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Cardio protective effect of *Coriandrum sativum* L. on isoproterenol induced myocardial necrosis in rats

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ABSTRACT

The preventive effect of *Coriandrum sativum* L. (CS) on cardiac damage was evaluated by Isoproterenol (IP) induced cardiotoxicity model in male *Wistar* rats. Rats were pretreated with methanolic extract of CS seeds at a dose of 100, 200 or 300 mg/kg orally for 30 days and they were subsequently administered (*s.c.*) with IP (85 mg/kg body weight) for the last two days. IP treated rats showed increased LPO, decreased levels of endogenous antioxidants and ATPases in the cardiac tissue together with increased plasma lipids and markers of cardiac damage. TTC staining showed increased infarct areas while HXE staining showed myofibrillar hypertrophy and disruption. CS (200 and 300 mg/kg body weight) pretreatment significantly prevented or resisted all these changes. Our results show that methanolic extract of CS is able to prevent myocardial infarction by inhibiting myofibrillar damage. It is also concluded that, the rich polyphenolic content of CS extract is responsible for preventing oxidative damage by effectively scavenging the IP generated ROS.

1. Introduction

Epidemiological studies predict an ominous prevalence of cardio vascular diseases globally as well as in India during next decade (Lopez and Murray, 1998; Gilski and Borkenhagen, 2005). Myocardial infarction, a highly prevalent ischemic condition characterized by tissue necrosis develops essentially due to an imbalance between oxygen need and actual supply (De Bono and Boon, 1992) and results in irreversible histopathological damages and subsequent cardiovascular complications (Gross and Auchampach, 2007).

Isoproterenol (IP), a synthetic catecholamine and β-adrenergic agonist increases heart rate and exhaust energy reservoir of cardiac myocytes leading to cell death. It induces myocardial necrosis via multiple modes of action in experimental animals. It is essentially manifest by its stimulation of sarcolemmal adenylate cyclase and Na^+ and Ca^{2+} channels resulting in exaggerated influx of Ca^{2+} and energy consumption and consequent cell death (Milei et al., 1978). Free radicals produced by IP initiate the peroxidation of membrane bound polyunsaturated fatty acids (PUFAs) leading to both structural and functional myocardial injury (Thompson and Hess, 1986). IP-induced myocardial necrosis serves as an excellent experimental model to study catecholamines induced cardiac dysfunction and also to evaluate the possible cardioprotective efficacy of various natural and synthetic agents.

Coriandrum sativum L. (Apiaceae) (CS) is an ubiquitous annual herb, the leaves and seeds of which form a key ingredient of Middle Eastern, Mediterranean, Indian, Latin American, African and Southeast Asian cuisines. Apart from its usage as a condiment, decoction and tincture of powdered seeds of CS find usage either alone or in combination with other herbals in the treatment of cough, dysentery, sore throat, convulsion, insomnia and anxiety (Grieve, 1971). An extract of CS seeds is also reported to have therapeutic potential against diabetes, cardiovascular and urinary disorders (Eguale et al., 2007; Emamghoreishi et al., 2005). Phytochemical analysis of CS seeds has revealed the presence of polyphenols (rutin, ferulic acid, galic acid, chlorogenic acid and caffeic acid derivatives), flavonoids (quercetin and isoquercetin) and β-carotenoids (Melo et al., 2003). The oil of CS seeds is rich in α and β-pinene, camphor, citronellol, coriandrol, *p*-cymene, geraniol, geranyl acetate, limonene, linalool, myrcene, α and β phellandrene and terpinene besides many water soluble compounds such as monoterpenoid glycosides and their derivatives (Sergeeva, 1975; Ishikawa et al., 2003). The reported pharmacological actions of CS are many with its oil shown to possess antifungal (Garg and Siddiqui, 1992) and antimicrobial (Baratta et al., 1998) properties and seed extract shown to possess hypoglycemic (Gray and Flatt, 1999), hypolipidemic (Chithra and Leelamma, 1997; Chithra and Leelamma, 1999; Lal et al., 2004), hypocholesterolemic (Dhanapakiam et al., 2008),

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anti-insulin resistance activity (Patel et al., 2011), antihypertensive (Medhin et al., 1986) and antioxidant (Melo et al., 2003; Ramadan et al., 2003; Bajpai et al., 2005) competence.

