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Research Article

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Interaction of Garlic with Carvedilol during Ischemia-Reperfusion Induced Myocardial Damage in Rats

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Abstract: Concurrent administration of herbs with drugs may magnify, oppose or mimic the pharmacological effect of each other. The current research was carried out to determine the cardio protective potential of garlic homogenate (GH) when administered with carvedilol (CAR) on ischemia-reperfusion injury (IRI) in isolated rat heart preparation. Pretreated male albino rats were anesthetized, hearts were excised and mounted on modified Langendorff setup, perfused with physiological salt solution, after initial stabilization, subjected to 15 min global no flow ischemia (IRI) and re-perfused. Prior treatment of animals with CAR, GH-125 and GH-250 showed significant recovery from IRI induced myocardial damage evident from significant decline in LDH and CK-MB in post-ischemic perfusate; this was further validated by incline in the above biomarkers in the heart tissue homogenate (HTH). Further, significant recovery of developed tension and heart rate were found in treated groups when compared to control. Furthermore, GH-250 treated groups with CAR showed significant increase in endogenous antioxidant enzyme like SOD and catalase activities. This enhanced antioxidant activities might be due to possible role of CAR in augmenting the role of GH to either increase synthesis of antioxidants or trigger degeneration of oxidants. However, high dose of GH-500 failed to provide similar results in presence of CAR. In conclusion, simultaneous administration of CAR and moderate dose of GH (250 mg/kg) provided enhanced protection to myocardium from myocardial injury when compared to their individual administration. Therefore, diet containing moderate quantities of garlic could prove beneficial to the heart and administration of garlic with CAR produces additive effect.

Keywords: Garlic; herb-drug interaction; ischemia-reperfusion; isolated heart; carvedilol

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1. INTRODUCTION

Administration of herbs with conventional drugs concurrently may lead to increase or decrease of the pharmacological effects of each other[1]. It is unequivocal fact that several herbs possess therapeutically effective potential in alleviating diseases and illness, however, they lack validation of their efficacy through established therapeutic trials. Additionally, their use in presence of conventional medicament may be sometimes detrimental and very often beneficial for patients. Hence, it is imperative to carryout in-depth and appropriate studies to validate their efficacy in the presence of modern medicines. Literature survey shows an inverse correlation between consumption of garlic and progression of cardiovascular diseases[2]. Various preparations of garlic have been widely reported for prevention and treatment of cardiovascular and other metabolic diseases such as atherosclerosis, arrhythmia, hyperlipidemia, thrombosis, hypertension and diabetes[3]. Garlic in the form of aqueous homogenate is recognized as cardioprotective[4], antioxidant[5], antineoplastic and antimicrobial agent[6]. Garlic is also found to possess significant antiarrhythmic effect in both ventricular and supraventricular arrhythmias[7]. Long term use of garlic is reported for augmenting endogenous antioxidants activities and depletes the oxidants damaging effects by either increasing the synthesis of endogenous antioxidants or decreasing the generation of oxidants like oxygen free radicals[8]. Furthermore, garlic was reported to exert anti-oxidant effect in isoprenaline-induced myocardial infarction in rat[9]. Garlic juice inhibits norepinephrine-induced contractions of rabbit and guinea pig aortic rings. It is also reported to inhibit the force of contraction of isolated rabbit heart in a concentration-dependent manner[10]. Earlier reports on the drug interaction studies of garlic indicate that it produces concentration dependent synergistic effect with calcium channel blockers[11]. Synergistic activity of captopril and hydrochlorothiazide was also found in literatures[12,13]. In our earlier study, we demonstrated the ability of garlic in potentiating cardioprotective action of the beta blocker, propranolol[14] in animal experimental models. Hence, present investigation was undertaken to demonstrate the protective effect of garlic and its interaction with selective beta-blocker, carvedilol (CAR), during IRI damage to myocardium using isolated perfused rat heart preparation.

2. MATERIALS AND METHODS

2.1 Chemicals

All chemicals used in the present research were of analytical grade and purchased from standard companies. Biochemical kits like LDH and CK-MB were procured from Crest Biosystems, Coral Clinical Systems, Goa, India).

2.2 Preparation of Extract

Garlic (*Allium sativum*) bulbs were purchased from a local market. The cloves were peeled, sliced, ground into a paste and then suspended in distilled water. Three different concentrations of the garlic homogenate were prepared corresponding to 125 mg/kg, 250 mg/kg and 500 mg/kg body weight[3]. The garlic homogenate (GH) was administered within 30 min of preparation.

