PHCOG RES. ORIGINAL ARTICLE

Cardioprotective effects of gallic acid in diabetes-induced myocardial dysfunction in rats

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Submitted: 30-03-2011 Revised: 09-05-2011 Published: 15-11-2011

ABSTRACT

Background: Normalization of hyperglycemia, hyperlipidemia, and oxidative stress is an important objective in preventing diabetes-induced cardiac dysfunction. **Objective:** This study was undertaken to examine the effects of gallic acid in myocardial dysfunctions associated with type-1 diabetes. **Materials and Methods:** Diabetes was induced by single intravenous injection of streptozotocin (STZ, 50 mg/kg i.v.). Gallic acid was administered daily at three different doses (100, 50, and 25 mg/kg p.o.) for 8 weeks at the end of which blood samples were collected and analyzed for various biochemical parameters. **Results:** Injection of STZ produced significant loss of body weight (BW), polyphagia, polydypsia, hyperglycemia, hypoinsulinemia, hyperlipidemia, hypertension, bradycardia, and myocardial functional alterations. Treatment with gallic acid significantly lowered fasting glucose, the $AUC_{glucose}$ level in a dose-dependent manner; however, the insulin level was not increased significantly at same the dose and prevented loss of BW, polyphagia, and polydypsia in diabetic rats. It also prevented STZ-induced hyperlipidemia, hypertension, bradycardia, structural alterations in cardiac tissue such as increase in force of contraction, left ventricular weight to body weight ratio, collagen content, protein content, serum lactate dehydrogenase, and creatinine kinase levels in a dose-dependent manner. Further, treatment also produced reduction in lipid peroxidation and increase in antioxidant parameters in heart of diabetic rats. **Conclusion:** The results of this study suggest that gallic acid to be beneficial for the treatment of myocardial damage associated with type-1 diabetes.

Key words: Antidiabetic, antihyperlipidemic, *Emblica officinalis,* left ventricular hypertrophy, myocardial dysfunction, oxidative stress, streptozotocin

Access this article online

Website: www.phcogres.com

DOI: 10.4103/0974-8490.89743

Quick Response Code:

INTRODUCTION

The frequency of myocardial dysfunction is two to five times higher in diabetic patients as compared to nondiabetics.[1] The mechanisms underlying the development of cardiovascular dysfunction, though unclear, appear to have a complex etiology.[2] Various hypotheses such as hypoinsulinemia, dysregulated carbohydrate and lipid metabolism, formation of advanced glycation end products, and oxidative stress have been proposed to explain the relationship between the diabetes and the occurrence of cardiac disease.[3] The occurrence of hyperglycemia, hyperlipidemia, and oxidative stress in diabetes has been extensively documented, and is implicated in the pathogenesis of various cardiovascular complications including cardiomyopathy.[4-6] Thus, among the various therapeutic strategies, antihyperglycemic, antihyperlipidemic, and antioxidant agents can be useful in the prevention of cardiomyopathy in STZ-diabetes.[2,7,8]

Gallic acid is a component of naturally occurring esters of gallic acid that belong to the larger group of plant polyphenols known as gallotannins. Gallotannins are polyphenolic compounds found in legumes, vegetables, fruits, and beverages.[9] Gallotannins were reported to possess multiple biological activities including anticancer, antioxidant, antimicrobial activities, and cardioprotective effects.[9-12] In recent years, gallotannins have been also studied for their antihyperglycemic, lipid lowering, and antioxidant activities.[13-15] Further, gallotannins are hydrolysable tannins which get hydrolyzed in the form of free gallic acid in the gastrointestinal tract.[16] Thus, we

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extended our study to investigate the antihyperglycemic, antihyperlipidemic, antioxidant, and cardioprotective effects of gallic acid on diabetes-induced myocardial dysfunction in streptozotocin (STZ)-induced type-1 diabetic rats. In this study, oral administration of gallic acid at three different doses for 8 weeks was evaluated for amelioration of heart-function defects in myocardial dysfunction associated with STZ diabetic rats.

