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Research Article

Role of Gender in the Protection Against Doxorubicin-Induced Oxidative Stress

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ABSTRACT

Background: There are gender differences in the oxidation-reduction reactions. Doxorubicin (Dox) is a chemotherapeutic drug that can produce oxidative stress which may require prevention by antioxidants. **Aim:** The study aimed to investigate the gender-dependent changes in Dox-induced oxidative stress, and the protective effects of coenzyme Q10 (CoQ10). **Materials and Methods:** Rats were administered CoQ10 orally for 17 days. On day 13, some rats receiving CoQ10 received a single intraperitoneal dosage of Dox, whereas other rats received normal saline. Glutathione (GSH), malondialdehyde (MDA), and total anti-oxidant capacity (T-AOC) were measured in both genders of albino rats. **Results:** Dox significantly reduced both GSH and T-AOC levels and caused a significant increase in MDA. The administration of CoQ10 significantly prevented these changes. Dox caused a larger reduction in GSH in males than in females, while CoQ10 caused more protection in females. Dox caused a higher increase in MDA levels in males. **Conclusion:** Pre-treatments with CoQ10 may protect against Dox-induced oxidative stress, with gender-dependent variations in the extent of these Dox/CoQ10 effects.
Key words: Coenzyme Q10, Doxorubicin, Gender difference, Oxidative stress.

INTRODUCTION

Gender differences are biological variations caused by hormonal, genetic, and epigenetic factors.[1,2] Elderly males and postmenopausal females have higher rates of cardiac disease, kidney disease, and hypertension compared to premenopausal females.[3,4] In addition, the risk of specific types of damage has been linked to sex differences in mitochondrial bioenergetics in several situations.[2,5,6] Tissue damage could result from mitochondrial dysfunction and its related harmful elements, such as oxidative stress.[7] Several indicators have been linked to oxidative stress like malondialdehyde (MDA), reduced glutathione (GSH), and total anti-oxidant capacity (T-AOC).[8-11] Additionally, gender differences in oxidative stress responses are associated with differences in severity of oxidative stress-related disorders. Previous studies suggested that hormonal and non-hormonal influences, such as sex chromosomal gene expression, are involved in sex differences in stress response.[12]

Dox is a cytotoxic antibiotic drug that belongs to the anthracycline family. It is one of the most popular and efficient chemotherapeutic medications for the treatment of various malignancies, like Hodgkin's lymphoma, soft tissue, bladder, thyroid, breast, acute lymphoblastic leukaemia, ovarian, gastric, pulmonary cancer, bone sarcomas, and myeloblastic leukaemia.[13,14] However, Dox clinical use is limited by its adverse effects, which include nephrotoxicity, cardiotoxicity, skin toxicity, and hepatotoxicity.[15] Although the specific mechanism of Dox-induced toxicity is unknown. Several studies show that doxorubicin-induced toxicity is caused by oxidative stress, which causes intracellular thiol cross-linking and oxidation, as well as membrane lipid peroxidation.[16] Furthermore, the increased free radical generation and lipid and protein oxidation can lead to apoptosis.[17] As a result, adding a concomitant therapy with Dox can potentially improve the effectiveness of cancer chemotherapy and reduce its adverse effects.[18,19]

Coenzyme Q-10 (CoQ10) is an endogenously generated lipid-soluble antioxidant and a vitamin-like molecule that is involved in the mitochondrial respiratory chain. Previous studies have shown that it possesses antioxidant and anti-inflammatory properties.[20,21] CoQ10 acts as an acceptor of electrons in oxidative phosphorylation and serves to transform metabolic products into adenosine triphosphate (ATP) during the cellular respiration process for the synthesis of ATP.[22] As a result, organs with greater metabolic activity, like the heart, kidneys, and liver, have the greatest concentration of CoQ10 for cellular ATP generation.[23] CoQ10 may have antioxidative properties through rapid protective action against lipid peroxidation by lowering malondialdehyde (MDA) level, which is an indicator of damage caused by free radicals.[24] In fact, the associations between CoQ10 and the improvement of general health has well defined, however, the role of CoQ10 as a protective agent against drug-induced adverse effects, and the extent of protection with regard to sex difference has not yet clearly defined.[25-28] The purpose of this study is to examine the gender differences in Dox-induced oxidative stress and the possible protective effect of CoQ10 against this Dox's adverse effect.

