

Effect of Cyclodextrin Garcinol Complex on Pressure Overload- Induced Cardiotoxicity and Cardiac Hypertrophy by Aortic Stenosis in Rats



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ABSTRACT

Background: Garcinol is a polyisoprenylated benzophenone derived from rinds of fruit of *Garcinia* species namely *Garcinia indica* (common name 'Kokum') and *Garcinia cambogia* (common name 'Gombogee'). Garcinol is not stable and has poor bioavailability which can be improved by complexing garcinol with cyclodextrin (cyclodextrin-garcinol complex).

Objective: The objective of the present study was to investigate effect of cyclodextrin-garcinol complex (20 mg/kg) on pressure overload-induced cardiotoxicity and cardiac hypertrophy by aortic stenosis in rats.

Methods: Male Wistar rats (250-300g) were divided into following four groups such as: control, sham, stenosis and cyclodextrin-garcinol complex. Daily body weights were recorded. Cyclodextrin-garcinol complex (20 mg/kg/day) in distilled water, was administered orally to rats daily for 18 days and then the animals underwent surgery with aortic binding, the treatment was continued up to 4-6 weeks.

Haemodynamic changes and electrocardiogram (ECG) were recorded in anaesthetized rats.

Results: Pressure overload induced by aortic stenosis in rat resulted in significant myocardial hypertrophy and decreased endogenous antioxidants when compared with the control and sham group animals. Cyclodextrin-garcinol complex (20 mg/kg) showed significant cardioprotective activity by lowering the myocardial hypertrophy, level of lipid peroxidation (MDA content) as well as elevated the level of GSH. The results suggest pre-treatment of cyclodextrin-garcinol complex (20 mg/kg), may offer potential benefits in the management of cardiotoxicity and cardiac hypertrophy.

Conclusion: It is concluded that cyclodextrin-garcinol complex (20 mg/kg) protected the haemodynamics of stenosed heart of rats by reduction of lipid peroxidation and preservation of endogenous antioxidants in rat heart.

Keywords: Antioxidants, Cardiac hypertrophy, cyclodextrin-garcinol Complex (20 mg/kg), Aortic Stenosis.

INTRODUCTION

Increased cardiovascular mortality is a serious problem in modern societies. Minimizing the risk of cardiac disease and alleviating the complications of cardiovascular dysfunction are the main therapeutic aim in modern medicine.¹ Our understanding of the mechanisms of pathophysiology of cardiovascular diseases has been gaining significant advances and a wealth of knowledge implicates sustained overload pressure and oxidative stress as a key causative agent.

Small animal models are the most preferred tools for the study of chronic changes in the development of cardiac hypertrophy.² Constriction of the ascending aorta is one of the most common and successful surgical models for creating pressure overload.³

Clinically occurrence of chronic pressure overload is a recurrent that leads to left ventricular hypertrophy (LVH). Initially, LVH was considered to be a compensatory mechanism that allows the generation of the required cardiac output and

normalization of wall mechanical stress.⁴ Therefore, aortic stenosis-induced LVH and persistence systemic hypertension can become maladaptive and herald the onset of heart failure.⁵ In rats, gradual aortic constriction for four to eight weeks has been reported to produce stable LV hypertrophy.⁶

The literature shows that in the heart, Ang II (Angiotensin-II) is playing a crucial factor in the development of cardiac fibrosis via collagen deposition and induction of fibroblast proliferation leads to progress of cardiac cell hypertrophy.⁷

It is reported that *in vitro* acute release of Ang II within 10 min and the expression of AGT gene (Angiotensin) after 6 h from cardiomyocytes is induced by the mechanical stretch.⁸ It also showed that Ang II acts as an initial mediator of the stretchinduced hypertrophic response.

