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Coenzyme Q10 prevents Oxidative Stress and Cardiac Disorders in ISO- treated Male Rats

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Abstract: The affliction of heart-ailment and metabolic diseases is amassed every single year. heart-ailment are an energy-depleted state allied with little myocardial-adenosine-triphosphate (A.T.P) production, mitochondria dysfunction, Oxidative stress, augmented reactive oxygen species generation, and endothelial dysfunction. There is a prerequisite for innovative approaches to prophylaxis and treatment. Coenzyme-Q.10 (Co.Q10) is a crucial compound for the body. There is upward substantiation that Co.Q10 is compactly allied to cardiac disorders. It can be baptized as the strategic constituent of the electron transport chain in mitochondria necessary for ATP production. As well, it dramas a key-part in protons 'transfer in the inner mitochondrial membrane. Consequently, this study targets to appraise the role of CoQ10 *vs* myocardial infarct in male rats. Rats were categorized into four groups vs. Control group, Q10 treated group, ISO treated group, and CoQ10 + ISO treated group, each comprising of 6 rats. Lipid profile, biochemical functions of heart and liver, oxidative stress markers, and anti-oxidative stress indicators were scrutinized. Administration of ISO occasioned an increase in total lipid profile. Serum levels of biochemical tests bared significant results, and oxidative stress markers showed a significant increase in ISO-treated rats. Treatment with CoQ10 expressively value-added the oxidative stresses in ISO-treated rats. In conclusion, it was pragmatic that administering the CoQ10 exhibited deterrent results contrary to myocardial infarct instigated by injection with isoproterenol (ISO)

keywords: Cardiac, CoQ10, Oxidative

1.Introduction

Heart-ailment endure the foremost root of death universally. more than i17million people died from CVD in 2008, whereas an estimated 17.5 million people died from CVD in 2012, secretarial for 31% of all global deaths [1]**.** European Society of Cardiology and W.H.O information prophesied that virtually 23.i6 1M-a-year decease from CVD every-one year by 20i30 [2]. Cardiac alteration is habitually methodized thru genomic expression, and vicissitudes in molecular statuses, which eventually results in size, shape, and function fluctuations of the heart which considered as the conjoint proceedings that befell numerous CVD together with M.I, aortic-stenosis, HT.N, myocarditis, idi**o**pathic cardio-myopathy. Impairment to the myocardial cells ascends attributable to the generation of toxic reactive oxygen species (ROS) such as superoxide radicals, hydrogen peroxide, and hydroxyl radicals [3]**.**

Acute myocardial infarct (AM.I) befalls throughout the period at what time circulation to a region of the heart is stuffy and necrosis ensues. AM.I is methodized by severe pain (angina pectoris), habitually allied with nausea, shortness of breath, and dizziness. A precursor state of AM.I is myocardial ischemia, in which

barricade of coronary artery clues to severe oxygen deprivation of the myocardium before necrosis [4]**.** The model of Isoproterenol (ISO) induced MI is well-thought-out as one of the most extensively rummage-sale experimental models to study the beneficial effects of many drugs and their cardiac function**.** Hypodermic injection of I.S.O, which imitators the β-adrenergic receptor activity, can yield myocardial necrosis [5].

Oxidative strain and seditious reactions are specific to the fundamental mechanisms of myocardial transformation in the heart. Additional making of RO.S and inflammatory cytokines might cause alteration in the extra-cellular matrix by activating matrix metalloproteinase (M.M.P) eventually fallouts in collagen synthesis and heart myocardial fibrosis [6]. Cumulative shreds of evidence have advocated that at high doses surges myocardial oxidative stress thru ISO treatment, pro-inflammatory cytokine synthesis, and arouses mitogen-activated protein kinases [7].

Much ordinary merchandise and dietetic additions comprehending anti-oxidant properties verified RO.S in rats. Q.10 (CoQ.10) is amalgamated anti-oxidant and mend heart death by dwindling all cases of mortality by half [8]. Q.10 deeds as an electron carrier in the mitochondrial electron transport chain. CoQ.10 plays a key-role in the biochemical mechanism intricate in furnishing cells thru energy, acting in conjunction with enzymes, henceforth the name CoQ.10, to convert sugars and fat into energy [6]. Q.10 (CoQ.10) can rally the ischemia damage of revascularization coronary [10]. In addition to its anti-oxidant bustle, Q.10 (CoQ.10) is also used for intracellular energy production, liable for the perfection of endothelial dysfunction as well as imperative for triggering mitochondrial uncoupling proteins [11]. Bearing in mind, the Cardio-protective effect of Co-Q10, investigations were accompanied to gage the consequence of Q.10 (CoQ.10) contrary to isoproterenol-induced cardiac remodeling in male rats.

