Interdisciplinary Research in Medical Sciences Specialty
ISSN: 3062-4401
2022, Volume 2, Issue 1, Page No: 26-32

Available online at: www.galaxypub.co/page/journals

Galaxy Publication

Coenzyme Q10 Modulates Gene Expression in Myocardial Infarction Induced by Isoproterenol

Ahmed O. Babalghith[1]*

[1] Department of Medical Genetics, College of Medicine, Umm Al-Qura University, Makkah, Saudi Arabia.

***E-mail** ✉ aobabalghith@uqu.edu.sa

Received: 24 February 2022; **Revised:** 26 May 2022; **Accepted:** 03 June 2022

ABSTRACT

Cardiac remodeling involves alterations in gene expression, molecular, cellular, and interstitial changes that ultimately affect heart function. Coenzyme Q10 (CoQ10) plays a critical role in the mitochondrial electron transport chain, which is essential for ATP production. This study aimed to evaluate the effect of CoQ10 on myocardial infarction (MI) in male rats induced by isoproterenol (ISO). The rats were divided into four groups: control, CoQ10-treated, ISO-treated, and CoQ10+ISO-treated. Various biochemical markers were evaluated, including liver function indicators (AST, ALT, ALP, albumin, and total protein), cardiac biomarkers, electrolytes, TNF levels, oxidative stress (malondialdehyde [MDA]), and antioxidant markers (superoxide dismutase [SOD], reduced glutathione [GSH]). In addition, qPCR was used to measure the expression of key genes involved in angiogenesis (vascular endothelial growth factor [VEGF]), migration (matrix metalloprotease 9 [MMP9]), and antioxidants (heme oxygenase-1 [HO-1]) in heart tissue. CoQ10 treatment in ISO-treated rats resulted in a significant reduction in liver injury, as evidenced by improved liver function markers, decreased MDA levels, elevated GSH and SOD levels, and upregulated VEGF, MMP9, and HO-1 expression. These findings suggest that CoQ10 has a protective role against myocardial injury caused by the ISO-induced model.

Keywords: HO-1, Gene expression, Oxidative stress, CoQ10, VEGF, MMP9

How to Cite This Article: Babalghith AO. Coenzyme Q10 Modulates Gene Expression in Myocardial Infarction Induced by Isoproterenol. Interdiscip Res Med Sci Spec. 2022;2(1):26-32. https://doi.org/10.51847/PWaCUiUjJ6

Introduction

Cardiovascular diseases (CVDs) remain the leading global cause of death [1]. Acute myocardial infarction (MI), resulting from a blocked coronary artery, is a significant contributor to both morbidity and mortality worldwide [2]. Common symptoms of MI include chest pain, often described as deep pain, along with nausea, dizziness, ischemia, and shortness of breath [3]. Following an ischemic episode, the inflammatory process plays a crucial role in cardiac tissue damage. Neutrophils invade the infarcted area, releasing proteolytic enzymes and reactive oxygen species that contribute to the injury of cardiac cells [4].

Cardiac remodeling refers to the changes in gene expression, as well as alterations in the molecular, cellular, and interstitial environment, all of which impact the heart's function [5]. The isoproterenol (ISO)-induced myocardial infarction model is commonly employed to study the effects of various treatments on heart function. ISO, which mimics adrenergic receptor activation, can induce myocardial necrosis when administered subcutaneously [6]. Oxidative stress and inflammatory responses are key contributors to myocardial remodeling following ischemia [7]. The excessive production of reactive oxygen species and inflammatory cytokines activates matrix metalloproteinase, leading to changes in the extracellular matrix (MMP) [8].

Several natural compounds and dietary supplements with antioxidant properties have shown promise in counteracting oxidative stress in the ISO-treated model. Coenzyme Q10 (CoQ10), a naturally occurring antioxidant in the body, has been shown to halve heart mortality rates in various studies. CoQ10 plays a critical role in cellular energy production and is beneficial in mitigating ischemia and reperfusion injuries linked to

coronary revascularization [9]. Additionally, CoQ10 supports intracellular energy generation, reduces endothelial dysfunction, and activates mitochondrial uncoupling proteins [10].
This study aims to assess the effects of CoQ10 on myocardial infarction induced by ISO, focusing on biochemical markers, genetic alterations, and other biochemical changes to evaluate its effectiveness in treatment.