Several pre-clinical and clinical studies involving pretreatment with vitamins and antioxidants have demonstrated their potential to prevent myocardial damage (Singh et al., 1994; Senthil et al., 2004). Previously Hashim et al. (2005) have investigated that hydro-methanolic extract of CS seed had strong antioxidant property and it had prevented oxidative damage induced by H_2O_2 to lymphocytes. The present study was designed to assess cardioprotective potential of hydro-methanolic extract of the customarily used spice CS seeds in IP induced multifocal myocardial necrosis in rats.

2. Materials and methods

2.1. Plant material and preparation of extract

CS plants were collected in the seedling months (February and March) and Dr. P.S. Nagar, Department of Botany, The M.S. University of Baroda identified the plant and a sample specimen was deposited in the herbarium of the Department of Botany. Hundred grams of powdered dry seeds soaked in methanol:water (80:20 v/v) at room temperature was allowed to stand for seven days. Resultant extract filtered through a muslin cloth was concentrated in a rotary evaporator under reduced pressure to obtain a thick semisolid brown paste (Qaiser et al., 2009). The final yield obtained was 8.3 g (w/w).

2.2. Experimental animals

Adult male *Wistar* rats (150–200 gm; obtained from Zydus Cadila Research Centre, Ahmedabad, Gujarat, India) were housed under standard animal house conditions (23 ± 2 °C; LD 12:12 and 45–50% humidity) and provided with pelleted diet (M/S Pranav agro, Ltd., Baroda, India) and water *ad libitum*. The animals were maintained as per the guidelines of the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA) India and the experimental protocol approved by the animal ethical committee of the Department of Zoology, The M.S. University of Baroda, Vadodara (Approval No.827/ac/04/CPCSEA).

2.3. Experiment design

Thirty animals were randomly divided into five groups of six animals each. Group I (NC) served as control and received 0.5% Carboxy methyl cellulose (CMC; *p.o.*) for 28 days and normal saline (*s.c.*) on days 29 and 30. Group II (IP) served as positive control rats and received 0.5 CMC (*p.o.*) for 28 days and isoproterenol (85 mg/kg body weight, *s.c.*) on days 29 and 30 while, the remaining groups [Group III (IP + CS100), Group IV (IP + CS200) and group V (IP + CS300)] received respectively 100, 200 and 300 mg/kg body weight of CS extract daily for 28 days (*p.o.*) and IP (85 mg/kg, *s.c.*) on days 29 and 30. The protocol for IP treatment schedule was as per the previous works from this laboratory (Jadeja et al., 2010; Thounaojam et al., 2011). At the end of the experimental period (i.e. 31st day), animals were fasted overnight (12 h) and blood samples were collected from retro-orbital sinus under mild ether anesthesia. Plasma was obtained by cold centrifugation of samples at 3000 rpm for 10 min. Later, animals were sacrificed by cervical dislocation under mild anesthesia and heart was excised and stored at −80 °C for further evaluations. A piece of cardiac tissue was fixed in 10% paraformaldehyde for paraffin wax histology.

2.4. Plasma markers of cardiac damage

Plasma levels of creatine phospokinase- MB (CK-MB), lactate dehydrogenase (LDH), aspartate transaminase (AST), alanine transaminase (ALT) and uric acid were ascertained by using commercially available kits (Reckon Diagnostic Ltd., Vadodara, India).

2.5. Plasma lipid profile

Triglyceride (TG), total cholesterol (TC) and high density lipoprotein (HDL) content were assayed by using commercially available kits (Recon Diagnostic, Ltd., Vadodara, India). Lowdensity lipoprotein (LDL) and Very low-density lipoprotein (VLDL) were calculated by Friedewald"s formula (Friedewald et al., 1972).

