



# International Journal of Pharmacology

ISSN 1811-7775

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## Protective Effects of *Lagenaria siceraria* (Molina) Fruit Juice in Isoproterenol Induced Myocardial Infarction

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**Abstract:** Present study was carried to evaluate the protective effect of *Lagenaria siceraria* fruit juice (LSFJ) in isoproterenol (ISO) induced myocardial infarction in rats. Rats treated with ISO (200 mg kg<sup>-1</sup>, s.c.) for two consecutive days at an interval of 24 h resulted in a significant ( $p < 0.001$ ) alteration in cardiac marker enzymes (alkaline phosphatase, Lactate dehydrogenase, creatine kinase-MB, serum Aspartate Transaminase and alanine Transaminase), lipid peroxidation and endogenous antioxidants activities (reduced glutathione, glutathione peroxidase, glutathione s-transferase, superoxide dismutase and catalase). It also showed alteration in electrocardiographic and hemodynamic parameters. Treatment with LSFJ (400 mg/kg/day, p.o.) for 30 days and challenged with ISO on 29th and 30th day showed a protective effect on serum marker enzymes, LPO, endogenous antioxidants activity, electrocardiographic and hemodynamic changes. These findings indicate the protective effect of LSFJ during isoproterenol induced myocardial infarction and associated oxidative stress in rats.

**Key words:** *Lagenaria siceraria*, antioxidant activity, isoproterenol, myocardial infarction, blood pressure, oxidative stress, cardioprotective

### INTRODUCTION

Myocardial infarction is the condition which occurs due to the imbalance between coronary blood supply and myocardial demand (Boudina *et al.*, 2002). Isoproterenol, a  $\beta$ -adrenergic agonist, has been found to cause severe stress in the myocardium resulting in infarct like necrosis of the heart muscle due to its auto-oxidation (Rona *et al.*, 1959). Some of the mechanisms proposed to explain ISO induced damage to cardiac myocytes includes hypoxia due to myocardial hyperactivity and coronary hypotension, calcium overload, depletion of energy reserve and excessive production of free radicals resulting from oxidative metabolism of catecholamine (Rona *et al.*, 1959; Adameova *et al.*, 2009). Several studies had shown the effects of natural products in the management of isoproterenol induced myocardial infarction in rats Farvin *et al.* (2009), Asdaq *et al.* (2008), Nandave *et al.* (2007) and Ojha *et al.* (2008).

*Lagenaria siceraria* (LS) commonly known as Bottle gourd Syn. Doodhi, Syn. Lauki (Hindi), Kadoo (Marathi) this is official in Ayurvedic Pharmacopoeia. It is one of the excellent fruit for human being made and gifted by the nature having composition of all the essential constituents that are required for normal and good human

health. Traditionally the fruit of LS is used for its cardioprotective, cardiostimulant, diuretic, aphrodisiac, antidote to certain poisons and scorpion sting. It cures pain, ulcers, fever and used for pectoral cough, asthma and other bronchial disorders-especially syrup prepared from the tender fruits (Nadkarni, 1992; Duke, 1985).

A modern pharmacological study shows that *Lagenaria siceraria* fruit possesses various beneficial effects. Chloroform and alcoholic extract of *L. siceraria* showed significant effects in lowering total cholesterol, triglyceride and low density lipoproteins along with an increase in HDL level in triton induced hyperlipidemia in rats (Ghule *et al.*, 2006a). *Lagenaria siceraria* Stand. fruit juice extract (LSFJE) shows analgesic effect in acetic acid induced writhing and formalin induced pain in mice. It also showed anti-inflammatory activity against acute inflammatory models (Ghule *et al.*, 2006b). Vacuum dried extract and methanol extract of *L. siceraria* fruit also shows diuretic activity (Ghule *et al.*, 2007). *Lagenaria siceraria* fruit showed maximum antioxidant activity against *in vitro* model using DPPH. The juice as such and its ten times dilution showed radical scavenging activity (Deshpande *et al.*, 2007). Extract is also effective in CCl<sub>4</sub> induced liver damage and Doxorubicin induced cardiotoxicity where it maintained the level of endogenous

antioxidant enzymes (superoxide dismutase, catalase and glutathione peroxidase) and marker of lipid peroxidation to that of normal (Fard *et al.*, 2008).

