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Research Article

NARINGIN ATTENUATES OXIDATIVE STRESS AND PROTECT AGAINST MYOCARDIAL ISCHEMIA-REPERFUSION INJURY IN DIABETIC RAT

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ABSTRACT

Objective: The relative risk of coronary heart disease in diabetic patients is more than in non-diabetic population. The present study was undertaken to explore the cardioprotective effect of Naringin on ischemia-reperfusion injury in the diabetic model of rat.

Methods: Adult Wistar rats (either sex) divided into six groups. Diabetes was induced by 5 weeks combine exposure to a high-fat diet with a low dose of streptozotocin (30 mg/kg i.p.), administered on the 1st day of starting of the 5th week. Naringin treatment 25 mg/kg and 50 mg/kg was given simultaneously for 5 weeks. On the 36th day, the study animals were subjected to induction myocardial ischemia-reperfusion injury induced by the ligation of the left anterior descending coronary artery ligation in anesthetizing rat. Serum glucose level and cholesterol level measured before performing of ischemic reperfusion. After reperfusion injury, the animals were sacrificed and estimate change in the heart in the course of biochemical alterations, in creatine kinase-muscle/brain (CK-MB) and lactate dehydrogenase, lipid peroxidation (LPO), glutathione (GSH), superoxide dismutase (SOD) and infarct size in the heart.

Results and Conclusion: Naringin treatment significantly reduced the body weight, blood glucose, cholesterol, cardiac injury biomarkers, and LPO level and increased in antioxidant (GSH and SOD) level and also significantly increased in mean arterial pressure heart rate, reduced the myocardial infarction size. The present study concludes that Naringin 50 mg/kg being more prominent action to reduce the cardiotoxicity risk in ischemia-reperfusion injury state and increases myocardial susceptibility through having more prominent antioxidant potential properties.

Keywords: Diabetes, Ischemia-reperfusion injury, Naringin.

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INTRODUCTION

Cardiovascular diseases are the major cause of death and disability in people with diabetic patients [1]. The mortality rate of the diabetic patient after coronary bypass grafting is about twice that of the non-diabetic patient [2]. The diabetic heart is more prone to develop ventricular tachyarrhythmia and high-degree atrioventricular block [3]. Diabetes mellitus increases susceptibility to ischemia-reperfusion injury and also modifies myocardial responses to ischemic conditioning strategies by disruption of intracellular signaling responsible for the enhancement of resistance to cell death [4,5]. Endothelial dysfunction has received increasing attention as a potential contributor to the development of vascular disease in diabetes mellitus [3]. It caused the activation of major molecular signaling mechanisms protein kinase C, hexosamine flux, polyol pathway flux, and increased advanced glycation end product formation [6]. The diabetic heart is more sensitive for the coronary heart disease due to decreased glycolysis and alters the sarcolemmal Na^+/H^+ and Na^+/Ca^{2+} exchange activities and diabetic heart also increases the free fatty acid and an inflammatory mediator which is responsible for the cell damage and death during the ischemia condition [7]. Susceptibility to coronary heart disease is also increased due to the altered cardioprotective mechanism. An *in vivo* small rodent model for myocardial ischemia-reperfusion injury-induced damage in diabetes mellitus in which administration of high-fat diet (HFD) with a low dose of streptozotocin (STZ) and surgical occlusion of coronary artery followed by reperfusion more closely to the real clinical setting.

A therapeutic approach such as antihyperglycemic, antihyperlipidemic, and antioxidant compound can be beneficial in the prevention of cardiovascular complication associated with diabetes mellitus. Flavonoids are an important group of secondary metabolites and a source of bioactive compounds in plants. It was first discovered in the flowers of grapefruit. Naringin is major flavanone glycoside obtained from tomatoes, grapefruits, and many other citrus fruits, it presents in grape juice up to concentrations of 800 mg/L. It experimentally documented to possess numerous biological properties such as antioxidant, anti-inflammatory, and antiapoptotic activities [8]. It is potential to be a useful dietary supplement in the management of the signs of metabolic syndrome. The molecular mechanism involved in the activation of the adenosine monophosphate (AMP) kinase, peroxisome proliferator-activated receptor-γ, suppressed fatty acid synthesis, and lowering blood glucose and cholesterol concentrations [9]. Naringin markedly suppressed HG-triggered cytotoxicity and apoptosis and it was suggested that contributed to cardioprotection by attenuating mitochondrial dysfunction. Naringin is a potent antioxidant effect by activation of novel antioxidant defense mechanism. It can play an important role in the management of hyperglycemia [8]. It also used in the treatment of atherosclerosis through inhibition of the HMG-CoA reductase, the release of tumor necrosis factor (TNF-α), and nuclear factor-kβ activation and protected against the endotoxic shock and blocked the lethal shock [10]. Naringin protects against lipopolysaccharide-induced acute lung injury in mice through suppression of iNOS activity, TNF-α secretion, and myeloperoxidase [11]. Experimental studies reported the protective effect of Naringin against ischemia-reperfusion-induced injury in rat [12].