MATERIAL AND METHODS

Materials

Gallic acid and STZ were purchased from Sigma Chemicals (St. Louis, MO, USA), glucose, triglyceride, and total cholesterol kits were purchased from Span Diagnostics Ltd., India. Radioimmunoassay kit for rat insulin was obtained from Bhabha Atomic Research Centre, Mumbai, India. Cholesterol-high density lipoprotein (HDL) kit was purchased from Lab-care Diagnostics Pvt. Ltd., India. Lactate dehydrogenase (LDH) and creatinine kinase (CK-MB) kits were purchased from Bayer Diagnostics Ltd., Baroda, India. Other chemicals used were of analytical reagent grade.

Experimental animals

Male Wistar rats weighing 200–250g were obtained from the animal facility of Zydus Research Centre, Ahmedabad, India. They were maintained under standard environmental conditions (12 h light/dark cycle at 20–25 C and controlled humidity) and provided with feed and purified water *ad libitum*.

Experimental protocol

All experiments and protocols described in this study were approved by Institutions Animal Ethics Committee (IAEC) and are in accordance with guidelines as per "Guide for the care and use of laboratory animal" and with permission from Committee for the purpose of control and suppression of experiments on Animals (CPCSEA). Diabetes was induced by single intravenous injection of STZ (50 mg/kg i.v) dissolved in normal saline. The control animals were injected with equal volume of vehicle. After 48 h of STZ injection animals showing glucosuria (>2%) were consider as diabetic. Animals were divided into five groups: normal control, diabetic control, diabetic animals treated with gallic acid (25 mg/kg/p.o./day), gallic acid (50 mg/kg/p.o./day), and gallic acid (100 mg/kg/p.o./day) Treatment was started after 3 days of STZ injection and it was given daily for 8 weeks. Weekly food water intake and body weight (BW) gain were measured. Mean and systolic blood pressure and heart rate were measured noninvasively by the tail-cuff method using the Harward blood pressure monitor (Kent, UK) in all the above-mentioned groups at the end of 8 week treatment.

Blood sampling and biochemical analysis

At the end of 8 week treatment, the animals were kept for an overnight fasting and the blood samples were collected from retro-orbital sinus and allowed to clot for 30 min at room temperature. These blood samples were centrifuged at 5000 rpm for 20 min, and serum was separated and stored at–20 °C until analysis was done. Serum samples were analyzed spectrometrically for serum glucose, triglyceride, total cholesterol, HDL-cholesterol, lactate dehydrogenase (LDH), and creatinine kinase (CK-MB) using their respective kits and an UV-visible spectrophotometer (Shimadzu UV-1601, Japan). Low density lipoprotein (LDL) and very low density lipoprotein (VLDL) were calculated from the values of total cholesterol, triglyceride, and HDL. Serum insulin was estimated by a radioimmunoassay technique using the gamma counter (Packard).

Oral glucose tolerance test

The same animals were subjected to oral glucose tolerance test (OGTT).[17] To perform OGTT, the animals were orally administered with 1.5 g/kg glucose and blood samples were collected from the tail vein under light ether anesthesia before, i.e. 0 min and 30, 60 and 120 min after oral glucose administration. Samples were analyzed for glucose and insulin. Plotting the glucose concentration versus time gives a curve showing rise and fall in glucose and insulin levels with time and expressed as integrated area under the curve for glucose and insulin ($AUC_{glucose}$, $AUC_{insulin}$).

Isolated heart experiment

After 3–4 days following OGTT, the animals were killed and the heart was isolated and mounted as per the Langendorff heart technique. The heart was perfused with Chenoweth-Koelle buffer (119.8 mmol/L NaCl, 5.6 mmol/L KCl, 2.88 mmol/L $CaCl_2$, 4.5 mmol/L $MgCl_2$, 3.8 mmol/L $NaHCO_3$, and 5 mmol/L glucose) and was continuously bubbled with 95% O_2 and 5% CO_2 carbogen. The responses were recorded using a transducer attached to the student's physiograph. At the end of study, the hearts were taken out, blotted with a filter paper to remove excess of water, remaining extraneous tissues were removed and weight of the heart was noted down to calculate the index of hypertrophy as wet left ventricular weight to body weight, (LV/BW), heart weight to body weight (HW/BW) and subjected to assessment of antioxidant parameters and estimation of LV collagen and protein content.

