elevation ($P < 0.0001$) of heart ICAM-1 level with DOX and DOX + CoQ10 groups compared to the control group. However, there were no significant differences in the DOX + CoQ10 group compared to the DOX group. Also, the TNFα level significantly increased ($P < 0.0001$) in the groups treated with DOX and DOX + CoQ10 compared to the control group. While the DOX + CoQ10 group showed a significant decrease ($P < 0.0001$) compared to the DOX group.

Table 1. **Effects of apoptotic marker caspase-3 after 2 weeks**

Bonferroni's multiple comparison tests	Mean ± SEM
Control	0.7672 ± 0.03141****
DOX	1.690 ± 0.06614 ns
DOX + CoQ10	0.9995 ± 0.03822####

The data are presented as the mean ± standard error means for each group of eight rats, employing one-way ANOVA in conjunction with the Bonferroni post hoc test. (****$P < 0.0001$) and (####$P < 0.0001$) groups, respectively, when compared to the DOX and control groups.

Table 2. **Effects of oxidative stress markers SOD & GSH after 2 weeks**

Bonferroni's multiple comparison tests	Mean ± SEM for SOD	Mean ± SEM for GSH
Control	2.662 ± 0.1374*	176.3 ± 3.360****
DOX	1.562 ± 0.1008 ns	100.8 ± 2.598 ns
DOX + CoQ10	3.027 ± 0.2205 ###	163.7 ± 3.765####

The data are presented as the mean ± standard error means for each group of eight rats, employing one-way ANOVA in conjunction with the Bonferroni post hoc test. (****$P < 0.0001$) and (####$P < 0.0001$) groups, respectively, when compared to the DOX and control groups.

Table 3. **Effects of inflammatory markers ICAM-1 & TNFα after 2 weeks**

Bonferroni's multiple comparison tests	Mean ± SEM for ICAM-1	Mean ± SEM for TNFα
Control	1.621 ± 0.1917****	124.8 ± 4.168****
DOX	2.750 ± 0.07003****	176.4 ± 4.854****
DOX + DAPA	2.470 ± 0.05760 ns	57.89 ± 5.200****

The data are presented as the mean ± standard error means for each group of eight rats, employing one-way ANOVA in conjunction with the Bonferroni post hoc test. (****$P < 0.0001$) and (####$P < 0.0001$) groups, respectively, when compared to the DOX and control groups.