2. Materials and methods

2.1 Experimental animals:

The experiment was carried out on healthy adult male Wister albino rats weighing 190-215 g of the male sex. Rats were maintained under standardized conditions. The rats were set aside in a controlled temperature atmosphere with a 24 h cycle. All rats were reformed to the place for two weeks afore the preparatory of the experiment. The animals were delivered with a normal diet and water *ad libtium* thru period of experiment

2.2 Experimental design:

Infarcted rats were arbitrarily alienated into the following groups each entailing of six animals.

1. **The control group (C):** Rats were fed on the normal laboratory rat diet through the experiment.
2. **Q.10 group (Q10):** Rat received Q10 (10mg/kg b.w), daily via oral gavage.
3. **Isoproterenol group (I.S.O):** Rats fed on the ordinary rat diet and injected subcutaneously (SC) with (ISO) at a dose of (150 mg/kg in 2ml saline solution) weekly for 8 weeks
4. **Q10 + ISO group:** Rats received (10mg\kg b.w) of Coenzyme Q10 for 2 weeks via oral gavage before their injection subcutaneously (S.C) with isoproterenol (ISO) at a dose of (150mg/kg b.w in 2ml saline, S.C) weekly for 8 weeks.
5. **ISO + Q1O group:** Rats received (10mg/kg b.w) of Coenzyme Q10 daily via oral gavage and injected subcutaneously with isoproterenol concomitantly at a dose of (150 mg/kg b.w in 2ml saline) weekly for 8 weeks.

2.3 Blood sampling:

At the culmination of the experimental period (8 wks.) overnight abstained rats have forfeited 24 hrs. After the last treatment and blood obtaining, were gathered in a separator at 4000 r.p.m for 15 min. The clear non hemolysis sera were quickly removed and put in labeled Eppendorf's tubes; the sera were frozen αTP 20oC for diverse biochemical analyses.

2.4 Valuation of biochemical parameters:

Lipid profile and liver functions, and TNF activities were determined. The kits for assessing the biochemical parameters in serum were also purchased and keep an eye on the manufacturer’s ordinary procedure.

2.5 Estimation of oxidative stress biomarkers

To describe the markers of oxidative stress, the clear supernatant obtained was used for assay of R.O.S, H202, M.D.A, and NO.

2.6 Estimation of antioxidative stress markers

To define the antioxidative stress markers, the clear supernatant of heart tissue was used for the valuation of superoxide dismutase (SOD), catalase (CAT), glutathione-S-transferase (GST), and Glutathione (GSH).

2.6 Analysis of data

The collected data were coded, tabulated, and statistically analyzed using the **Minitab software version 19.** Descriptive statistics were thru parametric quantitative data my mean, standard deviation, and standard error of the mean (SEM). Analyses were done for non-parametric quantitative data using the Kruskal Wallis test between the groups. The level of significance was taken at (P-value ≤ 0.05).

3 Results

3.1 Effect of Coenzyme Q10 treatment on lipid profile in rat groups:

As publicized in **Table (1)**, the fallouts demonstrated that all parameters of lipid profile concentration in the ISO treated group significantly augmented than its concentration in control group. However, there was significant betterment (diminution) in Q10 treated groups (ISO +Q10) and (Q10+ISO) at a dose (200 mg/kg b.w) that was extra manifest in group (Q10+ISO) for TC and TG. While the concentration was stagnant significantly higher than the concentration of the control group. What's more, no significant conversion in Q10 treated group equated to the control one

Table (1): Comparison of lipid profiles in different rat groups**.**

groups	CN=6	Q10N=6	ISON=6	Q10+ISON=6	ISO+Q10N=6
TC, mg/dl, mean±SEM	106.4±3.05[a]	103.6±1.24[a]	144.3±2.11[b]	108.6±0.19[c]	116.4±0.13[c]
TG, mg/dl, mean±SEM	95.18±0.42[a]	95.24±0.44[a]	166.2±0.44[b]	100.5±1.36[c]	126.8±1.44[c]
HDL-C mg/dl , mean±SEM	44.18±0.34[a]	44.80±0.44[a]	33.24±0.21[b]	41.04±0.22[c]	37.54±0.09[c]
LDL-C, mean±SEM	38.29±0.75[a]	37.91±0.59[a]	29.12±0.35[b]	38.30±0.21[c]	29.5±0.08[c]

In each group results for 6 rats are expressed by means ± SE. Small (a-c) letters

showing the marked change at P ≤ 0.05. The same letters showing (non-significant) and the significant are expressed by dissimilar letters.TG: Triglyceride; TC: Total cholesterol. HDL-C; high density lipoprotein cholesterol, LDL-C; low density lipoprotein cholesterol

