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EFFECT OF COENZYME Q10 AND CARVEDILOL ON CYCLOSPORINE A INDUCED CARDIOTOXICITY IN RATS

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ABSTRACT

Cyclosporine-A is most frequently used in transplant medicine. However, the major limiting factors in its use are nephrotoxicity, hepatotoxicity and cardiotoxicity. **Aim:** The aim of this work is to study the effect of each of coenzyme Q10 and carvedilol alone and in combination on cyclosporine-A induced cardiotoxicity in rats. **Methods:** This study was carried out on 50 male albino rats divided into 5 equal groups: Group 1 (Normal control), Group 2 (Received Cyclosporine-A), Group 3 (Received Cyclosporine-A + Carvedilol), Group 4 (Received Cyclosporine-A + CoQ10), Group 5 (Received Cyclosporine-A + CoQ10+ Carvedilol). Tissue SOD, CAT, GSH-Px activity, MDA, NO and serum CK-MB and AST were measured. Histopathological examination of the heart was performed. **Results:** Cyclosporine-A induced significant decrease in tissue SOD, CAT, GSH-Px activities and significant increase in tissue MDA, NO and serum CK-MB and AST compared to normal control group. Administration of either carvedilol or Q10 induced significant increase in tissue SOD, CAT, GSH-Px activities and significant decrease in tissue MDA, NO and serum CK-MB and AST compared to CsA group. Concomitant administration of carvedilol and Q10 induced significant increase in tissue SOD, CAT, GSH-Px activities and significant decrease in tissue MDA and NO and serum CK-MB and AST compared to CsA group which was more marked than each of coenzyme Q10 and carvedilol alone. **Conclusion:** This demonstrates the cardioprotective effect of coenzyme Q10 and carvedilol alone and in combination against cyclosporine A induced cardiotoxicity.

KEYWORDS: Coenzyme Q10, Carvedilol, Cyclosporine A, cardiotoxicity, rats.

INTRODUCTION

Cyclosporine A is the most frequently used immunosuppressive agent in transplant medicine and in the treatment of autoimmune diseases because of its specific inhibitory effect on the signal transduction pathways of the T cell receptor **(Guada, Melissa, 2016)**. However, the major limiting factors for its clinical use are the adverse effects, which include nephrotoxicity, hypertension, hepatotoxicity and cardiotoxicity which are related to generation of reactive oxygen species**(Jadon, 2019).** Moreover, theuse of cyclosporine A may lead to increased vasoconstriction andvascular endothelial dysfunction **(Su, Jin Bo., 2015).**

CoQ10 is an essential cofactor in mitochondrial oxidativephosphorylation and is necessaryfor adenosine triphosphate (ATP)production. The reduced form ofCoQ10 is also an antioxidant, membrane stabilizer and is the onlyendogenouslysynthesisedlipophilic antioxidant. It can act as an antioxidant directly by protecting biological membranes against oxidation, as well as inhibiting the peroxidation of lipoprotein lipids present in the circulation **(Zaki, Noha M., 2016)**. It has also been shown to preserve myocardial sodium-potassium ATP-ase activity and to stabilize myocardial calcium- dependent ion channels **(Tosaki, Arpad, 2020).**

Indeed, supplementation with exogenous CoQ10 has been shown to ead to an increase in the reduced CoQ10 content of LDL, and a decrease of their peroxidisability. As an antioxidant, reduced CoQ10 may also have a role in recycling α- tocopherol **(Florkowski, 2015).**

Carvedilol, a third generation non-selective β-blocker with both β1- and β2-adrenoreceptor and α1- adrenoceptor blocking properties, is widely used as anti-hypertensive **(shireman, Theresa I., et al**., **2016)**. Carvedilol has also demonstrated antioxidant effects possibly due to stimulation ofendothelial nitric oxide production or reduced nitric oxide inactivation **(Fergus, Icilma V, 2015).** Furthermore, carvedilol may protect against reactive oxygen species (ROS) through scavenging of free radicals, suppression of free radical generation and prevention of ferric ion-induced oxidation **(Zhang, Zhongtian, et al,2020).**

Aim of the work

The aim of this work is to study the effect of each of Coenzyme Q10and carvedilol alone and combination of both on cyclosporine-A induced cardiotoxicity in rats.