2.3 Experimental Animals

All animal experiments were carried out in accordance and approval of institutional ethical committee of the college of Pharmacy (UM150819). Laboratory bred male Wistar albino rats weighing between 200-250 g were housed at 25° ± 5°C in a well-ventilated animal house under 12:12 hour light and dark cycle. The rats had free access to standard rat chow and water *ad libitum*. There was no significant difference in the body weight of the treated rats when compared with control, either at the beginning or at the end of the study period.

2.4 Experimental Protocol

Male Wistar albino rats used in the present study were divided into following groups: Group I: Normal– vehicle ; Group II : CAR (carvedilol 10 mg/kg)[15]; Group III : GH-125 (GH 125 mg/kg); Group IV GH- 250 (GH 250 mg/kg); Group V: GH-500 (GH 500 mg/kg); Group VI: GH-125 + CAR; Group VII : GH-250 + CAR and Group VIII: GH-500+ CAR. GH treatments was done for 30 days (p.o) whereas CAR treatments (p.o) were done during the last seven days of the GH treatment.

2.5 Experimental Procedure

A modified Langendorff apparatus for the isolated perfused heart was set up as mentioned elsewhere [16]. The heart was isolated from each animal 2 hr after the last dose of the drugs under ketamine (70 mg/kg, i.p) and xylazine (10 mg/kg, i.p) anesthesia. The isolated heart was perfused with Kreb-Henseleit solution gassed with carbogen (95% O_2 and 5% CO_2) at 37 °C with a constant flow rate of 5 ml/min. The composition of K-H solution was (mM) NaCl 118, KCl 4.7, $NaHCO_3$ 25, $NaHPO_4$ 1.0, $MgSO_4.7H_2O$ 0.57, $CaCl_2$ 2.5 and glucose 11. The pH of K-H solution was adjusted to 7.4 to avoid K-H buffer acidosis that may occur after prolonged gassing with carbogen. The heart was allowed to equilibrate for 10 min and then regular recordings were taken for a perfusion period of 15 min. Measurement of contractile force was done using force displacement transducer and recorded on a Student Physiograph (INCO, Mumbai, India). After the initial pre-ischemic perfusion, the animal heart was subjected to 15 min of global no-flow ischemia[17]by blocking the flow of K-H solution and carbogen supply followed by 15 min of reperfusion. The heart rate and developed tension were measured during pre-ischemic and post-ischemic period and % recovery was calculated. Lactate dehydrogenase (LDH) and creatine kinase-MB (CK-MB) activity were measured in the perfusate during pre-ischemic and post-ischemic period. The heart was then homogenized to prepare heart tissue homogenate (HTH) using sucrose (0.25 M) [18] and the activity of LDH, CK-MB, superoxide dismutase (SOD) [19] and catalase[20] was determined. Microscopic slides of myocardium were prepared for studying volume fraction of interstitial space (VFITS) in myocardial tissue after staining with hematoxylin and eosin (H &E) stain by using the equation[21].

$$VFITS = \frac{(100\% \times \text{Area of interstitial space})}{\text{Total tissue area.}}$$

3. STATISTICAL ANALYSIS

Results were expressed as mean SEM. Statistical significance was assessed using One-way Analysis of variance (ANOVA) followed by Tukey multiple comparison tests. $p<0.05$ was considered significant.

4. RESULTS

4.1 Effect on LDH & CK-MB Levels

The activity of LDH and CK-MB enzymes during pre-ischemia were increased significantly in the perfusate of animals pretreated with GH 500 mg/kg and decreased with GH 125 mg/kg and GH 250 mg/kg administered alone or with CAR when compared to control. During post-ischemia, there was a significant decline in enzyme activity with GH 250 mg/kg and in groups treated with different doses of GH along with CAR when compared to control (Table 1). High dose of GH (500 mg/kg) was also found to deplete the activities of these enzymes in heart tissue homogenate when compared to control. However, there were elevation in the activities of the enzymes in the heart tissue homogenate of animals pretreated with GH 250 mg/kg and GH 250 mg/kg with CAR when compared to control (Table 1).

Table-1 Effect on LDH and CK-MB activities in rat heart perfusate

Treatment	LDH Activity (U/L)		CK-MB (U/L)	
	Pre-ischemia	Post- ischemia	Pre-ischemia	Post- ischemia
Control	205.22±7.42	456.75±11.89	22.21±0.49	48.16±1.02
CAR	156.12±4.69***	299.24±7.15***	13.61±0.23***	25.40±0.74***
GH-125	198.99±4.15	333.66±5.68***	18.10±0.65**	36.81±0.35***
GH-250	158.51±3.63***	312.49 ± 3.32***	13.65±0.45***	26.58 ± 0.85***
GH-500	385.81±8.55***	576.70±9.57*	28.06±0.56***	42.48±0.85***
GH-125+ CAR	165.34±1.27***	320.75±9.86***	12.64±0.26***	30.40±0.55***
GH-250+ CAR	151.46±1.35***	265.33±8.13***	10.48±0.19***	20.64±0.24***
GH-500+ CAR	322.33±3.91***	421.16 ± 6.60***	26.69±0.27***	33.93 ± 0.64***

