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Full Length Article

Cardioprotective and Antilipidemic Potential of *Cyperus rotundus* in Chemically Induced Cardiotoxicity

NAZISH JAHAN[1], KHALIL-UR-RAHMAN AND SHOUKAT ALI
Department of Chemistry and Biochemistry, University of Agriculture, Faisalabad-38040, Pakistan
[1]Corresponding author's e-mail: nazishjahanuaf@yahoo.com

ABSTRACT

Cardioprotective potential of methanol extract of *Cyprus rotundus* on serum cardiac marker enzymes (CK-MB, LDH, AST, ALT), serum lipids (cholesterol, triglycerides, LDL, HDL) and antioxidant enzymes in heart tissues (SOD, CAT, peroxidase) was evaluated in isoproterenol (ISO) induced myocardial infarction in rabbits. Isoproterenol (85 mg kg^{-1}) significantly increased the level of cardiac marker enzymes and lipids and decreased the antioxidant enzymes in heart tissues of rabbits. Male albino rabbits were pretreated with three different doses of *C. rotundus* (100, 150 & 200 mg kg^{-1}) daily for a period of 21 days and then intoxicated with Isoproterenol (85 mg kg^{-1}) for two consecutive days. The treatment with different doses of *C. rotundus* extract significantly ($p<0.001$) reduced the ISO induced elevated level of lipids (cholesterol triglycerides, LDL) and cardiac enzymes (ALT, AST, LDH, CK-MB) and restored the level of antioxidant enzymes in heart tissues. The highest effect was observed @ 200 mg/kg b.wt, which was near to normal. The present study concluded that *C. rotundus* may be used as therapeutic agent for the treatment of hyperlipidemia and myocardial infarction. © 2012 Friends Science Publishers

Key Words: Cardioprotective; Antilipidemic; *Cyperus rotundus;* Isoproterenol

INTRODUCTION

Cardiovascular diseases are leading cause of 17.1 million fatalities each year and it will reach upto 20 million in 2020 (Velavan *et al*., 2008; Gunjal *et al.,* 2010; Upaganlawar *et al.,* 2011). In Pakistan, the situation has become really alarming as cardiac diseases contribute to about 25% of deaths in the country. High concentration of cholesterol is a big risk factor for heart diseases. Hyperlipidemia leads to progressive atherosclerosis, which results in blockage of coronary arteries, interruption of blood supply to parts of heart leading to ischemia and myocardial infarction (Maruthappan & Shree, 2010; Radhika *et al*., 2011; Manimegalai & Venkatalakshmi, 2012). Atherosclerosis develops from oxidized form of low density lipoprotein (LDL), which in high concentrations is predictive risk factor for heart diseases (Attar, 2006; Mansour *et al.,* 2009; Maruthappan & Shree 2010).

Currently available cardioprotective/hypolipidemic drugs have been associated with a number of side effects and are very expensive. Some safe and cost-effective medicinal plants have been reported for their cardioprotective effects (Gauthaman *et al*., 2001) owing to their chemical composition. For example, polyphenols have been shown to be very good antioxidants and having cardio protective effects (Fuhrman, 2000). Many plants have shown potent antilipidemic and cardioprotective potential (Sun *et al*., 2002; Devi & Sharma, 2004; Parsad, 2005; Attar, 2006; Sivakumar *et al*., 2007; Muralidharan *et al.,* 2008; Mohanty *et al.,* 2009; Radhika *et al*., 2011).

Cyprus rotundus have good antioxidants potential (Pal & Dutta, 2006; Nagulendran *et al*., 2007; Jaziri *et al*., 2009). It is also reported as antiseptic (Nuryana *et al*., 2007), antidiabatic, antidiarrheal (Uddin *et al*., 2006) and antimicrobial agent (Tambekar *et al*., 2009). As far as could be ascertained, this is the first study on the hypolipidemic potential of *C. rotundus.*

MATERIALS AND METHODS

Extract preparation: Rhizomes of *C. rotundus* were collected from Botanical garden and authenticated by a plant taxonomist in the Department of Botany, University of Agriculture, Faisalabad-Pakistan. The collected sample (voucher # 6012-11) of rhizomes was air dried under shade and ground into fine powdered form. Plant material (30 g) was extracted with methanol (300 mL) in soxhlet extractor. After the extraction time the solvent was removed under reduced pressure and crude extract containing high fraction of total polyphenols was stored in refrigerator.

Evaluation of cardioprotective/antilipidemic activity: Healthy grownup male albino rabbits weighing 1-1.5 kg were selected for this study. Animal were kept under standard internationally recommended conditions. Animals were allowed for free access to standard diet and water.

Experimental protocol: Rabbits were housed in metallic

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cages with standard conditions of light food and water for one week acclimatization period and then divided into different groups of five rabbit each.

Group I: Normal controls; animals were given standard diet only.

Group II: ISO control group; rabbits were injected with isoproterenol (ISO, 85 mg/kg b.wt.) for two consecutive days.

