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Isoproterenol Induced Myocardial Infarction: Protective Role of Natural Products

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ABSTRACT

Cardiovascular Diseases (CVD) remain one of the leading causes of deaths despite several advancements in the medical interventions. Among these, the ischemic heart diseases, acute myocardial infarction (AMI) in particular, is one of the most alarming values. AMI, which arises out of a lot risk-factors working in concert, gives rise to a lot of unfavorable biochemical outcomes. The end-result of which is the ultimate morbidity of the patient or even death. The synthetic drugs that constitute the current pharmacological armamentarium are themselves effective in managing the condition but not without setbacks. These hunches have accelerated the need for natural products, which may be used as dietary supplement to prevent the development of an acute myocardial infarction. The isoproterenol-induced myocardial infarction in rodents offers a relevant model to study the effect of natural products. The model is simple in execution and the biochemical, histological and electrocardiographic changes closely mimic that seen in case of an AMI. The model has so far been widely used by many researchers to study the effect of drugs in AMI. Natural products, which include crude herbals, extracts, herbomineral formulations, polyherbal formulations, etc., have been used for the treatment of ischemic heart diseases in traditional systems of medicine. A range of natural products have been tried for activity against acute myocardial infarction with considerable success. The colossal collections of chemicals present in the natural products possess antioxidant, anti-inflammatory and other properties that prove useful in ameliorating the pathophysiology of acute myocardial infarction. Besides, these natural products may also augment the conventional treatment and offer better management of the condition with fewer side effects.

Key words: Myocardial infarction, isoproterenol, natural products, antioxidants

INTRODUCTION

Healthy human life is always cardinal for human being starting from his birth to the end of life. The numbers of diseases, minor to major, play a key role in disturbing the healthy human life. Along with the modernization as well as sophistication in the life, human health directly or indirectly faces challenge from several diseases resulting sometime in survival and sometimes in surrender to diseases. Cardiovascular Disease (CVD), remain the principal cause of death in both developed and developing countries. It may present as a typical `heart attack', as sudden death, or it may be detected at an advanced stage and be described as a silent infarct. CVD includes high

blood pressure, coronary heart disease, congestive heart failure, stroke and accounts for 17,000,000 deaths per annum worldwide (Reeve *et al.*, 2005). It is predicted that CVD will be the most important cause of mortality in India by 2020. In India, the numbers of patients being hospitalized for heart attack have increased over the past 35 years and male patients have shown a more striking rate of increase (Krishnaswami, 1998).

The contributing factors for the growing burden of CVDs are increase in prevalence of cardiovascular risk factors, especially hypertension, dyslipidemia, diabetes, overweight or obesity, physical inactivity and the use of tobacco. It is an area where major health gains can be made through the implementation of primary care interventions and basic public health measures targeting diet, lifestyles and environment (Saradha and Jhan, 2009). According to World Health Organization data, 16.7 million people die each year owing to heart attacks. The figure is one-third of the number of deaths worldwide. By 2020-30 more deaths will be caused by heart attacks and India will lead in the number of such deaths in the world (Gupta and Gupta, 1996).

Myocardial infarction, commonly known as heart attack is a disease that occurs when the blood supply to a part of the heart is interrupted, causing death of heart tissue. It means necrosis of a region of myocardium caused by an interruption in the supply of blood to the heart usually as a result of occlusion of a coronary artery also called as cardiac infarction (De Bono and Boon, 1992). AMI is usually characterized by varying degree of chest pain, sweating, weakness, vomiting, arrhythmia and sometimes causes loss of consciousness and even sudden death. Several factors increasing the risk of developing atherosclerosis and heart attack include elevated level of low density lipoproteins, triglycerides, reduced high density lipoproteins levels, increased blood cholesterol, high blood pressure, use of tobacco, diabetes mellitus, male gender, family history of coronary heart disease and change in life style (Smith *et al.*, 2004).

Isoproterenol induced Myocardial Infarction (MI): 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 cardiomyocytes and thus may result in biochemical and structural changes which are responsible for the development of irreversible damage.