Till date no study reports are available regarding the protective effect of LSFJ in isoproterenol induced myocardial infarction and associated oxidative stress. So, an attempt was made to evaluate the cardioprotective activity of LSFJ in isoproterenol induced myocardial infarction.

## MATERIALS AND METHODS

**Drugs and chemicals:** ( $\pm$ )-Isoproterenol hydrochloride (ISO) was purchase from Sigma Aldrich Co. St. Louis, MO, USA. Fresh fruits of *Lagenaria siceraria* (LS) were collected from nearby farm at Baroda, Gujarat. All the reagents and chemicals used in the entire study were of analytical grade.

**Collection and authentication of *Lagenaria siceraria* (LS) fruits:** Fresh fruits of LS were collected from nearby farm at Baroda. The fruits collected were semiripened, bottle shape, weighted between 500-700 g and of the same plant. The fruit of LS was authenticated by the authority from Botany Department, The M.S. University of Baroda, Vadodara. The complete work was carried out from August to October 2008 at Pharmacy Department, The M.S. University of Baroda, India.

**Preparation of Fruit Juice of *Lagenaria siceraria* (LSFJ):** The fresh juice of LS was prepared with the help of juicer without addition of water. Two hundred and fifty gram of fresh fruit was chopped into small pieces and 135 mL juice was collected. The juice was filtered with sterile cloth and the resultant filtrate was used for oral dosing to animals.

Ten milliliter of fresh juice was subjected for drying in previously dried and weighed petridish, then the juice was evaporated to complete dryness in a hot air oven (45°C) and then weight of petridish containing dry residue of juice was taken and milligram equivalent dose of 10 mL juice was calculated by subtracting initial weight of dried petridish. The same procedure was repeated for six times at different days. It was clear from the mean that, 10 mL of juice gives 602.00 mg of total solid residue in dried juice, which is equivalent to 250 g of fresh fruit of LS. The dose of fresh juice of *Lagenaria siceraria* in (mL) equivalent to 100, 200 and 400 mg was administered orally to rats mg/kg/day for 30 days.

**Fixation of optimum dosage of LSFJ:** A pilot study was carried out to establish the optimum dose of the drugs

which exhibits maximum cardioprotective effect during 30 days. Rats were treated with LSFJ (100, 200 and 400 mg/kg/day, p.o.) for 30 days and ISO on 29th and 30th day. At the end of treatment period serum lactate dehydrogenase and creatine phosphokinase-MB levels were evaluated. LSFJ (400 mg/kg/day, p.o.) was found to be most effective in functional recovery of above biochemical alterations and it was selected for further evaluation in the present study (Data not shown).

**Experimental animals:** All experiments were carried out on male albino Wistar rats weighing 200-250 g, obtained from in house animal breeding. They were housed in polypropylene cages (47×34×20 cm) lined with husk, renewed every 24 h under a 12:12 h light dark cycle at around 22°C and had free access to water and food. The animals were fed on a standard pellet diet (Pranav Agro Industries Ltd., Maharashtra, India). The pellet diet consisted of crude protein (22.12%), crude oil (4.05%), crude fibre (4.11%), ash (9.13%) and sand silica (0.75%) which provides the energy of 3630 Kcal/Kg. All the protocols of animal experiments were approved by the Institutional Animal Ethics Committee (IAEC) in accordance to the guidelines of Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), Ministry of Social Justice and Empowerment, Government of India, New Delhi.

### Experimental design:

- **Group 1:** Control rats received distilled water for 30 days and normal saline (1 mL kg<sup>-1</sup>, s.c.) on 29th and 30th day
- **Group 2:** Rats received distilled water for 30 days and ISO (200 mg kg<sup>-1</sup>, s.c.) in normal saline on 29th and 30th day at an interval of 24 h
- **Group 3:** Rats received LSFJ (400 mg/kg/day, p.o.) for 30 days
- **Group 4:** Rats received LSFJ (400 mg/kg/day, p.o.) for 30 days and ISO on 29th and 30th day

The change in body weight was recorded at the end of experimental period. After 24 h of second injection (i.e., on 48th h) of Isoproterenol, electrocardiographic changes were recorded. Blood was collected and serum was separated. The animals were sacrificed and the heart was dissected out and weighed. Serum and heart tissue homogenate was used for the estimation of following biochemical parameters.