MATERIALS AND METHODS

In this investigation, 62 adult albino rats of both genders were used. They weighed 250–50 g and were 10–12 weeks old. They were provided from the University of Mosul, college of Veterinary Medicine. The rats were kept in a controlled environment with a temperature of 25°C ± 2°C, humidity range of 45–

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50%, and housed for a week prior to the experiment 12-h light, 12-h dark cycle, lights on at 08:00 h, along with providing a normal amount of water and food. Dox (Saba-Turkey) with CoQ10 (21st Century-USA) were administered to the rats. Tween 80 (schlau-SPAN) in an aqueous phase at 1% was employed to dissolve CoQ10.

Rats were divided into four groups for each gender. As controls, Groups A was administered a 1% aqueous Tween 80 solution. CoQ10 (10 mg/kg) was given to groups B for 17 days.[29] On day 13, Dox (15 mg/kg) was administered intraperitoneally once to positive control group C.[30] Group D was administered CoQ10 (10 mg/kg) for 17 days, while Dox (single dose, 15 mg/kg) was administered on day 13 of the trial.

The animals were euthanized *via* dislocation of their cervical spine. Animal euthanasia regulations were followed during this treatment. Before sacrifice, blood samples were obtained from the retro-orbital venous plexus. These samples were kept at room temperature for 30 minutes before centrifugation at 3000 rpm for 15 minutes. Isoiated serum samples were kept at a temperature of -20°C in a freezer for the oxidative stress parameters assay.

Serum samples were used to calculate the amounts of MDA, GSH, and T-AOC. ELISA kits supplied by Elabscience USA were used to measure both MDA and GSH using the Competitive-ELISA principle strictly according to the manufacturers' instructions. The optical density of the final product was monitored spectrophotometrically at 450 nm. T-AOC plasma concentration was measured using a colorimetric method by an assay Kit supplied by Elabscience USA according to the manufacturer's protocol. The produced colour was determined by monitoring absorbance at 520 nm.

Statistical analysis

The GraphPad Prism application was used to analyse the data. The data were presented as Mean ± SD. To compare different groups, one-way analysis of variance (ANOVA) was utilized, with Tukey's multiple comparison tests as a post-hoc analysis. To compare data between different genders, two-way ANOVA with Tukey's multiple comparison tests as a post-hoc analysis was used. *P*-value of < 0.05 was accepted as the significant level.

RESULTS

The effect of gender difference on Dox/CoQ10- induced MDA levels

MDA levels in Dox-treated rats were considerably greater in both sexes than in control rats (Males: control, 64.8 ± 4.12 vs. Dox, 88.7 ± 2.84; Females: control, 63.9 ± 3.70 vs. Dox, 79.6 ± 6.56). Moreover, pre-treatment with CoQ10 prevented the rise in MDA levels in rats receiving Dox in both males (70.01 ± 4.877) and females (67.80 ± 5.131) (Figure 1 A and B). The increase in MDA levels due to Dox treatment was significantly higher in males (88.66 ± 2.841) in comparison with females (79.61 ± 6.565). (Figure 1C) However, no significant gender variation was present regarding CoQ10 protection against the MDA-inducing effect of Dox (Figure 1D).

The effect of gender difference on Dox/CoQ10-induced T-AOC levels

Dox administration resulted in a significant reduction in T-AOC compared to controls in both sexes (Males: control, 14.6 ± 0.6 vs. Dox, 4.9 ± 1.1; Females: 12.4 ± 2.16 vs. Dox, 4.1 ± 0.99). Serum T-AOC levels were significantly raised after pre-treatment with CoQ10 in both males (12.4 ± 1.53) and females (10.9 ± 0.79) (Figure 2: A and B). However, there is no significant gender difference in T-AOC level after Dox treatment or CoQ10 protection (Males: Dox (4.9 ± 1.11), Dox/CoQ10 (12.4 ± 1.53) vs. Females: Dox (4.1 ± 0.99), Dox/CoQ10 (10.9 ± 0.79)). (Figure 2: C and D)