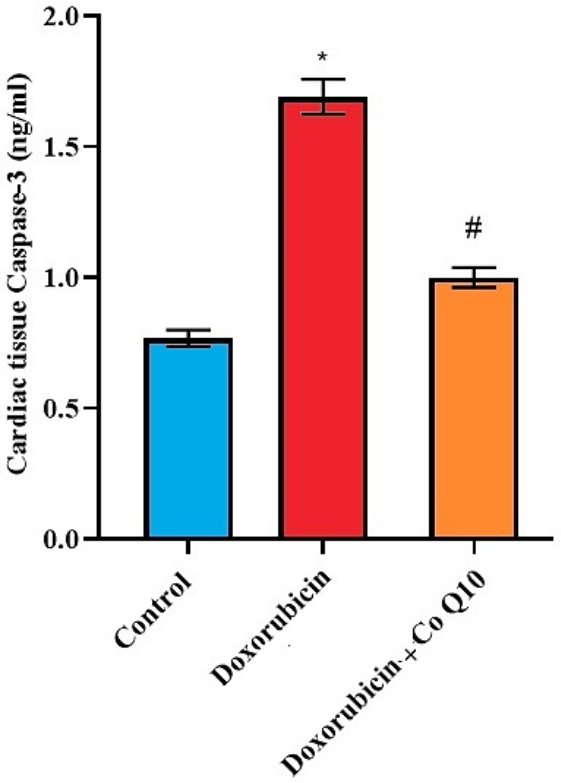

Fig. 1 **Level of Caspase-3 in heart tissue of the experimental groups.**

Discussions

DOX-induced cardiotoxicity, as evidenced by a statistically significant increase ($P < 0.0001$) in the concentrations of caspase-3, ICAM-1, and TNFα in the cardiac tissues of rats relative to the control group. Conversely, the concentrations of SOD and GSH decreased significantly ($P < 0.0001$) in the same group. Compared to the control group, the doxorubicin group also showed that the drug caused changes in histological lesions, which agreed with a recent study.[31] The pathophysiology of doxorubicin-induced cardiotoxicity has been associated with apoptosis.[32] Doxorubicin-induced oxidative stress triggers caspase-3 activation, leading to myocardial cell death via multiple signalling pathways.[33] Caspase-3 was activated to some degree in the current investigation. As a result, mitochondrial dysfunction is hypothesised to be at least possible. The activation of caspase-3 via the mitochondrial pathway may, therefore, be a mechanism by which DOX-induced apoptosis is achieved.

A notable reduction in cardiotoxicity was observed in the DOX + CoQ10 group ($P < 0.0001$) when compared to the DOX group, which can be attributed to the administration of coenzyme Q10 (Figure 1). These findings agreed with the study Chen et al.;[34] therefore, CoQ10 may prevent heart damage caused by doxorubicin and protect cardiomyocytes from fibrosis and cell death. In addition, Shabaan et al., [35] concluded that by modulating the expression of genes, CoQ10 protects against DOX-induced cardiotoxicity. The administration of CoQ10 in conjunction with DOX results in an increase in the Bax/Bcl-2 gene expression ratio, caspase-3 and iNOS immunoexpression, and MDA levels. The finding of a recent study (Zhao)[36] was that severe damage to the mitochondria caused by cardiotoxicity leads to the apoptosis of cardiomyocytes through caspase-dependent mechanisms; however, studies suggest that Coenzyme Q10 can improve this condition by inhibiting cell apoptosis and suppressing mitochondrial dysfunction. Additionally, the positive effects of CoQ10 on mitochondrial function in damaged cardiomyocytes were reported.[37,38]

The findings of the research demonstrated a significant increase in lipid peroxidation within the cardiac tissue of rodents that were treated with doxorubicin (Figure 2). This was confirmed by a decrease in the concentrations of GSH and SOD when compared to the control group. Antagonism

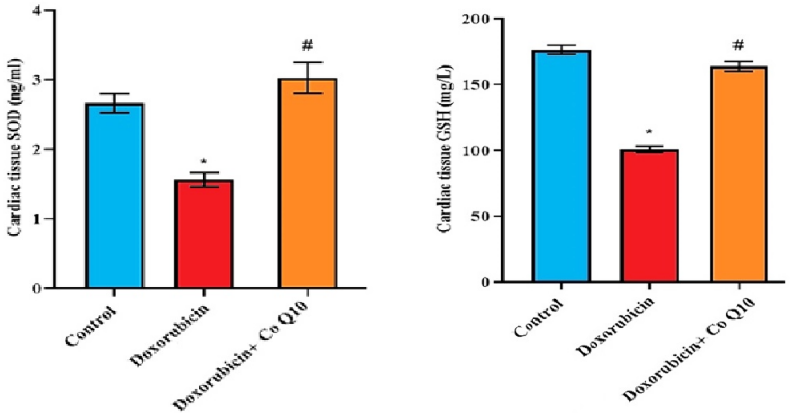

Fig. 2 **Oxidative stress marker levels in the heart tissue of the experimental groups.**

between oxidative stress and the body's antioxidant defence system is precipitated by the production of reactive nitrogen species (RNS) and reactive oxygen species (ROS). Cardiolipin, a phospholipid in the mitochondrial membrane, has a high affinity with DOX, leading to mitochondrial dysfunction mediated by oxidative stress.[39] The oxidative stress can be avoided by having an antioxidant defence system primarily involved in scavenging ROS.[40] Antioxidant enzymes, such as superoxide dismutase and glutathione peroxidase, are widely recognised as the principal cellular defence against free radical-mediated oxidative stress.[41]