2.6. Cardiac antioxidants and Lipid peroxidation (LPO)

Cardiac tissue from control and treated groups was weighed and homogenized (10%w/v) in chilled Tris buffer (10 mM; pH 7.4) and centrifuged at 10,000 g for 20 min at 0 °C. Clear supernatant was used to assay superoxide dismutase (SOD; Marklund and Marklund, 1974), catalase (CAT; Aebi, 1983), glutathione peroxidase (GPx; Rotruck et al., 1973), glutathione s-transferase (GST; Habig et al., 1974), reduced glutathione (GSH; Beutler, 1963), vitamin E (Vit. E; Baker and Frank, 1968), total protein content (Lowry et al., 1951) and lipid peroxidation levels (LPO; Buege and Aust, 1978). Total ascorbic acid content (AA) was measured as per Roe and Küether (1943) by preparing homogenates of fresh cardiac tissue in 6% Trichloro acetic acid.

2.7. Cardiac ATPases

Pellets obtained from tissue homogenate after centrifugation was re-suspended in ice-cold Tris buffer (10 mM, pH 7.4) to get a final concentration of 10% and was used for the estimation of Na^+ K^+ ATPase (Bonting et al., 1970), Ca^{2+} ATPase (Hjerken and Pan, 1983) and Mg^{+2}ATPase (Ohinishi et al., 1982). Protein was estimated according to the method of Lowry et al. (1951).

2.8. Macroscopic and microscopic evaluation of cardiac tissue

Heart tissue slices (approx. 2–3 mm thick) transversely cut across the ventricle were kept in a covered glass dish containing 1% TTC (2, 3, 5- triphenyltetrazolium chloride; Sigma, St. Louis, MO) solution and incubated at 37 °C for 20 min for differentiation of viable tissue from necrotic areas (Li et al., 2011).

Heart samples from control and treated rats were fixed in 4% buffered paraformaldehyde, dehydrated in graded alcohol series and embedded in paraffin wax. Five micrometer thick sections cut (by Leica RM2155 Microtome) and stained with haematoxylin-eosin, were photographed with Canon power shot S72 digital Camera (200×) attached to a Leica microscope.

2.9. Statistical analysis

Statistical analysis of data was done by one way ANOVA followed by Bonferroni's multiple comparison test and results were expressed as mean ± S.E.M (Using Graph Pad Prism version 3.0 for Windows, Graph Pad Software, San Diego California USA).

3. Results

3.1. Plasma markers of cardiac damage

IP treated rats showed significant ($p < 0.005$) increment in the plasma levels of CK-MB, LDH, AST, ALT and uric acid compared to NC rats. Pretreatment of IP rats with CS prevented the IP induced increase in the serum levels of these parameters in a dose dependent manner (Table 1).

3.2. Plasma lipid profile

IP treatment recorded significant ($p < 0.005$) increase in plasma TG, TC, LDL, and VLDL and decrement in HDL levels compared to the NC group. CS treatment showed dose dependent decrement

Table 1
Effect of CS seed extract on plasma markers of cardiac damage.

Parameters	NC	IP	IP + CS100	IP + CS200	IP + CS300
CkMB$^{\$}$	75.66 ± 6.91	218.20 ± 29.16^{c}	171.20 ± 9.19^{B}	133.10 ± 6.16^{C}	80.10 ± 9.03^{C}
LDH$^{\#}$	82.71 ± 6.50	189.60 ± 7.36^{c}	149.70 ± 4.32^{C}	126.00 ± 4.15^{C}	85.60 ± 6.35^{C}
AST*	30.33 ± 1.99	61.17 ± 2.24^{c}	50.33 ± 1.76^{B}	43.50 ± 1.91^{C}	31.67 ± 1.02^{C}
ALT*	19.33 ± 1.11	44.83 ± 2.18^{c}	36.67 ± 1.82^{A}	31.00 ± 1.73^{C}	22.17 ± 1.99^{C}
Uric acid$^{@}$	1.91 ± 0.21	7.01 ± 0.47^{c}	5.24 ± 0.41^{A}	3.72 ± 0.19 ^{C}	2.14 ± 0.21^{C}

Where, $ = IU/l, # = U/l, * = KA Units/l, @ = mg/dl. $n = 6$. Data were expressed as mean ± S.E.M. a ($p < 0.05$), b ($p < 0.01$), c ($p < 0.001$) when NC vs. IP and A ($p < 0.05$), B ($p < 0.01$), C ($p < 0.001$) when IP vs. IP + CS.