Values are expressed as mean ± SEM for eight rats in each group. Statistical Analysis: One-way ANOVA followed by Tukey multiple comparisons test. ***Significantly different from IRI group P< 0.001. GH- 125, 250 & 500 mg/kg (30 days treatment, p.o) CAR-10 mg/kg (7 days treatment, p.o)

4.2 Effect on SOD and catalase activity

The SOD and catalase activity in the heart tissue homogenate were significantly increased after treatment with GH 250 mg/kg and GH 125 mg/kg alone or along with CAR. However, high dose of GH (500 mg/kg) produced depletion of antioxidant enzymes and administration of CAR failed to reverse the depletion of enzymes produced by high dose of GH (Table 2).

Table-2 Effect on LDH, CK-MB, SOD and Catalase activities in heart tissue homogenate of isolated rat heart preparation

Treatment	LDH (U/L)	CK-MB (U/L)	SOD (Units/mg protein)	Catalase (Units/mg protein)
Control	656.92±35.12	48.76±0.97	1.67±0.00	2.10±0.05
CAR	847.82±24.04***	77.06±0.52***	3.49±0.03***	6.14±0.18***
GH-125	788.42±26.22	61.82±0.44	3.12±0.04***	4.32±0.10***
GH-250	879.32±4.42***	68.83±0.85***	4.31±0.04***	5.69±0.17***
GH-500	565.33±14.39	56.55±1.11*	1.85±0.00***	2.35±0.06
GH-125 + CAR	895.54±8.51*	65.96±1.29***	5.23±0.05***	6.87±0.12***
GH-250 + CAR	1094.82±21.35***	89.25±0.97***	7.76±0.12***	8.65±0.18***
GH-500 + CAR	786.41±12.34	53.77±0.20	2.01±0.01	2.27±0.09

Values are expressed as mean ± SEM for eight rats in each group. Statistical Analysis: One-way ANOVA followed by Tukey multiple comparisons test. ***Significantly different from IRI group P< 0.001. GH- 125, 250 & 500 mg/kg (30 days treatment, p.o) CAR-10 mg/kg (7 days treatment, p.o)

SOD Units: One enzymatic unit of SOD is the amount in the form of proteins present in 100 µl of 10 % heart tissue required to inhibit the reduction of 24 mM NBT by 50%. *Catalase Units:* One international unit of catalase is the amount, which catalyzes the decomposition of 1 mM hydrogen peroxide per minute at 37°C.

4.3 Developed Tension and Heart rate

Pretreatment of CAR significantly imparts the recovery of ischemic heart in terms of developed tension and heart rate. There was also a significant recovery from global ischemia in groups treated with GH 250 mg/kg alone or with CAR (table 3).

4.4 Percentage total tissue space and histological scores

There was a significant increase in VFITS in heart tissue of animals treated with high dose of GH (500 mg/kg). The pathological parameters were reduced in GH 250 mg/kg treated groups either alone or with CAR when compared to control (table 3).

Table-3 Effect on percentage recovery of developed tension & heart rate and volume fraction of interstitial space (VFITS)

Treatment	Percentage Recovery		VFITS[1]
	Developed Tension	Heart Rate	
Control	24.27±4.17	35.72±2.23	38.03±1.71
CAR	45.98±6.70***	44.66±1.63*	27.79±1.63***
GH-125	52.06±8.87	47.29±2.16*	27.23±0.69***
GH-250	65.02±9.23***	65.04±3.14***	21.24±0.93***
GH-500	23.68±6.22	31.04±1.71	36.49±0.54
GH-125 + CAR	56.44±5.94*	66.46±1.37***	22.39±0.60***
GH-250 + CAR	81.44±1.25***	85.42±1.32***	21.44±1.30***
GH-500 + CAR	47.72±4.78*	45.88±1.92*	30.49±0.50*

Values are expressed as mean ± SEM for eight rats in each group. Statistical Analysis: One-way ANOVA followed by Tukey multiple comparisons test. ***Significantly different from IRI group P< 0.001. GH- 125, 250 & 500 mg/kg (30 days treatment, p.o) CAR -10 mg/kg (7 days treatment, p.o).