MATERIALS AND METHODS

Drugs

1- Cyclosporine A

A product of Novartis, the content of the capsule is suspended in sunflower oil and given orally by gastro-oesophageal tube in a dose of25 mg/kg/day **(Gallo, Loreana, 2021).**

2- Carvedilol

A product of GNP/Biopharm, tablets suspended in gum tragacanth given orally by gastro-oesophageal tube in a dose 10mg/kg/day **(Huanget al., 2006)**.

3- Coenzyme Q10

A product of Arab CO. forPharm. & Medicinal Plants Egypt(Mepaco). The content of the capsule is suspended in sunflower oiland Given orally by gastro- oesophageal tube in a dose of 300 mg/kg per day **(Kon et al., 2007).**

The study was carried out on 50 adult male albino rats weighing 150-200 gram. The rats were housedin cages and received ordinary diet and water ad libitum. The rats were classified into 5 equal groups as follows:

Group 1: Normal control group, received sunflower oil (2 ml/kg/day for 21days orally).

Group 2: Received only cyclosporine A as a single dose dailyfor 21 days.

Group 3: Received cyclosporine-A and Carvedilol single dose daily for 21 days.

Group 4: Received Cyclosporine Aand Co Q10 single dose daily for 21days.

Group 5: Received Cyclosporine A,Co Q10 and Carvedilol single dose daily for 21 days.

All animals were sacrificed at theend of the study and blood samples were collected. Then, the serum wasseparated immediately by centrifugation at 1500×g, for 5 min. at 4° and stored at −30°C forbiochemical analysis. The heart wasrapidly removed, and divided equally into two longitudinal sections. One part was separated andthen stored at –80°C until the analysis time for further enzymatic analysis, while the other part was stored in 10% formalin for histopathological examination.

Specimen Collection & Methods

After weighing the sample tissues, homogenized in fivevolumes of ice-cold Tris-HCl buffer (50 mM, pH 7.4). Homogenization was carried out for 2 min at 13,000r.p.m. All procedures wereperformed at 4°C. Homogenate, supernatant and extracted sampleswere prepared and the

following determinations were made on the samples using commercial chemicals supplied by Sigma Chemical Co.

1. **Superoxide dismutase activities** were determined according to the method of **(Ahmed, et al., 2014)**. Resultswere expressed as U/mg protein.
2. **Catalase activity** was determined according to Aebi's method **(Gurel,et al., 2005).** Results were expressed asU/mg protein.
3. **Glutathione peroxidase (GSH- Px) activity** was measured by the method of **(Zararsiz, et al. 2006).** Results were expressed as U/gprotein.
4. **Lipid peroxidation assay:**The malondialdehyde (MDA) levels were determined by a method basedon the reaction of MDA with thiobarbituric acid at 95–100°C **(Domijan, et al., 2015)**.Results were expressed as nmol/gprotein.
5. **Nitric oxide**. Tissue nitrite and nitrate were estimated as an index of nitric oxide production **(Ozcan, et al., 2004)**. Results were expressed as micromol/g protein.
6. **Serum CK-MB:** Determinedaccording to **(Sultan, et al. 2022)**, expressedas U/L.
7. **Serum Aspartate Transaminase (AST)**: Measured According To**(Mousa, Y. J., and M. H. I. Al-Zubaidy. 2019**). Results Were Expressed As U/L.

