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Protective Effect of Medicinal Garlic Against Isoprenaline Induced Myocardial Infarction in Rats

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Abstract: The present study was undertaken to evaluate the cardioprotective effect of medicinal garlic (MG) against isoprenaline (ISO) induced myocardial damage in rats. Sprague dawley male rats were orally given MG 250 and 500 mg kg^{-1} once daily for 3 weeks and losartan (LTN, 30 mg kg^{-1}) for one week orally in their respective groups. Myocardial damage was induced by subcutaneous administration of isoprenaline (100 mg kg^{-1}) for two consecutive days. A change in biomarkers and antioxidants levels reflects the influence of prophylactic treatment with MG. The lactate dehydrogenase (LDH) and creatine phosphokinase-MB (CK-MB) activities were fallen in serum and elevated in heart tissue of animals treated with low and high doses of MG as well as LTN compared to ISO control. Further, high and low doses of MG caused significant elevation in superoxide dismutase and catalase activities and reduction in thiobarbituric acid reactive species levels compared to ISO control. Hence it is concluded that *medicinal garlic* possesses potential to ameliorate the myocardial damage induced by isoprenaline in rats.

Key words: Antioxidants, cardioprotection, isoprenaline, medicinal garlic, myocardial infraction

INTRODUCTION

Natural drugs are gaining greater acceptance from the public and the medical profession due to greater advances in understanding the mechanism of action by which herbs can positively influence health and quality (Nivethetha *et al*., 2009). Cardiovascular diseases (CVDs) such as hypertension and myocardial infarction (MI) are the most important cause of mortality in developing countries due to changing lifestyles (Rajadurai and Prince, 2007). MI is the acute condition of myocardial necrosis that occurs as a result of imbalance between coronary blood supply and myocardial demands (Upaganlawar and Balaraman, 2010), it increases the generation of reactive oxygen species in ischemic tissue, bringing about oxidative damage of membrane lipids, proteins, carbohydrates and DNA and brings changes in the mechanical, electrical, structural and biochemical properties of the heart (Wang *et al*., 2009). Although modern drugs are effective in preventing the cardiovascular disorders, their use is often limited because of their side effects and adverse reactions (Thippeswamy *et al*., 2009).

Epidemiologic studies show an inverse correlation between herbal therapies such as Garlic (*Liliaceae*) and progression of cardiovascular diseases. Garlic has acquired a special position in the folklore of many cultures as a formidable prophylactic and therapeutic medicinal agent (Rahman and Lowe, 2006). The preparations of garlic have been widely recognized as agents for prevention and treatment of cardiovascular and other metabolic diseases such as atherosclerosis, arrhythmia, hyperlipidemia (Khan *et al*., 2008), thrombosis, hypertension and diabetes (Banerjee and Maulik, 2002; Karim *et al*., 2011). Further, dietary garlic preparations were reported for wound healing (Jalali *et al*., 2008) and immunomodulatory (Jafari *et al*., 2009) activities. Furthermore, garlic was also reported to possess cardioprotective, antioxidant, antineoplastic and antimicrobial properties (Rahman and Lowe, 2006) and it has significant antiarrhythmic effect in both ventricular and supraventricular arrhythmias (Rietz *et al*., 1993). Moreover, garlic also exerts anti-oxidant effect during isoprenaline induced myocardial infarction in rat (Asdaq and Inamdar, 2010a; Anoush *et al*., 2009). One of the varieties of garlic is Medicinal Garlic (MG), usually found in Himalayas and china. It has milder and slightly perfumed flovour when compared to regular garlic. In spite of its traditional medicinal claims like prophylactic for bird flu (www.prettygarlic.com/products/singleclove), rarely explored for their role as cardioprotective agent.

ISO is a synthetic adrenergic agonist that causes severe stress in the myocardium resulting in infarct like necrosis of the heart muscle. The rat model of ISO induced

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myocardial necrosis serves as well accepted standardized model to evaluate several cardiac dysfunctions and to study the efficacy of various natural and synthetic cardioprotective agents (Upaganlawar *et al*., 2011).