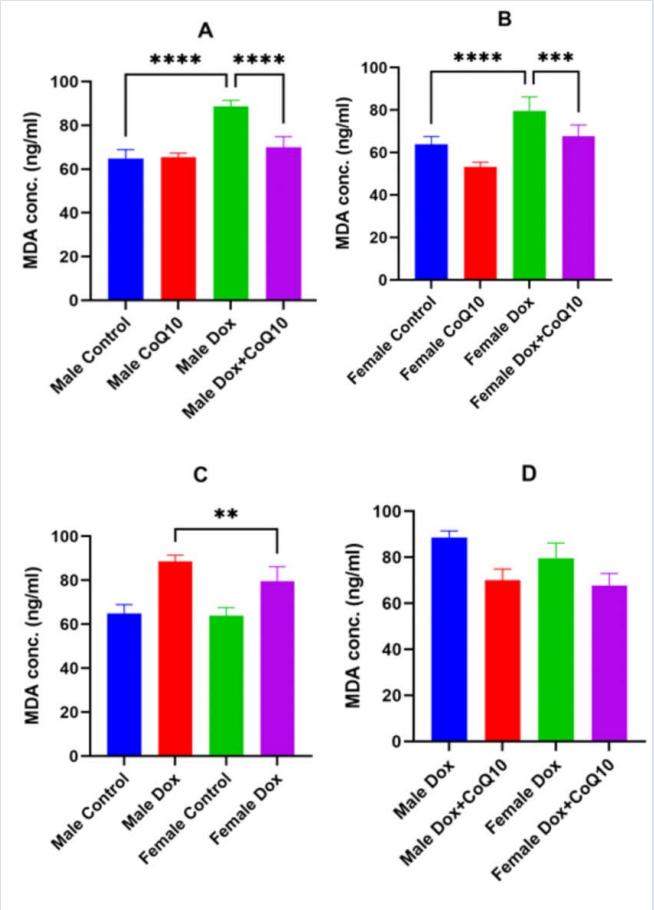

Figure 1: Gender difference in the protective effect of CoQ10 against Dox effects on serum MDA levels. Following a single dose of Dox (15 mg/kg) or a placebo, as well as with the presence or absence of CoQ10 pre-treatment with (10mg/kg orally daily), serum MDA levels are assessed. The resulting data is represented by mean ± S.D. The symbols **, ***, and **** denote p values below 0.01, 0.001, and 0.0001, respectively, one-way ANOVA for A and B, and a two-way ANOVA for C and D, followed by a Tukey's post hoc test vs. control values.

The effect of gender difference on Dox/CoQ10- induced GSH levels

GSH levels is significantly decreased in Dox-treated rats compared to controls in both males (control: 12.2 ± 3.6 vs. Dox: 5.8 ± 1.1) and females (control: 13.6 ± 2 vs. Dox: 9.3 ± 1.65). Furthermore, a substantial decrease in the Dox-induced rise in GSH levels was seen after pretreatment with CoQ10 in both males (10.3 ± 2.50) and females (13.4 ± 1.69) of Dox-treated rats (Figure 3: A and B). Comparison between genders showed that Dox can significantly decrease GSH levels in males (5.76 ± 1.1) more than in females (9.3 ± 1.65) (Figure 3C). However, CoQ10 could increase GSH levels much higher in females (13.4 ± 1.69) compared to males (10.3 ± 2.50). (Figure 3D)

DISCUSSION

The present study examined the role of gender difference on the protective effect of CoQ10 against Dox-induced oxidative stress in rats. Dox caused a significant increase in oxidative stress while pre-treatment with CoQ10 resulted in significant protection against this effect. In addition, gender difference has an impact on the Dox and CoQ10 effects.

In the present study, Dox demonstrated oxidative stress *via* elevation of the oxidative stress marker MDA, a product of lipid peroxidation. This

