

BENEFICIAL INTERACTION OF POMEGRANATE JUICE AND GLIBENCLAMIDE IN DIABETES INDUCED CARDIOMYOPATHY

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Abstract

Diabetes mellitus, a chronic metabolic disorder, is a growing global health crisis that causes cardiomyopathy through chronic hyperglycemia, oxidative stress, and reactive oxygen species (ROS), damaging heart tissue. Pomegranate juice (*Punica granatum*), rich in polyphenols and antioxidants, combined with glibenclamide, can target these alloxan-induced complications in rats. This study evaluated the cardioprotective effects of pomegranate juice with glibenclamide against alloxan-induced diabetic complications in rats. Objectives included assessing antinociception via thermal tests, serum biomarkers (LDH, CK-MB), ECG parameters, and antioxidants after 28 days of treatment. Diabetes was induced intraperitoneally with alloxan monohydrate (125 mg/kg); rats exhibiting fasting glucose levels of 210-220 mg/dl were randomised into groups (n=6): normal control, diabetic control, glibenclamide (0.5 mg/kg p.o.), pomegranate juice (3 ml/kg p.o.), and their combination. Cardioprotection was assessed via serum LDH/CK-MB, ECG recordings (heart rate, RR, QT, QRS, ST intervals using physiograph). Diabetic controls showed significant ($p < 0.001$) hyperalgesia, elevated LDH/CK-MB, antioxidant depletion, and ECG changes (increased QRS/PR/QT, decreased RR). Combination therapy reduced biomarkers, restored antioxidants, and corrected ECG, outperforming monotherapies. The combination therapy exhibited potent cardioprotective effects (normalised biomarkers, ECG, antioxidants). Pomegranate juice (3 ml p.o.) + glibenclamide (0.5 mg/kg p.o.) provided superior protection against alloxan-induced diabetic cardiomyopathy compared to monotherapies, suggesting synergistic antioxidant and hypoglycemic mechanisms. These promising preclinical findings warrant further pharmacokinetic, toxicological, and clinical investigations for therapeutic translation.

1. INTRODUCTION

India is a measureless storehouse of medicinal plants that are used in traditional medical treatments. The various native systems, such as Siddha, Ayurveda, Unani and Allopathy, use several plant species to treat different ailments. Herbal medicines as a major remedy in the traditional system of medicine, have been used in medical practices since antiquity.[1,2]

Diabetes mellitus is a metabolic disorder characterised by chronic hyperglycaemia (fasting blood glucose level > 126 mg/100 ml (6.1mmol/l)) with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action, or both. The chronic hyperglycaemia of diabetes is associated with long-term damage, dysfunction, and failure of

various organs, especially the eyes, kidneys, nerves, heart, and blood vessels, which result in significant morbidity and mortality. In India, diabetic patients are increasing day by day, and according to the World Diabetes Foundation, it has the world's largest diabetes population, followed by China with 43.2 million.[3,4]

Experimental evidence has supported that reactive oxygen species play a role in both pathogenesis and numerous pathophysiological mechanisms that trigger diabetic complications, primarily categorised into macro and micro vascular complications, the latter of which includes retinopathy, nephropathy, neuropathy, and microvascular damage to the cerebral artery.[5,6]The possible biochemical mechanisms include activation of the polyol pathway, activation

of protein kinase C (PKC), formation of glycation end products and increased oxygen stress.[7,8]

Ethno-botanical studies have identified more than 1,200 species of plants with hypoglycaemic activity throughout the world. Before the discovery of insulin, dietary measures and the traditional medicines derived from plants were the major forms of treatment. Among the anti-diabetic plants, Pomegranate (*Punica granatum*), belonging to the Lythraceae family, is one of the most efficacious plants, which is an herbaceous perennial plant native to subtropical and tropical rainforest areas of northern Africa, the Indian subcontinent and central Asia.[9–11]

In the Indian subcontinent's ancient Ayurveda system of traditional medicine, the pomegranate has been used extensively as a source of traditional remedies. The seeds and juice are considered a tonic for the heart and throat, the rind of the fruit and the bark of the pomegranate tree are used as a traditional remedy against diarrhoea, dysentery and intestinal parasites. It consists of various phytoconstituents, and the most abundant polyphenols are the hydrolysable tannins called ellagitannins. The red colour of juice can be attributed to anthocyanins, such as delphinidin, cyanidin, and pelargonidin glycosides. [12–14]

The present study was designed to evaluate the combined effect of pomegranate juice and glibenclamide in the management of diabetic complications such as cardiomyopathy against alloxan-induced diabetes using rats as experimental animals.