Group III: Baseline group A; rabbits were orally fed with 100 mg/kg b.wt. *C. rotundus* extract once daily for 21 days.

Group IV: Baseline group B; rabbits were orally fed with 150 mg/kg b.wt. *C. rotundus* extract once daily for 21 days.

Group V: To this group 200 mg/kg b.wt *C. rotundus* was given daily by oral gavage for 21 days.

Group VI: Rabbits were pretreated with *C. rotundus* extract 100 mg/kg b.wt. once daily by oral gavage for 21 days and then ISO (85 mg/kg) was administered by injection for two consecutive days.

Group VII: Rabbits were pretreated with *C. rotundus* extract 150 mg/kg b.wt. once daily by oral gavage for 21 days and then ISO (85 mg/kg) was administered by injection for two consecutive days.

Group VIII: Rabbits were pretreated with *C. rotundus* extract 200 mg/kg b.wt. once daily for 21 days and then ISO (85 mg/kg) was administered by injection for two consecutive days.

Biochemical Assessment

Cardiac enzymes in serum: At the end of experimental period, the blood samples were taken and serum was separated for analysis of different enzymes related to myocardial infarction such as creatinine kinase-MB fraction (CK-MB), lactate dehydrogenase (LDH), aspartate transaminase (AST), alanine transaminase (ALT). All analyses were performed with commercially available kits using chemistry analyzer.

Estimation of lipids: Serum total cholesterol, triglycerides, low density lipoprotein (LDL), and high density lipoprotein (HDL) were determined by using commercial kits with chemistry analyzer.

Statistical analysis: Each sample was analyzed in triplicate and data is expressed as mean ± SD.

Data were analyzed using analysis of variance ANOVA in SPSS 15 software. Tukey Multiple Comparison test was selected for comparison of means of different experiments ($p < 0.05$, $p < 0.001$).

RESULTS AND DISCUSSION

Effect of *C. rotundus* extracts on serum cardiac markers (enzymes): ISO significantly ($p < 0.001$) increased the level of serum cardiac marker enzymes (CK-MB, LDH, AST, ALT) in the ISO induced group as compared to normal control group indicating myocardial infarction in rabbits (Table I). ISO, a synthetic catechol amine, is β- adrenergic receptor agonist (Radhika *et al.,* 2011). Its high dose has ability to destruct myocardium and causes cardio toxicity due to oxidative stress (Upaganlawar *et al.,* 2011). As a result of myocardium destruction, cytosolic enzymes (CK-MB, LDH, AST & ALT) are released in to blood and function as diagnostic biomarkers of cardiotoxicity. Pathophysiological changes including cell necrosis, contractile failure, ventricular arrhythmias and subcellular changes in rabbits are comparable to those taking place in human myocardial ischemia/infarction (Nandave *et al*., 2007; Senthil *et al*., 2007; Panda & Niak 2008; Ojha *et al*., 2011; Subhashini *et al*., 2011).

Three week prior administration of three different doses (100, 150, 200 mg/kg b.wt.) of *C. rotundus* extract significantly decreased the ISO induced elevated level of enzymes (CK-MB, LDH, AST, ALT). All the doses of *C. rotundus* extract were found to reduce the ISO induced elevated enzymes level. *C. rotundus* treated groups showed decrease level near to normal group, which was highly significant ($P < 0.001$) decline as compared to ISO treated control group. The highest effect was demonstrated by treatment of dose 200 mg/kg b.wt which was near to the normal control. Treatment with *C. rotundus* extract also significantly ($P < 0.001$) restored the level of antioxidant enzymes in heart tissues (Table II).

Baseline group were treated with only *C. rotundus* extracts doses (100, 150 & 200 mg/kg) for three weeks. Enzymes like CK-MB, LDH, AST, ALT levels in the serum and antioxidant enzymes in heart tissues of baseline groups were not significantly ($P< 0.001$) changed when compared to normal.

Effect of *C. rotundus* on lipids profile: Significant increase ($P< 0.001$) was noted in the level of cholesterol, triglyceride and LDL cholesterol in serum of ISO injected group when compared to normal control group. The level of HDL cholesterol was significantly lower in ISO induced group of rabbits as compared to normal group (Table I). These finding support the earlier studies (Sasikumar *et al*., 2001; Sivakumar *et al*., 2007; Kareem *et al*., 2009).

Lipid peroxidation, as a result of excessive free radicals, has been identified as one of the major destructive reaction in cellular mechanism of the myocardial ischemia. Highly oxidative metabolite of ISO accelerates rate of peroxidation in membrane phospholipids and releases free fatty acids into plasma by the action of phospholipase A_2, and it is a major causative factor of ISO-induced hyperlipidemia (Sivakumar *et al*., 2007).