Assessment of oxidative stress-related markers

Heart tissues were finely sliced and homogenized in chilled Tris buffer. The homogenate were centrifuged and a clear supernatant was used for estimation of various antioxidant

parameters such as superoxide dismutase (SOD), catalase, lipid paroxidation or malondialdehyde (MDA), reduced glutathione (GSH). SOD was determined by the method of Mishra and Fridovich,[18] catalase was determined by the method of Aebi,[19] and GSH was determined by the method of Moron *et al.*[20] MDA formation was determined by the method of Slater and Sawyer.[21] The result of antioxidant activity in liver was expressed in terms of protein content which was measured as per the method of Lowry *et al.*[22]

Statistical analysis

Values are expressed as mean ± SEM. The results were analyzed using one-way factorial analysis of variance (ANOVA) followed by Tukey's multiple comparison test using Graphpad Prism 5 software. The value of $P < 0.05$ was considered as statistically significant.

RESULTS

Effects of gallic acid on general features and biochemical parameters

STZ administration produced cardinal signs of diabetes like loss of BW, increase in food and water intake as compared to control animals. Chronic treatment with gallic acid prevented the loss of BW and elevated food intake and water intake of diabetic rats in a dose-dependent manner [Table 1]. STZ diabetic rats were found to exhibit significant hyperglycemia, hypoinsulinemia, with hypertriglyceridemia and hypercholesteremia. It also produced an increase in serum LDL-cholesterol, VLDL-cholesterol levels and a decrease in HDL-cholesterol levels in diabetic rats. Treatment with gallic acid produced significant decrease in elevated serum glucose, triglyceride, total cholesterol, LDL-cholesterol, VLDL-cholesterol levels at all doses found to be decreased significantly at 50 and 100 mg/kg doses in diabetic rats. There was an increase in insulin and HDL-cholesterol levels at the same dose level but it was not statistically significant at any dose [Table 2]. There was a greater decrease in these parameters by 50 mg/kg gallic acid as compared to 25 mg/kg. However, 100 mg/kg gallic acid produced identical alteration in these parameters. Thus, 50 mg/kg appears to produce maximum effects in STZ diabetic rats.

Oral glucose tolerance test

Administration of glucose produced a significant increase in $AUC_{glucose}$ of the diabetic control group compared to that of normal control. Treatment with gallic acid in all doses produced a significant decrease in $AUC_{glucose}$ of diabetic rats compared to that of diabetic control [Table 2].

Effects on hemodynamic parameters

Mean blood pressure, force of contraction was found to be increased and heart rate was found to be decreased in diabetic rats as compared to control animals. Chronic treatment with gallic acid showed a significant increase in heart rate and decrease in blood pressure and force of contraction as compared to diabetic control animals in a

Table 1: Effect of treatment of gallic acid (25, 50 and 100 mg/kg) on general features of non-diabetic control and diabetic rats

Parameters	Non-diabetic control	Diabetic control	Diabetic treated with gallic acid 25 mg/kg	Diabetic treated with gallic acid 50 mg/kg	Diabetic treated with gallic acid 100 mg/kg
Body weight after treatment (g)	214.8 ± 0.38	168.6 ± 2.45	189.7 ± 0.77*	199.4 ± 0.90*	203.1 ± 0.83*
Food intake (g/animal/day)	23.2 ± 0.39	43.5 ± 0.83	31.3 ± 1.17*	25.9 ± 0.85*	23.5 ± 0.73*
Water intake (ml/animal/day)	24.9 ± 0.43	73.9 ± 1.03	54.2 ± 2.17*	38.8 ± 1.20*	32.8 ± 0.86*

Values are expressed as mean ± SEM, *Significantly different from diabetic control ($P < 0.05$)

Table 2: Effect of treatment of gallic acid (25, 50, and 100 mg/kg) on biochemical parameters of non-diabetic control and diabetic rats