Isoproterenol (L-β-(3, 4-dihydroxyphenyl)-α-isopropylaminoethanol hydrochloride), a sympathomimetic β-adrenergic receptor agonist, causes severe stress to the myocardium resulting in an infarct like necrosis of heart muscle (Sushma *et al*, 1989). The rat model of isoproterenol-(ISO) induced myocardial necrosis serves as a well accepted standardized model to evaluate several cardiac dysfunctions (Wexler, 1978) and to study the efficacy of various natural and synthetic cardioprotective agents (Rathore *et al.*, 1998). ISO induced myocardial infarction is widely used experimental model for several reasons. The model is characterized by an extraordinary technical simplicity, an excellent reproducibility as well as an acceptable low mortality (Grimm *et al.*, 1998). Myocardial infarction induced by ISO has been reported to show many metabolic and morphologic aberrations in the heart tissue of the experimental animals similar to those observed in human myocardial infarction (Nirmala and Puvanakrishnan, 1996). ISO induced necrosis is maximal in the subendocardial region of the left ventrical and in the interventricular septum. Continuous infusion of ISO in rats elicits typical cardiac gene expression similar to that observed in cardiac hypertrophy caused by pressure overload (Boluyt *et al.*, 1995).

Mechanisms of ISO induced myocardial infarction: Several mechanisms for the cardiotoxic effects of high levels of ISO have been suggested. These mechanisms include: (1) functional

hypoxia and ischemia, (2) coronary insufficiency, (3) alterations in metabolism, (4) decreased level of high-energy phosphate stores, (5) intracellular Ca^{2+} overload, (6) changes in electrolyte contents and (7) oxidative stress. Although these changes represent individual pathological states, they are known to affect each other and thus are interpreted as complex entities.

Oxidative stress is, more probably, one of the main mechanisms through which catecholamines exert their toxic effects. Spontaneous oxidation of catecholamines results in the formation of catecholamine-o-quinones, which generate aminochromes through cyclization. Adrenochrome (which results from the cyclization of epinephrine-o-quinone) can be oxidized to several other compounds such as adrenolutin, 5, 6-dihydroxy- 1-methylindole (DHMI) or adrenochrome-adrenolutin dimmer. All these redox reactions generate free radicals. Consequently, catecholamine-o-quinones, aminochromes and the radical species resulting from the oxidation of catecholamines are thought to be involved in catecholamine-related toxicity (Dhalla *et al*., 1992). The aminochrome undergo further oxidation similarly to that of adrenochrome which isomerizes to adrenolutin this oxidative reactions produce free radicals (Rupp *et al*., 1994).

The oxidized products have the ability to interact with sulphydryl groups of various proteins and also lead to production of superoxide anions and subsequently hydrogen peroxide. This results in changes in microsomal permeability, mitochondrial Ca^{2+} uptake, decrease in ATP production and the formation of highly reactive hydroxyl radicals which causes protein, lipid and DNA damage (Takeo *et al*., 1980; Bindoli *et al*., 1992; Dhalla *et al*., 2010). ISO produces a number of biochemical and electrophysiological alterations which precede the histological changes in the heart. The primary disturbances of ISO induced myocardial infarction has been reported to enhance adenyl cyclase activity, resulting in increased cAMP formation, which in turn would lead to the higher lipid accumulation in the myocardium (Subash *et al*., 1978). Several early events, such as ultrastructural changes, histological, biochemical, electrolyte and membrane changes, have been shown to occur within 48 h after the injection of isoproterenol. Glycogen depletion and fat deposition have been reported. Histological changes induced by excessive amounts of isoproterenol include degeneration and necrosis of myocardial fibres, accumulation of inflammatory cells, interstitial edema, lipid droplets and endocardial hemorrhage (Lehr, 1972).

Biochemical alterations in ISO-induced cardiomyopathy represent a complex pattern of changes in cardiac marker enzymes, lipid profile, lipid metabolizing enzymes, enzymatic and non-enzymatic antioxidants levels, glycoproteins levels, decrease in ATP store and changes in electrolyte levels in the blood as well as in the myocardial tissue (Fleckenstein *et al*., 1974; Lehr, 1972). Changes including those in sarcolemma, sarcoplasmic reticulum and mitochondria, are mainly mediated by oxidative stress, which is known to result in alterations of enzyme activity and transport systems and cause disturbances in cellular homeostasis (Takeo *et al*., 1980). Lipolysis is also one of the important determinants of ISO induced myocardial injury. Study also provides evidence that chronic **β**-AR stimulation markedly shows iNOS up-regulation, CRP release and nitrative stress and that iNOS-mediated nitrative stress functions as a main interface linking chronic **β** -AR activation and myocardial cell apoptosis (Hu *et al*., 2006).