Preventive treatment (three week pretreatment) of different doses of *C. rotundus* extract significantly reduced the ISO induced elevated level of cholesterol triglycerides and LDL cholesterol. Three weak pretreatment of rabbits with *C. rotundus* extracts significantly ($P<0.001$) increased the HDL level in ISO induced decrease in HDL level. Low dose (100 mg/kg b.wt.) was also active against hyperlipidemia; however, highest effect was observed @ 200 mg/kg b.wt which was near to normal. Free fatty acids liberated from adipose tissues enter into myocardium. As peroxidation of membrane increase, phospholipids liberate

Table I: Effect of *C. rotundus* on the level of cardiac marker enzymes and lipids in different experimental group

	Control (normal)	ISO control	IP.100 mg+ISO	P.150 mg+ISO	P.200 mg+ISO	BSL P100 mg	BSL P.150 mg	BSL P.200 mg
CK-MB(IU/L)	147.500±1.065	281.260+1.396*	231.900+1.75†	203.08+ 2.696†	172.560+0.66†	141.14 + 0.9	143.48 + 1.639	36.700 + 1.204
LDH(IU/L)	258.200±9.244	521.60±1.418*	436.360±8.97†	392.0±1.768†	300.70±1.76††	239.92±0.89	250.860±0.773	242.360±3.999
AST(IU/L)	32.560 ± 0.760	70.780±5.188*	66.840 ±1.20†	56.400 ± 0.8†	48.98 ± 1.19††	34.0±1.204	31.840 ± 1.514	30.040 ± 1.193
ALT(IU/L)	35.700 ± 0.875	85.580 ± 0.64*	72.940 ± 0.730	62.760 ± 1.19†	53.760 ± 0.6†	36.340±1.22	36.060 ± 1.031	35.180 ± 1.291
cholesterol (mg/dL	66.900±1.738	141.64±1.376*	103.42±1.13†	99.060±3.783†	73.82±2.562†	66.98±1.415	60.060±1.539	74.540±2.793
Triglycerides (mg/dL)	53.340±1.359	105.84±1.757*	82.70±1.230†	77.5204.244†	66.60±2.074††	52.54±2.293	47.060±1.679	49.060±3.601
LDL (mg/dL)	35.920±2.441	74.800±1.531	64.900±1.746	65.180±1.426	51.260±1.479	30.86±3.033	33.460±1.720	34.860±2.727
HDL (mg/dL	42.580±1.222	22.520±1.912*	29.980±1.56†	32.120±4.487†	38.00±1.581††	45.2±5.263	46.460±1.122	49.1801.470

Results are expressed as mean± SD for 5 rabbits in each group
*Significantly different from normal control group (p<0.001). † Significantly different from ISO control group (p< 0.001)
Control; received normal diet and water. ISO control; received two doses of 85mg/kg isoproterenol
Groups P,100, 150, 200 + ISO, received plant extract doses for three weeks and then two doses of 85mg/kg ISO was given
BSL groups received only plant extracts doses

Table II: Effect of *C. rotundus* on the antioxidant enzymes in heart tissues of different experimental group

	Control (normal)	ISO control	CR 200 mg+ISO
SOD (IUmg^{-1} protein)	11.02±1.05	4.14±.54*	8.93±.05†
CAT (IUmg^{-1} protein)	34.82±048	14.820±1.004*	225.6±1.2†
Peroxidase (IUmg^{-1} protein)	1.55±2.58	0.652±2.01*	1.9±0.58†

Results are expressed as mean± SD for 5 rabbits in each group
*Significantly different from normal control group (p<0.001). † Significantly different from ISO control group (p< 0.001)
Control; received normal diet and water. ISO control; received two doses of 85 mg/kg isoproterenol
Groups CR, 200 + ISO, received plant extract doses 200 mg for three weeks and then two doses of 85 mg/kg ISO was given
BSL groups received only plant extracts doses

free fatty acid by the action of the enzyme phospholipase A_2. Ca^{2+} ions are important inducers of phospholipase A_2, so the resulted increase in free fatty acid amount could have been due to the indirect effect of calcium level, which was reported to be changed in isoproterenol-treatment. Hence, the significant increase was observed in the level of lipids in serum of ISO treated group of rabbits (Sasikumar *et al*., 2001; Sivakumar *et al*., 2007; Kareem *et al*., 2009). Prior administration of plant extracts significantly decreased the ISO induced elevated level of cholesterol.

Treatment of different groups of rabbits with extracts of *C. rotundus* significantly blocked the ISO induced secretion of all cardiac diagnostic marker enzymes (CK-MB, LDH, AST, ALT) dose dependently. Extracts treatment has shown significant reduction in ISO-induced elevation in cholesterol, triglyceride and LDL and restored the HDL level. *C. rotundus* contained remarkable antioxidant compounds and showed antioxidant activity (Jahan *et al.*, 2011). The decline in enzymes and lipids levels could be due to potential of extracts to repair and maintain the membrane due to antioxidant polyphenols.

CONCLUSION

The present study concluded that *Cyperus rotundus* showed good cardioprotective and hypolipidemic potential.

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