Materials and Methods

Animals
The study received approval from the research ethics committee at Umm Alqura University (2021/021AO), Saudi Arabia, following the institutional animal care and use guidelines. ARRIVE principles were observed throughout the experiment. Male rats, with a weight range of 115–125 g, were selected for the study. They were kept in a controlled environment with a constant temperature and a 24-hour light/dark cycle, with free access to regular food and water.

Myocardial infarction induction
To induce myocardial infarction in the rats, a subcutaneous injection of 150 mg/kg of isoproterenol (ISO) dissolved in saline was administered daily for 2 consecutive days. This dosing regimen was based on established protocols in the existing literature [11].

Experimental design
The rats with induced infarction were randomly divided into six groups, each consisting of six animals:

1. *Control group (C):* These rats were provided with a standard laboratory diet throughout the experiment.
2. *CoQ10 group (CoQ10):* The rats in this group received coenzyme Q10 (10 mg/kg body weight) daily via oral gavage.
3. *Isoproterenol group (ISO):* Rats in this group were fed a regular rat diet and received subcutaneous injections of isoproterenol (ISO) at a dose of 150 mg/kg in 2 ml of saline for 2 consecutive days.
4. *CoQ10 + ISO group:* These rats were given coenzyme Q10 (10 mg/kg body weight) daily via oral gavage for two weeks before receiving the same ISO treatment (150 mg/kg in 2 ml saline, subcutaneously) for 2 consecutive days.

Blood collection
Blood was obtained in centrifuge-compatible glass tubes and allowed to clot before being centrifuged at 4000 rpm for 15 minutes. The clear serum, free from hemolysis, was swiftly extracted and placed into pre-labeled Eppendorf tubes, which were stored at -20 °C for further biochemical testing. Following blood collection, the heart was immediately excised, homogenized for biochemical analysis, or preserved at -80 °C for RNA extraction.

Biochemical parameter evaluation
Biochemical analyses were conducted using commercially available kits. Liver function markers, including aspartate transaminase (AST) and alanine transaminase (ALT), along with albumin and total proteins, were quantified (Roche Diagnostics, Saudi Arabia). Serum levels of cardiac markers, TNF, and electrolytes were also measured. Additionally, markers of antioxidant activity, such as glutathione (GSH) and superoxide dismutase (SOD), were assessed, while lipid peroxidation was determined by measuring malondialdehyde (MDA) in tissues, utilizing kits from Roche Diagnostics.

Gene expression analysis in cardiac tissues
Gene expression levels of VEGF, MMP9, and HO-1 in the heart tissues from all experimental groups were assessed via real-time PCR. Initially, total RNA was isolated, then transcribed into cDNA using Thermo Scientific kits (#L0852 and #EL0331, respectively).
The sequences of primers were as follows: F: 5` CACATCCAGACAGACACCAGT 3` and R: 5` CTACAAATGGGAATGTCTCTGC 3` for HO-1; F: 5` TCGAAGGCGACCTCAAGTG 3` and R: 5` TTCGGTGTAGCTTTG GATCCA 3` for MMP9; F: 5` GATCATGCGGATCAAACCTCACC 3` and R: 5` CCTCCGGACCCAAAGTGCTC 3` for VEGF; F: 5` CATGGATGACGATATCGCT 3` and R: 5` CATGAGGTAGTCTGTCAGGT 3` for β actin (internal control).

Statistical analysis

Data analysis was conducted using GraphPad Prism 5.0. The results are expressed as the mean ± standard error of the mean (SEM). One-way analysis of variance (ANOVA) was used to analyze the data, followed by the Tukey test for comparisons between variables. Statistical significance was determined at a P-value of 0.05.

Results and Discussion

Effect of coenzyme Q10 on liver function tests

ISO-treated rats exhibited a significant rise in the enzyme activities of ALT, AST, Alb, and ALP when compared to the control group **(Table 1)**. Following CoQ10 treatment, the activities of ALP, AST, and ALT enzymes were notably diminished. Additionally, in the CoQ10+ISO group, there was a slight change observed in the activity of Alb and TP.