**Assessment of general parameters:** The final body weight along with heart weight was recorder. From this values heart weight to body weight ratio was calculated.

**Electrocardiographic measurements:** After 48 h of the first injection of either isoproterenol or vehicle, ECG was recorded under light ether anesthesia through needle electrodes (Lead II) using Biopac MP30 data acquisition system (Biopac Systems, Santa Barbara, CA). The changes in ST interval, QT interval, QRS complex and Heart rate were determined from ECG.

**Measurement of blood pressure by Noninvasive method (indirect method):** For arterial blood pressure measurements using tail cuff method, rats were trained for at least one week until the blood pressure was recorded with minimal stress and restraint. Systolic BP, Diastolic BP and Mean BP were measured at the end of treatment period (Tail cuff) using LE 5002 storage pressure meter.

**Assessment of serum parameters:** On day 31, blood was collected from the retro-orbital plexus under mild ether anesthesia. Serum was separated and lactate dehydrogenase (LDH), creatine phosphokinase-MB (CK-MB), Alkaline Phosphate (ALP) were determined by using standard kits (Reckon Diagnostic Ltd., India) while serum Aspartate Transaminase (AST) and serum Alanine Transaminase (ALT) were estimated by using the standard kit (Span Diagnostic Pvt Ltd., India).

**Assessment of markers of oxidative stress:** The excised heart was then weighed and homogenized in chilled Tris buffer (10 mM, pH 7.4) at a concentration of 10% (w/v). The homogenates were centrifuged at 10,000×g at 0°C for 20 min using Remi C-24 high speed cooling centrifuge. The clear supernatant was used for the assay of lipid peroxidation (LPO) (Slater and Sawyer 1971), superoxide dismutase (SOD) (Misra and Fridovich, 1972), catalase (CAT) (Aebi, 1984), reduced glutathione (GSH)

(Moron *et al.*, 1979), glutathione peroxidase (GPx) (Rotruck *et al.*, 1979) and glutathione S transferase (GST) (Habig and Jakoby, 1981).

**Statistical analysis:** Results are presented as Mean±SEM. One-way Analysis of Variance (ANOVA) followed by Bonferroni multiple comparisons using a computer based fitting program (Prism). Differences were considered to be statistically significant when  $p < 0.05$ .

**RESULTS**

**Effect of LSFJ on body weight, heart weight and heart/body weight ratio:** Rats injected with ISO for two consecutive days showed a significant ( $p < 0.01$ ) decrease in body weight ( $p < 0.01$ ) and a significant ( $p < 0.01$ ,  $p < 0.001$ ) increase in heart weight and heart to body weight ratio as compared to control rats. Treatment with LSFJ in ISO injected rats (LSFJ+ISO) did not show significant improvement in body weight, heart weight and heart to body weight ratio as compared to ISO injected rats (Table 1).

**Effect of LSFJ on ECG changes:** The effect of LSFJ on ECG pattern and alteration in ECG parameters in normal and ISO injected rats is shown in Fig. 1 a-d and Table 2.

Table 1: Effect of LSFJ (400 mg/kg/day, p.o.) for 30 days on body weight, heart weight and heart to body weight ratio in normal and ISO (200 mg kg<sup>-1</sup>, s.c.) injected rats

Groups	Body weight (g)	Heart weight (g)	HW/BW
Control	232.5±3.39	0.667±0.031	0.00286±0.0091
ISO	214.2±3.48 <sup>###</sup>	0.920±0.054 <sup>###</sup>	0.00429±0.0155 <sup>###</sup>
LSFJ	229.3±7.21	0.669±0.072	0.00291±0.0099
LSFJ+ISO	221.3±7.21 <sup>ns</sup>	0.806±0.092 <sup>ns</sup>	0.00364±0.0127 <sup>ns</sup>