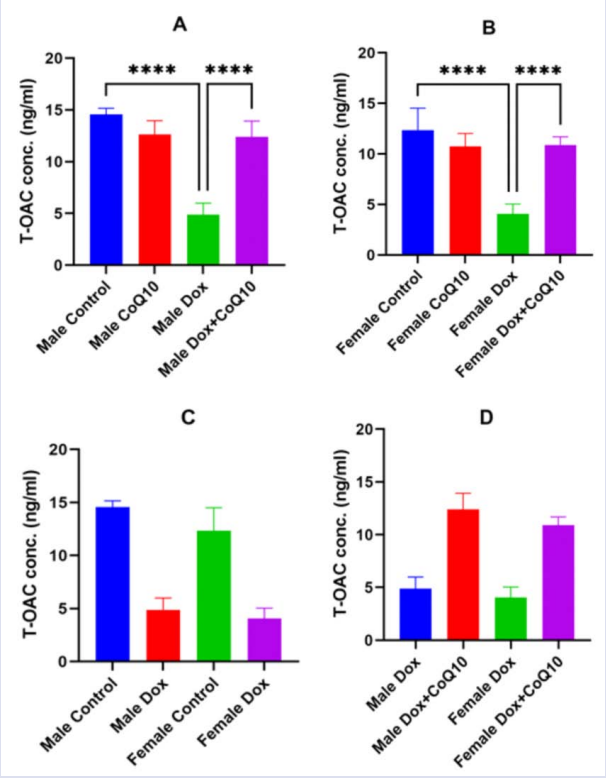

Figure 2: Gender difference in the protective effect of CoQ10 against Dox effects on serum T-AOC levels. Following a single dose of Dox (15 mg/kg) or a placebo, as well as with the presence or absence of CoQ10 pre-treatment with (10mg/kg orally daily), serum T-AOC levels are assessed. The resulting data is represented by mean ± S.D. **** denotes $p < 0.0001$. One-way ANOVA for A and B and two-way ANOVA for C and D were used, followed by a Tukey's post hoc test against control values.

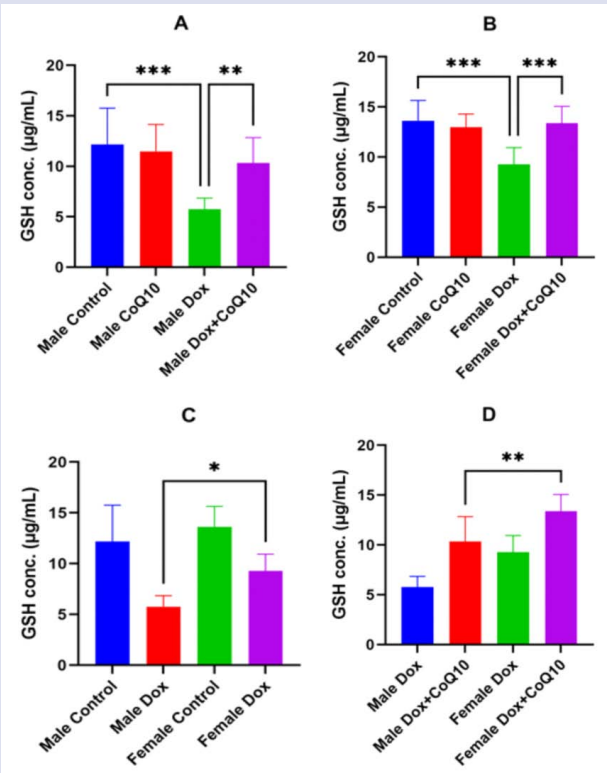

Figure 3: Gender difference in the protective effect of CoQ10 against Dox effects on serum GSH levels. Following a single dose of Dox (15 mg/kg) or a placebo, as well as with the presence or absence of CoQ10 pre-treatment with (10mg/kg orally daily), serum GSH levels are assessed. The data is shown as mean ± S.D. * means $p < 0.05$; ** means $p < 0.01$; *** means $p < 0.001$; one-way ANOVA for A and B, and a two-way ANOVA for C and D, followed by a Tukey's post hoc test vs. control values.

is consistent with recent research by Khan *et al.*, (2020).[31] MDA is a key indicator of oxidative stress and cellular membrane damage and bodily aging.[9-11] In the current study, CoQ10 prevented the elevation of Dox-related MDA. The elimination of these ROS is one of the mechanisms through which CoQ10 acts as an antioxidant.[32] Interestingly, this study showed that the effect of Dox on MDA level is gender dependent as Dox increased MDA level in males more than in females. With regard to MDA levels, the gender dimorphism was seen in a previous study on humans in which the MDA levels were substantially lower in females than in males. Females had lower MDA levels because they have more oestrogen, which is known to exhibit antioxidant capabilities *in vitro* and is associated with the overexpression of endogenous antioxidants.[33,34] In addition, this variation in MDA concentration could be attributed to gender differences in NADPH-oxidase activity which produces MDA, or other yet-to-be-identified processes.[35]