Till now there is no scientific evidence of cardioprotective activity of medicinal garlic during MI. Hence, the current research was undertaken to demonstrate the protective effect of different doses of MG during isoprenaline mediated cardiac dysfunction in rats.

MATERIALS AND METHODS

The research work was carried out from 12/08/2010 to 16/11/2010 in Krupanidhi College of Pharmacy, Bangalore, India as part of post graduate research programme.

Chemicals: Isoproterenol was purchased from Sigma-aldrich, U.S.A. LDH and CKMB Kits for enzyme estimation was purchased from Crest Biosystems, Coral clinical systems, Goa, India. All chemicals used in the present study were of analytical grade.

Experimental animals: Adult male rats of Sprague dawley strain weighing 175-250 g were housed at 25°±5°C in a well-ventilated animal house under 12:12 h light dark cycle. Institutional Animal Ethics Committee approved the experimental protocol. They were fed with commercial pelleted rat chow and given water *ad libitum*. The animals were maintained under standard conditions in an animal house as per the guidelines of Committee for the Purpose of Control and Supervision on Experiments on Animals (CPCSEA).

Plant extract: Medicinal garlic bulbs were purchased from the local vegetable market and the bulbs were peeled, sliced, ground into a paste and suspended in distilled water. Two different concentrations of the medicinal garlic homogenate (MGH) were prepared, 0.1 and 0.2 g mL^{-1}, corresponding to 250 and 500 mg kg^{-1} body weight of animal (Banerjee *et al*., 2002). MGH was administered within 30 min of preparation.

Phytochemical estimations of the MGH: The medicinal garlic homogenate were subjected to qualitative analysis for various phytoconstituents like alkaloids, carbohydrates, glycosides, phytosterols, saponins, tannins, proteins, amino acids and Flavonoids as per (Kokate, 1991; Finar, 1993; Mukherjee, 2002).

Acute toxicity study: The dose selection of MGH was based on acute toxicity studies, carried out according to OPPTS (Office of Prevention, Pesticide and Toxic Substance) following the limit test procedure (http://www.epa.gov/opptsfrs . 2009 Nov 15.). The animals were fasted over night prior to the studies. Mice were divided into two groups of three each. Test dose of 2 g kg^{-1} body weight and 5 g kg^{-1} body weight were given orally to either group of mice. Mice were observed for 72 h for mortality. 1/10th and 1/20th of the maximum safe dose corresponding to 500 and 250 mg kg^{-1} body weight were selected as high and low doses respectively.

Experimental protocol: The animals were divided into five groups of six each. Group I and Group II received saline for three weeks and termed as normal control and ISO control respectively; Group III and Group IV were administered MG 250 and 500 mg kg^{-1} orally respectively for three weeks. Group V was treated with standard Losartan (LTN) 30 mg kg^{-1} (Kaneko *et al*., 1996), p.o. for one week after two week of saline treatment.

Experimental procedure: At the end of treatment as mentioned above, animals of all groups except group I were administered ISO (100 mg kg^{-1} s.c) for 2 consecutive days (De Sanchez *et al*., 1997). Blood was withdrawn from retro orbital vein 48 h after the first dose of ISO under anesthesia. Serum was separated by centrifugation and biological markers lactate dehydrogenase (LDH) and creatine phosphokinase-MB (CK-MB) were estimated. The heart was isolated from each animal under ketamine (70 mg kg^{-1}, i.p) and xylazine (10 mg kg^{-1}, i.p.) anesthesia and homogenized to prepare heart tissue homogenate (HTH) using sucrose (0.25 M) (Buerke *et al*., 1998). The activity of LDH, CK-MB, superoxide dismutase (SOD) (Erich and Heupel, 1976), catalase (Link, 1988) and thiobarbituric acid reactive species (TBARS) (Walter *et al*., 2004; Sedlakova *et al*., 2009) activities was determined in heart tissue homogenate (HTH).