Table 1. Liver function in ISO treated rats after treatment with CoQ10

Groups	Control (n = 6)	CoQ10 (n = 6)	ISO (n = 6)	CoQ10 + ISO (n = 6)
ALT, U/L (mean ± SEM)	12.52 ± 0.22^{a}	13.81 ± 0.20^{a}	49.210 ± 0.62^{b}	36.79 ± 1.15^{c}
AST, U/L (mean ± SEM)	44.65 ± 0.34^{a}	45.89 ± 0.52^{a}	81.77 ± 0.66^{b}	44.61 ± 1.26^{c}
Albumin, g/dl (mean ± SEM)	3.98 ± 0.25^{a}	3.88 ± 0.21^{a}	2.52 ± 0.06^{b}	3.13 ± 0.15^{c}
ALP, mg/dl (mean ± SEM)	143.65 ± 0.13^{a}	145.6 ± 0.21^{a}	281.13 ± 1.52^{b}	234.67 ± 12.5^{c}
TP, g/dL (mean ± SEM)	4.73 ± 0.17^{a}	4.98 ± 0.21^{a}	3.31 ± 0.21^{b}	3.81 ± 0.13^{c}

Data are expressed by means ± SEM; small (a-c) letters show the marked change at $P \leq 0.05$; the same letters show (non-significant), and the significant are expressed by dissimilar letters.

Cardiac Indicators and serum electrolytes in ISO-treated rats after therapy with coenzyme Q10

ISO-treated rats demonstrated a significant increase in CK-MB activity when compared to the control group ($P < 0.05$). Coenzyme Q10 administration notably lowered CK-MB levels in ISO-treated rats **(Table 2)**. Similar reductions were observed in LDH and CK levels. Regarding TNF, CoQ10 treatment combined with ISO led to a decrease in TNF activity compared to the CoQ10+ISO group. Additionally, in rats receiving CoQ10+ISO therapy, serum levels of K and Na were significantly reduced.

Table 2. The effects of CoQ10 on cardiac indicators, serum electrolytes, and TNF

Groups	Control (n = 6)	CoQ10 (n = 6)	ISO (n = 6)	CoQ10+ISO (n = 6)
LDH, U/L (mean ± SEM)	198.12 ± 4.13^{a}	204.23 ± 4.23^{a}	492.65 ± 2.24^{b}	220.12 ± 3.22^{c}
K, mmol/L (mean ± SEM)	3.56 ± 0.72^{a}	3.99 ± 0.22^{a}	8.96 ± 2.04^{b}	6.21 ± 1.22^{c}
Na, mmol/L (mean ± SEM)	139.52 ± 1.05^{a}	135.98 ± 0.96^{a}	159.41 ± 2.56^{b}	144.90 ± 0.87^{c}
CK-MB, IU/L (mean ± SEM)	12.99 ± 0.75^{a}	15.02 ± 0.62^{a}	24.85 ± 0.45^{b}	14.82 ± 0.21^{c}
CK, U/L (mean ± SEM)	141.13 ± 0.62^{a}	143.02 ± 0.60^{a}	235.23 ± 1.89^{b}	148.54 ± 2.91^{c}
TNF, pg./ml (mean ± SEM)	5.01 ± 0.91^{a}	4.92 ± 0.88^{a}	9.14 ± 0.12^{b}	5.96 ± 0.23^{c}

Data are expressed by means ± SEM. Small (a-c) letters show the marked change at $P \leq 0.05$. The same letters show (non-significant), and the significant are expressed by dissimilar letters.

Effect of CoQ10 on oxidative and antioxidative markers

ISO-treated rats displayed a marked increase in cardiac MDA levels, indicating higher lipid peroxidation, and a significant decrease in the levels of antioxidant markers, GSH and SOD, compared to the control group **(Table 3)**. After CoQ10 administration, these oxidative and antioxidative markers were restored to levels similar to those observed in the control animals.