Natural products-A promising approach: Herbal medicine is increasingly gaining greater acceptance from the public and medical profession due to greater advances in the understanding of the mechanisms by which herbs positively influence health and quality of life (Berman, 2000). Leading the way in the new understanding is the discovery of herbs as potent free radical

scavenger, antioxidants. Natural antioxidants, especially phenolics and flavonoids, are safe and also bioactive. Therefore, in current years, substantial attention has been directed towards credentials of plants with antioxidant ability that may be used for human expenditure. The task of free radicals in many disease conditions has been well customary. Several biochemical reactions in our body generate reactive oxygen species and these are capable of damaging critical bio-molecules (Pinn, 2000). In recent years one of the areas, which attracted a great deal of attention, is antioxidant in the control of degenerative diseases in which oxidative stress has been implicated.

In recent decades, substantial interest has been focused on antioxidant therapeutic strategies for cardiovascular disease. It is imperative to emphasize effective preventive strategies for the cardiovascular disease epidemic. In years past, vegetable, fruit and antioxidant-rich Mediterranean diets have been highlighted, since a number of epidemiological studies have shown a strong inverse relationship between cardiovascular disease and vegetable and fruit rich diets (Weisburger, 2002). The World Health Organization recommends 500 g of fresh fruits and vegetables per day (NRC, 1989). Antioxidant micronutrients have attracted special attention, particularly vitamin E, vitamin C, **β**-carotene and other carotenoids, such as lutin, zeaxanthin and lycopene, which have the greatest singlet oxygen-quenching properties (Halliwell and Gutteridge, 1989). More recently, there has been increased interest in putative dietary antioxidants like bioflavonoids, flavonals like quercetin or special phenol derivatives in red wine and oxygen-sensitive B complexes, which are involved in the metabolism of homocysteine and L-arginine (Hirvonen *et al*., 2001; Hinderliter and Caughey, 2003). Following is the list of natural products and polyherbal formulations which has been proved to prevent isoproterenol induced myocardial infarction (Table 1).

Table 1: Plant and plant products in the management of ISO induced myocardial infarction

Drugs	Dose	Parameters protected	References
Salvianolic acid A from dried root of *Salvia miltiorrhiza* Bunge (Family: Lamiaceae)	0.3,1 and 3 mg kg^{-1}, i.v. for 8 days	Improved cardiac marker enzymes (LDH, CK-MB, AST), antioxidant enzymes (MDA, SOD, CAT, GPX), Mitochondrial respiratory dysfunction, Left ventricular function, ECG and histopathological alteration	Wang *et al.* (2009)
Gallic acid an endogenous plant phenol	15 mg kg^{-1} for 10 days	Protects cardiac marker enzymes(LDH, CK-MB, AST, ALT), antioxidant enzymes (MDA, SOD, CAT,GPX,GST), troponin-T and histopathological alteration Lysosomal enzymes: The activities of β-glucuronidase, β-N-acetylglucosaminidase, β-galactosidase, cathepsin-B and D were significantly ($p<0.05$) protected in the serum and heart of rats	Priscilla and Prince (2009), Prince *et al.* (2009)
Mangiferin from *Mangifera indica* Linn. Leaves (Family: Anacardiaceae)	10 mg/100 g for 28 days 100 mg kg^{-1} b.w. i.p. for 28 days	Prevents Serum cardiac marker enzymes (LDH, CK-MB, AST, ALT), enzymatic and non-enzymatic antioxidants (Lipid peroxidation, SOD, CAT, GPX, GST, Vitamin E and C), infarct area, Mitochondria: Prevented mitochondrial alterations, oxidation with energy metabolism and restored the TCA cycle enzyme activities (isocitrate dehydrogenase , α-ketoglutarate dehydrogenase, succinate dehydrogenase, malate dehydrogenase, NADH dehydrogenase and cytochrome-C-oxidase . Mitochondrial NADH oxidation and Oxygen consumption. ADP/O ratio and respiratory control ratio (RCR), ATP content. It also prevents ultrastructure (TEM) of the heart tissue mitochondria specimen	Prabhu *et al.* (2006a, b)