3.2 Effect of coenzyme Q10 on biochemical tests:

I.S.O management in rats sizably up-surged A.L.T, A.S.T, and A.L.P enzyme conc. equated to the control rats **Table (2)**. Furthermore, CoQ10 administration significantly decrease the ALT, AST, and ALP activities. Likeness, ISO administered rats publicized significantly higher activity of CK-MB compared to control rats. CoQ10 administration in group Q10+ISO significantly let down the C.K and C.K-M.B in ISO-administered rats compared to the group of ISO+Q10**.** Also, analogous results were instituted for LDH, and electrolytes (Na and K). TNF, it was pragmatic that the outcome of administration of Q10 in consort with ISO dropped the activity of TNF than the group of Q10+ISO. Captivatingly, the CoQ10 behavior meaningfully abridged the level of most biochemical parameters in the serum of a group of Q10+ISO administered rats

Table (2): Comparison of biochemical tests in different groups regarding the control group

Group	ControlN=6	Q10N=6	ISON=6	Q10+ISON=6	ISO+Q10N=6
ALT, U/L, mean±SEM	13.72±0.42[a]	14.71±0.19a	48.30±0.52b	36.79±1.44c	45.04±1.93c
AST, U/L, mean±SEM	43.55±0.34[a]	43.59±0.52a	75.98±0.87b	49.54±1.47c	55.21±5.54c
ALP, mg/dl,mean±SEM	144.75±0.513[a]	144.6±0.31a	288.14±3.63b	234.67±13.5c	224.97±17.3c
CK, U/Lmean±SEM	145.45±0.513a	144.92±0.513a	252.43±0.412b	142.53±0.180c	179.33±0.202c
CK-MB, IU/Lmean±SEM	13.89±0.513a	14.42±0.513a	28.90±0.369b	15.91±0.144c	26.32±0.237c
LDH, U/L, mean±SEM	202.05±3.43a	200.46±3.19a	486.54±3.15b	220.12±3.22c	248.75±8.06c
Na, mmol/Lmean±SEM	134.94±0.27a	136.17±0.26a	167.57±0.11b	142.20±0.14c	154.52±0.17c
K, mmol/L,mean±SEM	26.23±0.513[a]	25.81±0.31[a]	136.19±3.63[b]	99.15±13.5[c]	106.33±17.3[c]
TNF, pg./mlmean±SEM	4.52±0.130[a]	4.32±0.08[a]	8.78±0.138[b]	6.26±0.193[c]	5.24±0.208[c]

In each group results for 6 rats are expressed by means ± SE. Small (a-c) letters showing the marked change at P ≤ 0.05. The same letters showing (non-significant) and the significant are expressed by dissimilar letters.

3. Results and Discussion

ResultofQ.10onoxidativestressmeasurements

The oxidative stress markers were studied, M.DA, NO, and G.SH levels in tissue samples (heart) were scrutinized. I.SO treatment in rats bared an improved level of lipid peroxidation product M.DA in tissues matched to the control rats **Table (3)**. I.SO treatment also upturned the nitric oxide in tissues equaled to control rats. However, GSH concentration was diminished in tissues of I.SO +Q10 treated rats paralleled to control rats. Co.Q.10 treatment vetoed the upsurge of M.DA, and NO concentration knowingly in tissues. Moreover, the Co.Q.10 treatment meritoriously reinstated G.S.H level in I.SO -administered rat

Table (3): Comparison of oxidative stress markers in different groups regarding the Control group.

Group	ControlN=6	Q10N=6	ISON=6	Q10+ISON=6	ISO+Q10N=6
HeartROS,nmol/g,mean±SM	1.03±0.02[a]	1.02±0.05[a]	1.64±0.06[b]	0.91±0.04[c]	1.04±0.03[c]
HeartH2O2,mM/gmean±SEM	27.56±0.11[a]	23.51±0.15[a]	35.94±0.12[b]	26.95±0.61[c]	26.92±2.77[c]
Heart MDA,nmol/g,mean±SE	367.63±0.43[a]	367.86±0.44[a]	519.77±0.26[b]	382.7±8.91[c]	387.58±3.82[c]

In each group results for 6 rats are expressed by means ± SE. Small (a-c) letters showing the marked change at P ≤ 0.05. The same letters showing (non-significant) and the significant are expressed by dissimilar letters

3.4 Relation between Q10 and antioxidative stress biomarkers.

Table (4) spectacles the activity of antioxidative stress biomarkers of S.O.D, C.A.T, GS.T, and GSH in heart cells of control and other groups. From the obtained results we perceived that there was a significant diminution in S.O.D and C.A.T activity in I.SO group paralleled to control group. Whereas, Q10 to rat groups (ISO+Q10) and (Q10+ISO) occasioned a significant upsurge in S.O.D and CAT activity associated with ISO group. Also, SOD and CAT activity in Q10 + ISO group enhanced more than in ISO + Q10 group. Administration of Q10 only presented no significant modification compared to the control group. Equally, Heart GST and GSH have exhibited a significant lessening in ISO group. Administration of Q10 bounces rises to a significant surge in GST and GSH activity compared to ISO group.