The CoQ10 administration showed a significant increase in GSH and SOD levels in the cardiac tissue of rats compared to the DOX group. As in the study (Botelho et al. and Mustafa et al.),[28,42] the results of the study revealed a notable elevation in lipid peroxidation in the cardiac tissue of rodents that received doxorubicin treatment, as indicated by a reduction in GSH and SOD concentrations in comparison to the control group. An imbalance between the antioxidant defence system of the body and oxidative stress is caused by the generation of reactive nitrogen species (RNS) and reactive oxygen species (ROS).[43]

The findings of our study agree with other studies, which present a significant increase ($P > 0.0001$) in ICAM-1 and TNF-α levels in the DOX + CoQ10 group compared with the control group (Figure 3). In contrast, the DOX + CoQ10 group presents no significant differences compared to the DOX group. ROS produced by DOX might trigger inflammatory responses, primarily via NF-B, which causes the release of cytokines, including interleukin one beta [IL-1] and tumour necrosis factor-alpha [TNF-alpha]. This may account for the observed outcomes.[44,45] The study of Tsuneki et al.[46] revealed that coenzyme Q10 reduces the increased expression of ICAM-1. In its absence, ICAM-1 and VCAM-1 levels increase 1.3 and 1.5-fold, respectively. However, coenzyme Q10 effectively restores the elevated levels of it. CoQ10 significantly decreases lipid and antioxidation levels, as determined by rodents' serum lipid and oxidation levels. Additionally, inflammatory proteins, including IL-6, TNF-α, ICAM-1, VCAM-1, and NLRP3, may be inhibited by CoQ10, thereby preventing atherosclerosis. Subsequently, it identified the expression of proteins linked to energy metabolism.[47]

In addition, the administration of CoQ10 to rats treated with DOX resulted in a 10% reduction in moderate hypotrophic lesions within cardiac muscle fibres, this was determined by histopathology by comparing (Figures 4, 5, and 6) between the control and doxorubicin group and the group treated with CoQ10, respectively. Other DOX-induced cardiac tissue alterations were mitigated by CoQ10, including cardiomyocyte degeneration, intracellular autophagosomes, ECG changes, oxidative stress, and lipid peroxidation.[28]

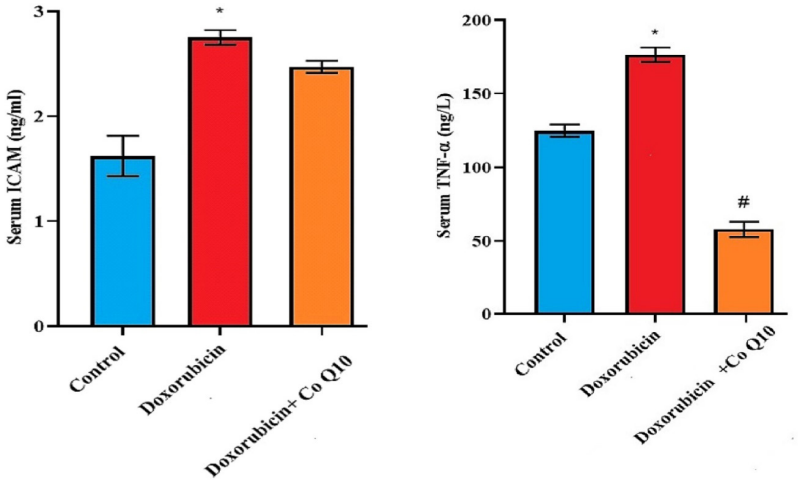

Fig. 3 **Inflammatory markers level in heart tissue of the experimental groups.**