Table 3. The effects of CoQ10 on oxidative and antioxidative markers

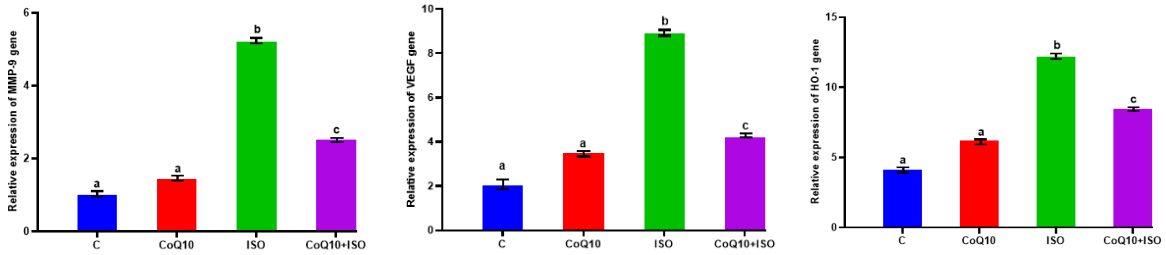
Groups	MDA (nmol/ g tissue)	GSH (nmol/ g tissue)	SOD (U/ g tissue)
Control	367.63 ± 0.43^{a}	4.31 ± 0.26 ^{a}	59.63 ± 1.34 ^{a}
CoQ10	367.86 ± 0.44^{a}	4.22 ± 0.33 ^{a}	61.09 ± 1.75 ^{a}

ISO	519.77 ± 0.26[b]	2.06 ± 0.29 [b]	50.28 ± 1.81 [a]
CoQ10+ISO	382.7 ± 8.91[c]	5.13 ± 0.38 [c]	57.21 ± 2.12 [a]

Data are expressed by means ± SEM; small (a-c) letters show the marked change at $P \leq 0.05$; the same letters show (non-significant), and the significant are expressed by dissimilar letters.

Effect of CoQ10 on the expression of VEGF, MMP-9, and HO-1 genes

ISO-treated rats showed a significant elevation in the cardiac expression of HO-1, MMP-9, and VEGF when compared to the control groups **(Figure 1)**. CoQ10 administration led to a restoration of these gene expression levels to those observed in the control group.



a b c

Figure 1. Real-time PCR analysis of changes in the expression of VEGF, MMP9, and HO-1 genes in cardiac tissues from various groups; β-actin served as the internal control; the fold changes are represented by the mean ± SEM for expression levels; small letters (a-c) indicate significant differences at $P \leq 0.05$, with identical letters denoting non-significant differences, while distinct letters represent statistically significant changes.

A major factor contributing to adverse cardiac remodeling is the altered expression of inflammatory mediators and the inability of cells to respond to growth factors [12]. The objective of this research was to evaluate the potential protective and therapeutic effects of CoQ10 against ISO-induced cardiac damage and blood parameter alterations. CoQ10 may serve as a promising treatment for individuals with heart disease. Evidence suggests that CoQ10 plays a vital role in ATP synthesis, acts as a potent anti-inflammatory agent, and could improve endothelial function [13].

In this study, ISO was administered subcutaneously to rats to induce cardiac remodeling. Catecholamines exert a positive inotropic effect, helping the heart function at lower levels [14]. However, excessive ISO causes energy depletion in the heart, resulting in structural and biochemical alterations in cardiomyocytes [15]. Rats treated with ISO exhibited significantly higher serum levels of liver enzymes ALT, AST, and ALP, and a notable decrease in serum albumin and total protein levels. These results are consistent with those reported by Barman *et al.* [16]. The increased levels of ALT, AST, and ALP may be due to ISO's cytotoxic effects, which damage liver cells and canaliculi, causing the release of these enzymes into the bloodstream. Since ALT and AST are found in hepatocyte cytoplasm [17], their elevated levels indicate liver damage.

Supporting findings by Omnia *et al.* [18], this study observed a significant decrease in Alb and TP levels in ISO-treated rats compared to the control group. The decline in protein levels reflects the degenerative impact of ISO on liver cells, as Alb and TP are indicators of the liver's biosynthetic function, or possibly due to increased protein consumption [19].