Table 2
Effect of CS seed extract on plasma lipid profile.

Parameters	NC	IP	IP + CS100	IP + CS200	IP + CS300
TC[@]	54.50 ± 1.72	90.83 ± 2.58[c]	75.83 ± 2.16[B]	65.33 ± 2.88[C]	59.50 ± 2.23[C]
TG[@]	33.17 ± 2.37	53.00 ± 2.67[c]	50.67 ± 1.82[NS]	44.67 ± 2.60[C]	35.00 ± 1.48[C]
VLDL [@]	6.63 ± 0.47	10.60 ± 0.53[c]	10.13 ± 0.36[NS]	8.93 ± 0.52[A]	7.00 ± 0.29[C]
LDL[@]	34.30 ± 0.52	90.27 ± 2.83[c]	70.97 ± 2.62[C]	58.10 ± 3.92[C]	43.67 ± 2.75[C]
HDL[@]	26.83 ± 0.98	11.17 ± 1.04[c]	15.00 ± 0.73[NS]	16.17 ± 1.35 [A]	22.83 ± 0.79[C]

Where, @ = mg/dl. $n = 6$. Data were expressed as mean ± S.E.M. a ($p < 0.05$), b ($p < 0.01$), c ($p < 0.001$) when NC vs. IP and A ($p < 0.05$), B ($p < 0.01$), C ($p < 0.001$) when IP vs. IP + CS.

Table 3
Effect of CS seed extract on Cardiac LPO levels and enzymatic and non-enzymatic anti-oxidant.

Parameters	NC	IP	IP + CS100	IP + CS200	IP + CS300
LPO*	0.96 ± 0.53	3.22 ± 0.27[c]	2.05 ± 0.73[B]	1.61 ± 0.28[B]	1.27 ± 0.57[B]
SOD	8.06 ± 0.63	3.46 ± 0.60[c]	6.12 ± 0.37[B]	6.54 ± 0.19[C]	6.98 ± 0.17[C]
CAT[@]	5.15 ± 0.43	1.92 ± 0.31[c]	2.23 ± 0.14[NS]	3.06 ± 0.29[A]	4.40 ± 0.34[C]
GPx[$]	3.08 ± 0.05	1.03 ± 0.06[c]	1.22 ± 0.06[A]	1.81 ± 0.07[C]	2.80 ± 0.04[C]
GST[#]	787.4 ± 14.41	423.6 ± 12.63[c]	541.4 ± 10.19[C]	625.7 ± 11.34[C]	760.7 ± 16.06[C]
GSH[@]	9.27 ± 0.17	3.81 ± 0.22[c]	4.79 ± 0.26[A]	5.87 ± 0.31[C]	7.81 ± 0.18[C]
AA[€]	250.0 ± 5.0	114.0 ± 7.0[c]	140.0 ± 8.0[A]	195.0 ± 12.0[C]	229.0 ± 9.0[C]
Vit E[€]	5.29 ± 0.23	1.33 ± 0.31[c]	2.65 ± 0.36[NS]	3.32 ± 0.21[C]	4.91 ± 0.29[C]

* = µmol/mg protein, @ = nmol/mg protein, $ = unit/mg protein, # = µmol/min/mg protein, € = mg/100 g tissue Where, $n = 6$. Data were expressed as mean ± S.E.M. a ($p < 0.05$), b ($p < 0.01$), c ($p < 0.001$) when NC vs. IP and A ($p < 0.05$), B ($p < 0.01$), C ($p < 0.001$) when IP vs. IP + CS.

Table 4
Effect of CS seed extract on Cardiac ATPases.