Histopathological examination

Tissue samples were fixed in 10% neutral buffered formalin. Following dehydration in ascendingseries of ethanol, tissue samples were cleared in xylene and embedded in paraffin. Tissue sections of 4μ m were deparaffinized, rehydrated and stained with haematoxylin and eosin, periodic acid-Schiff and trichrome staining procedure. The severity of changes was quantified based on the degree of inflammation, interstitial fibrosis and myocardial disorganization. The scoring system was as follows: (−) no damage; (+) minimal inflammatory cell infiltration, focal minimal interstitial fibrosis and mild myocardial disorganization (less than 5%); (++) moderate inflammatory cell infiltration, patchy multifocal interstitial fibrosis and moderatemyocardial disorganization (5– 20%); (+++) widespread inflammatory cell infiltration, severe interstitial fibrosis and myocardial disorganization (more than 20%) **(Selcoki et al., 2007)**.

Statistical analysis

Data were presented as means ± standard deviation (SD). Student's t- test was used for evaluating the statistical significance of differences in means. P value of <0.05 was considered to be statistically significant.

RESULTS

Effect of administration of Carvedilol, Coenzyme Q10 and combination of both on different oxidative stress markers [Tissue superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GSH-Px) activities, MDA and NO levels] and serum **CK-MB and AST (Table 1,Fig.1,2,3,4,5,6,7):**

Cyclosporine A inducedsignificant decrease ($p< 0.05$) in tissue superoxide dismutase (SOD), catalase (CAT), glutathioneperoxidase (GSH-Px) activities and significant increase ($p< 0.05$) in tissue MDA, NO levels and serum CK-MB and AST compared to normal control group.

Administration of either carvedilol and Q10 alone induced significant increase ($p< 0.05$) in tissue superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GSH-Px) activities, and significant decrease ($p< 0.05$) in tissue MDA, NO levels and serum CK-MB and AST compared to CsA group.

Concomitant administration of carvedilol and Q10 induced significant increase ($p< 0.05$) in tissue SOD, CAT, GSH-Px activitiesand significant decrease ($p< 0.05$) intissue MDA and NO levels and serum CK-MB and AST compared to CsA group which was more marked than each of coenzyme Q10and carvedilol alone.

DISCUSSION

Histopathological findings (Table 2): Histopathological changes in the heart tissue of the CsA treated rats and after administration of carvedilol, Q10 and ccombination of them were quantified and summarized in table 2. The hearts of control rats had a normal morphology with striated muscle fibers and connective tissue among them (Fig.8). Pathological evidence of myocardial damage was observed in all rats treated with cyclosporine-A (Fig.9). Inflammatory cell infiltration, disorganization of myocardial muscle fibers and interstitial fibrosis wereseen in this group.

The cellular infiltrate was mostly composed of mature lymphocytes.

Connectivetissue was clearly increased and fibrosis was evident around myocardial fibres.

Number of infiltrated cells, disorganization of myocardial fibers and interstitial fibrosis was diminished in the heart of the CsA- treated rats given each of carvedilol or Q10 alone and in combination of both (Fig.10, 11,12).

The results in the present studyshowed that administration of cyclosporine to rats induced marked cardiotoxic effect as evidenced by significant decrease in the activities of SOD, CAT and GSH-Px andincreased level of MDA and NO incardiac tissue.

Also significantincrease in the level of serum CK-MB and AST.

