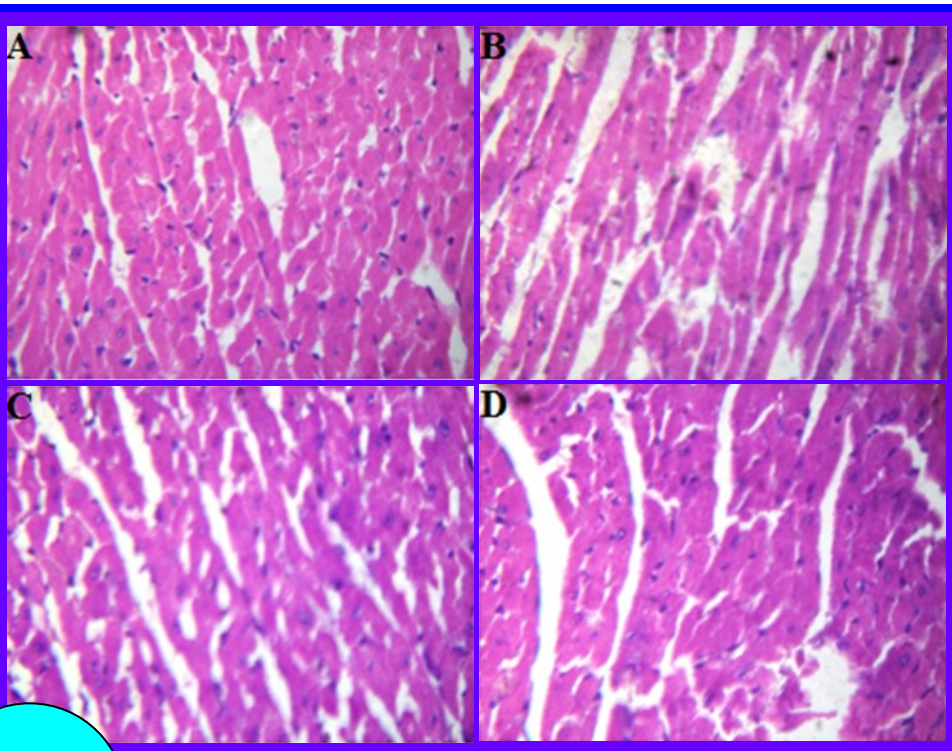

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Cardioprotective activity of fruits of *Sechium edule*

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Abstract

The present work deals with the study of the ethanolic extract of fruits of *Sechium edule* for cardioprotective activity. Cardioprotective activity of the ethanolic extract of fruits of *S. edule* was determined by the administration of isoproterenol (60 mg/kg, s.c) for two days. Pretreatment with *S. edule* (200 mg/kg, p.o and 100 mg/kg, p.o) for 28 days in significantly ($p<0.01$) reduce the levels of serum transaminases, alkaline phosphates, lactate dehydrogenase, creatinine kinase, total cholesterol, triglycerides, LDL-cholesterol, VLDL-cholesterol and increase the levels of HDL-cholesterol. Histopathological studies of the hearts of isoproterenol treated rats have shown infiltration of inflammatory cells and continuity in muscle fiber was lacking suggesting an irreversible cell injury. Animals treated with ethanolic extract of *S. edule* showed less degenerative changes compared to isoproterenol-treated animals.

Introduction

Myocardial infarction is a major public health concern and the leading cause of death throughout the world. By 2020, heart disease and stroke will become the leading causes of both death and disability worldwide, with the number of fatalities projected to increase to more than 20 million a year, and to more than 24 million a year by 2030 (Farvin et al., 2006). Developing countries like India are struggling to manage the impact of infectious diseases simultaneously with the growing burden on society and health system caused by non communicable diseases such as myocardial infarction. Due to changing lifestyles in developing countries, such as India, and particularly in urban areas, myocardial infarction is making an increasingly important contribution to mortality statistics (Lopez and Murray, 2000).