Parameters	Non-diabetic control	Diabetic control	Diabetic treated with gallic acid 25 mg/kg	Diabetic treated with gallic acid 50 mg/kg	Diabetic treated with gallic acid 100 mg/kg
Serum glucose (mg/dl)	119.2 ± 5.91	450.8 ± 22.1	241.8 ± 30.9*	187.3 ±37.6*	185.2 ± 10.0*
Serum insulin (μU/ml)	51.8 ± 5.30	26.0 ± 5.61	29.8 ± 4.47	26.7 ± 6.58	29.83 ± 4.64
$AUC_{glucose}$ (mg/dl//min) × 10^3	12.5 ± 0.48	53.4 ± 1.97	40.4 ± 3.63*	34.0 ± 3.72*	23.2 ± 2.12*
$AUC_{insulin}$ (μU/ml/min) × 10^3	5.47 ± 0.13	9.15 ± 0.44	8.38 ± 0.55	7.88 ± 0.51	7.97 ± 0.35
Serum triglyceride (mg/dl)	80.9 ± 10.8	197.3 ± 19.8	147.4 ± 6.29*	104.8 ± 13.7*	101.1 ± 12.0*
Serum cholesterol (mg/dl)	86.4 ± 4.95	124.5 ± 5.15	105.3 ± 3.29*	88.4 ± 4.01*	80.5 ± 8.83*
HDL cholesterol (mg/dl)	37.8 ± 3.53	31.8 ± 1.87	34.8 ± 3.22	35.3 ± 4.42	36.5 ± 4.82
LDL cholesterol (mg/dl)	35.6 ± 1.72	59.2 ± 5.22	41.08 ± 1.88*	34.7 ±7.75*	36.4 ± 5.32*
VLDL cholesterol (mg/dl)	16.2 ± 2.15	39.5 ± 3.95	29.5 ±1.26*	21.05 ± 2.75*	20.2 ± 2.41*

Values are expressed as mean ± SEM; *Significantly different from diabetic control ($P < 0.05$)

dose-dependent manner [Figure 1]. Gallic acid, 100 mg/kg and 50 mg/kg doses, showed similar alteration in these parameters.

Cardiac hypertrophy index

The LV/BW, LV collagen content and protein content were found to be increased significantly in diabetic rats. Treatment with gallic acid significantly decreased the LV/BW, LV collagen and protein content in a dose-dependent manner [Figure 2].

Effects on serum LDH and CK

Diabetic rats showed a significant increase in the serum CK-MB activity level as compared to the control rats. Administration of gallic acid decreased significantly the diabetes-induced increase in the serum CK-MB activity level in diabetic animals in a dose-dependent manner. The serum LDH activity level of diabetic animals was also increased significantly as compared to the control animal. Gallic acid administration to diabetic rats significantly attenuated the LDH serum activity level compared to diabetic control animals in a dose-dependent manner [Figure 2].

Effects antioxidant parameters in heart

STZ diabetic rats were found to have decreased SOD, GSH, and catalase enzyme levels in heart as compared to control rats. Treatment with gallic acid produced a significant increase in these enzyme levels at 50 and 100 mg/kg doses. STZ-diabetic rats were found to exhibit a significant increase in MDA levels in heart as compared to control rats. Treatment with gallic acid produced a significant decrease in the MDA level at the same dose level [Table 3]. There was a significant increase in antioxidant activity, which was observed with 25, 50, and 100 mg/kg doses as compared to control. The effect of 50 and 100 mg/kg doses of gallic acid were found to be identical which indicates that with 50 mg/kg produce maximum antioxidant effects.