2. MATERIALS AND METHODS:

2.1. Procurement of pomegranate and dose selection:

Fresh pomegranate was procured from the local market. Pomegranate juice was made by crushing the pomegranate using the Prestige Mixer and straining through a sieve. The juice was administered orally to the animals by gastric intubation using a force-feeding needle. Glibenclamide was purchased from Shreeji Pharma International, Vadodara, India. Based on earlier literature review, a therapeutic dose of pomegranate juice (3ml, p.o), glibenclamide (0.5 mg/kg) was found in rats and the same dose was selected for the present study.[7]

2.2. Experimental animals

Rats of either sex weighing 175-250 g were housed in standard polypropylene cages and maintained under controlled room temperature ($25^{\circ} \pm 5^{\circ}\text{C}$) and humidity ($55 \pm 5\%$) in a well-ventilated animal house under a 12:12 h light and dark cycle. All the rats were provided with a commercially available standard pellet diet, water *ad libitum*. Before each study, the animals were fasted for 12–14 h but had free access to water. The guidelines of the Committee for the Control and Supervision of Experiments on Animals (CPSCEA), Govt. of India, were followed.

Experimental models:

2.2.1. Alloxan-induced cardiomyopathy

Diabetes was induced by intraperitoneal injection of a freshly prepared aqueous solution of 5% alloxan monohydrate (125mg/kg body weight) in normal Saline. After 24h fasting, blood was withdrawn from the tail vein for glucose analysis. 48h after alloxan administration, and rats with fasting glucose ranging from 210-220 mg/dl, showing clear signs of polyuria, polyphagia and polydipsia were considered diabetic. Animals with fasting blood glucose levels less than 200 mg/dl were not used for experimentation.[15,16]

The rats were divided into the following groups containing 6 animals in each.

Group I: Normal control

Group II: Diabetic control (5% Alloxan 125mg/kg, i.p.)

Group III: Glibenclamide (0.5mg/kg, p.o.)

Group IV: Pomegranate juice (3ml, p.o)

Group V: Pomegranate juice (3ml, p.o) + glibenclamide (0.5mg/kg, p.o.)

Treatment with Pomegranate juice was started 48h after alloxan injection for 4 weeks. 24 hours after the last day of treatment, a blood sample was collected by retroorbital puncture, and serum was separated by centrifugation. Animals were sacrificed, and the hearts were collected, and for half of the heart samples, heart tissue homogenate (HTH) was prepared.[15,17]

The parameters determined were as follows:

- Blood glucose level was measured in serum on days 7, 14, 21 and 28.
- Electrocardiographic changes were measured on days 7, 14, 21 and 28.
- Serum: Lactic acid dehydrogenase (LDH), Creatinine kinase- MB (CKMB)

Statistical analysis

Results were expressed as mean \pm SEM. Statistical assessment was done by using One-way Analysis of variance (ANOVA) followed by Tukey-Kramer multiple comparison tests. $P < 0.05$ was considered significant.

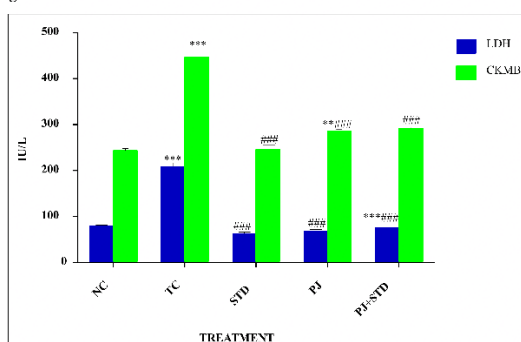
3.RESULT

3.1 Effect on hemodynamic parameters

i. Effect on serum LDH

Comparison of the normal control group with the toxic control (5% alloxan 125mg/kg, i.p) illustrated an extremely significant ($p < 0.001$) increase in serum LDH activity. The treated groups, like standard (glibenclamide 0.5mg/kg, p.o.), pomegranate juice (3ml, p.o), and pomegranate juice (3ml, p.o) + standard glibenclamide (0.5mg/kg, p.o.) demonstrated an extremely significant ($p < 0.001$) decrease in serum LDH activity compared with toxic control. (Figure 1)

Figure 1: Combined effect of pomegranate juice and standard glibenclamide on serum LDH and CKMB levels in alloxan-induced DCM