Angiotensin II acts via AT1 receptor for inducing cardiac hypertrophy. Which is associated with increased expression of many immediate-early

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Cite This Article: Kushawaha, S.K., Thakurdesai, P., Mohan, V., Bodhankar, S.L. 2018. Effect of Cyclodextrin Garcinol Complex on Pressure Overload- Induced Cardiotoxicity and Cardiac Hypertrophy by Aortic Stenosis in Rats. *Diabesity* 4(2): 17-24. DOI: [10.15562/diabesity.2018.XXX](https://doi.org/10.15562/diabesity.2018.XXX)

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genes (c-fos, c-jun, junB, Egr-1, and c-myc) and fetal marker genes of cardiac hypertrophy (ANF, skeletal α -actin, β -MHC) conferring a pathological phenotype.^{9,10}

Additional evidence suggests that phosphorylated Akt/glycogen synthase kinase 3 β (GSK3 β), extracellular signal-regulated kinases 1 or 2 (ERK1/2) and GATA binding protein 4 (GATA4) pathways play important roles in the process of cardiac hypertrophy and ventricular remodeling induced by pressure overload.^{11,12} All these alterations lead to a worsening of cardiac function, associated with diminished contractility.

The literature shows that chalcones having antioxidant, anti-inflammatory and ACE inhibitor property can reverse the pressure overload induced hypertrophy produced by aortic stenosis, pathogenic conditions and sedentary life style. Garcinol is a polyisoprenylated benzophenone derived rinds fruit of *Garcinia* species namely *Garcinia indica* (common name 'Kokum') and *Garcinia cambogia* (common name 'Gombogee'). It is a potent antioxidant has a limitation of poor stability and bioavailability.¹³ There are several methods to improve these limitations and complexation is one of them.

Literature shows that cyclodextrin is a (α -1, 4)-linked α -D-glucofuranose unit, which is able to form inclusion complexes with many drugs by taking up the drug molecule into the central cavity. No covalent bonds are formed or broken during complex formation. The complexed drug molecule remains in rapid equilibrium with free solvated and complexed forms in the solution. The complexation of garcinol with cyclodextrin is reported in literature. Cyclodextrin enhances the drug permeability by direct action on the biological membrane. It also increases the garcinol stability by restricting the drug solvent interaction. The overall result is increased bioavailability.¹⁴

The aim of present study was to investigate effect of cyclodextrin garcinol complex (cyclodextrin-garcinol complex) on the pressure over induced cardiotoxicity and cardiac hypertrophy by stenosis in rats with a purpose to assess its cardioprotective effect.

MATERIALS AND METHODS

Material

The animals were housed under standard housing conditions of temperature (25°C), relative humidity (60%) and photo period of 12 h dark/12 h light. Pellet diet (Chakan Oil Mills, Pune, India) and water were provided *ad libitum*. Male Wistar albino rats (250-300 g) were obtained from National Toxicological Centre (NTC) Pune. The Institutional

Animal Ethics Committee (IAEC) 'approved protocols of animal experiments.

Chemicals and sample

Cyclodextrin-garcinol complex was obtained as gift sample from Indus Biotech Private Limited, Pune, Epinephrine hydrochloride, and malondialdehyde were purchased from Sigma Chemical Co., USA. Reduced glutathione (GSH), 5,5'-dithiobis (2-nitro benzoic acid) (DTNB) and thiobarbituric acid (TBA) were obtained from Hi media, India. All chemicals used were of analytical grade.

Procedure

Abdominal aortic coarctation was carried out as described by Cordelia *et al* (2007).¹⁵ Rats were anesthetized with thiopental 25 mg/kg (i.p.). Under sterile conditions, the skin was cut open along the abdominal midline. Aortic constriction was created via a left thoracotomy by placing a ligature using sterilized silk suture of size 4-0 (purchased locally from Pune). After that a 40 mm long cannula of diameter 0.9 mm was placed longitudinally in the aorta & tied loosely with it. Then cannula was slowly removed, leaving an aortic lumen of 0.9 mm diameter. The skin was then closed by stitching. The presence of the ascending aortic constriction precludes left ventricular catheterization by a carotid approach in this model.