Table (4): Comparison of antioxidative stress markers in groups regarding the Control group**.**

Group	ControlN=6	Q10N=6	ISON=6	Q10+ISON=6	ISO+Q10N=6
Heart SOD, U/gmean±SEM	174.3±0.14[a]	174.4±0.13[a]	135.6±0.11[b]	167.1±3.03[c]	155.0±4.43[c]
Heart CAT, U/gmean±SEM	174.3±2.13[a]	184.4±3.15[a]	145.6±6.15[b]	167.2±4.03[c]	155.0±4.83[c]
Heart GST, U/gmean±SEM	5.48±0.31[a]	4.91±0.03[a]	2.00±0.03[b]	4.73±0.18[c]	3.79±0.09[c]
Heart GSH, mmol/g, mean±SEM	4.22±0.03[a]	4.52±0.15[a]	2.18±0.03[b]	4.21±0.17[c]	3.80±0.14[c]

In each group results for 6 rats are expressed by means ± SE. Small (a-c) letters showing the marked change at P ≤ 0.05. The same letters showing (non-significant) and the significant are expressed by dissimilar letters

4.Discussion

Heart-ailment is a retrogressive process that is allied with an on-going buildup of detrimental vicissitudes with time, fallouts in a lessening of physiological such as cardiovascular, renal, neurological, endocrine function with the increase of chances of disease and death. One of the most enervating is the forfeiture of myocardial function. Dwindled cardiac elasticity and incompetence to retort the changes in pressure to the arterial system influence the heart function allied with aging [12]. Reformed intermediary expresion and incapacity to retort to cell growth factors are crucial mechanisms of adversative cardiac remodeling [13].

This study intended to manifest the possible defensive and health-giving possessions of Coenzyme Q10 (CoQ10) on heart-ailment and blood parameters toxicity persuaded by ISO. Oppositely, (CoQ10) may embody a therapeutic option to treat individuals with heart-ailment. Some statistics advocate that CoQ10 has a perilous role in ATP production, a potent anti-inflammatory agent, and may rally endothelial function. Inferior CoQ10 levels are

seen in patients thru advanced cardiac-disease symptoms and with lower ejection fractions [14]. The cardiac restoration in rats was tempted by S.C. injection of isoproterenol. By squat dosages, catecholamine wields a +ve. Inotropic upshot that is favorable for heart function. Nonetheless, high doses of isoproterenol cause energy lessening of the heart follow-on biochemical and vicissitudes structure of cardio myocytes [15].

In the contemporary study, lipids play a chief role in heart-ailment, by subsidizing the expansion of atherosclerosis and by amending the structure, and firmness of the celular-membrane. Abundant levels of circulating cholesterol and its accretion in the heart've remained allied with circulatory impairment [16]. Rats pickled with I.S.O revealed a substantial surge in the serum levels of T.C, T.G, and LD.L-C, as hitherto conveyed [17]. In general, the mechanisms of actions of lipolytic hormones comprising ISO on fat cells are alleged to be refereed by the cAMP cascade, in which lipolysis hormones actuate adenylate cyclase and thereby intensifier cAMP formation. At that moment, cAMP upholds lipolytic bustle by initiating cAMP-dependent protein kinase, which phosphorylates hormone-sensitive lipase [18], and fallouts in the hydrolysis of stored triacylglycerol, in so doing subsidizing to discernible hyperlipidemia [19].

An intensification in LDL-C with a decrease in HDL-C was experiential in ISO-induced rats. HDL-C impedes the uptake of LDL-C by the arterial wall and eases the conveyance of cholesterol as of peripheral tissue to the liver, where it is catabolized and abolishes waste from the body [19].

Likewise, in this study, there was a significant escalation in serum and liver ALT, AST ALP, and LDH and a significant decrease in serum albumin and total protein in the animal group-administered ISO. These domino effects are in covenant with Hariri *et al*. (2010) [20]**.** The intensities of ALT, AST ALP, and LDH may be owing to the cyto-toxic spur of ISO which steered to the grievance of hepatic cells, canaliculi and the discharge of these enzymes leading to their increase in the liver and bloodstream; since ALT and AST are confined in the cytoplasm of the hepatocyte.