Regarding the mechanism by which cyclosporine induced cardiotoxicity it has been demonstrated that CsA is able to generate reactive oxygen species and lipid peroxidation, which directlyinduce cardiotoxicity **(Pari & Sivasankari, 2008).**Similar results were obtained by **Rezzani et al. (2006)** who demonstrated that CsA administration for 21 days producedelevated levels of MDA, markeddepletion ofcardiac antioxidant enzymes and caused morphologicalalterations in myocardial fibers. Also, the depletion of glutathione induced by cyclosporine is thought to be able to induce irreversible injury by oxidative intoxication andby free radicals which can result inlipid peroxidation, protein oxidation and inactivation, disturbances in calcium homeostasis and loss of cell viability **(Ebru et al., 2008).** It has been demonstrated that high NO production, especially by inducible nitric oxide synthase (iNOS) activity in myocardium was present during CsA therapy **(Rezzani et al., 2003).** In the present study administration of carvedilol induced cardioprotective effect as evidencedbysignificant increase in the activities of SOD, CAT and GSH-Px and significant decrease in the levelof MDA and NO in cardiac tissue,also significant decrease in serum CK-MB and AST. These results are in accordance with **Huang et al.(2006)** who reported that carvediloltreatment increased activities of antioxidant enzymes and decreased the level of MDA. Furthermore,these results are Supported by **(Zheng, et al., 2019)**. They reported that carvedilol preventslipid peroxidation in the brain andheart membranes both in vitro and invivo and as a result of the anti-oxidant activity, carvedilol preventsthe depletion of the endogenous anti- oxidants, α-tocopherol (vitamin E) and glutathione, from tissues subjected to oxidative stress**.** Attenuation of iron-mediated free radical formation is other possible antioxidant mechanism as reported by **Yoshioka et al. (2000)** who reported that becaue of its unique ability to interact with free radicals, carvedilol has been proposed to be a useful adrenergic antagonist in the treatment of hypertension and cardiac diseases in which oxidative stress prevails. Also, **Yoshioka et al.(2000)** reported that highconcentrations of NO are effectivelyeliminated by carvedilol. Thus, carvedilol may function as an anti- NO agent at least in conditions wherehigh biologicalconcentrations of NO prevail.

On the other hand, other studies reported that carvedilol can exert pro-oxidant effects. These

studies reported that this drug can induce, in isolated mitochondria, marked inhibition of mitochondrial respiration by NAD-dependent substrates and specific inhibition of mitochondrial complex I activity, with these effects being associated with an increased production of ROS**(Sgobbo et al., 2007)**.

In the present study, administration of Coenzyme Q10 induced cardioprotective effect as evidenced by significant increase in the activities of SOD, CAT and GSH-Px and decrease in the level of MDA and NO in cardiac tissue with significant decrease in serum CK- MB and AST. These results can be explained on the basis that Coenzyme Q10, a fat-soluble, vitamin-like, benzo-quinonecompound that functions primarily as an antioxidant, membranestabilizer and a cofactor in the oxidative phosphorylation and production of ATP **(Higashi et al., 2009).** Coenzyme Q stimulatescell growth and attenuates cell death**(Kalenikova et al., 2007).** It has alsobeen shown to help preservation of myocardial sodium-potassium ATPase activity and to stabilize myocardial calcium-dependent ion channels **(Higashi et al., 2009)**. Coenzyme Q10 is the most important fat soluble antioxidant. Inall membranes, the antioxidant effectof Coenzyme Q10 consists of direct interaction of its reduced form with free radicals (lipid radicals, hydroxyl radical, peroxynitrite) or regeneration of α tocopherol and ascorbate **(Kalenikova et al., 2007)**. These properties of Co Q limit lipid peroxidation in biomembranes and protect DNA and proteins against thedamaging effect of free radicals **(Kalenikova et al., 2007).** Similar results were reported by other studies which demonstrated that CoQ10 appears to be involved in thecoordinated regulation between oxidative stress and antioxidant capacity of heart tissue. When the heart is subjected to oxidative stress in various pathogenic conditions the amount of CoQ10 is decreased **(Maulik et al., 2000).** Exogenously administered CoQ10 produced significant increase in myocardial CoQ10 and CoQ10 is nonspecifically incorporated into the cell membranes and into various subcellular fractions and organelles **(Maulik et al., 2000**), such as mitochondrial membranes and sarcoplasmic reticularmembranes and oxidative stress wassignificantly suppressed **(Wang etal., 2021**).