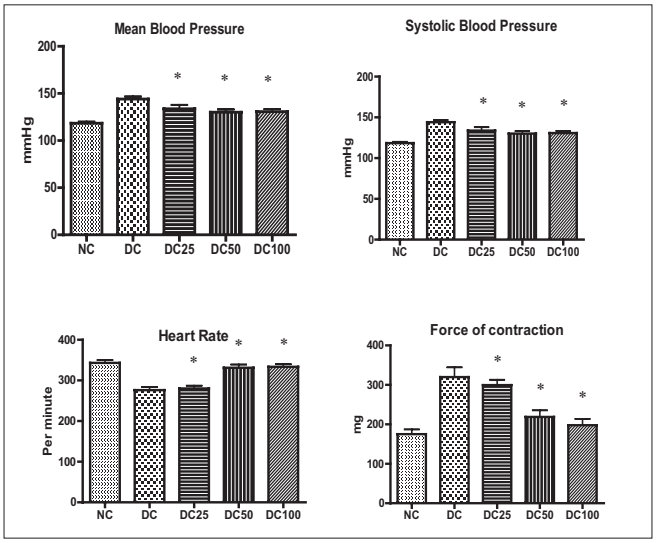

Figure 1: Effect of treatment of gallic acid (25, 50, and 100 mg/kg) on cardiac performance of non-diabetic control and diabetic rats. Each bar represents mean ± SEM of six animals. NC = Non-diabetic control; DC = Diabetic control; DC25 = Diabetic treated with gallic acid 25 mg/kg p.o.; DC50 = Diabetic treated with gallic acid 50 mg/kg p.o.; DC100 = Diabetic treated with gallic acid 100 mg/kg p.o. $P < 0.05$; *significantly different from diabetic control.

DISCUSSION

Intravenous injection of STZ produces clinical symptoms of hyperglycemia and hypoinsulinemia and diabetic hearts have a primary defect in the stimulation of glycolysis, reduction in myocardial glucose supply, and utilization.[23,24] Increasing evidence suggests that altered glucose supply and utilization by cardiac myocytes could be the primary injury in the pathogenesis of this specific heart muscle disease.[2] Therefore, it is necessary to increase glucose utilization or increase the rate of glucose transport in the diabetic heart. In this study, STZ produced a significant increase in glucose levels associated with a decrease in insulin levels in type-1 diabetic rats. Treatment with gallic acid significantly reduced the serum glucose levels and increased serum insulin levels of STZ-diabetic rats. However, the insulin

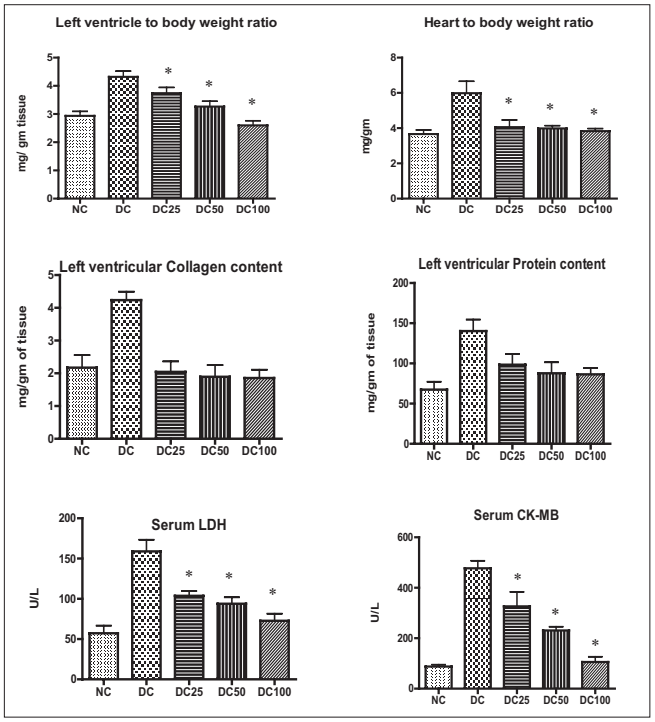

Figure 2: Effect of treatment of gallic acid (25, 50, and 100 mg/kg) on morphological and hemodynamic parameters of control and diabetic rats. Each bar represents mean ± SEM of six animals. NC = Non-diabetic control; DC = Diabetic control; DC25 = Diabetic treated with gallic acid 25 mg/kg p.o.; DC50 = Diabetic treated with gallic acid 50 mg/kg p.o.; DC100, diabetic treated with gallic acid 100 mg/kg p.o. $P < 0.05$; *significantly different from diabetic control

Table 3: Effect of treatment of gallic acid (25, 50, and 100 mg/kg) on antioxidant parameters of non-diabetic control and diabetic rats