Parameters	NC	IP	IP + CS100	IP + CS200	IP + CS300
Na^+/K^+ATPase[@]	5.00 ± 0.50	2.11 ± 0.17[c]	2.51 ± 0.14[NS]	2.96 ± 0.33[A]	4.40 ± 0.28[C]
Mg^{2+} ATPase[@]	2.74 ± 0.02	0.45 ± 0.03[c]	0.84 ± 0.05[C]	1.02 ± 0.08[C]	2.09 ± 0.09[C]
Ca^{2+} ATPase[@]	2.03 ± 0.18	0.98 ± 0.02[c]	1.29 ± 0.02[C]	1.46 ± 0.04[C]	1.83 ± 0.04[C]

Where, @ = µmol phosphate liberated/ mg protein. $n = 6$. Data were expressed as mean ± S.E.M. a ($p < 0.05$), b ($p < 0.01$), c ($p < 0.001$) when NC vs. IP and A ($p < 0.05$), B ($p < 0.01$), C ($p < 0.001$) when IP vs. IP + CS.

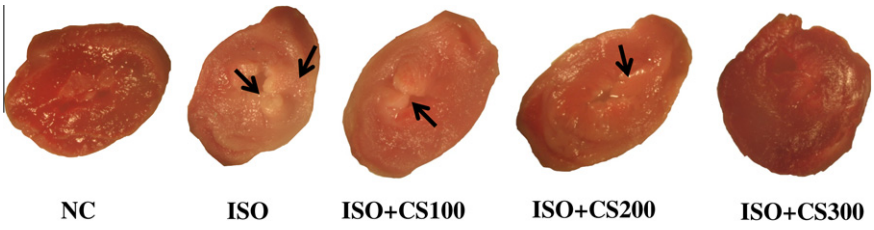

Fig. 1. Effect of CS seed extract on triphenyltetrazolium chloride (TTC) stained cardiac tissue slices. Arrows indicate necrotic tissue.

in TC, TG, LDL, VLDL and significant increment in HDL compared to IP treated rats (Table 2).

3.3. Cardiac anti-oxidants and LPO

IP treated group recorded significant ($p < 0.001$) increment in LPO level, as well as significant ($p < 0.001$) decrement in the activities of enzymatic antioxidants (SOD, CAT, GPx and GST) and content of non-enzymatic antioxidants (GSH, AA and Vit. E) compared to NC rats. Administration of CS (100, 200 and 300 mg/kg body weight, respectively) markedly prevented all the alterations with respect to antioxidants and LPO in IP treated rats and maintained them to the near normal levels (Table 3).

3.4. Cardiac ATPase

The cardiac tissue of IP treated rats depicted significant ($p < 0.005$) decrement in the activities of Na^+/K^+, Mg^2 and Ca^{2+}ATPases compared to that of NC rats while, IP + CS treated cardiac tissue recorded significant resistance (Table 4).

3.5. TTC and HE staining of cardiac tissue

TTC staining of heart of control rats showed brick red coloration indicative of more number of viable cells whereas, IP treated rats showed large area of pale yellow coloration was suggestive of necrosis. However, IP rats pretreated with CS showed a protective effect with a minimal or no pale yellow coloration in a dose dependent manner (Fig. 1).

HE staining of cardiac tissue from NC rats showed histoarchitecture of myofibers that were characteristically multinucleated and intact. IP treatment resulted in focal myocardial necrosis (encircled area) and disrupted myofibers. However, IP + CS treated groups showed relatively less disruption of myofibers with IP + CS 300 showing maximum fiber integrity. (Fig. 2).