Table 1: Continued

Drugs	Dose	Parameters protected	References
Epigallocatechin gallate (EGCG) from the leaves of *Camellia sinensis* (Green tea)		ECG protects Membrane bound phosphatase (Na^+/K^+ATPase, Mg^{+2}ATPase and Ca^{+2}ATPase), serum marker enzymes, lipid profile, enzymatic and non-enzymatic antioxidants, histopathological and ultrastructure changes Mitochondria: it protects mitochondrial thiobarbituric acid reactive substances, lipid hydroperoxides, superoxide dismutase, catalase, glutathione peroxidase, glutathione-*S*-transferase, glutathione reductase and reduced glutathione. Also, it significantly prevents activities of tricarboxylic acid cycle enzymes such as isocitrate, succinate, malate and α-ketoglutarate dehydrogenases and respiratory chain marker enzymes such as NADH-dehydrogenase and cytochrome-*c*-oxidase Lysosomal enzymes: the activities of activities of lysosomal enzymes (β-glucuronidase, β-N-acetylglucosaminidase, β-galactosidase, cathepsin-B and cathepsin-D) were also maintained towards normal	Devika and Prince (2008a)
Hydro alcoholic extracts of *Tribulus terrestris* Linn. (Fam. Zygophyllaceae)		It protects Biochemical, hemodynamic and ultrastructure changes	Ojha *et al.* (2008)
Ethanolic extracts of *Curcumis trigonus* Roxb. (Fam. Cucurbiateace)	75 and 150 mg kg^{-1}, p.o. for 14 days	Serum marker enzymes, electrocardiographic changes (ST elevation, QRS complex, P wave, RR interval and heart rate) and histopathological changes were well protected after administration of *Curcumis trigonus* extract	Thippeswamy *et al.* (2009)
Ethanol extract of stem-bark and stem-wood of *Premna serratifolia* Lin., (Fam: Verbenaceae)	100 mg/100 g, i.p. for 28 days	Maintained ECG changes in rat heart, serum protein, serum Albumin/Globulin (A/G) ratio, heart tissue proteins, glycogen, nucleic acids and blood glucose	Rajendran and Basha (2008)
Tender coconut water (Fam. Arecaceae)	4 mL/100 g, for 45 days	Lipid profile, serum marker enzymes and histopathological histopathological studies were improved	Anurag and Rajamohan (2003)
Ethanol extract of *Picrorrhiza kurroa* Royle ex Benth. (Fam. Scrophulariacae) rhizomes and roots	80 mg kg^{-1}, p.o. for 15 days	Serum and tissue lipid profile (TC, TG, HDL, PL, FFA)	Kumar *et al.* (2001)
Hydroalcoholic leaf extract of *Ocimum sanctum* (Family: Lamiaceae)	25, 50, 75, 100, 200 and 400 mg kg^{-1}	Serum marker enzymes, TTC staining, histopathological study, antioxidant enzymes (SOD, CAT, LPO, GSH, GPX and GST)	Sharma *et al.* (2001)
Quercetin a bioflavonoid	10 mg kg^{-1}, p.o. for 14 days	Significantly protects Serum and heart lipid profile (TC, TG, HDL, PL, FFA), the activity of plasma and liver 3-hydroxy-3-methylglutaryl-coenzyme-A reductase and the activity of plasma and liver lecithin cholesterol acyl transferase. significantly reduced the levels of hexose, hexosamine, fucose and sialic acid in the serum and heart. Quercetin significant decrease plasma thiobarbituric acid reactive substances and lipid hydroperoxides	Punithavathi and Prince (2009)