Male Wistar rats (250-300g) were divided into following 4 groups. Group 1 was control (pre-treated with vehicle i.e. cyclodextrin for 18 days then treatment was continued up to 4-6 weeks). Group 2 was Sham (pre-treated with vehicle i.e. cyclodextrin for 18 days & then under went surgery without aortic banding, treatment was continued up to 4-6 weeks). Group 3 was stenosis (pre-treated with vehicle i.e. cyclodextrin for 18 days & then underwent surgery with aortic banding, treatment was continued up to 4-6 weeks). Group 4 was cyclodextrin-garcinol complex (pre-treated with, cyclodextrin-garcinol complex 20 mg/kg/day for 18 days & then underwent surgery with aortic banding, treatment was continued up to 4-6 weeks). Daily body weights were recorded. Cyclodextrin-garcinol complex (20 mg/kg/day) in distilled water was administered orally to group 4 rats daily for 18 days then treatment was continued up to 4-6 weeks. On the basis of previous pilot study the dose was selected. The literature showed that the therapeutic potential of the cyclodextrin-garcinol complex at a dose of 20 mg/kg is comparable to that of administration of 100 mg/kg (p.o.) of garcinol.¹⁶ It confirms that the chemically cyclodextrin-garcinol complex increases its therapeutic index by making it more efficacious. Moreover, this activity of cyclodextrin-garcinol

complex was achieved without any mortality of the animals indicating elimination of toxicity.

The rats were anaesthetized by anesthetic ether. The ECG, heart rate and blood pressure were recorded using 8 channels Power Lab System (AD Instruments Pvt. Ltd., Unit 13, 18-22 Lexington Drive, Bella Vista NSW 2153, Australia). The animals were sacrificed with overdose of thiopental. Randomly hearts from animals were selected for tissue parameter measurement. The heart of each animal was cut in to small pieces, placed in chilled 0.25M sucrose solution and blotted on a filter paper. The tissues were homogenized in 10% chilled Tris hydrochloride buffer (10mM, pH 7.4) by tissue homogenizer (Remi Motors, Mumbai, India) and centrifuged at 7500 rpm for 15 minutes at 0°C using Eppendorf 5810-R high speed cooling centrifuge. The clear supernatant was used for the measurement of GSH and MDA content.

Tissue parameters

Lipid peroxidation assay (MDA content)

Lipid peroxidation was evaluated by the production of thiobarbituric acid-reactive substances (TBARS).¹⁷ To 2.0 ml of the tissue homogenate (supernatant) was added to 2.0 ml of freshly prepared 10% w/v trichloroacetic acid (TCA). The mixture was allowed to stand for 15 minutes in an ice bath, followed by centrifugation at 2500 rpm for 10 minutes at 0°C. Then 2.0 ml of freshly prepared 0.67%w/v thiobarbituric acid was mixed with 2.0 ml of clear supernatant solution. The resulting solution was heated in boiling water bath for 10 minutes. It was immediately placed for 5 minutes in ice bath to cool the solution. The absorbance of colour developed was measured against reagent blank by UV/VIS spectrophotometer (JASCO-V-530, Japan) at 532 nm using 1, 1, 3, 3-tetraethoxypropane as a standard.

Measurement of GSH

GSH was estimated by method of Moron *et al*(1979).¹⁸ Firstly, 1.0 ml of tissue homogenate

(supernatant) and 1 ml of 20% trichloroacetic acid (TCA) were mixed. It was centrifuged at 2500 rpm for 15 minutes at 0°C. After that to 25 ml of supernatant, 2 ml of 5, 5'-dithiobis (2-nitro benzoic acid) (0.6M) reagent was added. The final volume was made up to 3 ml with phosphate buffer (pH 8.0). The colour developed was read at 412 nm against reagent blank. The amount of reduced glutathione was expressed as µg of GSH /gm of protein.

Determination of organ weight ratio

Body weight was recorded before sacrifice of animal. Heart weight was recorded after keeping the heart in cold saline and squeezing out the blood followed by drying on tissue paper. The weight of left ventricle was recorded. The left ventricular weight/body weight ratio was calculated.

Statistical analysis

The statistical analysis was performed by 'Graph pad prism' software. All values were expressed as mean ± SEM. One way ANOVA was applied to test the significance of biochemical data of different groups and multiple comparisons were determined by the Bonferroni Post hoc test. P < 0.05 was considered statistically significant.