All values are mean \pm SEM, $n=6$, * $p < 0.05$, ** $p < 0.01$ and *** $p < 0.001$ when compared to normal control and **** $p < 0.001$ compared to toxic control.

ii. Effect on serum CKMB

The toxic control (5% alloxan 125mg/kg, i.p) illustrated an extremely significant ($p < 0.001$) increase in serum

CKMB levels when compared to the normal control group. The treated groups, like standard (Glibenclamide 0.5mg/kg, p.o.) and pomegranate juice (3ml p.o), and pomegranate juice (3ml, p.o) + standard glibenclamide (0.5mg/kg, p.o.) demonstrated an extremely significant ($p < 0.001$) decrease in serum CKMB levels compared with toxic control. (Figure 1)

Table 1: Combined effect of pomegranate juice and standard glibenclamide on serum LDH and CKMB levels in alloxan-induced DCM.

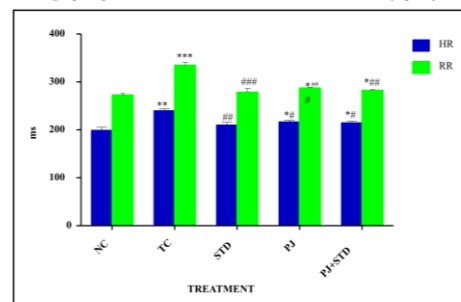
Treatment	Blood serum level (IU/L)	
	LDH	CKMB
Normal control (NC)	79.06 \pm 2.25	242.83 \pm 5.29
Toxic control (TC)	208.66 \pm 7.53***	446.33 \pm 7.22***
Standard <u>glibenclamide</u> (0.5mg/kg p.o.) (STD)	62.80 \pm 3.60 ###	245.80 \pm 2.72 ###
Pomegranate juice (3ml p.o.) (PJ)	68.13 \pm 4.23###	285.53 \pm 2.65***###
Pomegranate juice (3ml p.o) + <u>glibenclamide</u> (0.5mg/kg p.o.) (PJ+STD)	75.23 \pm 5.20***###	291.60 \pm 3.02###

3.2. Effect on ECG parameters

1. Heart Rate

Electrocardiographic determination revealed a moderately significant ($p < 0.01$) increase in heart rate of toxic control (5% alloxan 125 mg/kg, i.p) compared to normal control. A moderately significant ($p < 0.01$) fall in

Figure 2: Combined effect of pomegranate juice and standard glibenclamide on electrocardiographic parameters in alloxan-induced diabetic cardiomyopathy in rats



All values are mean \pm SEM, $n=6$, * $p < 0.05$, ** $p < 0.01$ and *** $p < 0.001$ when compared to normal control and **** $p < 0.001$ compared to toxic control.

heart rate was observed with standard group (glibenclamide 0.5mg/kg, p.o.) group while a significant ($p < 0.05$) fall was seen with that of pomegranate juice

(3ml p.o), and pomegranate juice (3ml, p.o) + standard (glibenclamide (0.5mg/kg, p.o.) when compared with the toxic control. (Figure 2) (Figure 4)

2. RR interval

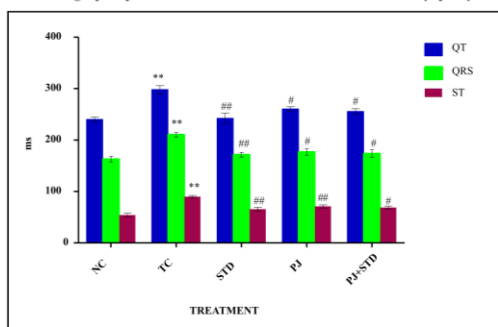
An extremely significant ($p < 0.001$) enlargement of RR interval was observed with toxic control (5% alloxan 125 mg/kg, i.p) on comparison with normal control, whereas an extremely significant ($p < 0.001$) reduction was observed with standard (Glibenclamide 0.5mg/kg, p.o.) on comparison with toxic control. pomegranate juice(3ml, p.o), and pomegranate juice (3ml, p.o) + standard (glibenclamide (0.5mg/kg, p.o.) showed a moderately significant ($p < 0.01$) reduction in RR interval on comparison with the toxic control. (Figure 2) (Figure 4)

3. QT interval

A moderately significant ($p < 0.01$) enlargement of the QT interval was observed in the case of toxic control (5% alloxan 125 mg/kg, i.p) on comparison with the normal control.