On behalf of previous reports, Naringin could be a less toxic and more selective therapeutic approach for the treatment of diabetic-induced cardiovascular complications. The aim of this study was to assess whether treatment with the Naringin glycoside can prevent or mitigate the changes on infarct size, hemodynamic, and biochemical alterations in ischemia-reperfusion injury under diabetic state and its deleterious effects on cardiovascular disease.

METHODS

Drugs and chemicals

Naringin, STZ, glutathione (GSH), and triphenyltetrazolium chloride (TTC) were purchased from Sisco Research Laboratories. Thiobarbituric acid (TBA) and dithiobis-2-nitrobenzoic acid were purchased from Himedia, Mumbai. Cholesterol kit was purchased from Erba Diagnostic and glucose, creatine kinase-muscle/brain (CK-MB), and lactate dehydrogenase (LDH) kits purchased from Reckon Diagnostic.

Study animals

The research protocol of this study has been approved by the Institutional Animal Ethics committee (IAEC) vide approval No-ASCB/IAEC/10/17/119. Adult Wistar rats (either sex), weighing between 200 and 250 g, were procured from registered breeder.

Experimental design

Experimental Groups-1 and 2: Rats were administered 0.9% normal saline (p.o.) with normal chow diet and HFD was administered for 5 weeks, on the 36th day, rats were subjected to thoracotomy and thread passed beneath the left anterior decent coronary artery (LADCA) but no ligation performed, respectively. Group-3: Rats were administered 0.9% normal saline (p.o.) with HFD was administered for 5 weeks and STZ was administered on starting of the 5th week, on the 36th day, rats were to LADCA ligation for 30 min and reperfusion for 60 min to induce myocardial I-R injury. Groups - 4 and 5: Rats were administered Naringin 25 and 50 mg/kg, p.o. [9], respectively, with HFD was administered for 5 weeks and STZ was administered on starting of the 5th week, on the 36th day, rats were to LADCA ligation for 30 min and reperfusion for 60 min to induce myocardial I-R injury. Group-6: Rats were administered glibenclamide 20 mg/kg, p.o. with HFD was administered for 5 weeks and STZ was administered on starting of the 5th week, on the 36th day, rats were to LADCA ligation for 30 min and reperfusion for 60 min to induce myocardial I-R injury.

Induction of diabetes

Diabetes was induced by combining exposure to an HFD with low dose of STZ. Rats were fed with high-fat containing diet (HFD) for 5 weeks and STZ was administered on starting of the 5th week. Composition of HFD (normal chow diet 67%, sucrose 20%, pig lard 10%, and custard powder 2.5%) STZ was administered at a dose 30 mg/kg, i.p. was prepared by freshly dissolved in 0.1 M citrate buffer, pH 4.5. HFD-induced insulin resistance and STZ destroyed a portion of pancreatic β-cell. The plasma glucose was measured after 72 h of STZ injection (the blood samples were collected through retro-orbital plexus technique using capillary glass tube). Animal showing blood glucose more than 250 mg/dL was considered as diabetic [13].

Induction of myocardial ischemic reperfusion injury

On the 36th day, after induction of diabetes in rat was subjected to induction of myocardial I-R. Rat was anesthetized with urethane at dose of 1.5 g/kg, i.p. and body temperature was maintained at 37°C using heating pad throughout the experiment. Neck was opened and tracheotomy and left thoracotomy were performed at the fifth intercostals space using rib cuter and retractor. Pericardium was opened to expose the heart and a 5/0 surgical suture attached to a 16 mm needle (circle cutting) was quickly placed under the left coronary artery. The animal was then stabilized for 10–15 min before the left coronary artery ligation. The left coronary artery was ligated 2–3 mm from its origin between the pulmonary artery cones and left atrium with needle-suture by pressing the polyethylene tubing against the ventricular wall. The animal then underwent 30 min of ischemia and reperfusion for a period of 60 min [13].