RESULTS

Effect of cyclodextrin-garcinol complex on Systolic BP and Diastolic BP (mmHg) in male Wistar rats

The Systolic BP (SBP) was significantly (p<0.01) reduced in the stenosis group compared with normal group or sham. The diastolic BP (DBP) was significantly (p<0.01) reduced in the stenosis group compared with normal group and Sham. Pretreatment for 18 days and post stenosis treatment for 28 days with cyclodextrin-garcinol complex (20 mg/kg) resulted in significant (p<0.05) decrease in systolic where as non- significant decrease in diastolic BP was non-significant in rats (Table 1).

Table 1 Effect of cyclodextrin-garcinol complex on myocardial SBP and DBP

Enzyme	Control group	Sham group	Stenosis group	Cyclodextrin-garcinol complex (20 mg/kg) group
Systolic BP (mmHg)	86.36 ± 2.2	81.75 ± 2.6ns	115.72 ± 6.3 ##	95.612 ± 2.2*
Diastolic BP (mmHg)	74.31 ± 2.47	64.80 ± 6.48ns	94.03 ± 3.48 ##	79.93 ± 3.48ns1

SBP- Systolic blood pressure, DBP- Diastolic blood pressure (n = 8), data are mean (SEM)]

ns- non significantas compared with control group

p<0.01 significant as compared with control and sham group,

*p <0.05 significant as compared with stenosis group.

p <0.01 significant as compared with control and sham group,

ns1-

Table 2 Effect of cyclodextrin-garcinol complex on myocardial MABP

Enzyme	Control group	Sham group	Stenosis group	Cyclodextrin-garcinol complex (20 mg/kg) group
MABP (mmHg)	77.994 ± 4.58	70.45 ± 4.58ns	101.40 ± 4.06##	91.128 ± 3.04ns1

MABP- Mean arterial blood pressure
(n = 8), data are mean (SEM)]

ns- non significant as compared with control group

p<0.01 significant as compared with control and sham group,
non significant as compared with stenosis group.

Table 3 Effect of cyclodextrin-garcinol complex on heart rate of rats

Ratio	Control group	Sham group	Stenosis group	Cyclodextrin-garcinol complex (20 mg/kg) group
Heart rate (beats/min)	4.583 ± 7.413	-13.05 ± 12.8ns	-88.79 ± 12.31 ###	-45.64 ± 4.673*

[(n = 8), data are mean (SEM)]

ns non significant compared with control group

p<0.001 significant as compared with control and sham group,

* p<0.05 significant as compared with stenosis group.

Table 4 Effect of cyclodextrin-garcinol complex on ECG of rats

Interval	Control group (msec)	Sham group (msec)	Stenosis group (msec)	Cyclodextrin-garcinol complex (20 mg/kg) group (msec)
QT	-0.0012 ± 0.00067	-0.0011 ± 0.0009ns	0.0187 ± 0.001 ###	0.0067 ± 0.0017***
ST	-0.0011 ± 0.002	-0.0024 ± 0.002ns	0.014 ± 0.0017###	0.006 ± 0.002 *

[(n = 8), data are mean (SEM)]

ns non significant compared with control group

p<0.001 significant as compared with control and sham group,

*** p<0.001 significant as compared with stenosis group.

p<0.001 significant as compared with control and sham group,

* p<0.05 significant as compared with stenosis group.

Table 5 Effect of cyclodextrin-garcinol complex on heart to body weight ratio of rats

Ratio	Control group	Sham group	Stenosis group	Cyclodextrin-garcinol complex (20 mg/kg) group
Heart to body weight mg/g	3.135 ± 0.078	2.985 ± 0.0769 ns	4.085 ± 0.037###	3.42 ± 0.0486***

[(n = 8), data are mean (SEM)]

ns non significant compared with control group

p<0.001 significant as compared with control and Sham group,

*** p<0.001 significant as compared with Stenosis group.

Table 6 Effect of cyclodextrin-garcinol complex on left ventricular weight to body weight ratio of rats