Similar results were demonstrated by other studies whichreported that, the administration of CoQ10 significantly attenuated the increase of oxidative and nitrative stress markers and inflammatory markers in a dose-dependent manner. These studies demonstrate the potential value of CoQ10 in prophylaxisand therapy of various disorders related to oxidative stress and its beneficial effect in hypertension and heart failure **(Kunitomo et al., 2008).**

In the present study, combined administration of Coenzyme Q10 and carvedilol induced

augmentedcardioprotective effect which is more marked than each of these drugs alone, as evidenced bysignificant increase in the activities of SOD, CAT and GSH-Px and significant decrease in the level of MDA and NO in cardiac tissue, alsodecrease in CK-MB and AST in the serum. This can be explained by the combined antioxidant effect of carvedilol and coenzyme Q10 with their abilities to prevent depletionand regenerate endogenous antioxidant as α tocopherol, ascorbate and glutathione (**Feuerstein & Ruffolo, 1996;Kalenikova et al., 2007**). On other hand, **Dandona et al .(2007)** reported that carvedilol may protect against reactive oxygen species (ROS) through scavenging of free radicals, suppression of free radical generation, and prevention of ferric ion-induced oxidation.

In conclusion, the present study demonstrates the cardioprotective effect of each of coenzyme Q10 and carvedilol alone and its additive antioxidant effect in combination against cyclosporine A induced cardiotoxicity.

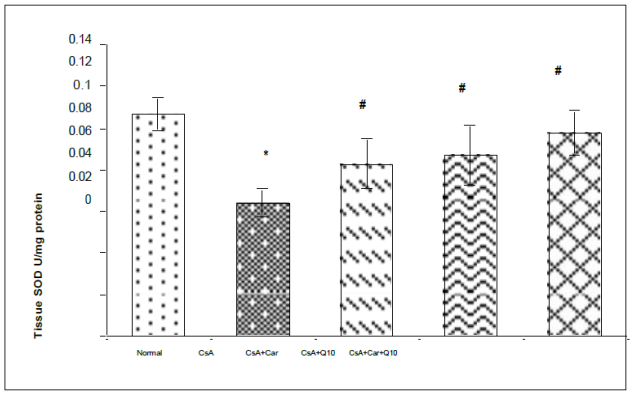

Fig. 1: Tissue SOD (U/mg protein)Mean ± SD in all studied groups.

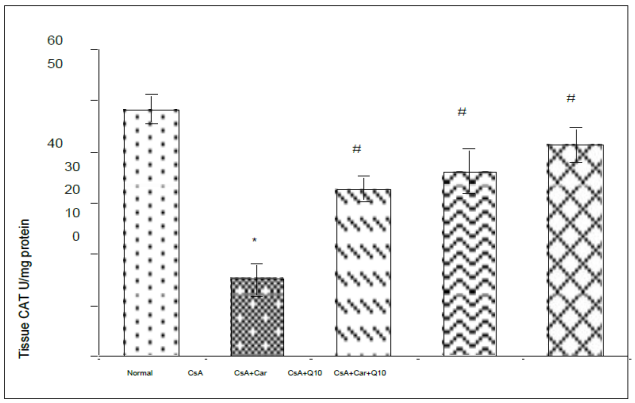

Fig. 2: Tissue Catalase (U/mg pro tein) Mean±SD in all studiedgroups.

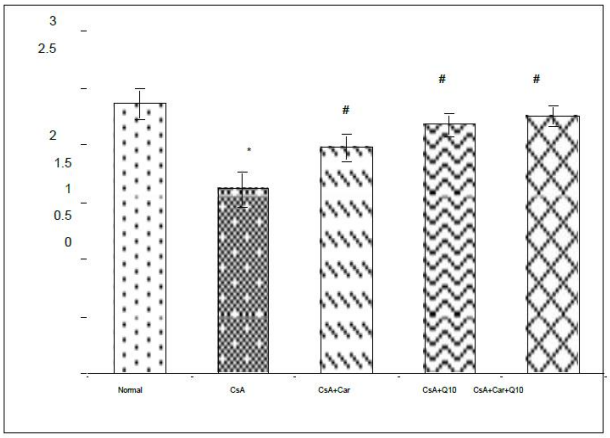

Fig. 3: Tissue GSH-Px (U/g protein) mean ±SD in all studied groups.