Additionally, when ISO dissociates into Na ions, ammonium ions are generated, contributing to cardiac injury [20]. Elevated ammonium ion (NH+4) levels damage heart tissue, leading to an increase in serum cardiac enzyme activity. This increase in enzymes may have been mitigated by the oxidative stress and injury caused by ISO on the heart, which results in the leakage of cardiac cytosolic enzymes into the bloodstream [21].

CK-MB and CK are key markers of myocardial necrosis [22]. In this study, ISO treatment led to an increase in CK-MB and CK activity in rat serum. However, CoQ10 administration prevented the rise in CK-MB and CK activity. Previous research supports the finding that CoQ10 reduces CK-MB activity in ISO-induced cardiotoxicity and cardiac hypertrophy in male rats [9, 23, 24].

The levels of malondialdehyde (MDA), a marker of lipid peroxidation, were reduced in ISO-treated rats following CoQ10 treatment. Lipid peroxidation plays a crucial role in myocardial necrosis and the accumulation of lipid hydroperoxides in heart injury. CoQ10 acts as an antioxidant, scavenging free radicals, inhibiting hydrogen

peroxide and tumor necrosis factor, reducing xanthine oxidase activity, disrupting the oxidative cascade, and preventing lipid peroxidation [25]. Additionally, CoQ10 functions as an oxygen quencher, limiting its availability for oxidative reactions, and inhibits cytochrome P450 during oxidative stress conditions [26].

In this study, ISO-treated rats showed a significant reduction in GSH and SOD levels in the heart compared to the control group. CoQ10 treatment notably restored the GSH levels. The decrease in GSH and SOD could initially be explained by glutathione reductase enzyme activity, which converts GSH into GSSG in the liver, acting to protect liver cells from damage [27]. The reduced SOD activity may be due to the elevated production of reactive oxygen species (ROS) such as hydrogen peroxide and superoxide, which impair these enzymes [28]. CoQ10 administration improved SOD activity, effectively scavenged superoxide radicals, and reduced cardiac damage induced by free radicals [29].

Additionally, the anti-inflammatory effects of CoQ10 against ISO induction were confirmed by a significant increase in VEGF expression. CoQ10 also activated the antioxidant genes HO-1 and MMP-9. HO-1, a crucial enzyme, regulates oxidative and inflammatory processes commonly associated with ISO-induced nephrotoxicity. CoQ10's effects on oxidative stress, inflammation, and apoptosis are thought to be mediated through the Nrf2/HO-1 pathway, as described by Khodir *et al*. [30]. Pala *et al*. [31] further supported that CoQ10's cytoprotective action is due to alterations in HO-1 expression, which highlights its anti-inflammatory and antioxidant roles.

ROS are key factors in the regulation of MMP and VEGF expression. CoQ10 acts as an effective antioxidant, reducing ROS levels and inhibiting cytokine and MMP production [32]. Therefore, the modulation of MMP-9 and VEGF observed in this study may be attributed to CoQ10's interaction with ROS mediators [33].

Conclusion

This research highlights that the administration of CoQ10 in rats reduces cardiac inflammation and offers protection against heart damage induced by the ISO model. The treatment with CoQ10 led to improvements in liver function, cardiac health, and gene expression, potentially through the reduction of oxidative stress and the restoration of antioxidant defense mechanisms in the tissues.

Acknowledgments: The writer acknowledges the Deanship of Scientific Research at Umm Al-Qura University for their financial support through Grant Code: 22UQU4280303DSR02.

Conflict of Interest: None

Financial Support: The financial backing for the research and writing of this study was provided by the Deanship of Scientific Research at Umm Al-Qura University.

Ethics Statement: The research was approved by the Research Ethical Committee at the Faculty of Medicine, Umm Al-Qura University, Saudi Arabia (Approval No. 2021/021AO).