Parameters	Non-diabetic control	Diabetic control	Diabetic treated with gallic acid 25 mg/kg	Diabetic treated with gallic acid 50 mg/kg	Diabetic treated with gallic acid 100 mg/kg
Superoxide dismutase (units/min/mg protein)	10.0 ± 1.22	4.33 ± 0.68	8.71 ± 0.56*	9.30 ± 0.93*	10.1 ± 0.72*
Catalase (units/min/mg protein)	11.7 ± 1.57	4.89 ± 0.97	10.2 ± 0.63*	11.2 ± 1.26*	11.5 ± 1.13*
Malondialdehyde (nmoles/mg protein)	0.64 ± 0.25	1.37 ± 0.15	0.69 ± 0.08*	0.59 ± 0.05*	0.59 ± 0.10*
Reduced glutathione (µg/mg protein)	10.8 ± 0.90	4.81 ± 0.72	8.24 ± 0.74*	9.09 ± 0.47*	9.83 ± 0.58*

Values are expressed as mean ± SEM; *Significantly different from diabetic control ($P < 0.05$)

levels were still statistically nonsignificant as compared to control groups. This indicates gallic acid may produce glucose lowering effects either due to increased sensitivity of peripheral tissue to insulin or direct insulin-like effects and it has been reported that cardiac dysfunction may be corrected using insulinomimetics or insulin sensitizer which produce increase in glucose utilization in the diabetic heart and increase in the rate of glucose transport across the sarcolemmal membrane into the myocardium.[25] The results of the OGTT also clearly indicate improved glucose tolerance with treatment of gallic acid to diabetic rats. These results are in complete accordance with all previous data indicating esters of gallic acid from *Lagerstroemia speciosa* (banaba) and *Punica granatum* flower extract produced antidiabetic activity in *in vivo* and in *in vitro* models of diabetes.[26,27] This study suggests that diabetes results in progressive, marked changes in the myocardium that can be prevented by gallic acid treatment either by increasing glucose utilization or glucose transport in diabetic heart. Earlier studies have shown that in STZ-diabetic rats, hyperglycemia is associated with hypercholesterolemia and hypertriglyceridemia.[8] Abnormalities in lipid metabolism have been demonstrated in cardiomyopathy in which the rate of free fatty acid (FFA) uptake by myocardium is inversely proportional to the severity of the myocardial dysfunction.[28] Elevated lipid levels are believed to be one of the major contributing factors in the pathogenesis of diabetic cardiomyopathy. The elevated circulating FFA produces inhibition of glucose oxidation, abnormal high oxygen requirements during FFA metabolism, and the intracellular accumulation of potentially toxic intermediates of FFA, all of which lead to impaired myocardial performance and severe morphological changes.[2,29] Thus, strategy to be employed to produce improvement in cardiac function is to improve upon these metabolic disarrangements. Chronic treatment with gallic acid in diabetic rats decreased elevated lipid profiles. These results of this study correlate with the previous reports that esters of gallic acid increase peripheral insulin sensitivity in rat adipose tissue by inhibiting lipogenesis[26] or by increase in activity of lipoprotein lipase.[30] This therapeutic approach had two major metabolic consequences. First, an increase in glucose utilization and second, a decrease in the lipid level. Thus, it is possible that increased glucose use and a reduction in lipid level have major contribution in improvement of cardiac function. Thus, antidiabetic and antihyperlipidemic activities may be one of the important reasons of the effectiveness of gallic acid in preventing cardiac dysfunctions because carbohydrate and lipid metabolic abnormalities have been attributed to development of cardiac dysfunction in diabetes mellitus.[5,6]