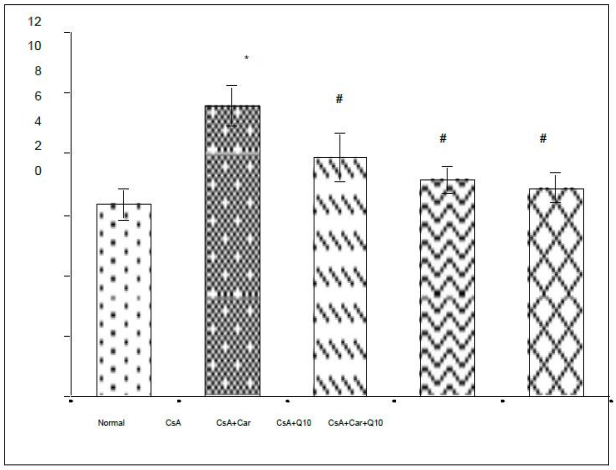

Fig. 4: Tissue MDA (nmol/g protein)Mean±SD in all studied groups.

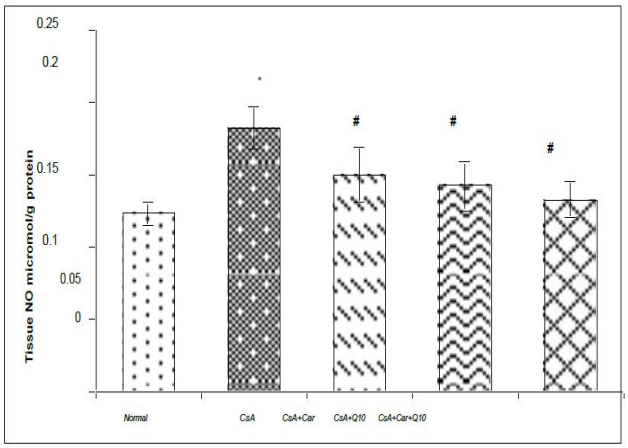

Fig. 5: Tissue NO (micromol/g protein)Mean±SD in all studied groups.

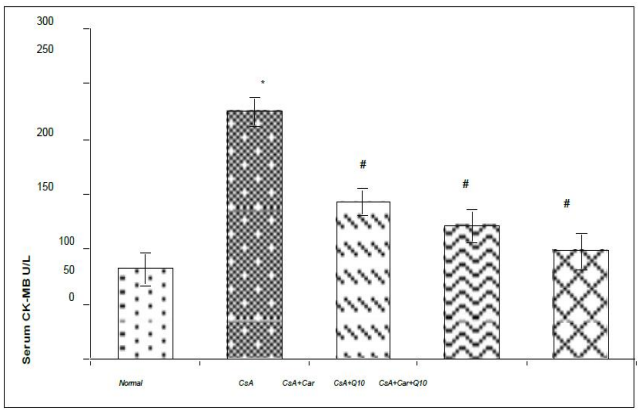

Fig. 6: Serum CK-MB (U/L) Mean ±SDin all studied groups.

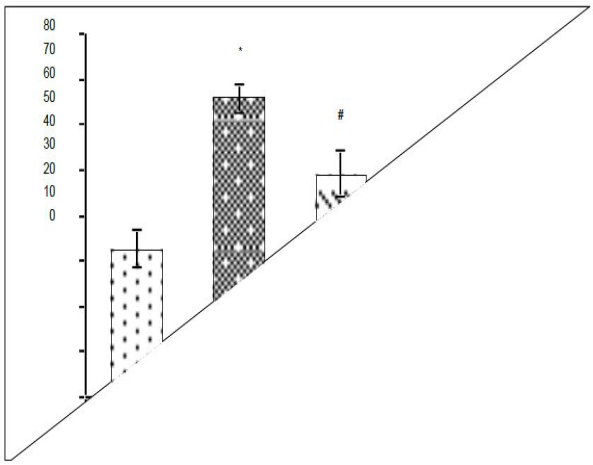

Fig. 7: Serum AST (U/L) Mean±SD inall studied groups.