Reactive oxygen species (ROS) play a critical role in the pathogenesis of various diseases such as cardiovascular injury associated with circulatory disturbance. Isoproterenol-induced myocardial necrosis has the mechanism of generating ROS causing lipid peroxidation damage to the proteins due to the production of carbonyl derivatives. Myocardial infarction is associated with ischemic necrosis of cardiac muscles due to a decrease in the supply of blood to a portion of myocardium below a critical level necessary for viability and proper physiological function. A disparity between the oxygen requirement of the myocardium and the ability of the coronary artery to meet it results in the ischemic necrosis of heart muscle (Thippeswamy et al., 2009).

Sechium edule is an edible plant that belongs to the family Cucurbitaceae also known as sayote, choko, chocho, chow-chow, and vegetable pear. The fruits and the seed especially, are rich in several important amino acids. A lectin from the exudate of *S. edule* was purified (Vozari-Hampe et al., 1992). Eight flavonoids, including three *C*-glycosyl and five *O*-glycosyl flavones, were detected (Siciliano and De Tommasi, 2004). Twenty known Gibberellins' have been identified in extracts of the seeds of *S. edule* (Albone et al., 1984). The leaves and fruits have diuretic, cardiovascular and anti-inflammatory properties, the leaves has been used in the treatment of arteriosclerosis and hypertension, and to dissolve kidney stones (Kamble et al., 2008; Gordon et al., 2000). The fruits of *S. edule* have been reported for

hepatoprotective (Firdous et al., 2012), antiulcer (Firdous et al., 2012), antiepileptic and central nervous system depressant (Sayeed et al., 2012), nephroprotective (Sayeed et al., 2013), antidiabetic (Maity et al., 2013) and free radical scavenging and anti-oxidant activity (Ordonez et al., 2006).

So, in the present study, the cardioprotective effect of ethanolic extract of fruits of *S. edule* in isoproterenol-induced myocardial infarction in rats.

Materials and Methods

Plant material

Fruits of *S. edule* were collected from Reliance Fresh, Secunderabad and also from Bangalore. The fruit material was taxonomically identified and authenticated by Dr. N. Shiddamallayya at Regional Research Institute (Ay.), Bangalore, where the voucher specimen is conserved under the reference number (RRCBI/MCW/7/2008).

Preparation of extracts

The leaves were washed thoroughly with tap water and air dried in shade at room temperature. They were mechanically powdered and sieved. The aqueous extract was prepared by cold maceration (72 hours). The liquid extract obtained was concentrated under vacuum at 40°C. The yield of extract was 24.0% and the extract was phytochemically investigated (Harbone, 1998).

Drugs and chemicals

Isopreterenol was obtained from Himedia, Mumbai, India. Total cholesterol, triglycerides, transaminases, alkaline phosphates, lactate dehydrogenase, creatinine kinase kits were obtained from Span Diagnostics, Surath, India. All other chemicals used in this study were obtained commercially and were of analytical grade.

Experimental animals

Albino rats (Wistar) weighing 150–200 g either sex were used in this study. Animals were maintained under controlled conditions of temperature (23 ± 2°C) and humidity (50 ± 5%) and a 12-hour light–dark cycle, were used for the experiment. They were housed in sanitized polypropylene cages containing sterile paddy husk as bedding. They had free access to standard rat pellet diet and water *ad libitum*. The animals were given a week's time to get acclimatized to the laboratory conditions.

Acute toxicity studies

Animals were kept overnight fasting prior to drug administration and then they received a single oral dose (2,000 mg/kg) of aqueous extract of *S. edule* leaves. After the administration of extract, food was withheld for further 3–4 hours. Animals were observed individually at least once during the first 30 min after dosing, periodically during the first 24 hours (with special attention during the first 4 hours) and daily thereafter for a period of 14 days. Once daily cage side observations included changes in skin and fur, eyes and mucous membrane (nasal) and also respiratory rate, circulatory (heart rate and blood pressure), autonomic (salivation, lacrimation, perspiration, piloerection, urinary incontinence, and defecation) and central nervous system (ptosis, drowsiness, gait, tremors and convulsion) changes. Mortality, if any, was determined over a period of 2 weeks (OECD, 2002).