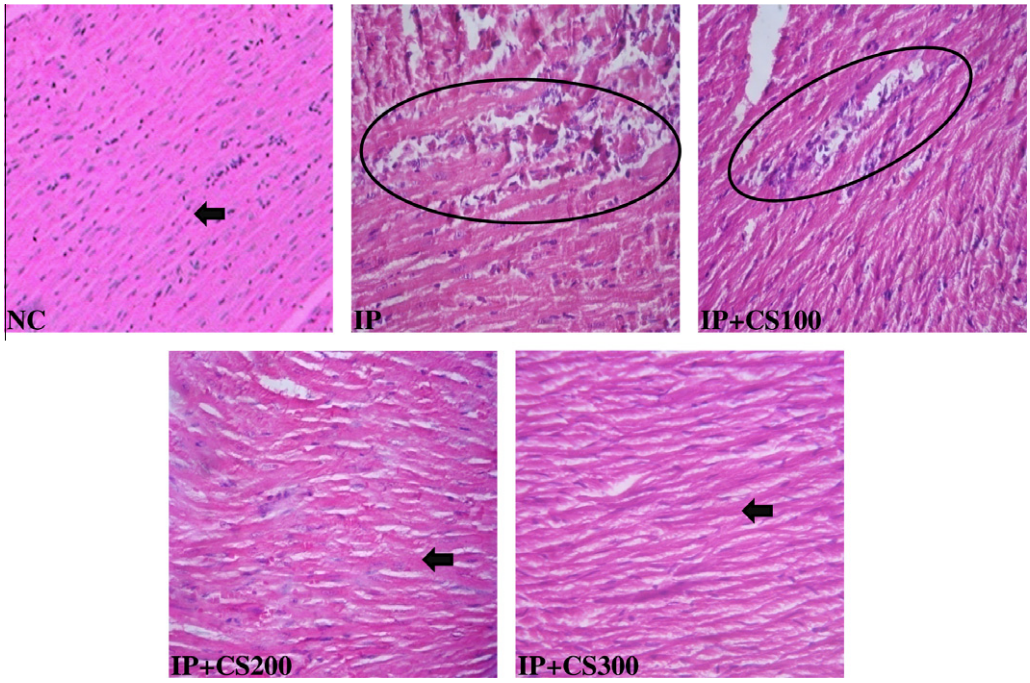

Fig. 2. Effect of CS seed extract on cardiac histopathology of cardiac tissue. Tissue sections (7 μM) are stained with hematoxylin-eosin (400×). Encircled area indicates focal myocardial necrosis whereas, arrows indicate healthy myofibers.

4. Discussion

Administration of higher doses of IP to rats induces increment in heart rate, systolic and diastolic irregularities and abnormal ECG pattern (Rona, 1985; Karthick and Prince, 2006). These events epitomized by hypoxia, calcium over load and increased production of reactive oxygen species (ROS) lead to degenerative changes in cardiac tissue that culminate in necrosis.

Accordingly, IP treated rats herein recorded significant increment in plasma levels of CK-MB, LDH, AST, ALT and uric acid, which is in keeping with the known IP induced deficiency of oxygen supply and increased sarcolemmal permeability and consequent leaching of CK-MB and LDH into the blood stream along with increased plasma levels of AST, ALT and uric acid (Mathew et al., 1985; Weir et al., 2003). The recorded ability of CS to effectively prevent these alterations clearly points towards its cardio-protective competence and maintenance of sarcolemmal integrity.

Also the activity levels of 3-hydroxy-3-methyl-glutaryl-CoA (HMG CoA) reductase and Lecithin-cholesterol acyltransferase (LCAT) have been reported to undergo significant alterations following IP treatment which resulted in altered lipid and lipoprotein profiles (Rajadurai et al., 2006). Hence, the observed decrement in lipid profile in IP + CS treated groups indicates at possible modulatory influence of CS on activity levels of HMG CoA and LCAT that requires further investigations.