Hemodynamic parameters measurement

Separation of carotid artery attached with vagus nerve was done by pointed curve forceps, and then, carotid artery cannulated with polyethylene tube (internal diameter 0.30 mm and outer diameter 0.40 mm) attached to a three-way cannula. The cannula was heparinized (Heparin 300 IU/ml) and connected to power lab 4/30 (AD instruments, NSW, Australia) system using a pressure transducer for the measurement of hemodynamic parameters.

Assessment of blood glucose, cholesterol, CKMB, and LDH level

Blood sample was collected from the rats at end of the experimentation. The blood was collected by puncturing retro-orbital plexus under chloroform anesthesia and collected in Eppendorf tubes (1.5 ml) and centrifuged (4000 rpm for 10 min) for the estimation of glucose and cholesterol using assay kits on autoanalyzer (Microlab 300). The 2nd time blood was collected from the carotid artery after the myocardial reperfusion procedure and prepare sample as similar above-mentioned method, and estimation of LDH and CK-MB by assay kits.

Evaluation of myocardial infarct size

The myocardial infarct size measured using TTC staining method. The heart was transversely cut to obtain slices no >0.1 cm in thickness. The heart slices were placed in the glass dish containing pre-warmed (1%) TTC in phosphate buffer solution (the 1% TTC powder diluted in a phosphate buffer). The image of TTC slices was captured with a digital camera and analyzed by Image J software [14].

Studies of rat heart parameters

Animal was sacrificed and heart tissue was removed, washed with the chilled isotonic saline, and dried with filter paper. After this heart was diced and homogenized in 0.05 chilled cold phosphate buffers. After centrifugation, supernatant was used for the analysis of antioxidant enzymes TBARS [15], GSH [16], and superoxide dismutase (SOD) [17].

Statistical analysis

All the results are expressed as mean±standard error of mean (SEM). The data of all the groups were analyzed by one-way ANOVA followed by Tukey's multiple comparison tests using software GraphPad Prism. A value of $p<0.05$ was considered to be statistically significant.

RESULTS

Effect of Naringin on body weight

Diabetic control rats show significant ($p<0.05$) increase in body weight in the 1st and 5th weeks and significantly ($p<0.001$) gain in body weight 2nd–4th weeks as compare to sham control groups. On treatment with Naringin (25 mg/kg), a significant ($p<0.05$) decreased in body weight in the 3rd and 5th weeks, as well as similar treatment significant ($p<0.01$) decreased but maintained body weight in final 4th week as compare to diabetic I-R rats. On treatment with Naringin (50 mg/kg), a significant ($p<0.01$) decreased but maintained body weight was observed in the 1st week, further observe ($p<0.001$) over the duration of the 2nd–5th weeks as compared to diabetic IR rats. Treatment with the standard glibenclamide (20 mg/kg), a significant ($p<0.05$) decreased but maintained body weight was observed in the 1st week, further observe a decrease in body weight ($p<0.001$) over the duration of the 2nd–5th weeks as compared to diabetic IR rats.

Following the injection of STZ (dose) on day 1 of the 5th week, decrease in body weight of diabetic control and diabetic IR rats was observed, but STZ (dose) administration did not alter body weight or weight gain in the Naringin (25 and 50 mg/kg) and glibenclamide (20 mg/kg) treated rats in final week as compared to diabetic IR rats (Fig. 1).

Effect of Naringin on water intake

Diabetic control rats show significant ($p<0.001$) increase in water intake over the duration of 5 weeks as compared to the sham control group. The water intake significant ($p<0.05$) reduces in Naringin (25 mg/kg) treated rats in the 1st and 3rd weeks and also significantly ($p<0.01$) increased in water intake at the 4th week, as well as similar treatment significant ($p<0.001$) decreased over the duration of the 2nd and 5th weeks as compare to diabetic I-R rats. Naringin 50 mg/kg and glibenclamide 20 mg/kg treated rats show significant ($p<0.001$) increase in water intake over the duration of the 5th week as compared to diabetic I-R control rats (Fig. 2).