Table 1: Continued

Drugs	Dose	Parameters protected	References
Echinocystic acid (EA), a pentacyclic triterpene, isolated and identified from the fruits of *Gleditsia sinensis* Lam (Family: Fabaceae)	30 and 15 mg kg^{-1}, i.v.	EA prevents the ST-segment changes and Bcl-2 mRNA level	Wu *et al.* (2010)
Aqueous extracts of *Embelia ribes*. Burm fruit (Family: Myrsinaceae)	100 mg kg^{-1}, p.o. for 40 days	Heart rate, systolic blood pressure, endogenous antioxidants levels, histopathological changes, serum marker enzymes were improved	Bhandari *et al.* (2008)
Aqueous extract of *Desmodium gangeticum* (L)DC Fam.(Fabaceae)	3 mL/100 g p.o. for 30 days	Serum and tissue marker enzymes (AST,ALT,LDH,CK), lipid profile, lipid metabolizing enzymes, endogenous antioxidants	Kurian *et al.* (2005)
Aqueous leaf extract of *Azadirachta indica* A. Juss. (Fam.Meliaceae)	250, 500, 1000 mg kg^{-1}, p.o. for 30 days	Improved mean arterial blood pressure (MAP), systolic arterial blood pressure (SAP), diastolic arterial blood pressure (DAP) and heart rate (HR). maintained cardiac marker enzymes, lipid profile (TC,TG,FFA.PL.HDL) and histopathological changes	Peer *et al.* (2007)
Alcoholic extract of the latex obtained from *Calotropis procera*. Fam. (Asclepidaceae)	100 to 400 mg kg^{-1} for 30 days	Improved levels of CK-MB, LDH, SGOT and SGPT in serum and lipid peroxide and reduced glutathione content in heart homogenates. Microscopical examination (histopathology) of heart tissue showed good protection	Ahmed *et al.* (2004)
Curcumin from *Curcuma longa* (Family: Zingiberaceae)	200 mg kg^{-1} b. wt. for 2 days	Lysosomal hydrolases: activities of P-glucuronidase, P-N-acetylglucosaminidase, cathepsin B, cathepsin D and acid phosphatase in serum and heart were protected.	Nirmala and Rengarajulu (1996)
		It also maintain myocardial marker enzymes, lipid peroxidation	Nirmala *et al.* (1999)
	100, 200 and 400 mg kg^{-1} or 15 days	and activities of endogenous antioxidant enzymes.also maintain ultrastructure Histopathological studies of the infarcted rat heart also showed a decreased degree of necrosis after curcumin treatment. Restored the cardiac function as evident by improved contractile functions, decreased left ventricular end-diastolic pressure, restored arterial pressures and heart rate. In addition, it also increase the activities of SOD, CAT, GSH and decreased production of thiobarbituric acid reactive substances and leakage of cardiac necroenzyme Ck-MB isoenzyme and LDH. It also shows stabilization of cytoskeleton structure which in turn is attributed to Hsp27 expression. Curcumin treatment decrease the degree of degradation of the existing collagen matrix and collagen synthesis	Ansari *et al.* (2007) Tanwar *et al.* (2010a, b)
Garlic (*Allium sativum*, (Fam.liliaceae) oil	75 mg kg^{-1} for 60 days	Prevented serum iron content, plasma iron binding capacity, ceruloplasmin activity and glutathione (GSH) level, lipid peroxides levels, SOD, CAT,GPX and GST	Saravanan and Prakash (2004)
Green tea	100 mg kg^{-1}, 30 days	Prevented heart weight, body weight, serum marker enzymes (AST, ALP, ALT, LDH and CK-MB), lipid peroxidation, endogenous antioxidants (SOD, CAT, GPX and GST.) and membrane bound ATPases (Na^+/K^+ATPase, Mg^{+2}ATPase and Ca^{+2}ATPase), serum and heart lipid profile (TC, TG, HDL, PL, FFA,VLDL and LDL), lipid metabolizing enzymes (LCAT, LPL and CES), histopathological alteration	Upaganlawar *et al.* (2009) Upaganlawar and Balaraman (2009)