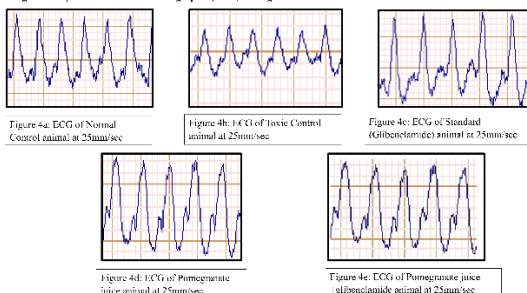
The standard group (Glibenclamide 0.5mg/kg, p.o.) showed a moderately significant ($p < 0.01$) decrease in QT interval while a significant ($p < 0.05$) decrease was

Figure 3: Combined effect of pomegranate juice and standard glibenclamide on electrocardiographic parameters in alloxan-induced diabetic cardiomyopathy in rats



All values are mean ± SEM, n=6, ** $p < 0.01$ and *** $p < 0.001$ when compared to normal control and # $p < 0.05$, ## $p < 0.01$ and ### $p < 0.001$ compared to toxic control.

Figure 4: Representative electrocardiographic (ECG) tracings



observed with pomegranate juice (3ml, p.o), and pomegranate juice (3ml, p.o) + standard glibenclamide

(0.5mg/kg, p.o.) treated group on comparison with the toxic control. (Figure 3)(Figure 4)

Table 2: Combined effect of pomegranate juice and standard glibenclamide on electrocardiographic parameters in alloxan-induced diabetic cardiomyopathy in rats

Treatment	Heart rate (Beats/min)	RR interval (ms)
NC	199.33 ± 6.00	272.33 ± 3.48
TC	240.16 ± 3.63**	334.33 ± 6.20***
STD	210.50 ± 5.20 ###	278.26 ± 7.95###
PJ	217.00 ± 2.88*#	287.00 ± 1.60 ***
PJ+STD	215 ± 3.23*###	282.16 ± 1.73*###

All values are mean ± SEM, n=6, * $p < 0.05$, ** $p < 0.01$ and *** $p < 0.001$ when compared to normal control and ### $p < 0.001$ compared to toxic control.

Treatment	QT interval (ms)	QRS duration (ms)	ST segment (ms)
NC	240.00 ± 4.35	162.76 ± 5.85	54.16 ± 3.3
TC	298.00 ± 7.63**	210.50 ± 4.53**	89.73 ± 2.60***
STD	242.16 ± 9.83###	171.50 ± 4.44##	65.66 ± 3.32##
PJ	260.33 ± 4.16 #	176.83 ± 6.50#	70.93 ± 2.88##
PJ+STD	255.43 ± 5.23#	173.67 ± 7.15#	68.77 ± 3.01#

All values are mean ± SEM, n=6, ** $p < 0.01$, *** $p < 0.001$ when compared to normal control, # $p < 0.05$, ## $p < 0.01$ ### $p < 0.001$ compared to toxic control.

4. QRS duration

The toxic control group (5% alloxan 125 mg/kg, i.p) showed a moderately significant ($p < 0.01$) increase in QRS interval when compared with the normal control and a moderately significant ($p < 0.01$) reduction in QRS interval is observed with standard group (Glibenclamide 0.5mg/kg, p.o.) on comparison with toxic control group. pomegranate juice(3ml, p.o), and pomegranate juice +

standard (glibenclamide (0.5mg/kg, p.o.) showed a significant ($p < 0.05$) decrease in QRS interval on comparison with toxic control. (Figure 3) (Figure 4)

5. ST segment

Toxic control group (5% alloxan 125 mg/kg, i.p) showed an extremely significant ($p < 0.001$) enlargement of ST interval when compared with normal control whereas Standard (Glibenclamide 0.5mg/kg, p.o.) and pomegranate juice (3ml, p.o), and pomegranate juice + standard (glibenclamide (0.5mg/kg, p.o.) showed moderately significant ($p < 0.01$) reduction of ST interval when compared to toxic control group. (Figure 3) (Figure 4)

Representative electrocardiographic (ECG) tracings of the normal control (Figure 4a), Toxic control (Figure 4b), Standard glibenclamide (Figure 4c), Pomegranate juice (Figure 4d), pomegranate juice + glibenclamide (Figure 4e) are shown below. (Figure 4)