Statistical analysis: Results are expressed as Mean±SEM. Statistical significance was assessed using analysis of variance (ANOVA) followed by bonferroni multiple comparison tests. $p<0.05$ was considered significant (Sadeghnejad *et al*., 2009).

RESULTS

Preliminary Phytochemical investigation: The preliminary phytochemical investigation of the MGH showed the presence of alkaloids, carbohydrates, flavonoids, cardiac glycosides, proteins, saponnins, tannins and terpenoids.

Effect on LDH and CK-MB activities: The biological activities of endogenous enzymes like LDH and CK-MB

Table 1: Effect of MG and LTN on LDH and CKMB level in serum and heart tissue homogenate against Isoprenaline induced acute myocardial damage

	LDH activity		CKMB activity	
Treatment	Serum (U/lt)	HTH (U g^{-1})	Serum (U/lt)	HTH (U g^{-1})
Normal control	25.56±15.6	8.78±1.0	144.30±40.4	47.00±4.6
ISO control	1339.66±108.0^{c}	1.00±0.3^{c}	1130.66±69.8^{c}	5.27±2.3^{c}
MGLD	13.80±5.8^{3}	1.42±0.3^{c}	720.90±69.7^{c3}	14.40±4.7^{c3}
MGHD	55.98±45.8^{3}	4.30±0.6^{a}	158.30±20.5^{3}	21.30±1.4^{c3}
LTN	241.50±103.6^{3}	5.60±0.8^{1}	19.40±0.6^{3}	31.20±0.6^{c3}

All values are Mean±SEM, n = 6, $^{a}p<0.05$, $^{b}p<0.01$, $^{c}p<0.001$ when compared normal control; $^{1}p<0.05$, $^{2}p<0.01$, $^{3}p<0.001$ compared to ISO control. MGLD: Medical garlic low dose, MGHD: Medical garlic high dose, LTN: Losartan

Table 2: Effects on SOD, Catalase and TBARS in heart tissue homogenate against Isoprenaline induced acute myocardial damage

Treatment	SOD (Units/mg protein)	Catalase (Units/mg protein)	TBARS(ng mg^{-1})
Normal control	4.50±0.26	14.32±0.63	18.60±1.15
ISO control	0.26±0.14^{c}	7.20±0.32^{c}	31.30±5.90^{a}
MGLD	1.62±0.35^{a}	13.70±0.85^{2}	9.50±5.60^{3}
MGHD	3.95±0.45^{2}	12.20±0.24^{1}	18.80±2.20^{3}
LTN	5.00±1.51^{3}	14.14±0.26^{2}	3.60±4.60^{b3}

All values are Mean±SEM, n = 6, $^{a}p<0.05$,^{b} $p<0.01$, $^{c}p<0.001$ when compared to nnormal control; $^{1}p<0.05$, $^{2}p<0.01$, $^{3}p<0.001$ compared to ISO control. MGLD: Medical garlic low dose, MGHD: Medicinal garlic high dose, LTN: Losartan

were evaluated in serum as well as in heart tissue homogenate (HTH).The LDH activity of MGLD and MGHD were compared with normal and ISO control. No significant change in the serum LDH activity was observed with MGLD, MGHD and LTN compared with normal control, whereas, significant ($p<0.001$) fall in serum LDH activity was seen with MGLD, MGHD and LTN compared with ISO control. In the HTH, a significant ($p<0.001$) fall in the LDH activity was found in the ISO control group and MGLD treated group where as brief ($p<0.05$) fall is observed in MGHD group compared to normal control (NC). A significant ($p<0.05$) increase in the LDH levels were observed in groups treated with LTN but MGHD and MGLD treatment failed to show the similar effect compared to ISO control (Table 1).

CKMB levels in the serum were significantly increased ($p<0.001$) in ISO control and MGLD group but decreased in LTN treated group compared to NC where as MGHD treatment showing almost the same CKMB level as NC. The groups treated with MGLD, MGHD and LTN were showed a significant ($p<0.001$) decrease in the serum CKMB level compared to ISO control. In HTH all the treated groups were showing significant ($p<0.001$) decline in the CKMB level compared to NC. Where as a significant ($p<0.001$) rise in the CKMB activity was observed in all pretreated groups compared to ISO control.