In addition to the oxidative stress indicators, antioxidants measurement is very critical in evaluating oxidative stress. Serum T-AOC levels were found to provide an integrated measure rather than a simple sum of detectable antioxidants.[36] The presented study showed that Dox could decrease the antioxidant biomarker T-AOC in consistent with a previous study.[37] T-AOC marker takes into account the synergistic effects of all antioxidants found in biological fluids, resulting in an integrative system of these molecules. When compared to the activity of a single antioxidant, T-AOC has the better predictive ability and biological significance.[8] Several pathogenic disorders linked to oxidative stress also have been shown to significantly reduce T-AOC.[38-40] Moreover, the hydroquinone and quinone groups in the Dox chemical structure produce semiquinone radical intermediates, increasing ROS and depleting antioxidant defences.[41] Pre-treatment with CoQ10 could significantly reverse the Dox-induced reduction in T-AOC. Additionally, CoQ10 could mediate another defence pathway that includes reduction of apoptosis and upregulation of glycoprotein in doxorubicin-induced toxicity. All of these findings support the protective effect of CoQ10 against Dox-induced toxicities.[42] Furthermore, the current study showed that gender difference has no impact on either Dox or CoQ10 effects on T-AOC plasma levels.

According to our findings, Dox therapy resulted in considerable depletion of GSH as another antioxidant defence in the body.[43] The glutathione system, which includes glutathione oxidase, glutathione reductase, and glutathione, provides optimal levels of $O_2^{\bullet}$ and H_2O_2 for tissue regeneration and immunological defence.[44] As a result, the balance of oxidized to reduced glutathione (GSH) reveals the homeostasis of the cell redox and could be used to detect oxidative stress and as a target for drug-based antioxidant therapy.[45] The current study found that CoQ10 can exert chemo protective activity against the Dox-induced GSH reduction. Previous clinical investigations have found that taking CoQ10 orally has positive effects on a variety of conditions related to low CoQ10 levels and high oxidative stress, including neurodegenerative, mitochondrial, and cardiovascular diseases.[46] Interestingly, the present study showed that both Dox and CoQ10 effects are gender-dependent. In males, Dox has reduced GSH more than in females. This is in line with previous studies, which found that the lower toxicity might be due to the stronger potential of cellular defences in female rats against oxidative stress than in male rats.[35] In addition, female mice were more resistant to anticancer toxic effects than male mice.[47] CoQ10 could prevent the GSH reduction in females more than in males. A previous study on mice showed that females have higher GSH content in tissues that are sensitive to oestrogen. The authors concluded that this finding could be due to that females have significantly higher plasma oestrogen levels than males.[48] According to Xu *et al.*, (2018), the results showed that CoQ10 pretreatment significantly reduced gonadotropin requirements and elevated peak levels of estradiol (E2),[49] which in turn has protection against oxidative stress. This has been shown to protect many organs from experimentally induced lipid peroxidation regardless of tissue type. In fact, the ovary has a lower baseline of oxidative damage to membrane lipids compared to other organs.[50]

Although our study showed that there is no significant difference in the basal level of GSH between genders, CoQ10 could elevate the level of GSH more in females compared to males due to also the different sex hormonal profiles.

Moreover, the variation in the results in different genders could be due to other causes. According to several studies, males show a greater basal metabolic rate than females since their bodies have greater energy demands. This requirement accelerates male metabolism at the expense of producing more free radicals in the mitochondria during oxidative phosphorylation. This makes the male antioxidant system more susceptible to free radical-mediated damage than the female antioxidant system, despite the fact that both genders' antioxidant and detoxifying systems are similarly effective and physiologically strong. Furthermore, females are thought to have greater stress resistance due to their sex hormones (oestrogen and progesterone), which contain antioxidant, anti-aging, and perhaps even anticancer effects.[51,52]

CONCLUSIONS

According to the current study, the anticancer drug doxorubicin can lead to oxidative stress which can be prevented by pre-treatment with CoQ10 in both genders. However, the extent of the Dox/CoQ10 effects varied in the different genders as females show more resistance to the deleterious effect of Dox and more sensitivity to the protective effect of CoQ10. Finally, current study suggests that supplementing with CoQ10 may be helpful in lowering Dox-induced oxidative stress in both sexes.