Ratio	Control group (mg/g)	Sham group (mg/g)	Stenosis group (mg/g)	Cyclodextrin-garcinol complex (20 mg/kg) group
Left ventricular to body weight mg/g	1.516 ± 0.023	1.569 ± 0.0305 ns	1.968 ± 0.0324 ###	1.711 ± 0.0312***

[(n = 8), data are mean (SEM)]

ns non significant compared with control group

p<0.001 significant as compared with control and sham group,

*** p<0.001 significant as compared with stenosis group.

Table 7 Effect of cyclodextrin-garcinol complex on myocardial MDA and GSH levels

Enzyme	Control group	Sham group	Stenosis group	Cyclodextrin-garcinol complex (20 mg/kg) group
MDA, nM/mg protein	2.729± 0.1250	3.399 ± 0.2121ns	4.546± 0.1797###	3.458 ± 0.9755**
GSH, µg/mg protein	30.39 ± 1.605	26.09 ± 0.6497ns	18.73 ± 0.7187 ###	25.53 ± 1.700 *

MDA- malondialdehyde, GSH- glutathione.

[(n = 8), data are mean (SEM)]

ns non significant compared with control group

p<0.001 significant as compared with control and sham group,

** p<0.01 significant as compared with stenosis group.

p<0.001 significant as compared with control and sham group.

*p<0.05 significant as compared with stenosis group,



Rat heart without aortic stenosis Sham group H.wt – 804.3 mg, animal wt-284g	Rat heart with aortic stenosis stenosis group H wt- 1219.5 mg, animal wt-289g	Rat heart with aortic stenosis cyclodextrin-garcinol Complex group H wt- 983.6 mg, animal wt-282g
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Figure 1 Effect of Cyclodextrin-garcinol complex (20 mg/kg) on heart weight in rats in experimentally induced cardiac hypertrophy by rat aortic stenosis.

Effect of garcinol complex on MABP (mmHg) in male Wistar rats

The mean arterial blood pressure (MABP) was significantly ($p<0.01$) reduced in the stenosis group compared with normal group or sham). Pretreatment for 18 days and post stenosis treatment for 28 days with garcinol complex (20 mg/kg) resulted in non-significant increase in the MABP as compared with stenosis group in male wistar rats (Table 2).

Effect of cyclodextrin-garcinol complex (20mg/kg) on heart rate of male Wistar rats

Heart rate was significantly ($p<0.001$) higher in the stenosis group compared with the control group and sham group Pretreatment for 18 days and post stenosis treatment for 28 days with cyclodextrin-garcinol complex (20 mg/kg) resulted insignificant ($p<0.05$) reduction in heart rate as compared with stenosis group (Table 3).

Effect of cyclodextrin-garcinol complex on electrocardiograph of rats

The mean (SEM) QT interval was significantly ($p<0.001$) higher in the stenosis group compared with the control group, respectively. The ST interval was also significantly ($p<0.001$) higher in the

stenosis group. Pretreatment for 18 days and post stenosis treatment for 28 days with cyclodextrin-garcinol complex (20 mg/kg) lowered QT and ST intervals significantly ($p<0.05$), compared with the stenosis group (Table 4 and Figure 2).

Effect of cyclodextrin-garcinol complex (20 mg/kg) on heart weight/body weight ratio

Heart to body weight ratio was significantly ($p<0.001$) higher in the stenosis group compared with the control group and Sham group. Pretreatment for 18 days and post stenosis treatment for 28 days with cyclodextrin-garcinol complex (20 mg/kg) resulted in significant ($p<0.001$) reduction in the ratio of heart weight/body weight as compared with stenosis group (Table 5).