Induction of myocardial infarction

Myocardial infarction was induced by intraperitoneal injection of isoproterenol (60 mg/kg), dissolved in saline, for two consecutive days (29th and 30th day).

Experimental design

Twenty four male Wistar rats were divided into four groups of 6 animals in each group as follows (Koneri et al., 2008): Group I: Served as a control (saline p.o); Group II: Rats were administered with isoproterenol dissolved in normal saline (60 mg/ kg) on 29th and 30th day with 24 hours interval between the administrations; Group III: Rats were administered with ethanolic extract of *S. edule* (200 mg/kg) for a period of 28 days and then isoproterenol was administered intraperitoneally on 29th and 30th day; Group IV: Rats were administered with ethanolic extract of *S. edule* (100 mg/kg) for a period of 28 days and then isoproterenol was administered intraperitoneally on 29th and 30th day.

Biochemical assessment

Blood was drawn from retro-orbital vein 48 hours after the first dose of isoproterenol under anesthesia and serum was separated by centrifugation and utilized for the estimation of various biochemical parameters namely: serum glutamate oxaloacetate transaminase, serum glutamate pyruvate transaminase, alkaline phosphates, lactate dehydrogenase, creatinine kinase, total cholesterol, serum triglycerides, LDL-cholesterol, HDL-cholesterol and VLDL-cholesterol.

Histopathological study

At the end of the study, all the rats were sacrificed by cervical decapitation and the hearts were dissected out, washed in ice-cold saline. Then myocardial tissue was immediately fixed in 10% formalin solution. After fixation, tissues were embedded in paraffin and serial sections (4-5 µm thick) were taken and each section is then stained with hematoxylin and eosin. Then the slides were examined under light microscope and photographs were taken.