References

1. Roth GA, Mensah GA, Johnson CO, Addolorato G, Ammirati E, Baddour LM, et al. Global burden of cardiovascular diseases and risk factors, 1990–2019: update from the GBD 2019 study. J Am Coll Cardiol. 2020;76(25):2982-3021.
2. Golforoush P, Yellon DM, Davidson SM. Mouse models of atherosclerosis and their suitability for the study of myocardial infarction. Basic Res Cardiol. 2020;115(6):1-24.
3. Hyun K, Negrone A, Redfern J, Atkins E, Chow C, Kilian J, et al. Gender difference in secondary prevention of cardiovascular disease and outcomes following the survival of acute coronary syndrome. Heart Lung Circ. 2021;30(1):121-7.
4. Kalogeris T, Baines CP, Krenz M, Korthuis RJ. Ischemia/reperfusion. Compr Physiol. 2016;7(1):113.
5. Torrealba N, Aranguiz P, Alonso C, Rothermel BA, Lavandero S. Mitochondria in structural and functional cardiac remodeling. Mitochondrial Dyn Cardiovasc Med. 2017:277-306.
6. Derbali A, Mnafgui K, Affes M, Derbali F, Hajji R, Gharsallah N, et al. Cardioprotective effect of linseed oil against isoproterenol-induced myocardial infarction in Wistar rats: a biochemical and electrocardiographic study. J Physiol Biochem. 2015;71(2):281-8.

7. Neri M, Fineschi V, Di Paolo M, Pomara C, Riezzo I, Turillazzi E, et al. Cardiac oxidative stress and inflammatory cytokines response after myocardial infarction. Curr Vasc Pharmacol. 2015;13(1):26-36.
8. Tauffenberger A, Magistretti PJ. Reactive oxygen species: beyond their reactive behavior. Neurochem Res. 2021;46(1):77-87.
9. Ulla A, Mohamed MK, Sikder B, Rahman AFMT, Sumi FA, Hossain M, et al. Coenzyme Q10 prevents oxidative stress and fibrosis in isoprenaline induced cardiac remodeling in aged rats. BMC Pharmacol Toxicol. 2017;18(1):1-10.
10. Alam MA, Rahman MM. Mitochondrial dysfunction in obesity: potential benefit and mechanism of Co-enzyme Q10 supplementation in metabolic syndrome. J Diabetes Metab Disord. 2014;13(1):1-11.
11. Lobo Filho HG, Ferreira NL, Sousa RB de, Carvalho ER de, Lobo PLD, Lobo Filho JG. Experimental model of myocardial infarction induced by isoproterenol in rats. Brazilian J Cardiovasc Surg. 2011;26:469-76.
12. Bujak M, Kweon HJ, Chatila K, Li N, Taffet G, Frangogiannis NG. Aging-related defects are associated with adverse cardiac remodeling in a mouse model of reperfused myocardial infarction. J Am Coll Cardiol. 2008;51(14):1384-92.
13. Littarru GP, Tiano L. Bioenergetic and antioxidant properties of coenzyme Q10: recent developments. Mol Biotechnol. 2007;37(1):31-7.
14. Krenek P, Kmecova J, Kucerova D, Bajuszova Z, Musil P, Gazova A, et al. Isoproterenol-induced heart failure in the rat is associated with nitric oxide-dependent functional alterations of cardiac function. Eur J Heart Fail. 2009;11(2):140-6.
15. Sumi FA, Sikder B, Rahman MM, Lubna SR, Ulla A, Hossain MH, et al. Phenolic content analysis of aloe vera gel and evaluation of the effect of aloe gel supplementation on oxidative stress and fibrosis in isoprenaline-administered cardiac damage in rats. Prev Nutr Food Sci. 2019;24(3):254.
16. Barman NR, Nandy S, Datta R, Kar PK. Cardioprotective effect of ethanolic extract of Urtica parviflora Roxb. against isoproterenol-induced myocardial infarction in rats. Indian J Pharmacol. 2013;45(5):513.
17. Veisi S, Johari SA, Tyler CR, Mansouri B, Esmaeilbeigi M. Antioxidant properties of dietary supplements of free and nanoencapsulated silymarin and their ameliorative effects on silver nanoparticles induced oxidative stress in Nile tilapia (Oreochromis niloticus). Environ Sci Pollut Res. 2021;28(20):26055-63.
18. Omnia M, Elhamid A, Hatem B, Rania HM, Elnaga A. Biochemical effect of garlic oil administration in heart necrosis induced experimentally in rats. Benha Vet Med J. 2014;27:264-76.
19. Elasoru SE, Rhana P, de Oliveira Barreto T, de Souza DLN, Menezes-Filho JER, Souza DS, et al. Andrographolide protects against isoproterenol-induced myocardial infarction in rats through inhibition of L-type Ca2+ and increase of cardiac transient outward K+ currents. Eur J Pharmacol. 2021;906:174194.
20. Lekshmi VS, Kurup GM. Sulfated polysaccharides from the edible marine algae Padina tetrastromatica protects the heart by ameliorating hyperlipidemia, endothelial dysfunction, and inflammation in isoproterenol-induced experimental myocardial infarction. J Funct Foods. 2019;54:22-31.
21. Jain PG, Mahajan UB, Shinde SD, Surana SJ. Cardioprotective role of FA against isoproterenol-induced cardiac toxicity. Mol Biol Rep. 2018;45(5):1357-65.
22. Wu YW, Ho SK, Tseng WK, Yeh HI, Leu HB, Yin WH, et al. Potential impacts of high-sensitivity creatine kinase-MB on long-term clinical outcomes in patients with stable coronary heart disease. Sci Rep. 2020;10(1):1-9.
23. Attalla DM, Ahmed LA, Zaki HF, Khattab MM. Paradoxical effects of atorvastatin in isoproterenol-induced cardiotoxicity in rats: role of oxidative stress and inflammation. Biomed Pharmacother. 2018;104:542-9.
24. Ghule AE, Kulkarni CP, Bodhankar SL, Pandit VA. Effect of pretreatment with coenzyme Q10 on isoproterenol-induced cardiotoxicity and cardiac hypertrophy in rats. Curr Ther Res. 2009;70(6):460-71.
25. MacCarthy PA, Shah AM. Oxidative stress and heart failure. Coron Artery Dis. 2003;14(2):109-13.
26. Moßhammer D, Schaeffeler E, Schwab M, Mörike K. Mechanisms and assessment of statin-related muscular adverse effects. Br J Clin Pharmacol. 2014;78(3):454-66.
27. Eftekhari A, Ahmadian E, Azarmi Y, Parvizpur A, Hamishehkar H, Eghbal MA. In Vitro/Vivo studies towards mechanisms of risperidone-induced oxidative stress and the protective role of coenzyme Q10 and N-acetylcysteine. Toxicol Mech Methods. 2016;26(7):520-8.
28. Costa TJ, Barros PR, Arce C, Santos JD, da Silva-Neto J, Egea G, et al. The homeostatic role of hydrogen peroxide, superoxide anion and nitric oxide in the vasculature. Free Radic Biol Med. 2021;162:615-35.