Effect of Naringin on feed intake

Diabetic control rats show significant ($p<0.05$) increase in feed intake in the 2nd week and also increase ($p<0.01$) in feed intake over the duration of the 3rd and 5th weeks, as well as similar treatment significant ($p<0.001$) increase over the duration of the 4th week compare to sham control groups. On treatment with Naringin (50 mg/kg), a significant ($p<0.05$) decreased in feed intake over the duration of the 2nd and 5th weeks and also decreased ($p<0.01$) in the 3rd week, as well as significantly decreased ($p<0.001$) in the 4th week as compared to diabetic IR rats (Fig. 3).

Effect of Naringin on blood glucose and cholesterol level, CK-MB, and LDH

Blood glucose and cholesterol level were significant ($p<0.001$) increase in diabetic rats as compared to sham control group. Naringin (25 and 50 mg/kg, p.o.) and glibenclamide (20 mg/kg, p.o.) treated rats show significant ($p<0.001$) decrease in glucose level, as compare to diabetic I-R control rats. Cholesterol level was significantly ($p<0.001$) decreased in Naringin-treated rats (25 and 50 mg/kg, p.o.), as compared to diabetic I-R control rats. The level of CK-MB and LDH was significantly elevated ($p<0.001$) in diabetic rats as compared to sham control group. Remarkably, CK-MB and LDH level were elevated significantly ($p<0.001$) in diabetic I-R rats as compare to diabetic control rats. Naringin low and high dose and reference drug glibenclamide-treated rats CK-MB and LDH level was significantly ($p<0.001$) decreased as compared to the diabetic I-R control group. Naringin 50 mg/kg treated rats show significantly ($p<0.001$) decreased cholesterol and LDH level as compare to glibenclamide-treated rats (Table 1).

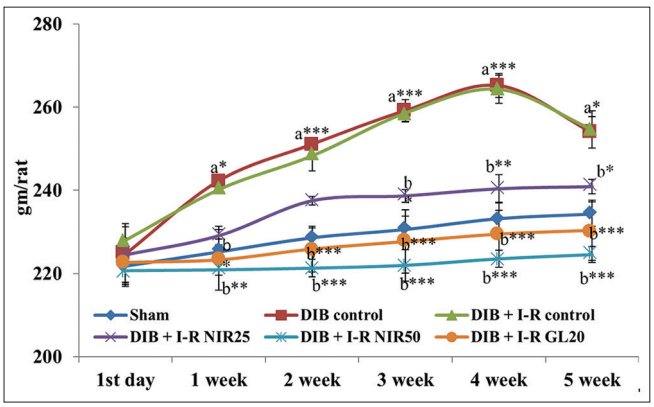

Fig. 1: Effect of Naringin on body weight. Value is expressed as mean±SEM. n=6; (a) *(p<0.05), *(p<0.001) versus sham control group; (b) *(p<0.05), **(p<0.01), ***(p<0.001) versus diabetic I-R control group (One-way ANOVA followed by Tukey's test)**

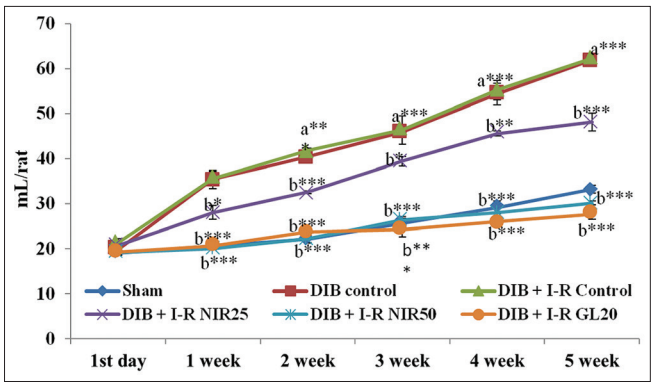

Fig. 2: Effect of Naringin on water intake. Value is expressed as mean±SEM. n=6; (a) *(p<0.05), *(p<0.001) versus sham control group; (b) *(p<0.05), **(p<0.01), ***(p<0.001) versus diabetic I-R control group (One-way ANOVA followed by Tukey's test)**

Effect of Naringin on biochemical estimations (TBARS, GSH, and SOD level)

TBARS activity significantly ($p<0.001$) increased and GSH and SOD level significantly ($p<0.001$) decreased in diabetic control rats and as compared to the sham control group. As similar manner, more potentially TBARS level significantly ($p<0.001$) increased and GSH and SOD activity significantly ($p<0.05$, $p<0.001$) decreased, respectively, in diabetic I-R control rats as compared to diabetic control rats. Naringin 25 and 50 mg/kg, p.o. treated group showed significantly ($p<0.001$) decreased TBARS, GSH level, and SOD activity as compared to diabetic I-R. Glibenclamide-treated group showed significantly ($p<0.001$) decreased GSH level and SOD activity as compared to diabetic I-R. Naringin 50 mg/kg treated rats show significantly ($p<0.001$) decreased TBARS, GSH level, and SOD activity as compared to glibenclamide-treated rats (Table 2).