Values are expressed as Mean±SEM (n = 6). \* $p < 0.05$ , \*\* $p < 0.01$ , \*\*\* $p < 0.001$  values compared to control groups, \* $p < 0.05$ , \*\* $p < 0.01$ , \*\*\* $p < 0.001$  values compared to ISO groups.  $p > 0.05$  was considered as non-significance (ns)

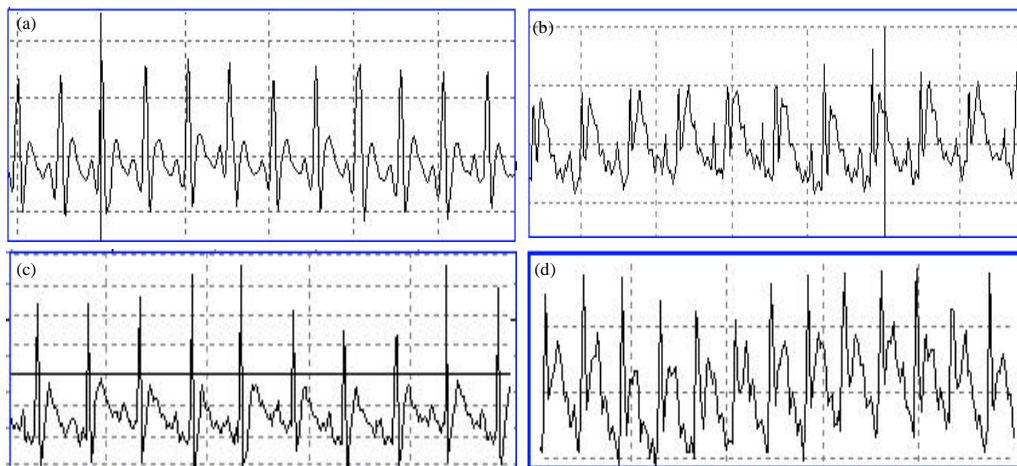


Fig. 1: Effect of LSFJ (400 mg/kg/day, p.o.) for 30 days on ECG pattern in normal and ISO (200 mg kg<sup>-1</sup>, s.c.) injected rats. (a) Control, (b) ISO, (c) LSFJ and (d) LSFJ+ISO

Table 2: Effect of LSFJ (400 mg/kg/day, p.o.) for 30 days on alteration in ECG parameters and heart rats in normal and ISO (200 mg kg<sup>-1</sup>, s.c.) injected rats

Groups	ST elevation	QRS complex	QT interval	Heart rate
Control	0.184±0.0022	0.0416±0.005	0.071±0.0006	338.30±12.88
ISO	0.302±0.0040 <sup>###</sup>	0.0285±0.007 <sup>###</sup>	0.081±0.0012 <sup>###</sup>	400.09±14.32 <sup>ns</sup>
LSFJ	0.181±0.0012	0.0418±0.009	0.070±0.0023	335.10±12.66
LSFJ+ISO	0.272±0.0081 <sup>**</sup>	0.0312±0.010 <sup>ns</sup>	0.078±0.0032 <sup>ns</sup>	371.00±14.08

Values are expressed as Mean±SEM for 6 animals in each group. The ECG parameters are expressed in seconds (sec), heart rate as Beats per minutes (BPM), ST elevation in milivolt (mv). <sup>#</sup>p<0.05, <sup>##</sup>p<0.01, <sup>###</sup>p<0.001 values compared to control group. <sup>\*</sup>p<0.05, <sup>\*\*</sup>p<0.01, <sup>\*\*\*</sup>p<0.001 values compared to ISO injected group