29. Sanoobar M, Eghtesadi S, Azimi A, Khalili M, Jazayeri S, Reza Gohari M. Coenzyme Q10 supplementation reduces oxidative stress and increases antioxidant enzyme activity in patients with relapsing-remitting multiple sclerosis. Int J Neurosci. 2013;123(11):776-82.
30. Khodir AE, Atef H, Said E, ElKashef HA, Salem HA. Implication of Nrf2/HO-1 pathway in the coloprotective effect of coenzyme Q10 against experimentally induced ulcerative colitis. Inflammopharmacology. 2017;25(1):119-35.
31. Pala R, Orhan C, Tuzcu M, Sahin N, Ali S, Cinar V, et al. Coenzyme Q10 Supplementation Modulates NFκB and Nrf2 pathways in exercise training. J Sports Sci Med. 2016;15(1):196.
32. Bahar M, Khaghani S, Pasalar P, Paknejad M, Khorramizadeh MR, Mirmiranpour H, et al. Exogenous coenzyme Q10 modulates MMP-2 activity in MCF-7 cell line as a breast cancer cellular model. Nutr J. 2010;9(1):1-8.
33. Sanoobar M, Eghtesadi S, Azimi A, Khalili M, Khodadadi B, Jazayeri S, et al. Coenzyme Q10 supplementation ameliorates inflammatory markers in patients with multiple sclerosis: a double-blind, placebo, controlled randomized clinical trial. Nutr Neurosci. 2015;18(4):169-76.