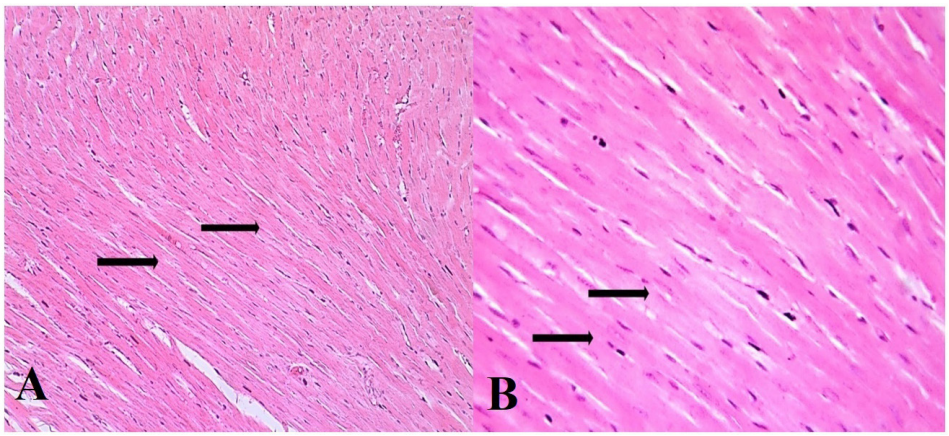

Fig. 4 **The histological section with H&E stain of the rat's heart for the control group with magnification scale (A) 10X, (B) 40X.**

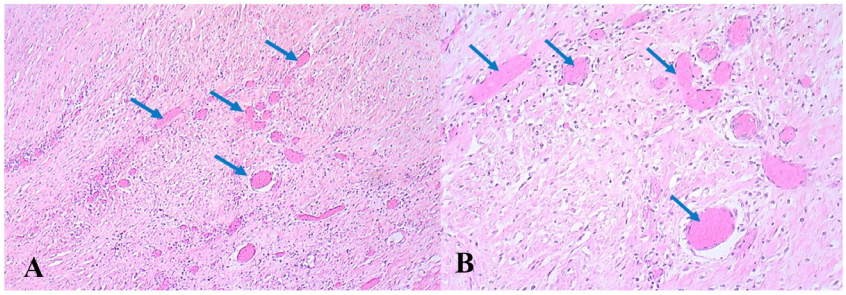

Fig. 5 **The histological section with H&E stain of the rat's heart for the DOX group with magnification scale (A) 10X, (B) 40X.**

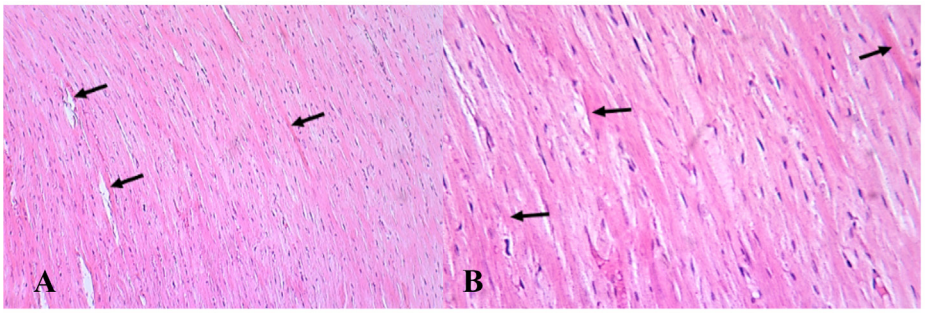

Fig. 6 **The histological section with H&E stain of the rat's heart for the DAPA group with magnification scale (A) 10X, (B) 40X.**

Conclusion

In this investigation, coenzyme Q10 exhibited cardioprotective effects against DOX-induced damage to the mouse heart. This phenomenon potentially pertains to inhibiting and safeguarding against oxidative stress, the pathway of apoptosis, and the inflammatory response.

Conflicts of Interest

According to the authors, no conflicts of interest exist.

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