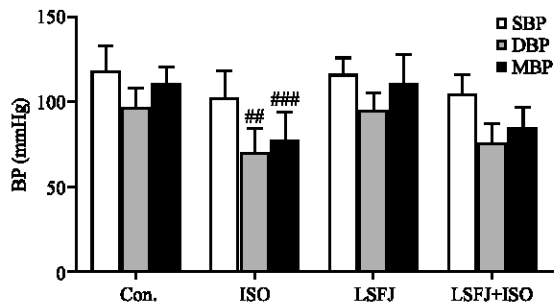


Fig. 2: Effect of LSFJ (400 mg/kg/day, p.o.) for 30 days on systolic, diastolic and mean blood pressure in normal and ISO (200 mg kg<sup>-1</sup>, s.c.) injected rats. Values are expressed as Mean±SEM (n = 6). <sup>#</sup>p<0.05, <sup>##</sup>p<0.01, <sup>###</sup>p<0.001 values compared to control groups, <sup>\*</sup>p<0.05, <sup>\*\*</sup>p<0.01, <sup>\*\*\*</sup>p<0.001 values compared to ISO injected groups

ISO injected rats showed a significant (p<0.01) increase in ST-interval, QT interval and a significant (p<0.01, p<0.001) decrease in QRS complex as compared to control group. Treatment with LSFJ in ISO injected rats (LSFJ+ISO) showed a significant (p<0.01) decrease in ST-elevation compared to control rats. Heart rate was increased in ISO injected rats compared to control rats, it was found to be non-significant.

**Effect of LSFJ on systolic, diastolic and mean blood pressure:** ISO injected rats showed a significantly (p<0.001) decrease in diastolic and mean blood pressure. However, systolic pressure was decrease, it was found to be statistically non significant compared to control rats. Treatment of LSFJ in ISO injected rats (LSFJ+ISO) did not show significant improvement in blood pressure as compared to ISO injected rats (Fig. 2).

**Effect of LSFJ on serum cardiac marker enzymes:** A significant (p<0.001) increased in the activities of serum AST, ALT, ALP, LDH and CK-MB were observed in ISO injected rats. Treatment with LSFJ in ISO injected rats (LSFJ+ISO) showed significant (p<0.01) decrease in the activities of serum AST, ALT, ALP, LDH and CK-MB compared to ISO injected rats. LSFJ alone treatment did not produce any significant effects on serum marker enzymes levels (Fig. 3a-c).

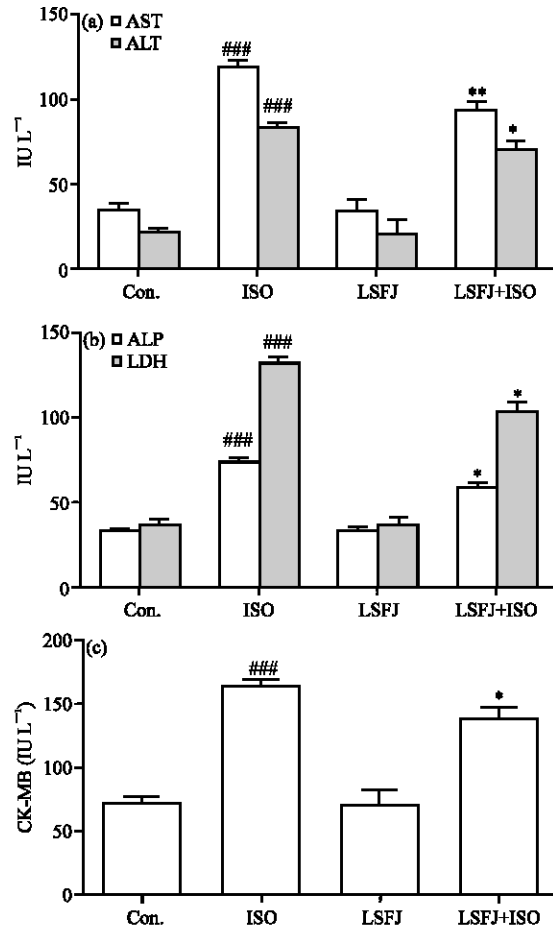


Fig. 3: (a-c) Effect of LSFJ (400 mg/kg/day, p.o.) for 30 days on serum (a) AST and ALT (b) ALP and LDH and (c) CK-MB levels in normal and ISO (200 mg kg<sup>-1</sup>, s.c.) injected rats. Values are expressed as Mean±SEM (n = 6). <sup>#</sup>p<0.05, <sup>##</sup>p<0.01, <sup>###</sup>p<0.001 values compared to control groups, <sup>\*</sup>p<0.05, <sup>\*\*</sup>p<0.01, <sup>\*\*\*</sup>p<0.001 values compared to ISO injected groups