Effect on SOD, Catalase and TBARS: The SOD and Catalase activity were estimated in the heart tissue homogenate. SOD activities were reduced significantly ($p<0.001$) and ($p<0.01$) in the ISO control and MGLD treated group compared to NC, where as the groups treated with MGHD($p<0.01$) and LTN ($p<0.001$) were showing significant incline in the SOD activities compared to ISO control but MGLD treatment causes no significant changes.

ISO control group was showing a significant ($p<0.001$) decline in the catalase level compared to NC where as groups treated with MGLD and LTN were showing significant ($p<0.01$) rise in catalase activity but MGHD group was showing a brief rise compared to ISO control.

TBARS levels increased significantly ($p<0.001$) upon ISO administration and significant ($p<0.01$) decline was observed in LTN treated group compared to NC where as MGHD group was showing no changes in TBARS activity compared to NC. All the pretreated groups were showing a significant (p0.001) fall in thiobarbituric acid reactive species (TBARS) activity compared to ISO control (Table 2).

DISCUSSION

The research envisaged was carried out to determine the effect of high and low dose of MG and its comparison with standard drug LTN using ISO induced myocardial damage model in rat. The results of the present study demonstrate that both high dose of MG (500 mg kg^{-1}) and low doses of MG (250 mg kg^{-1}) dose dependently protect the myocardium against ISO damage in rat heart.

Catecholamines at low concentrations are considered to be beneficial in regulating heart function by exerting a positive inotropic effect. Catecholamines administration at high doses or excess release of it from the endogenous stores may deplete the energy reserve of cardiomycytes and thus may result in biochemical and structural changes which are responsible for the development of irreversible damage (Upaganlawar *et al*., 2011). By administering a sympathetic activator such as isoprenaline myocardial

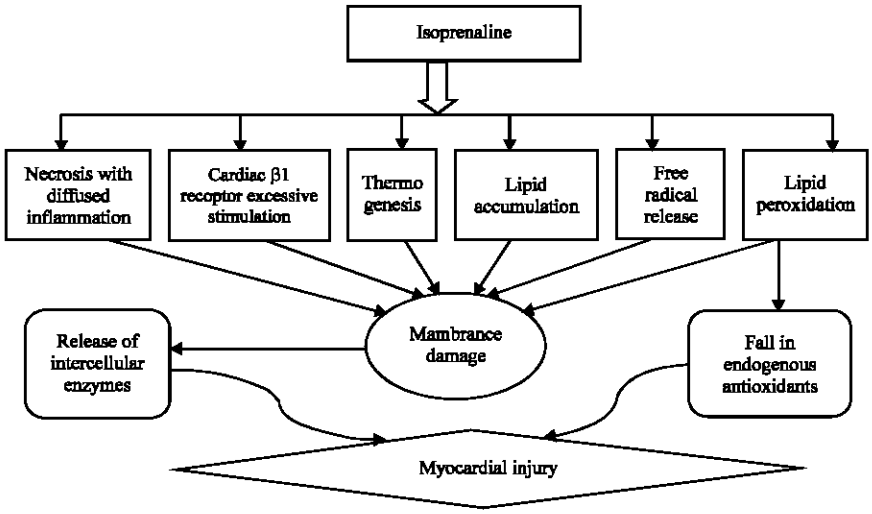

Fig. 1: Mechanism of induction of myocardial injury by ISO

ischemia and infarction can be caused by increased inotropic activity (Fig 1) (Farvin *et al*., 2010; Pinelli *et al*., 2004). Animals were pretreated with varying doses of MG and LTN, which is a competitive and selective Angiotensin II receptor antagonist (Bumpus *et al*., 1991).