[1]VFITS = 100X Area of Interstitial space/Total tissue

5. DISCUSSION

This research was done to explore the role of different doses of garlic homogenate (GH) in presence and absence of carvedilol (CAR). The outcome of the research demonstrates that the high dose of GH (500 mg/kg) aggravates the ischemia reperfusion injury (IRI) as exhibited by increase in the levels of biological markers of myocardial infarction, LDH and CK-MB activities in the perfusate and a decrease in the activities of the antioxidant enzymes; SOD and catalase along with a decrease in the activities of biological markers in the heart tissue homogenate. The moderate dose of GH (250 mg/kg) and the low dose of GH (125 mg/kg) reduced the IRI as shown by changes in the activities of biological markers and antioxidant enzymes. Further, administration of moderate dose of GH (250 mg/kg) and low dose of GH (125 mg/kg) along with carvedilol, a known cardioprotective agent, produced synergistic effect. GH was administered at three different doses, which were reported to be safe (125 mg/kg, 250 mg/kg & 500 mg/kg)[3]. Earlier studies on the effect of GH on the cardiovascular system suggests that GH by virtue of the presence of its active organosulfur metabolites, S-allylcysteine (SAC) and S-allylmercaptocys-teine (SAMC), has potent antioxidant activity[22-24]. Allicin (allyl 2-propenethiosulfinate) was thought to be the principle bioactive compound responsible for the cardioprotective effect. However, recent studies suggest that allicin is an unstable and transient compound with oxidant activity[25] and it is virtually undetectable in blood circulation after garlic ingestion and it decomposes to form the active organosulfur compounds[26]. Since, the metabolites of garlic are effective, it was administered orally instead of introducing it into the perfusion fluid. The diagnostic marker enzymes of myocardial damage, estimated in this study were CK-MB and LDH[27]. Hearse[28] had reported that, of all the macromolecules that leak from the damages tissue, enzymes because of their tissue specificity and catalytic activity are the best markers of tissue damage. In the present study there was a decrease in the activities of these marker enzymes in heart tissue homogenate and increase in the activities in the perfusate in control groups due to IRI damage. The release of cellular enzymes reflects a non-specific alteration in the plasma membrane integrity, which results in the leakage of these enzymes in the perfusate. This accounts for the decreased activities of CK-MB and LDH in heart tissue homogenate and increased activity in perfusate. Oral pretreatment with GH (250 mg/kg) and incorporation of CAR with GH treatment restored the activities of these enzymes to near normal in heart tissue homogenate and perfusate. The reactive oxygen species like superoxide and hydrogen peroxide are produced in enormous amounts during IRI that contribute to myocardial tissue injury associated with decreased activities of endogenous antioxidants such as superoxide dismutase (SOD) and catalase[29]. Pretreatment of animals with GH (125 mg/kg & 250 mg/kg) alone or along with CAR produced remarkable elevation in SOD and catalase level when compared to control indicating cardioprotective effect. However, pretreatment of GH (500 mg/kg) produced a significant decrease in the antioxidant enzyme levels and CAR failed to reverse the GH (500 mg/kg) induced aggravation of myocardial damage. The result clearly demonstrates that GH in moderate and low doses reduces oxidative damage and in high doses aggravates oxidative damage. The increase in functional parameters like developed tension and heart rate at the end of 15 minutes reperfusion is an indication of good recovery from global ischemia[14]. CAR is known to reduce myocardial oxygen requirement and improve the stress tolerance in patients with MI[30]. This CAR tolerating ability was demonstrated in this study, which was evident from good recovery in functional parameters in CAR incorporated groups. Maximum recovery was seen in groups with GH (250 mg/kg) alone or along with CAR and good recovery was seen even at low dose GH (125 mg/kg) alone or along with CAR. GH (500 mg/kg) showed toxic effect, as indicated by poor recovery from IRI. The findings of the present study shows that garlic in low or moderate doses possess cardioprotective effect and in high doses aggravate IRI. Concurrent administration of garlic with CAR produces additive effect. However, further studies should be carried out to demonstrate the exact mechanism of the interaction of garlic with CAR and to determine whether doses of CAR could be reduced if administered along with garlic.

6. CONCLUSION

In conclusion, pretreatment of GH (250 mg/kg) offers protection from myocardial injury in IRI myocardial damage. Incorporation of CAR augments myocardial protection. However, high dose of GH was found to increase the oxidative stress that could aggravate the pathological

complications. Therefore, diet containing moderate doses of garlic could prove beneficial to the heart and administration of garlic with CAR produces additive effect.

7. AUTHORS CONTRIBUTION STATEMENT

Dr. Asdaq was responsible for conceptualization, designing, analyzing and interpreting the results as well as reviewing the manuscript, whereas, Dr. Yahya carried out the research study, evaluated the results and drafted the manuscript.

8. ACKNOWLEDGMENTS

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9. CONFLICT OF INTEREST

Conflict of interest declared none.

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