Statistical analysis

Statistical analysis was carried out using Graph pad

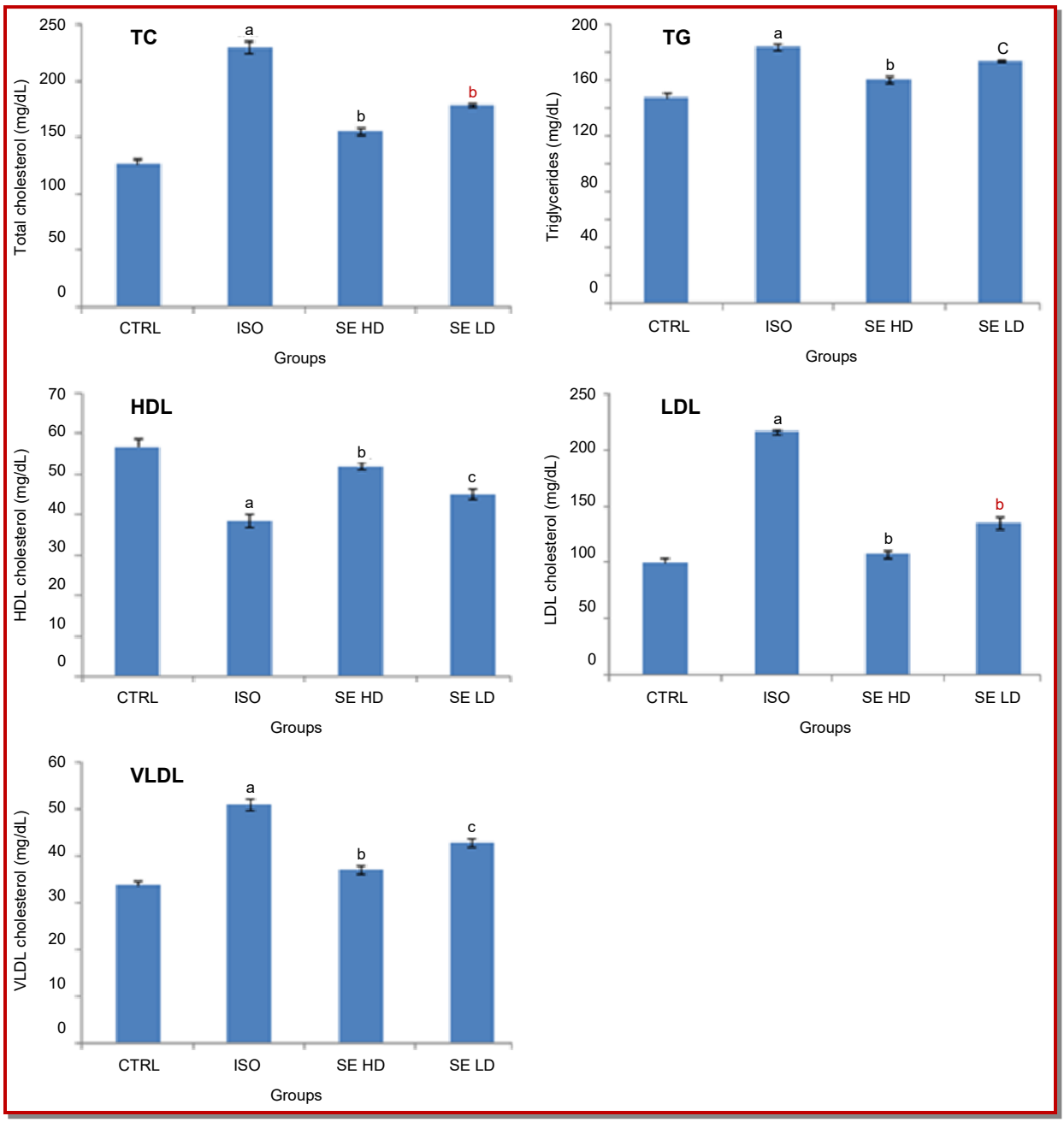

Figure 1: Effect of administration of ethanolic extract of *Sechium edule* on serum lipid profile in rats

CTRL: Normal control, ISO: Isoproterenol control, SE HD: *Sechium edule* higher dose (200 mg/kg) and SE LD: *Sechium edule* lower dose (100 mg/kg); Results are expressed as mean ± SEM for six animals in each group; [a]p<0.01 considered statistically significant as compared to normal control group; [b]p<0.01 considered statistically significant as compared to ISO treated group; [c]p<0.05 considered statistically significant as compared to ISO treated group

Prism software. All data were expressed as Mean ± SE. Groups of data were compared with an one-way analysis of variance followed by Dunnett 't' test .Values were considered statistically significant at p<0.05.

Results

In isoproterenol-induced cardiotoxicity, isoproterenol-treated group showed a significant (p<0.001) increase in total cholesterol, serum triglycerides, LDL-cholesterol and VLDL-cholesterol as compared to control group and the HDL-cholesterol concentration was significantly (p<0.01) lower in isoproterenol-treated group (Figure 1). The transaminases, alkaline phosphates, lactate dehydrogenase, creatinine kinase were also significantly (p<0.01) increased as compared to control group (Table I). Administering ethanolic extract of *S.*

Table I

Effect of *Sechium edule* on ISO induced alterations in serum levels of marker enzymes in rats

Treatment	SGOT (IU/L)	SGPT (IU/L)	ALP (KA)	LDH (U/L)	CK (U/L)
Normal control	92.5 ± 4.3	38.8 ± 1.5	17.5 ± 1.0	160.0 ± 4.6	35.3 ± 1.3
ISO control	207.5 ± 3.2[a]	77.5 ± 3.2[a]	45.3 ± 0.9[a]	282.5 ± 12.5[a]	57.3 ± 3.0[a]
Sechium edule (200 mg/Kg) + ISO	110.3 ± 2.1[b]	42.0 ± 2.5[b]	23.3 ± 0.6[b]	173.3 ± 5.9[b]	36.0 ± 1.7[b]
Sechium edule (100 mg/Kg) + ISO	125.0 ± 2.0[b]	53.5 ± 0.6[b]	31.0 ± 0.9[b]	192.5 ± 3.2[b]	43.3 ± 1.1[b]