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REFERENCES

1. Seifarth JE, McGowan CL, Milne KJ. Sex and life expectancy. Gend Med. 2012;9(6):390-401.
2. Ventura-Clapier R, Moulin M, Piquereau J, Lemaire C, Mericskay M, Veksler V, *et al.* Mitochondria: A central target for sex differences in pathologies. Clin Sci. 2017;131(9):803-22.
3. Maric C, Sullivan S. Estrogens and the diabetic kidney. Gend Med. 2008;5(Suppl A):S103-13.
4. Xue B, Johnson AK, Hay M. Sex differences in angiotensin II-and aldosterone-induced hypertension: the central protective effects of estrogen. Am J Physiol Integr Comp Physiol. 2013;305(5):R459-63.
5. Yang J-L, Mukda S, Chen S-D. Diverse roles of mitochondria in ischemic stroke. Redox Biol. 2018;16:263-75.
6. Mitchell T, De Miguel C, Gohar EY. Sex differences in redox homeostasis in renal disease. Redox Biol. 2020;31:101489.
7. Sultanova RF, Schibalski R, Yankelevich IA, Stadler K, Ilatovskaya DV. Sex differences in renal mitochondrial function: a hormone-gous opportunity for research. Am J Physiol Physiol. 2020;319(6):F1117-24.
8. Serafini M, Del Rio D. Understanding the association between dietary antioxidants, redox status and disease: Is the total antioxidant capacity the right tool? Redox Rep. 2004;9(3):145-52.
9. Gorrini C, Harris IS, Mak TW. Modulation of oxidative stress as an anticancer strategy. Nat Rev Drug Discov. 2013;12(12):931-47.