Table 1: Continued

Drugs	Dose	Parameters protected	References
Squalene, an isoprenoid molecule present in shark liver oil	2% level for a period of 45 days	Levels of diagnostic marker enzymes (ALT, AST, LDH and CPK) in plasma, lipid peroxides, GSH and the activities of GPx, GST,CAT, SOD) were maintained	Farvin *et al.* (2004)
Fish oil	0.05 mL day^{-1} for 45 day	Protects serum and heart tissue lipid profile, lipoprotein changes and myocardial membrane phospholipid fatty acid composition	Padma *et al.* (2006)
Alcoholic extract of *Terminalia chebula* (TCE) Fam: Combretaceae	50 mg/100 g for 30 days	Cardioprotective effect: Marker enzymes (AST, ALT, LDH and CK), lipid peroxidation and histopathological alteration were maintained Lysosomal enzyme: prevented lysosomal enzyme activities from the serum, heart and lysosomal fractions.TTC staining Mitochondria: level of lactate, activities of tricarboxylic acid cycle (TCA) enzymes, mitochondrial respiration, levels of adenosine triphosphate (ATP) and oxidative phosphorylation and electron microscopy (TEM) were maintained	Suchalatha and Devi (2005) Suchalatha and Shyamala (2004) Suchalatha *et al.* (2007)
Alcoholic extract of *Crataegus oxycantha* (family, Rosaceae)	0.5 mL/100 g for 30 days	Prevents the defective oxidative phosphorylation and diminished energy production mitochondrial Kreb's cycle enzymes, lipid peroxidative damage, antioxidant status and ultrastructural changes	Jayalakshmi and Devaraj (2004) Jayalakshmi *et al.* (2006)
Naringin from grape fruit	10, 20 and 40 mg kg^{-1} for 56 days	Prevented cardiac troponin T (cTnT), CK-MB, electrophoretic separation of lactate dehydrogenase (LDH)-isoenzymes, electrocardiographic (ECG)-patterns. heart weight, blood glucose, total proteins, albumin/globulin (A/G) ratio, serum uric acid, serum iron, plasma iron binding capacity and membrane bound enzymes (Na^+/K^+ ATPase, Ca^{2+} ATPase and Mg^{2+} ATPase) and glycoproteins such as hexose, hexosamine, fucose and sialic acid. SOD,CAT,GPX,GST in the heart and the levels of GSH, vitamin C and vitamin E in plasma and heart and ceruloplasmin in plasm lysosomal hydrolases: β-glucuronidase, β-*N*-acetyl glucosaminidase, β_-galactosidase, cathepsin-B and cathepsin-D)	Rajadurai and Prince (2006, 2007a, b)
Hydroalcoholic extracts of leaves of *Sida cordifolia* L. (Family: Malvaceae)	100 and 500 mg kg^{-1} for 30 days	Endogenous biomarkers (LDH and CK-MB) and antioxidants (SOD and catalase) were maintained in serum and heart tissue homogenate	Kubavat and Asdaq (2009)
S-allylcysteine from Garlic	50, 100 and 150 mg kg^{-1} of 45 days	Mitochondria: The activities of heart mitochondrial enzymes (isocitrate dehydrogenase, succinate dehydrogenase, malate dehydrogenase and α-ketoglutarate dehydrogenase) and respiratory chain enzymes (NADH dehydrogenase and cytochrome C oxidase). The activities of lysosomal enzymes (β-glucuronidase, β-N-acetyl glucosaminidase, β-galactosidase, cathepsin-D and acid phosphatase) were prevented. It also maintained ECG changes cardiac marker enzymes, lipids, lipoproteins, enzymes associated with lipid metabolism, lipid peroxides, antioxidants, lysosomal enzymes and ATPases	Padmanabhan and Prince (2007) Sangeetha and Darlin (2006a, b, 2007)