**Effect of LSFJ on lipid peroxidation and markers of oxidative stress:** ISO injected rats showed a significant (p<0.001) increase in LPO level and significant decrease in GSH, GPx, GST, SOD and CAT activities as compared to control group. Treatment with LSFJ in ISO treated rats (LSFJ+ISO) showed a significant (p<0.05) decrease in LPO level and a significant (p<0.05) increase in GSH, GPx

Table 3: Effect of LSFJ (400 mg/kg/day, p.o.) for 30 days on endogenous antioxidants activities in normal and ISO (200 mg kg<sup>-1</sup>, s.c.) injected rats

Groups	LPO	GSH	GPx	GST	SOD	CAT
Con.	1.093±0.119	7.401±0.480	6.102±0.206	110.40±5.712	4.496±0.203	6.290±0.331
ISO	4.053±0.318 <sup>###</sup>	4.338±0.260 <sup>###</sup>	4.032±0.231 <sup>###</sup>	68.91±4.829 <sup>###</sup>	2.272±0.166 <sup>###</sup>	3.687±0.219 <sup>###</sup>
LSFJ	1.010±0.789	7.101±0.476	6.460±0.654	112.43±4.226	4.102±0.621	6.122±0.821
LSFJ+ISO	3.140±0.867 <sup>*</sup>	5.555±0.178 <sup>*</sup>	5.007±0.292 <sup>*</sup>	79.11±2.424	2.952±0.220	4.208±0.366

Values are expressed as Mean±SEM, (n = 6). <sup>\*</sup>p<0.05, <sup>†</sup>p<0.01, <sup>‡</sup>p<0.001 values compared to control group. <sup>\*</sup>p<0.05, <sup>\*\*</sup>p<0.01, <sup>\*\*\*</sup>p<0.001 values compared to ISO injected group. LPO (nM of MDA/mg protein), GSH: (µg of GSH/mg protein), GPx: (µmoles of glutathione oxidized/min/mg protein), GST: (µmoles of CDNB conjugated/min/mg protein), SOD: (units/mg protein), CAT: (µmoles of H<sub>2</sub>O<sub>2</sub> consumed/min/mg protein)

activities as compared to ISO injected rats. LSFJ alone did not show significant effects on LPO level and markers of oxidative stress (Table 3).

### DISCUSSION

Many dietary antioxidants are increasingly being recognized as potential health promoters in reducing the risk of cardiovascular disease (CVD) and atherosclerosis. The prophylactic and therapeutic effects of many plant foods and extracts in reducing CVD have been reviewed (Ames *et al.*, 1993). Phytopharmaceuticals are gaining importance in allopathic as well as traditional medicine owing to their non-addictive and less-toxic nature. Novel antioxidants may offer an effective and safe means of counteracting some of the problems and boosting the body's defense against free radicals and CVD (Ying, 1997).

Present study shows, a significant increase in heart/body weight ratio in ISO injected rats. Increased heart/body weight ratio indicates cardiac hypertrophy (i.e., enlargement of heart) which may be due to ventricular stiffness, increased water content and extensive necrosis of cardiac muscle followed by invasion of the damaged tissue by inflammatory cells (Nirmala and Puvanakrishnan, 1996; Weber and Brilla, 1991). Increased generation of reactive oxygen species and oxidative stress is also implicated in the progression of cardiac hypertrophy and heart failure (Choudhary *et al.*, 2006). Treatment of LSFJ in ISO injected rats did not show significant effect on heart/body weight ratio. Indicated that it did not reduce the stimulus for hypertrophy.