10. Hyvärinen S, Uchida K, Varjosalo M, Jokela R, Jokiranta TS. Recognition of malondialdehyde-modified proteins by the C terminus of complement factor H is mediated via the polyanion binding site and impaired by mutations found in atypical hemolytic uremic syndrome. J Biol Chem. 2014;289(7):4295-306.
11. Rahimi O, Kirby J, Varagic J, Westwood B, Tallant EA, Gallagher PE. Angiotensin-(1-7) reduces doxorubicin-induced cardiac dysfunction in male and female Sprague-Dawley rats through antioxidant mechanisms. Am J Physiol Circ Physiol. 2020;318(4):H883-94.
12. Tower J, Pomatto LCD, Davies KJA. Sex differences in the response to oxidative and proteolytic stress. Redox Biol. 2020;31:101488.
13. Cagel M, Grotz E, Bernabeu E, Moretton MA, Chiappetta DA. Doxorubicin: nanotechnological overviews from bench to bedside. Drug Discov Today. 2017;22(2):270-81.
14. Sohail M, Sun Z, Li Y, Gu X, Xu H. Research progress in strategies to improve the efficacy and safety of doxorubicin for cancer chemotherapy. Expert Rev Anticancer Ther. 2021;21(12):1385-98.
15. Kaur A, Kaur M, Sharma R, Kumar S. Doxorubicin: a critical review on toxicity. Int J Appl Res Nat Prod. 2012;1:208-12.
16. Malarkodi DP, Balachandar AV, Varalakshmi P. The influence of lipoic acid on adriamycin induced nephrotoxicity in rats. Mol Cell Biochem. 2003;247(1):15-22.
17. Nagai K, Fukuno S, Otani K, Nagamine Y, Omotani S, Hatsuda Y, *et al.* Prevention of doxorubicin-induced renal toxicity by theanine in rats. Pharmacology. 2018;101(3-4):219-24.
18. Aydin B, Unsal M, Sekeroglu ZA, Gülbahar Y. The antioxidant and antigenotoxic effects of Pycnogenol® on rats treated with cisplatin. Biol Trace Elem Res. 2011;142(3):638-50.
19. Lee CK, Son SH, Park KK, Park JHY, Lim SS, Kim S, *et al.* Licochalcone A inhibits the growth of colon carcinoma and attenuates cisplatin-induced toxicity without a loss of chemotherapeutic efficacy in mice. Basic Clin Pharmacol Toxicol. 2008;103(1):48-54.
20. Zhang X, Shi Z, Liu Q, Quan H, Cheng X. Effects of coenzyme Q10 intervention on diabetic kidney disease: A systematic review and meta-analysis. Medicine (Baltimore). 2019;98(24):e15850.
21. Bentinger M, Tekle M, Dallner G. Coenzyme Q-biosynthesis and functions. Biochem Biophys Res Commun. 2010;396(1):74-9.
22. Fatima S, Suhail N, Alrashed M, Wasi S, Aljaser FS, AlSubki RA, *et al.* Epigallocatechin gallate and coenzyme Q10 attenuate cisplatin-induced hepatotoxicity in rats via targeting mitochondrial stress and apoptosis. J Biochem Mol Toxicol. 2021;35(4):e22701.
23. López-Lluch G, Rodríguez-Aguilera JC, Santos-Ocaña C, Navas P. Is coenzyme Q a key factor in aging? Mech Ageing Dev. 2010;131(4):225-35.
24. 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.
25. AL-Megrin WA, Soliman D, Kassab RB, Metwally DM, Dina DM, El-Khadragy MF. Coenzyme Q10 Activates the Antioxidant Machinery and Inhibits the Inflammatory and Apoptotic Cascades Against Lead Acetate-Induced Renal Injury in Rats. Front Physiol. 2020;11:64.
26. Sutken E, Aral E, Ozdemir F, Uslu S, Alatas O, Colak O. Protective role of melatonin and coenzyme Q10 in ochratoxin A toxicity in rat liver and kidney. Int J Toxicol. 2007;26(1):81-7.
27. Langsjoen PH, Langsjoen JO, Langsjoen AM, Lucas LA. Treatment of statin adverse effects with supplemental Coenzyme Q10 and statin drug discontinuation. Biofactors. 2005;25(1-4):147-52.
28. Izadi A, Ebrahimi S, Shirazi S, Taghizadeh S, Parizad M, Farzadi L, *et al.* Hormonal and metabolic effects of coenzyme Q10 and/or vitamin E in patients with polycystic ovary syndrome. J Clin Endocrinol Metab. 2019;104(2):319-27.
29. Güleş Ö, Kum Ş, Yıldız M, Boyacıoğlu M, Ahmad E, Naseer Z, *et al.* Protective effect of coenzyme Q10 against bisphenol-A-induced toxicity in the rat testes. Toxicol Ind Health. 2019;35(7):466-81.
30. Oyagbemi AA, Omobowale TO, Olopade JO, Farombi EO. Kolaviron and Garcinia kola attenuate doxorubicin-induced cardiotoxicity in Wistar rats. J Complement Integr Med. 2018;15(1).
31. Khan TH, Ganaie MA, Alharthy KM, Madkhali H, Jan BL, Sheikh IA. Naringenin prevents doxorubicin-induced toxicity in kidney tissues by regulating the oxidative and inflammatory insult in Wistar rats. Arch Physiol Biochem. 2020;126(4):300-7.
32. Matsura T, Yamada K, Kawasaki T. Difference in antioxidant activity between reduced coenzyme Q9 and reduced coenzyme Q10 in the cell: Studies with isolated rat and guinea pig hepatocytes treated with a water-soluble radical initiator. Biochim Biophys Acta (BBA)-Lipids Lipid Metab. 1992;1123(3):309-15.
33. Bloomer RJ, Fisher-Wellman KH. Blood oxidative stress biomarkers: Influence of sex, exercise training status, and dietary intake. Gend Med. 2008;5(3):218-28.
34. Vina J, Sastre J, Pallardo FV, Gambini J, Borras C. Role of mitochondrial oxidative stress to explain the different longevity between genders. Protective effect of estrogens. Free Radic Res. 2006;40(12):1359-65.
35. Kander MC, Cui Y, Liu Z. Gender difference in oxidative stress: A new look at the mechanisms for cardiovascular diseases. J Cell Mol Med. 2017;21(5):1024-32.
36. Brealey D, Brand M, Hargreaves I, Heales S, Land J, Smolenski R, *et al.* Association between mitochondrial dysfunction and severity and outcome of septic shock. Lancet. 2002;360(9328):219-23.
37. Hashish FER, Abdel-Wahed MM, El-Odemi MH, El-Naidany SS, ElBatsh MM. Possible protective effects of quercetin on doxorubicin-induced cardiotoxicity in rats. Menoufia Med J. 2021;34(1):333.
38. Yu X, Li Y, Mu X. Effect of quercetin on PC12 Alzheimer's disease cell model induced by Aβ25-35 and its mechanism based on sirtuin1/Nrf2/HO-1 pathway. Biomed Res Int. 2020;2020:8210578.
39. Han Q, Zhang J, Sun Q, Xu Y, Teng X. Oxidative stress and mitochondrial dysfunction involved in ammonia-induced nephrocyte necroptosis in chickens. Ecotoxicol Environ Saf. 2020;203:110974.
40. Yun S, Chu D, He X, Zhang W, Feng C. Protective effects of grape seed proanthocyanidins against iron overload-induced renal oxidative damage in rats. J Trace Elem Med Biol. 2020;57:126407.
41. Bayram C, Cetin I, Tavil B, Yarali N, Ekici F, Isık P, *et al.* Evaluation of cardiotoxicity by tissue Doppler imaging in childhood leukemia survivors treated with low-dose anthracycline. Pediatr Cardiol. 2015;36(4):862-6.
42. El-Sheikh AAK, Morsy MA, Mahmoud MM, Rifaai RA. Protective mechanisms of coenzyme-Q10 may involve up-regulation of testicular P-glycoprotein in doxorubicin-induced toxicity. Environ Toxicol Pharmacol. 2014;37(2):772-81.
43. Mallappa S, Neeli PK, Karnewar S, Kotamraju S. Doxorubicin induces prostate cancer drug resistance by upregulation of ABCG4 through GSH depletion and CREB activation: Relevance of statins in chemosensitization. Mol Carcinog. 2019;58(7):1118-33.
44. Nuhu F, Seymour A-M, Bhandari S. Impact of intravenous iron on oxidative stress and mitochondrial function in experimental chronic kidney disease. Antioxidants. 2019;8(10):498.
45. Peoples JN, Saraf A, Ghazal N, Pham TT, Kwong JQ. Mitochondrial dysfunction and oxidative stress in heart disease. Exp Mol Med. 2019;51(12):1-13.
46. Garrido-Maraver J, Cordero MD, Oropesa-Ávila M, Vega AF, De La Mata M, Pavón AD, *et al.* Coenzyme q10 therapy. Mol Syndromol. 2014;5(3-4):187-97.