Increases in blood pressure after treatment with STZ has been reported by several workers and the prevalence of hypertension is approximately doubled in diabetic patients compared with nondiabetic.[31,32] Hypertension may be secondary to diabetes is also associated with LV dysfunction, increased force of contraction, and development of bradycardia.[8,33] In our study, increased blood pressure and force of contraction and decreased heart rate were observed in STZ-diabetic animals as compared to nondiabetic control animals. Treatment with gallic acid significantly reduced blood pressure and force of contraction and increased the heart rate as compared to the diabetic control group, and this indicates gallic acid has beneficial effects in diabetic cardiomyopathy.Myocardial fibrosis and myocyte hypertrophy are the most frequently proposed mechanisms to explain cardiac changes in diabetic cardiomyopathy. Studies in various experimental animals have shown that experimentally induced diabetes cause an increase in collagen formation and accumulation of protein within the interstitium,[34] which results in anatomic and physiological changes in the myocardium. Collagen accumulation in the diabetic myocardium may be due in part to impaired collagen degradation resulting from glycosylation of the lysine residues on collagen.[35] In this study, an increase in LV collagen and protein content has been observed in diabetic rats and various studies have demonstrated that increases in LV collagen and protein content may produce cardiac wall stiffness and fibrosis resulting in cardiac dysfunction.[36,37] Treatment with gallic acid decrease LV collagen and protein content. Thus, gallic acid may produce protection against cardiac stiffness and fibrosis in cardiac dysfunction.

In the diabetic rat heart, increases in fibrous tissue

formation and accumulation of collagen cause an increase in the LV mass[38] which correlate with the biopsy study in diabetic patients.[39] In this study, diabetic rats were found to exhibit increased LV weight and heart weight. The wet LV/BW and HW/BW serves as an index of cardiac hypertrophy which was found to be increased in diabetic hearts.[40] After treatment with gallic acid produced, an improvement in the wet LV/BW and HW/BW may be due to increased breakdown of collagen and decrease in glycation of the lysine residue on collagen in the left ventricle suggesting that good diabetic control is associated with the improvement in LV hypertrophy.

Serum LDH and CK activities were found to be increased in STZ diabetic rats, this may be due to myocardial dysfunction because previously it has been reported that serum LDH and CK activities were found to be increased in cardiac muscular damage and serve as a cardiovascular risk-related marker.[41,42] In this study, a significant decrease in serum LDH and CKMB level was observed by treatment of gallic acid, which indicates beneficial effects in reducing the cardiovascular risk in diabetes mellitus.

Hyperglycemia also results in the production of reactive oxygen species (ROS), coexists with a reduction in antioxidant enzymes such as SOD, catalase, GSH, and an increase in lipid peroxidation.[43] Increased ROS generation may activate maladaptive signaling pathways, which may lead to cell death, which could promote abnormal cardiac remodeling, which ultimately may contribute to the characteristic morphological and functional abnormalities that are associated with diabetic cardiomyopathy.[44-45] Over expression of reduced glutathione, catalase and superoxide dismutase in the heart reversed diabetic cardiomyopathy in animal models of both type-1 and type-2 diabetes.[46-48] Thus, strategies that either reduce ROS or augment myocardial antioxidant defense mechanisms might have therapeutic efficacy in improving myocardial function in diabetes mellitus. Treatment with gallic acid increased the levels of endogenous antioxidants and decreased lipid peroxidation in diabetic rats. Numerous studies which have demonstrated that polyphenolic compounds of the plant origin are good antioxidants that inhibit the lipid peroxidation processes *in vitro* and *in vivo*.[49-51] Thus, this study shows that gallic acid exhibits protection against myocardial dysfunction associated with type-1 diabetes which may be also due to antioxidant activity of gallic acid. Thus diabetics, who have an increased risk of cardiac dysfunction, may benefit both from an improvement in glucose and lipid homeostasis as well as from the antioxidant effect of gallic acid.

In conclusion, gallic acid treatment ameliorates hyperglycemia, hyperlipidemia, and development of cardiac dysfunction associated with STZ-diabetes. These insights afford the opportunity to design therapeutic approaches targeted at specific pathogenic mechanisms including improving diabetic control, lipid-lowering therapy, antioxidant, and insulin-sensitizing drugs that might be effective for preventing or delaying the development of diabetic cardiomyopathy.

ACKNOWLEDGMENTS

This study was supported by National Facilities in Engineering and technology with Industrial collaboration (NAFETIC) scheme, AICET, New Delhi.

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Cite this article as: Patel SS, Goyal RK. Cardioprotective effects of gallic acid in diabetes-induced myocardial dysfunction in rats. Phcog Res 2011;3:239-45.

Source of Support: National Facilities in Engineering and technology with Industrial collaboration (NAFETIC) scheme, AICET, New Delhi., **Conflict of Interest:** None declared.