Table 1: Continued

Drugs	Dose	Parameters protected	References
Aqueous extract of *Oxalis corniculata* (Family: Oxalidaceae)	30 days	Cardiac injury marker enzymes (CPK, LDH), serum lipids. It also maintained the activity of lipogenic enzyme, glucose-6-phosphate dehydrogenase, activities of antioxidant enzymes (CAT,SOD, MDA and conjugated dienes), vitamin C, protein sulfhydryl groups and reduced glutathione (GSH) and Histopathological alteration were prevented.	Abhilash *et al.* (2010)
Phytosomes of *Ginkgo biloba* (Family: Ginkgoaceae)	100 and 200 mg kg^{-1} for 21 days	Levels of marker enzymes (AST, LDH and CPK) in serum and heart, antioxidant parameters (GSH, SOD, CAT, GPx and GR and MDA in heart homogenate were significantly protected	Panda and Naik (2008)
Betaine,widely distributed in plants	250 mg kg^{-1} for 30 days	Prevented Marker enzymes (ALT, AST, LDH,CPK) homocystein plasma, mitochondrial TCA cycle enzymes,lipid peroxidation and endogenous antioxidants activities	Ganesan *et al.* (2007)
Rutin a bioflavonoid	40 and 80 mg kg^{-1} for 42 days	Activities of serum cardiac marker enzymes (CK, LDH, AST and ALT), thiobarbituricacid reactive substances and lipid hydroperoxides, enzymatic (SOD,CAT,GPX) and non-enzymic (GSH and vitamin C). lipids, lipoproteins and ATPases (Na^+/K^+, ATPase,Mg^{2+} ATPase, Ca^{2+}ATPase)	Karthick and Prince (2006)
Crocin from *crocus sativus* L. (family: Iridaceae)	5, 10 and 20 mg kg^{-1} for 21	Crocin treatment significantly modulated hemodynamic (systolic, diastolic and mean arterial blood pressures. Isignificant decrease in maximum positive and negative rate of developed left ventricular pressure (+/-LVdp/ dt (max)) and an increase in left ventricular end-diastolic pressure (LVEDP) and antioxidant (SOD, CAT,GSH and MDA) levels and histopathological and ultrastructural changes.	Goyal *et al.* (2010)
Moringa oleifera leaf extract (Family: Moringaceae)	200 mg kg^{-1} for 1 month	Chronic treatment with M. oleifera demonstrated mitigating effects on hemodynamic (HR, (+) LV dP/dt, (-) LV dP/dt and LVEDP). Modulates biochemical enzymes (SOD, CAT, GPX, LDH and CK-MB) but failed to demonstrate any significant effect on reduced glutathione level. Moringa treatment significantly prevented the rise in lipid peroxidation and histopathological alterations in myocardial tissue.	Nandave *et al.* (2009)
Hydroalcoholic extract of *Commiphora mukul* (family: Burseraceae)		*C. mukul* preserved the structural integrity of myocardium. Reduced leakage of myocyte enzyme lactate dehydrogenase and maintenance of structural integrity of myocardium along with favorable modulation of cardiac function and improved cardiac performance	Ojha *et al.* (2008)
Hydro-alcoholic extract of *Withania somnifera* (Family: Solanaceae)	25, 50 and 100 mg kg^{-1} for four week	Pretreatment protects myocardial antioxidant status and significant restoration of most of the altered haemodynamic parameters	Mohanty *et al.* (2004)
Lagenaria siceraria (LS) fruit powder and fruit juice (Family: Cucurbitaceae)	500 mg kg^{-1}, p.o. for 51 days	Fruit powder was found to be less effective in maintaining isoproterenol induced myocardial infarction. However fruit juice of LS prevented marker enzymes, lipid peroxidation and ST elevation	Mali and Bodhankar (2010) Upaganlawar and Balaraman (2009)
Arjunolic acid, a new triterpene and a potent principle from the bark of *Terminalia arjuna* (Family: Combretaceae)	15 mg kg^{-1}, i.p.	Arjunolic acid at an effective dosage of 15 mg kg^{-1} effectively maintain serum enzyme levels and ECG changes towards normalcy. It also prevent the levels of SOD,CAT, GPX, ceruloplasmin, α-tocopherol, GSH, ascorbic acid, LPO, MPO and histopathological alterations	Sumitra *et al.* (2001)