Garlic (Allium sativum, family: Lilliaceae) is one of the herbs that are widely believed to hold promise as therapeutically effective medicament for CVDs (Rahman and Lowe, 2006). Garlic possesses potent cardio protective activity as a result of its active organ sulfur metabolites; S-allylcysteine (SAC) and Sallylmercaptocysteine (SAMC), which have potent antioxidant activity (Asdaq *et al*., 2010). Fresh garlic homogenate is known to possess the highest concentration of active constituent, so in the present study medicinal garlic homogenate preparation were used to study its effects on ISO induced myocardial damage.

The diagnostic marker enzymes of myocardial infarction (MI) are CK-MB and LDH, presence of these biomarkers in heart tissue homogenate (HTH) is indicative of myocardial integrity and their release in serum signifies myocardial injury (Asdaq and Inamdar, 2010b). Damage to the membrane induced by the ISO causes release of enzymes in the serum and deficiency of enzymes in HTH reflects the damage to the myocardium. Pretreatment with MGLD and MGHD decreased the ISO induced elevation of serum CKMB and LDH level may be by protecting the cell membrane from the destructive effect of free radicals and also by inhibiting the oxidative modification of LDL as well by balancing lipid profile (Rahman and Lowe, 2006).Both doses of MG causes rise in CK-MB activity in HTH but no significant change was observed in the activity of LDH in HTH.

During MI, reactive oxygen species like superoxide, hydrogen peroxide and TBARS are produced in enormous amount that contribute to myocardial tissue injury. ISO induced myocardial damage is associated with decreased endogenous antioxidants such as superoxide dismutase (SOD) and catalase in HTH which are structurally and functionally impaired by free radicals resulting in damage to myocardium. Inclination in endogenous antioxidant activities in HTH is indication for structural integrity and protection to the myocardium (Asdaq and Sowmya, 2010). Pretreatment of animals with low and high dose of MG (250 and 500 mg kg^{-1}) produced remarkable elevation in SOD and catalase activities when compared to ISO control indicating cardioprotective effect of garlic. *In vitro* studies revealed that garlic is able to capture the radical's dose dependently. The free-radical scavenger action of garlic can probably be explained by its germanium, glutathione, selenium and zinc content. The latter three are key components of the antioxidant enzymes, superoxide dismutase and glutathione peroxidase (Abdullah *et al*., 1988). Allicin the principle bioactive compound in garlic extract also showed potent free radical scavenging effect which may contribute to antioxidant activity of garlic (Sukandar *et al*., 2010). However, low dose of MG does not show the similar rise in SOD when compared to high dose indicating the dose dependent effect of MG. MGLD failed to show the beneficial effect probably because low dose failed to reduce the oxidative stress mediated through superoxide.

In our study, there was substantial fall in ISO induced TBARS levels in MG pretreated groups Aqueous garlic extract prevented the hydroxyl radical-induced formation of malondialdehyde (MDA), a lipid peroxidation product in a concentration-dependent manner (Banerjee *et al*.,

2003). The free radical scavenging action of fresh garlic homogenate is attributed to SAC, SAMC and other organosulfur compounds which are readily formed upon its administration (Asdaq *et al*., 2008).

Angiotensin II has been implicated as a factor in the pathogenesis of hypertension, MI, sudden death and end-stage heart disease (Nickenig *et al*., 2006). Losartan is the first orally available angiotensin receptor antagonist with out agonist properties (Kiran *et al*., 2010). Angiotensin receptor blocker LTN displace angiotensin II from the angiotensin I receptor and lowers the blood pressure by antagonizing angiotensin II-induced vasoconstriction, aldosterone release, catecholamine release, arginine vasopressin release, water intake and hypertrophic response (Burnier, 2001).

CONCLUSION

From the present results it may be concluded that both the doses of MG (250 and 500 mg kg^{-1}) possess cardioprotective efficacy when given prophylactically against ISO induced myocardial necrosis in rats. Further studies should be carried out to elucidate the active constituents responsible for the said effect with extensive evaluations of histological and ultra structural changes.

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