4. DISCUSSION

The present study was aimed to investigate effect of pomegranate juice on antidiabetic activity of glibenclamide against alloxan induced diabetic cardiomyopathy in rats. The oxygenated pyrimidine derivative, alloxan monohydrate is the most potent diabetogenic chemical agent in experimental diabetes research. Alloxan induces a multiphasic blood glucose response when injected in an experimental animal, which is accompanied by corresponding inverse changes in the plasma insulin concentration followed by sequential ultrastructural beta cell changes ultimately leading to necrotic cell death. It has been found to be selectively toxic to pancreatic beta cells as it preferentially accumulates in the beta cells as glucose analogues. In addition, the cytotoxic action of alloxan is mediated mainly by the generation of reactive oxygen species (ROS).[15,16]

Diabetic cardiomyopathy (DC) is the factor which leads to changes at the cellular level, leading to structural abnormalities. The biological markers like endogenous enzymes are organ specific and leak from the damaged organ during tissue necrosis. Different cardiac specific biomarker enzyme such as Creatinine kinase-MB (CK-MB), Creatinine kinase-NAC (CK-NAC), Lactate dehydrogenase elevation in serum is due to the leakage from the heart as a result of alloxan induced necrosis in myocardial cells. DC is invariably followed by several biochemical alterations such as expression and activity of regulatory proteins such as $\text{Na}^+/\text{Ca}^{2+}$ exchanger,

hyperglycaemia, hyperlipidaemia and leading to quantitative and qualitative alterations of myocardium.[15,18] In the case of alloxan induced diabetic cardiomyopathy model, the experimental results suggested that the glibenclamide+pomegranate juice combination showed comparatively better results compared to glibenclamide alone treated group by reducing the elevated marker enzyme level (LDH, CK-MB) and electrocardiographic parameters (heart rate, QRS complex, RR, QT and ST intervals) in combination dose. The present study also provides the evidence for glibenclamide + pomegranate juice combination pre-treatment reduces the myocardial injuries against alloxan induced diabetic complications like Cardiomyopathy. The probable mechanism of these actions may be due the cytochrome P450 (CYP) 2C9 inhibitory property (or bioenhancing property) of pomegranate juice on glibenclamide (as glibenclamide is metabolized by CYP2C9 enzyme) which may be responsible for potentiation of glibenclamide. Apart from those earlier studies also reported pomegranate juice is having antidiabetic, antioxidant and protective action on pancreatic β -cells.[7] These beneficial properties of pomegranate juice against diabetic conditions may be contributed to the observed results. However, further studies are required to understand the exact mechanism behind the cardioprotective effects of glibenclamide+pomegranate combination in diabetic complications.

5. CONCLUSION

With the findings of the present study, it can be concluded that pomegranate juice (3ml p.o) + Glibenclamide (0.5mg/kg p.o) possessed a significant protective effect against Alloxan-induced diabetic complications such as Cardiomyopathy in rats, when compared to glibenclamide (0.5mg/kg p.o) and pomegranate juice (3ml p.o). All models of Alloxan-induced diabetic complications in rats are evidenced by the physical, biochemical, functional and histological parameters. Evaluation of antioxidant activity was also performed to support the protective potential of Pomegranate juice. The findings of the present study illustrated a significant protective activity in all models. The reported protective effect of the Pomegranate juice may be due to the presence of glycosides, which is responsible for the scavenging of free radicals. The reported results were exciting but the exact mechanism for the cardioprotective activity of pomegranate juice is still not clear and further investigation is required to understand the clear pharmacological profile of the same and to interpret the findings in clinical

applications. The present study was designed to evaluate the combined effect of pomegranate juice with glibenclamide against alloxan-induced diabetic cardiomyopathy in rats. In the alloxan-induced diabetic cardiomyopathy model, diabetes was induced by using alloxan. Treatment was given for 28 days. 24 hours after the last day of treatment, a blood sample was collected by retroorbital puncture and serum was separated by centrifugation. Blood glucose level in serum and Electrocardiographic changes was measured on days 7, 14, 21 and 28. Then after sacrificing the animals for half of the heart samples collected, heart tissue homogenate (HTH) was prepared. Both serum and HTH were subjected to the estimation of different biochemical parameters. The report of the evaluation revealed that the toxic group showed an extremely significant increase of serum biomarker enzymes such as Lactic acid dehydrogenase (LDH) and Creatinine kinase- MB (CKMB), electrocardiographic parameters like heart rate, RR – interval, ST-interval, QT-interval and QRS-complex, when compared to vehicle control. The combined effect of pomegranate juice with glibenclamide-treated groups showed an extremely significant decrease in the level of elevated serum marker enzymes and electrocardiographic parameters compared to the toxic control group.

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