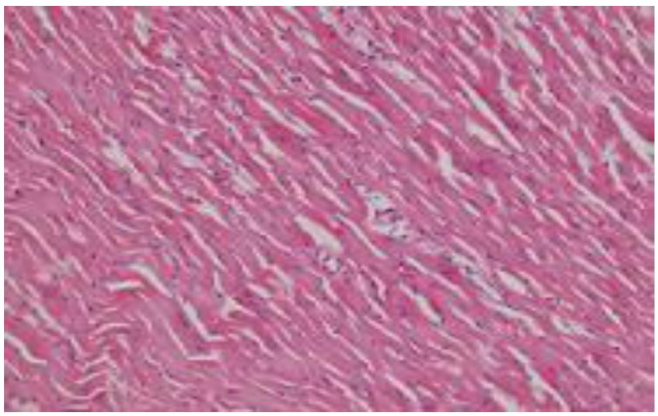

Fig. 8: Section from the heart of normal group stained with H&E stain showed normal morphology, consisting of striated muscle fibers and sparse connective tissue (H&E X 250).

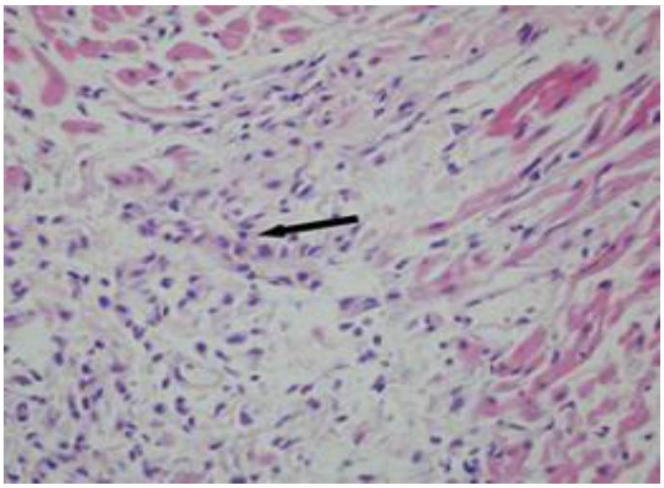

Fig. 9: Section from the heart of cyclosporine A treated group stained with H&E stain showed inflammatory cell infiltration and fibrosis among cardiac muscle cells (H &E ×400).

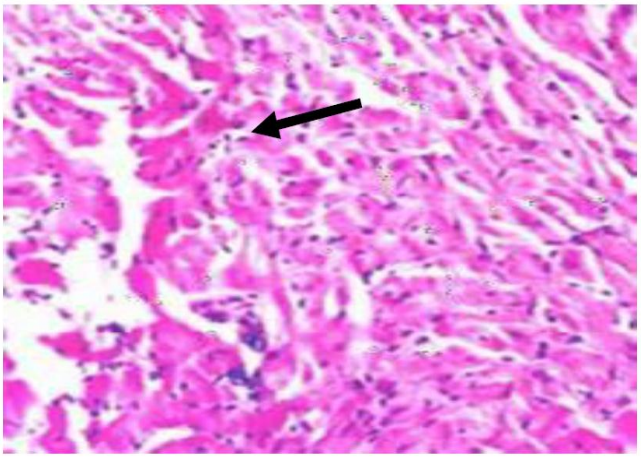

Fig. 10: Section from the heart of coenzymeQ10 + Cyclosporine A treated group stained with H&E stain showed significant decreasein inflammatory cell infiltration and fibrosis among cardiac muscle cells (H &E ×400).

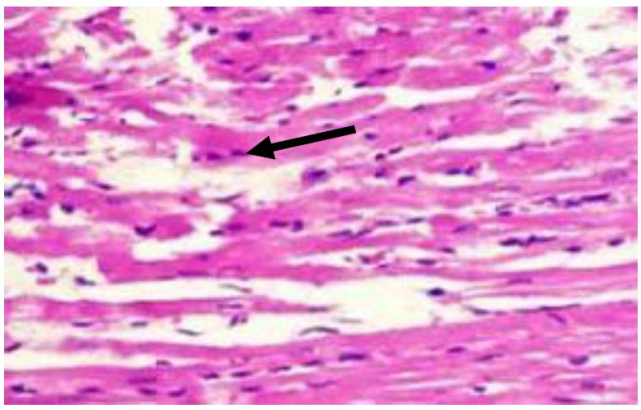

Fig. 11: Section from the heart of carvedilol + Cyclosporine A treated group stained with

H&E stain showed marked decrease in inflammatory cell infiltration and fibrosisamong cardiac muscle cells (H &E ×400).