Electrocardiograph (ECG)-abnormalities are the main criteria generally used for the definite diagnosis of MI. ST-segment elevation was observed in patient with acute myocardial ischemia and in ISO-induced MI in rat (Peacock *et al.*, 2007; Rajadurai and Prince, 2007). Present study shows significant alterations in ECG patterns of ISO injected rats. These alterations could be due to the consecutive loss of cell membrane potential in injured myocardium. Increased ST segment reflects a potential difference in the boundary between ischemic and non ischemic zones and consequent loss of cell membrane functions in the regional ischemic myocardium

(Kela *et al.*, 1980). ISO injected rats did not show statistically significant changes in heart rate which is supported by previous reports (Thippeswamy *et al.*, 2009). Treatment with LSFJ in ISO injected rats (LSFJ+ISO) shows a significant decrease in ST elevation. In this context Fard *et al.* (2008) reported that the fruit of *Lagenaria siceraria* prevents ECG changes in doxorubicin induced cardiotoxicity.

In the present study ISO injected rats produced myocardial infarction which is evident by significant fall in systolic, diastolic and mean blood pressure. These changes in hemodynamic parameters indicated the activation of sympathetic nervous system. The decrease in blood pressure in the present study is in line with previous reports (Asdaq and Inamdar, 2009; Thippeswamy *et al.*, 2009). Treatment with LSFJ in ISO injected rats did not show significant improvement in hemodynamic changes compared to ISO treated rats.

A significant increase was observed in the levels of CK-MB, LDH, ALP and transaminases in ISO injected rats is due to the leakage of enzymes from the heart as a result of oxidative stress and necrosis induced by ISO (Manjula and Devi, 1993). The myocardial membrane becomes permeable or may rupture, due to deficient oxygen supply or glucose, thereby resulting in the leakage of these enzymes into the blood stream, thus increasing their concentration in the serum (Wexler and Kittinger, 1963). Treatment with LSFJ alone in ISO injected rats significantly decreased cardiac marker enzymes. In this context it has been reported that *Lagenaria siceraria* fruit prevents elevation of serum marker enzymes in doxorubicin induced cardiotoxicity (Fard *et al.*, 2008) and CCl<sub>4</sub> induced hepatotoxicity (Deshpande *et al.*, 2008).

In the present study a significant increase in the lipid peroxidation products and a significant decreased in the activities of GSH, GPX, GST, SOD and CAT was observed following ISO injection. Elevation of lipid peroxides in ISO injected rats could be attributed to the accumulation of lipids in the heart and the irreversible damage to myocardial membranes (Sathish *et al.*, 2003). A significant decreased in the activities of markers of oxidative stress in ISO injected rats, suggested an enhanced oxidative stress after ISO injection. Present results are in agreement with previous reports (Rajadurai and Prince, 2006;

Saravanan and Prakash, 2004). Treatment of LSFJ in ISO injected rats (LSFJ+ISO) showed significant decrease in lipid peroxidation and an improvement in GSH level which might be due to the presence of polyphenols in the fruit. In this context Fard *et al.* (2008) and Deshpande *et al.* (2008) reported that administration of *Lagenaria siceraria* fruit extract and *Lagenaria siceraria* epicarp extract prevented biomarkers of oxidative stress in doxorubicin induced cardiotoxicity and CCl<sub>4</sub> induced hepatotoxicity owing to its polyphenolic contents. LSFJ also showed *in vitro* antioxidant activity against DPPH radical scavenging assay (Deshpande *et al.*, 2007). Previous investigations demonstrated that the fruits of LS contain flavonoids glycoside, Phenolic constituents, cucurbitane triterpens and saponins (Chen *et al.*, 2008; Ghule *et al.*, 2006a). The presence of various chemical constituents might be responsible for the cardioprotective activity of LSFJ in the present study. The present findings supports the previous reports (Fard *et al.*, 2008; Deshpande *et al.*, 2008) that LS fruit possesses cardioprotective property.

In conclusion, The present study reveal that administration of LSFJ for 30 days may prevent ISO induced myocardial infarction by preventing altered electrocardiographic, hemodynamic and biochemical parameters. Further study is required with higher dose and/or for long duration to confirm the cardioprotective activity of LSFJ in isoproterenol induced myocardial infarction.

#### ACKNOWLEDGMENT

This research was supported by grants from All India Council for Technical Education (AICTE), New Delhi, in the form of National Doctoral Fellowship (NDF) to the first author.

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