Values expressed as mean ±SEM for six animals in each group; [a]p<0.01 considered statistically significant as compared to normal control group; [b]p<0.01 considered statistically significant as compared to ISO treated group

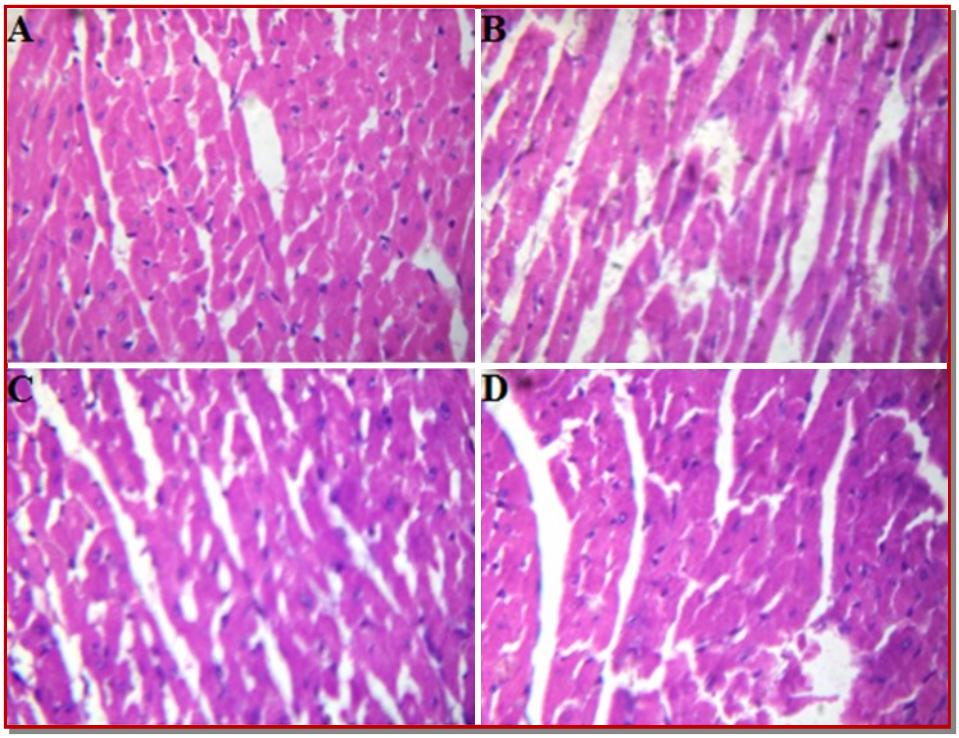

Figure 2: Effect of *Sechium edule* on ISO-induced cardiotoxicity in rats

A: Normal control; B: Treated with ISO (60 mg/kg, i.p.); C: Treated with *Sechium edule* (200 mg/kg) and ISO (60 mg/kg, i.p.); D: Treated with *Sechium edule* (100 mg/kg) and ISO (60 mg/kg, i.p.)

edule (200 mg/kg) significantly (p<0.01) reduced the levels of total cholesterol, serum triglycerides, LDL-cholesterol, VLDL-cholesterol, serum glutamate pyruvate transaminase, alkaline phosphates, lactate dehydrogenase, creatinine kinase in isoproterenol-treated rats as compared to the animals treated with isoproterenol-treated group alone and the total serum HDL-cholesterol concentration was significantly (p<0.01) increased.

Histopathological examination of heart tissue of control rats showed normal myocardial fibers and muscle bundles with normal architecture (Figure 2).