Effect of Naringin on hemodynamic evaluation

A significant ($p<0.001$) decrease in arterial pressure, significant ($p<0.01$) elevation in the heart rate (HR), and significant ($p<0.001$) elevation in the systolic arterial pressure (SAP) and diastolic arterial pressure (DAP) were observed in the diabetic control group when compared to sham control group. Significant ($p<0.001$) decreased in SAP, DAP, mean arterial pressure (MAP), and HR in diabetic I-R control rats as compared to diabetic control rats. On treatment with Naringin 25 and 50 mg/kg significantly ($p<0.001$) restore AP as compared to diabetic I-R control group. Naringin 50 mg/kg treated rats significant ($p<0.05$) restore MAP and HR as compared to diabetic I-R control. Glibenclamide-treated rats show significant ($p<0.001$) restore AP, and also significant ($p<0.01$) restore the SAP, DAP, and MAP and significantly ($p<0.05$) restore the HR when compared to diabetic I-R group (Table 3).

Effect of Naringin on infarct size in rat heat

The infarct size was significantly increased diabetic control groups as compared to the sham control group. Infarct size was significantly increased diabetic I-R control groups as compared to the diabetic control group. Naringin (50 mg/kg, p.o.) and glibenclamide (20 mg/kg, p.o.) treated groups show significantly reduced the infarct size as compared to the diabetic I-R group (Fig. 4).

DISCUSSION

Diabetes mellitus is a rapidly growing health concern which causes several cardiovascular complications including ischemic heart disease, diabetic cardiomyopathy, and stroke [2,3]. The relative risk of ischemic heart disease in the diabetic population is more vulnerable compare that in the non-diabetic population [5]. The enhanced susceptibility is partially due to an associated metabolic disorder characterized by high blood glucose, insulin resistance, and dyslipidemia in patients with diabetic, which aggravated myocardial injury after myocardial ischemia-reperfusion [3,16]. The proposed model combination of HFD with a low dose of STZ-treated rat after that performed myocardial ischemic reperfusion (I-R) injury-induced damage in diabetes animals; it is surgical occlusion of coronary artery followed by reperfusion more closely to the real clinical setting. Recently, tend to focus on; search for new cardioprotective molecules have targeted as well as less complication in therapy. In this contest, the present study was undertaken to explore the cardioprotective effect of Naringin on ischemia-reperfusion injury in a diabetic rat model.

In the study, animal treated with HFD-STZ increases feed intake, water intake, and body weight was found to be significantly elevated, due to increased intake of feed. Linked with weight gain in a hyperglycemic state, glucose from the blood cannot enter the cells due to an abnormality of diabetes associated dysfunction with that body cannot convert the energy from food this condition feel lack of energy and causes an increase in hunger [18]. Increase in body weight and fat deposition is the chief indicators for the gradual progress of metabolic abnormalities and onset of obesity. Naringin-treated rats reduced and maintained feed intake, water intake, and body weight as compared to diabetic I-R control rats'

Table 1: Effect of Naringin on blood parameters (glucose and cholesterol, CK-MB, and LDH)

Group	Glucose	Cholesterol	CK-MB	LDH
Sham	88.3±3.28	60.3±2.51	65.17±1.78	112.5±2.23
DIB control	331.0±7.49a***	180.0±2.38a***	87.33±3.69a***	573±2.99a***
DIB I-R control	330.1±7.61	181.8±2.60	121.20±2.21b***	810±2.94b***
NIR 25 mg/kg	170.0±8.66c***	113.0±1.75c***	76.17±1.30c***	309.7±3.44c***
NIR 50 mg/kg	105.5±2.58c***	80.3±3.79c***, d***	68.67±2.23c***	243.3±2.78c***, d***
GL 20 mg/kg	91.5±2.05c***	176.7±1.36	74±0.89c***	429.3±5.19c***