Furthermore, ISO detaches to Na ion, which produces ammonium ions which cause heart noxiousness [21]. The increased level of ammonium ions (NH+4) leads to mutilation to the heart tissues and consequently, surges the levels of serum cardiac enzymes [22]. Subsequently, the upsurge in these enzymes might have stopped the injury and oxidative stress persuaded by ISO on the heart somewhere copious cytosolic cardiac enzymes trickled into the blood. What is more, the intensification in the ALP enzyme may attributable to amassed biliary pressure and/or uplifting their production [23].

Congruently, our results offered that the induction of rats by ISO treatment unveiled a significant lessening in Alb and TP when matched to the control group, these effects settle with the ex-study of Younis and Mohamed (2019)**.** As per Alb and TP are pointers of the biosynthesis liver role or the upsurge in the deprivation of the degree of protein depletion, the reduction in proteins attests to the wasting consequence of ISO on hepatic cells [24].

The preceding study was also sustained by treatment with Q.10 (CoQ.10) can lessening enzyme actions thru serum [25]. C.K-M.B and C.K are superior and special markers, serve as a sign of heartnecrosis [26]. The boost of C.K-M.B and C.K activities on account of ISO treatment is experiential in the serum of rats [27]. In this study, treatment with Co.Q10 set aside the upswing of C.K-M.B and C.K activities in serum. This study is too strengthened thru earlier findings whiich too bared Co.Q10 can minimize C.K-M.B activity in I.SO-persuaded cardiotoxicity and cardiac hypertrophy in male.rats [28].

Indelibly, Catecholamine-induced intensification in the M.D.A level in myocardial tissue was pronounced in an erstwhile study [29]. Augmented M.D.A, a product of lipid peroxidation) content was grander than before in ISO-treated rats that were pointed by CoQ10 in our study. Besides, Nitric oxide is an alternative reactive molecule that can switch cardiovascular homeostasis, myocytes' growth, function, and remodeling [30]. Un-coupled N.O-synthase is the topmost donor of R.O.S generation which ultimately

knock-on effect in endothelial dysfunction [31]. This additional nitric oxide attentiveness be able to retort with superoxide radical and can construct peroxynitrite (˙ONOO-) a vastly lethal responsive classes equipped triggering cyto-toxic expansion including, protein oxidation, lipid peroxidation, and nitration lastly result in myo-heart grievance [32]. In this study, nitric oxide level was harmoniously instigated to be raised in ISO-treated rats however, mitochondrial component Co.Q10 positively legalized the upswing of nitric oxide level [32].

Anti-oxidant machinates the protection mechanism equipped decelerating or forestalling the unsteady free radicals from instigating toxic effects that simultaneously cause tissue damage. The prime endogenous antioxidants such as SOD (superoxide dismutase), CAT (catalase), G.S.H (reduced glutathione) are in charge of duping free radicals where SOD catalyzes the conversion of O_2 to H_2O_2 and H_2O; CAT converts H_2O_2 to H_2O and O_2; glutathione reduces H_2O_2 to H_2O. Myocardial injury induced by I.S.O treatment increases lipid peroxidation which in turn reduces these enzyme levels (Hamid et al., 2010). This study also exposed a significant reduction of CAT activity and GSH level in I.S.O -treated rats both in plasma and heart equaled to the control group. CoQ10 treatment reestablished the GSH level knowingly [33].

The augmented heart was pragmatic in ISO treatment which was standardized by Co.Q10. treatment. This study as well unveiled a significant drop in G.SH level in I.S.O -treated rats in the heart compared to the control group. Co.Q10 treatment reestablished the G.SH level significantly. These ex-findings were buttressed by extra investigator Ortiz et al. (2006) [33]. Momentarily, the pragmatic reduction in G.SH. content could be because of the alteration of most G.SH in the liver to G.S.S.G by glutathione reductase enzyme to shield the liver cells as of injury by toxic resources [34].

This study advocates that the Co.Q10 administration averts the heart-ailment of I.S.O.-treated rats. Value-added cardiac functions due to Co.Q10 administration could convict the perfection of oxidative stress and refurbishment of antioxidant defense in tissues [35].

5.Conclusion

This study publicized that coenzyme Q.10 treatment delivers remarkable cardiac and sheltering effects in the changeability of I.S.O-administered rats. Co.Q10 deferrals heart-liver impairment over decreasing the oxidation state and deterring cell damage in I.S.O-treated rats.

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