SOD and CAT are enzymatic antioxidants that act as the first line of cellular defense and help in scavenging free radicals. Therefore, a decrement in their activity levels results in free radical induced cellular damage. Other enzymatic antioxidants GPx and GST and non-enzymatic GSH also help maintain healthy cell functions by scavenging free radicals like peroxy radicals, superoxide ions and singlet oxygen formed by toxicants (Rathore et al., 1998). AA is a water soluble vitamin that acts as an antioxidant and scavenger of superoxide and other free radicals, getting transformed in the process to dehydroascorbate (Frei et al., 1986; Packer et al., 1979). Vitamin E is a lipid soluble antioxidant that protects membrane polyunsaturated fatty acids and other components from oxidation by free radicals (Tappel, 1972). Presently, we have observed increased LPO and decreased endogenous antioxidants (both enzymatic and non-enzymatic) in IP treated rats. Apparently, IP causes heightened oxidative damage of cellular macromolecules marked by elevated level of LPO by way of increased generation of free radicals as has also been inferred by Gokkusu and Mostafazadeh (2003). However, pretreatment of IP animals with CS prevented the decrease in antioxidant levels and increase in LPO significantly in a dose dependent manner. Plant based extracts that are rich in polyphenols and flavonoids are supposedly strong antioxidants and CS seed extract has been reported to be rich in flavonoids, terpenoids (Wangensteen et al., 2004) and polyphenols (Hashim et al., 2005). The latter workers have opined that alcoholic extract of CS has maximal content of the said antioxidants compared to other types of extract. The currently observed effects of CS may be attributable to the presence of these secondary metabolites.

ATPases, by maintaining differential levels of ions play important roles in the regulation of contraction–relaxation cycles of cardiac muscles and consequently, peroxidation of sarcolemmal lipids can result in their inactivation as suggested by Kako et al. (1988). Reduced activity of Na^+/K^+ ATPase with compromised Na^+ efflux can result in altered membrane permeability (Finotti and Palatini, 1986). A decrement in Ca^{2+}ATPase expectantly would decrease sarcoplasmic Ca^{2+} concentration and weaken the contractility of heart. Hence, loss of ATPase activity in the ischemic state could contribute to myofibrillar necrosis and functional damage. Even Chernysheva et al. (1980) have reported IP induced decrement in the activity levels of Na^+/K^+, Mg^{2+} and Ca^{2+} ATPase in rats. However, IP + CS treated rats show a dose dependent significant up keep of these ATPases, essentially attributable to the membrane stabilizing aproperty of CS extract that protects the sarcolemma and intracellular membranes from the deleterious effect of IP and consequent myocardial damage (Hashim et al., 2005).

TTC is a redox indicator that is commonly used to differentiate between metabolically active and inactive cells and tissues (Altman, 1976). Staining of cardiac tissue slices with TTC provides

insight regarding the infarct size and is a well accepted method to assess necrosis of myocardial tissue (Prabhu et al., 2006). TTC is enzymatically reduced to brick red precipitates of formazan dye or TPF (1,3,5-triphenylformazan). Active mitochondrial respiration generating reduced coenzymes is responsible for the reduction of TTC to TFP in all tissues including the cardiac tissue (Ramkissoon, 1996). Hence, appearance of patches of pale white color in cardiac tissue slices of IP treated rats indicates areas of focal necrosis due to non-reduction of TTC as observed in the present study in IP treated rats. The IP + CS rats (especially CS300) depicted minimal pale yellow patches suggestive of normal myocardial structure. Histological observations further confirm the IP induced necrotic changes affecting myofiber disruption and fraying of fibers. These deleterious changes seem ably resisted by pretreatment with CS with the highest dose affording maximal protection. These observations provide compelling macroscopic and microscopic evidences regarding the cardioprotective potential of CS seed extract.

Parameters investigated here in indicate that hydro-methanolic extract of CS is potent in mitigating IP induced myocardial necrosis. The same is evidenced inform of CS induced favourable alterations in biochemical and histo-morphological parameters. Although the observed results have been attributed to high content of polyphenols in hydro-methanolic extract of CS. Our further studies are aimed that isolating the active component of CS and to reassess its cardioprotective potential in more appropriate experimental model (coronary ligation) and using gold standard marker enzyme such as cardiac Troponin I that underlying mechanism of CS induced cardioprotection.

5. Conclusion

It can be concluded from the present study that hydro-methanolic extract of CS seeds has cardioprotective potential. The same is attributable to high polyphenol content in CS seeds.

Conflict of Interest

The authors declare that there are no conflicts of interest.

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