Cardiac sections of the isoproterenol-treated rats showed infiltration of inflammatory cells and continuity in muscle fiber was lacking suggesting an irreversible cell injury (Figure 2B). Rats pretreated with *S. edule* showed normal myofibrillar structures with striations and revealed a marked protection by the extract against myocardial necrotic damage (Figure 2C & 2D).

Discussion

Lipids play an important role in cardiovascular disease, not only by way of hyperlipidemia and the development of atherosclerosis, but also by modifying the composition, structure and stability of cellular membranes (Kareem et al., 2009). The increased levels of plasma cholesterol and triglycerides observed in isoproterenol-injected rats could be due to increased lipolysis. Plasma hypertriglyceridemia, which was observed in isoproterenol-treated rats, is due to

decrease in the activity of lipoprotein lipase, resulting in decreased uptake of triglycerides from to that of the circulation. Hypertriglyceridemia and increased levels of cholesterol in plasma might be responsible for altered cardiovascular functions which are often reported in isoproterenol-induced myocardial infarction (Sabeena et al., 2006).

Myocardium contains an abundant concentration of diagnostic marker enzymes of myocardial infarction viz., lactate dehydrogenase, creatinine kinase and transaminases and once metabolically damaged, releases its contents into the extracellular fluid. In this present study, a significant increase ($p<0.01$) in serum lactate dehydrogenase, creatinine kinase, transaminases and alkaline phosphates was observed in isoproterenol-treated rats (Group II) when compared with normal control rats (Group I). Pretreatment at the dose of 200 and 100 mg/kg with ethanolic extract of *S. edule* significantly ($p<0.01$) reduced the levels of serum lactate dehydrogenase, creatinine kinase, transaminases and ALP levels when compared with isoproterenol treated group.

The significant ($p<0.01$) increase observed in the levels of total cholesterol, triglycerides, LDL-cholesterol, VLDL-cholesterol and a significant decrease in the levels of HDL-cholesterol in the plasma of isoproterenol -treated rats was observed when compared with normal control treated rats (Vijaypadma and Shyamaladevi, 2000). Pretreatment at the dose of 200 and 100 mg/kg with ethanolic extract of *S. edule* significantly reduced ($p<0.01$) the levels of total cholesterol, triglycerides, LDL-cholesterol, VLDL-cholesterol and significantly increased the levels of HDL-cholesterol when compared with isoproterenol-treated rats, signifying that the myocardial membrane is intact and not damaged.

Myofilament alterations such as myocytosis and myofibrillar degeneration are reported in isoproterenol –treated rats. Cardiac sections of the isoproterenol–treated rats showed infiltration of inflammatory cells and continuity in muscle fiber was lacking suggesting an irreversible cell injury. Rats pretreated with *S. edule* showed the reduction of such pathological changes and revealed a marked protection by the extract against myocardial necrotic damage.

It has been reported that the anti-oxidant activity plays an important role in the protection against isoproterenol-induced myocardial infarction. The anti-oxidant property and the presence of flavonoids of *S. edule* were already reported (Ordonez et al., 2006). Flavonoids obtained from different plant sources possess anti-oxidant or free radical scavenging activity. Presumably the high reactivity of the phenolic or hydroxyl group of flavonoids is responsible for this free radical scavenging activity (Vandana and Suresh, 2009). Thus, the results of the present investigation clearly demonstrate that various biochemical changes produce in the serum in rats by isoproterenol treatment, were prevented or reversed by treatment with ethanolic extract of fruits of *S. edule* dose dependently, probably due to anti-oxidant or free radical scavenging property.

Conclusion

The ethanolic extract of fruits of *S. edule* has a protective effect against isoproterenol-induced myocardial infarction in rats.

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Ethical Issue

All the experimental procedures were performed according to the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), Ministry of Social Justice and Empowerment, Government of India, norms and approved by the Institutional Animal Ethics Committee (IAEC).

Conflict of Interest

Authors declare no conflict of interest

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