Values are expressed as mean±SEM. n=6; (a) ***(p<0.001) versus sham control; (b) ***(p<0.001) versus diabetic control group; (c) ***(p<0.001) versus diabetic I-R control group; (d) ***(p<0.001) versus glibenclamide 20 mg/kg (One-way ANOVA followed by Tukey's test). CK-MB: Creatine kinase-muscle/brain, LDH: Lactate dehydrogenase

Table 2: Effect of Naringin on TBARS, GSH, and SOD level

Group	TBARS	GSH	SOD
Sham	5.90±0.16	15.45±0.87	9.63±0.27
DIB control	21.93±0.37a***	5.48±0.37a***	4.32±0.11a***
DIB I-R control	31.81±0.16b***	2.84±0.53b*	2.78±0.28b***
NIR 25 mg/kg	12.87±0.15c***, d***	6.59±0.47c***	5.26±0.08c***
NIR 50 mg/kg	11.65±0.90c***, d***	14.73±0.56c*** , d***	14.45±0.13c***, d***
GL 20 mg/kg	27.60±0.46	10.17±0.22c***	6.93±0.19c***

Values are expressed as mean±SEM. n=6; (a) ***(P<0.001) versus sham control; (b) *(p<0.05) ***(p<0.001) versus diabetic control group; (c) ***(p<0.001) versus diabetic I-R control group; (d) ***(p<0.001) versus glibenclamide 20 mg/kg (One-way ANOVA followed by Tukey's test). GSH: Glutathione, SOD: Superoxide dismutase

Table 3: Effect of Naringin on hemodynamic parameters

Groups	AP	SAP	DAP	MAP	HR
Sham	115.7±1.65	124.3±1.36	84.67±1.09	97.88±1.46	426.2±1.14
DIB control	88.33±4.56a***	140.5±1.40a***	106.5±1.85a***	117.5±1.86a***	430.7±1.55a**
DIB I-R control	85.50±2.49	117.3±2.51b***	77.83±1.86b***	91.52±2.55b***	415.3±1.15b***
NIR 25 mg/kg	104.0±3.05c***	118.1±0.97	78.50±2.33	91.7±1.03	411.3±0.39
NIR 50 mg/kg	109.2±1.31c***	121.1±0.68	82.25±0.92	95±0.98c*	421.8±0.49c*
GL 20 mg/kg	114.4±2.08c***	123.6±0.57c**	83.16±0.69c**	96.64±0.78c**	422.1±2.06c*

Values are expressed as mean±SEM. n=6; (a) **(p<0.01), ***(p<0.001) versus sham control; (b) ***(p<0.001) versus diabetic control group; (c) *(p<0.05), **(p<0.01), ***(p<0.001) versus diabetic I-R control group (One-way ANOVA followed by Tukey's test). AP: Arterial pressure, SAP: Systolic arterial pressure, DAP: Diastolic arterial pressure, MAP: Mean arterial pressure, HR: Heart rate

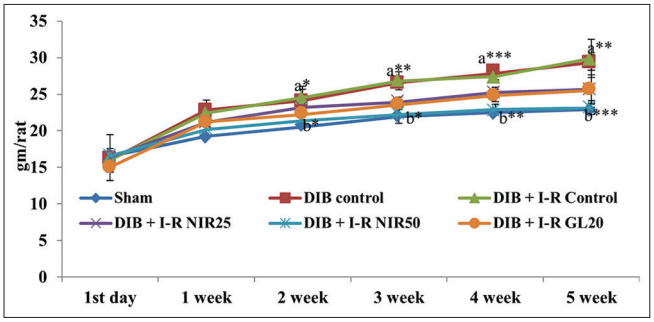

Fig. 3: Effect of Naringin on feed intake. Value is expressed as mean±SEM. n=6; (a) *(p<0.05), *(p<0.001) versus sham control group; (b) *(p<0.05), **(p<0.01), ***(p<0.001) versus diabetic I-R control group (One-way ANOVA followed by Tukey's test)**

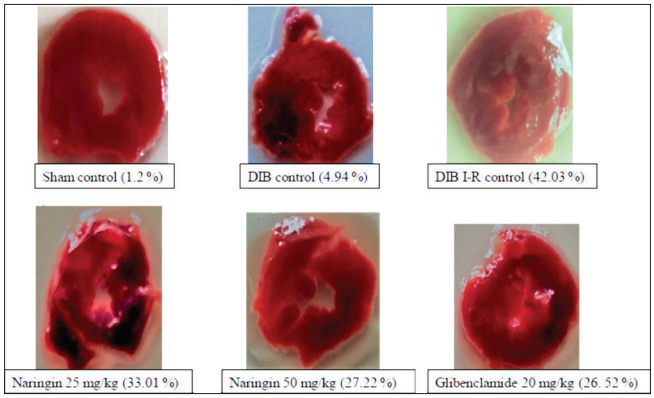

Fig. 4: Effect of Naringin on infarct size in rat heart

results are in agreement with other experimental studies [19].