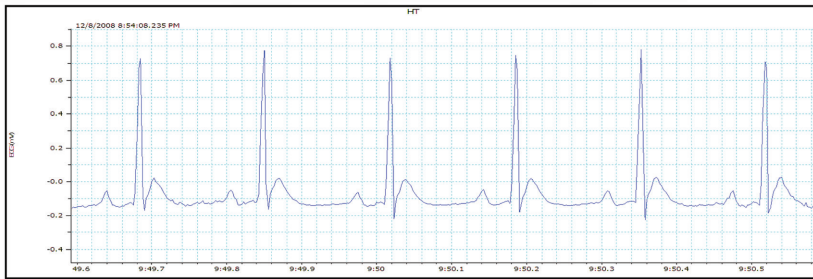
Effect of cyclodextrin-garcinol complex (20mg/kg) on Left ventricular weight/Body weight ratio

Left ventricular to body weight ratio was significantly ($p<0.001$) higher in the stenosis group compared with the control group and sham group Pretreatment for 18 days and post stenosis treatment for 28 days with cyclodextrin-garcinol complex (20 mg/kg) resulted insignificant ($p<0.001$) reduction in the ratio of left ventricular weight/body weight of the rats compared to stenosis group (Table 6).

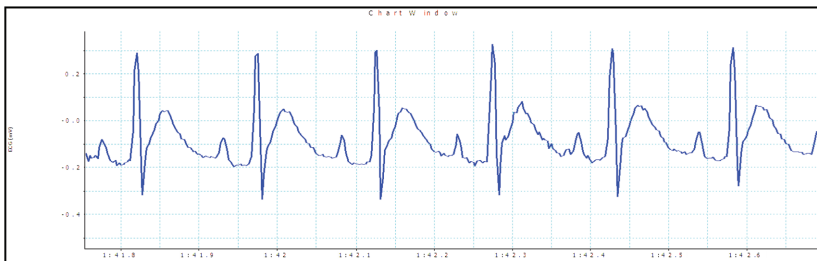
Effect of cyclodextrin-garcinol complex on myocardial MDA levels

Myocardial MDA concentration was significantly ($p<0.001$) higher in the stenosis group compared with the control group and sham group Pretreatment for 18 days and post stenosis treatment for 28 days with cyclodextrin-garcinol complex (20 mg/kg) resulted in lowering MDA concentration significantly ($p<0.01$) in the cyclodextrin-garcinol complex (20 mg/kg) group compared with the stenosis group (Table 7).

1) ECG of rat from Sham group on 44thday shows the normal response



2) ECG of rat from aortic stenosis group on 44thday shows the prolongation in QT and ST segment of the ECG.



3) ECG of rat from cyclodextrin-garcinol group on 44thday shows the reversal of the prolongation in QT and ST segment of the ECG.

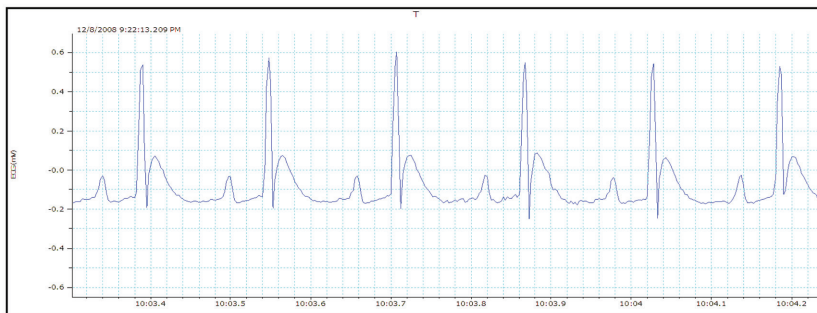


Figure 2 Effect of cyclodextrin-garcinol complex (20 mg/kg) on QT and ST interval of male Wistar rats in experimentally induced cardiac hypertrophy by rat aortic stenosis

Effect of cyclodextrin-garcinol complex on myocardial GSH levels

Myocardial GSH concentration was significantly ($p < 0.001$) lower in the stenosis group compared with the control group. Pretreatment for 18 days and post stenosis treatment for 28 days with cyclodextrin-garcinol complex (20 mg/kg) resulted in significantly ($p < 0.05$) higher myocardial GSH concentration in the cyclodextrin-garcinol complex (20 mg/kg) group compared with stenosis group (Table 7).

DISCUSSION

Haemodynamic, sustained pressure overload will override these adaptive mechanisms, leading to cardiac hypertrophy, decreased contractile function, and the development of heart failure. The

literature showed *in vivo* studies that, the molecular pathways involved in cardiac hypertrophy can be specifically by exposing rats to either biomechanical stress through transaortic constriction of the aorta. Although left ventricular hypertrophy is the most important compensation mechanism in chronic pressure overload, it has frequently been associated with heart failure and death.¹⁹ It occurs because the hypertrophied myocardium presents structural changes that lead to cardiac remodeling, such as a disproportional increase in the myocytes component compared to vascular component.