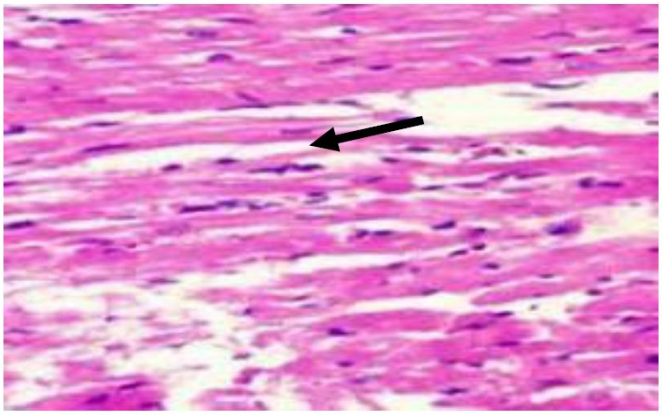

Fig. 12: Section from the heart of coenzyme Q10 + Carvedilol + Cyclosporine A treated group stained with H&E stain showed marked improvement in inflammatory cell infiltration and fibrosis among cardiac muscle cells (H &E ×400).

Table 1: Effect of administration of carvedilol, Q10 and combination of both on different oxidative stress markers (Tissue SOD, CAT, GSH-Px activites, MDA and NO levels) and serum CK-MB and AST in different groups (Mean±SD).

Group Parameter	G-1 Normal	G-2 CsA	G-3 CsA+ Car	G-4 CsA + Q10	G-5 CsA + Car +Q10
Tissue SOD U/mg protein	0.107 ± 0.008	* 0.064 ± 0.007	# 0.083 ± 0.012	# 0.087 ± 0.014	# 0.098 ± 0.011
Tissue CAT U/mg protein	48.32 ± 3.12	* 16.2 ± 2.04	# 32.6 ± 2.8	# 38.07 ± 4.21	# 41.24 ± 3.3
Tissue GSH-Px U/g protein	2.36 ± 0.14	* 1.61 ± 0.15	# 1.98 ± 0.12	# 2.18 ± 0.1	# 2.25 ± 0.09
Tissue MDA nmol/g protei	6.31 ± 0.52	* 9.56 ± 0.68	# 7.88 ± 0.78	# 7.15 ± 0.43	# 6.85 ± 0.48
Tissue NO cromole/g protein	0.123 ± 0.008	* 0.182 ± 0.015	# 0.15 ± 0.019	# 0.142 ± 0.017	# 0.133 ± 0.013
Serum CK-MB U/L	82.33 ± 15.55	* 225.21± 13.87	# 142.63 ± 12.41	# 121.34 ± 15.41	# 98.12 ± 17.12
Serum AST U/L	32.62 ± 4.1	* 65.86 ± 3.2	# 49.2 ± 5.3	# 42.77± 6.2	# 38.5 ± 5.6

* Significant compared to the control group

Significant compared to Cyclosporin A group

Table 2: Effect of administration of carvedilol, Q10 and combination of both on morphological changes assessed by histopathological examination of the heart in different groups.

Group	Inflammation	Myocardial disorganization	Interstitial fibrosis
Normal	(-)	(-)	(-)
CsA	(++) to (+++)	(++) to (+++)	(+) to (++)
CsA+ Car	(+) to (++)	(+) to (++)	(-) to (+)
CsA + Q10	(+) to (++)	(+) to (++)	(-) to (+)
CsA+Car +Q10	(-) to (+)	(-) to (+)	(-) to (+)

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