Various studies have reported that I-R injury sequence results in the generation of free radicals in the myocardium [5,7]. Ischemia reduced the activity of cellular defense systems against free radicals and reperfusion or restoration of oxygen further disturbs the delicate balance of oxidants/antioxidants and generates a burst of free radicals in the tissue [20]. Numerous studies suggested that increased oxidative stress, generation of reactive oxygen species (ROS), and imbalance in antioxidant and oxidant contribute to myocardial tissue injury which explains the decreased in heart weight due to myocardial loss [6,21]. The oxidative indicators GSH and SOD involved in heart disease have been previously reported [22]. Diabetic heart accelerates myocardial oxidative stress and subsequently aggravates heart damage and secondary to lead ischemia-reperfusion injury [5]. Hyperglycemia decreased the antioxidant capacity by reducing SOD and GSH activities [23]. We have observed decreased GSH and SOD level in the study group treated with a combination of HFD and a low dose of STZ plus I-R injury. In addition, HFD-STZ rats significantly increased the cardiac damaged enzymes level (CK-MB and LDH) possible indication of the increased severity of myocardial damage. It has been shown that the enhancement of CK-MB level and LDH attributed to the overproduction of free radicals and cell membrane injury that might have led to the release of cardiac toxic biomarkers [24]. Naringin

activates AMP-activated protein kinase and hypolipidemic effect due to reducing the HMG-CoA reductase [9,10]. Feeding Naringin could downregulate the expression of gluconeogenic enzymes and result in lower blood glucose concentration [19]. Reduction of glucose level and cholesterol level in Naringin treatment confirms in the study. In agreement with these reports, treatment with Naringin significantly increased the activities of SOD and GSH and decreased the levels of MDA in heart and reduced CK-MB and LDH levels were reverted to normal which shows the protective effect of Naringin through maintenance of cell integrity and prevented cell injury and protect the myocardium. LDH level in Naringin-treated groups shown its potential to reduce oxidative, intracellular Ca^{2+} overload, inflammation, and hyperglycemia-induced ischemia-reperfusion injury and our results are in accordance with other experimental reports [25]. Observed that in Naringin treatment preserve near to normal heart muscle architecture, and reduced to infarct size. The data showed that Naringin is capable of limiting infarct size when administered before the onset of ischemia-reperfusion and has shown cardioprotection in diabetes-induced myocardial I-R injury. Hyperglycemia condition associated with I-R, potentiate ROS generation increased the HR responsible for increased myocardial oxygen consumption and demand which leads to ischemic necrosis of the myocardium in animal [26,27]. Naringin treatment will help to preserve near normal heart functions, these were reflected by near normal the underlying the cardioprotective mechanisms effects of Naringin against diabetic IR-induced abnormality. There is evidence for an association between high dietary intakes of Naringin reduction of cardiac damage.

CONCLUSION

Therefore, the present study suggests a protective effect of Naringin at a higher dose on HFD-STZ-induced diabetes with myocardial ischemic reperfusion injury in rats. Naringin 50 mg/kg shown protected significantly for all parameters and it has a best effective dose. Further, we have concluded that Naringin at higher dose level effectively reduced the body weight it also reduced the blood glucose level and cholesterol level and showed a significant result in biochemical parameters, which effectively reduced the lipid peroxidation level and increased the GSH and SOD level and also shown significant result in hemodynamic parameters, MAP and HR. Naringin pre-treatment also reduced the myocardial infarction percentage and damage.

AUTHORS' CONTRIBUTIONS

All authors have equal contribution to this manuscript. The study conception and experimental design by Ajay Singh Kushwah, acquisition of data and drafting of manuscript analysis, and interpretation of data by Neelam Kumari.

CONFLICTS OF INTEREST

There are no conflicts of interest.

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