47. Naseem I, Hassan I, Alhazza IM, Chibber S. Protective effect of riboflavin on cisplatin induced toxicities: A gender-dependent study. J trace Elem Med Biol. 2015;29:303-14.

48. Wang H, Liu H, Liu R-M. Gender difference in glutathione metabolism during aging in mice. Exp Gerontol. 2003;38(5):507-17.

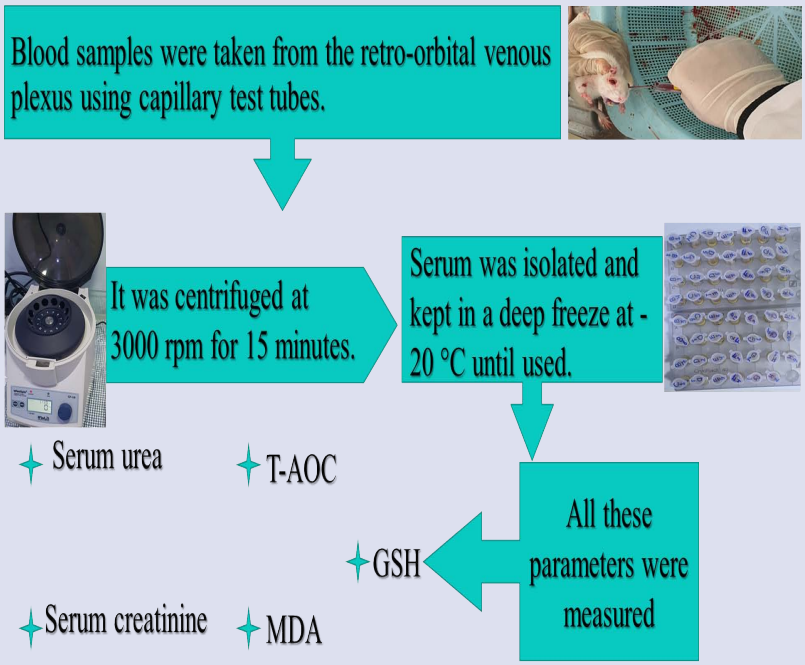
49. Xu Y, Nisenblat V, Lu C, Li R, Qiao J, Zhen X, *et al.* Pretreatment with coenzyme Q10 improves ovarian response and embryo quality in low-prognosis young women with decreased ovarian reserve: A randomized controlled trial. Reprod Biol Endocrinol. 2018;16(1):1-11.

50. Rynkowska A, Stępniak J, Karbownik-Lewińska M. Fenton reaction-induced oxidative damage to membrane lipids and protective effects of 17β-estradiol in porcine ovary and thyroid homogenates. Int J Environ Res Public Health. 2020;17(18):6841.

51. Viña J, Sastre J, Pallardó F, Borrás C. Mitochondrial theory of aging: Importance to explain why females live longer than males. Antioxidants Redox Signal. 2003;5(5):549-56.

52. Abplanalp W, Subbiah MTR. Uptake and protection against oxidative stress by estrogen esters in THP-1 human macrophage cell lines. Gynecol Obstet Invest. 2001;51(2):81-4.

GRAPHICAL ABSTRACT



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