One of the consequences is an imbalance between oxygen supply and consumption, which causes myocytes necrosis, apoptosis, and abnormal collagen accumulation. Fibrosis also occurs as a direct consequence of activation of the renin-angiotensin system in the myocardium.²⁰ The stimuli for developing cardiac remodeling also include mechanical and biochemical factors which, acting on receptors, ionic channels, and integrin present in the sarcolemma membrane.²¹ trigger cytosolic biochemical signals provoking increased protein synthesis and changes in gene expression.²² All these alterations lead to a worsening of cardiac function, associated with diminished contractility.

In the present investigation the cardiac hypertrophy was confirmed by the heart weight/body weight ratio and left ventricular weight/body weight ratio in rats. In the stenosis group significant increase in both the ratios was observed. Pretreatment for 18 days and post stenosis treatment for 28 days, resulted in the significant reduction in both ratios. Result thus indicated that complex (20mg/kg) possessed anti-hypertrophic effect. Aortic stenosis-sized rats showed decrease in heart rate.²³ These results were consistent with the earlier studies where it was hypothesized that aortic stenosis condition induced reactive oxygen species formation causes disturbance in calcium homeostasis.²⁴ This could lead to a reduction in heart rate because decrease in intracellular calcium reduced excitability of pacemaker cells in the sino atrial node and other cells in the cardiac conduction system.

In recent years, electrical remodeling has emerged as an important pathophysiological mechanism in the development of mechanical dysfunction, pump failure and sudden death. When detected by electrocardiography, cardiac hypertrophy and heart failure are commonly associated with the development of QT and ST interval prolongation or dispersion and life threatening arrhythmias.^{25,26} Clinical studies suggest that 50% of sudden deaths associated with heart failure are attributable to ventricular tachycardia or fibrillation, the other half being coupled to bradyarrhythmias or electromechanical dissociation.²⁷ The electrocardiographic parameter from

this study indicated that aortic stenosis significantly prolonged QT and ST intervals as compared to sham group, while treatment of cyclodextrin-garcinol complex resulted in significant reduction of the QT and ST interval prolongation.

In aortic stenosed rats significant increase in MDA content in cardiac tissues as well as highly significant reduction in cardiac tissue levels of protective biological antioxidant enzymes like GSH were compared to that of the sham group indicating oxidative stress. These results correlate with previous studies which have demonstrated the involvement of oxidative stress and lipid peroxidation in aortic stenosis induced cardiac hypertrophy.²⁸ The treatment with cyclodextrin-garcinol complex (20 mg/kg) significantly increased the GSH levels and decrease the MDA level, that producing a cardioprotective effect. Haemodynamic changes revealed that the aortic stenosis group showed significant increase in MABP, systolic and diastolic BP, as compared with sham group. While treatment of cyclodextrin-garcinol complex (20 mg/kg) showed non-significant decrease in the MABP, systolic blood pressure and diastolic blood pressure.

CONCLUSION

It is concluded that cyclodextrin-garcinol complex (20 mg/kg) protected the haemodynamics of stenosed heart of rats, restoration of normal function of stenosed heart is reflected by minimal (non significant) response change in MABP, Systolic BP, and Diastolic BP. It offered significant protection against cardiotoxicity and cardiac hypertrophy as well as reduced myocardial injury by reduction of lipid peroxidation and preservation of endogenous antioxidants in rat heart.

ACKNOWLEDGEMENTS

The authors acknowledge Dr. S.S. Kadam, Chancellor, Bharati Vidyapeeth Deemed University, Dr. K.R. Mahadik, Principal, Poona College of Pharmacy for keen interest for this work. We thank to Sunil Bhaskaran of Indus Biotech Private Limited, Pune, for financial support and Dr. Manish Sinha for their help in writing of manuscript.

There is no conflict of interest among the authors.

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