Table 1: Continued

Drugs	Dose	Parameters protected	References
Ethanolic extract of *Momordica cymbalaria* (Family: Cucurbitaceae)	250 and 500 mg kg^{-1}	Prevented the elevation of serum marker enzymes (LDH, CK-MB, AST, ALT, ALP) and alterations in the oxidative stress markers like (LPO, GSH, CAT and SOD) in rats	Raju *et al.* (2009)
Cichorium intybus (Family: Asteraceae)		Protects lactate dehydrogenase activity in ageing myocardium during isoproteranol induced myocardial infarction	Nayeemunnisa and Amarnath (2007)
Sida rhomboidea. Roxb (SR) extract (Family-Malvaceae)	400 mg kg^{-1}, p.o. for 30	Pre-treatment with SR extract showed significant decrease in heart weight, plasma lipid profile, plasma marker enzymes of cardiac damage, cardiac lipid peroxidation, Ca^{+2} ATPase and significant increase in plasma HDL, cardiac endogenous enzymatic and non-enzymatic antioxidants, Na^{+}–K^{+} ATPase and Mg^{+2} ATPase.	Thounaojam *et al.* (2010)
Caffeic acid		Mitochondria *Lysosomal dysfunctioning*	
Aqueous extract of *Oxalis corniculata* leaves Family: Oxalidaceae	250 mg kg^{-1}, p.o for 30 days	Prevented changes in marker enzymes (SGOT,SGPT,CPK and LDH), lipid profile, Glucose-6-phosphatase,lipid peroxidation, conjugated dines and endogenous antioxidant status	Abhilash *et al.* (2010) Sunitha and Raghu (2010)
Punica granatum L. (Punicaceae). Fruit juice extract and butanolic fraction	100 and 300 mg kg^{-1}, p.o. for 21 days	Treatment for 21 days signiicantly prevented the altered ECG pattern, cardiac marker enzymes(LDH and CK), heart rate, SOD, CAT, histopathological changes and infarct size. Further the treatment also shows protective effects on vascular activity	Mohan *et al.* (2010)
Dried stigams of *Crocus sativus* L. (Saffron)	100 mg kg^{-1}, p.o.	Shows protective effects by preventing altered MDA level and GPX and SOD activities. It also prevents troponin I level along with histopathological changes in heart tissue	Joukar *et al.* (2010)
Lycopene	10 mg kg^{-1}, p.o.	Lycopene alone and in combination with vitamin E synergistically prevents the altered levels of cardiac marker enzymes (CK-MB, LDH, SGOT, SGPR), endogenous antioxidant enzymes (SOD, CAT, GSH, GPX, GST), membrane bound phosphates (Na^{+}–K^{+} ATPase and Mg^{+2} ATPase, Ca^{+2} ATPase), LDH isoenzyme pattern and histopathological alteration in wistar rats	Upaganlawar *et al.* (2010)

Polyherbal and herbomineral formulations: Several scientific reports have showed that polyherbal and herbomineral formulations are also useful in the prevention of isoproterenol induced myocardial infarction in rats. Arogh a polyherbal formulation is a cocktail of nine herbs including *Nelumbo nucifera, Rosa damasana, Terminalia chebula, Zingeber officinalis, Eclipta alba, Hibiscus rosasinensis, Hemidesmus indicus, Querus infectoria* and *Glycrrhiza glabra.* Arogh treatment in isoproterenol induced myocardial infarction showed significant alteration in the activities of endogenous antioxidant enzymes and certain biochemical parameters (Suchalatha and Shyamala, 2004). DHC-1, a herbal formulation derived from the popular plants *Bacopa monniera, Emblica officinalis, Glycyrrhiza glabra, Mangifera indica and Syzygium aromaticum* was studied for its antioxidant activity. A significant reduction in the serum markers of heart and the extent of lipid peroxidation with a concomitant increase in the enzymatic (SOD and CAT) and non-enzymatic antioxidants (reduced glutathione) were observed in DHC-1 pretreated animals compared with the isoproterenol treated animals (Bafna and Balaraman, 2005). The

cardioprotective effect of Marutham, a polyherbal formulation on serum and heart tissue lipids, serum lipoproteins and heart membrane bound enzymes in isoproterenol induced myocardial infarction was studied in Wistar rats. Pretreatment with Marutham at different doses of 30, 60 and 90 mg kg^{-1} to isoproterenol treated rats significantly prevented the altered lipid profile and membrane bound enzymes to near normal status (Prince *et al.*, 2008). The effect of AO-8, a herbal formulation was investigated at dose levels of 250, 500 and 750 mg kg^{-1} p.o. in isoproterenol-induced myocardial infarction. Treatment with AO-8 for 15 days at a dose of 500 and 750 mg kg^{-1} offered marked protection in isoproterenol induced myocardial infarction by maintaining cardiac marker enzymes and the activities of endogenous antioxidants (Mitra *et al.*, 1999).

A herbomineral formulation containing extract derived from *Mucuna pruriens*, *Withania sominfera*, *Argyreia speciosa*, *Ceutella asiatica*, *Tribulus terrestris*, *Asparagus racemosus*, *Piper lengum*, *Anacyclus pyrethrus*, *Nux vomica* and *Tinospora cordifolia* and *Shring bhasma* was studied in isoproterenol model of myocardial infarction. It was found that Activit reduced the serum levels of creatine, urea, blood urea nitrogen and uric acid. It was further found that administration of Activit increased the level of superoxide dismutase, catalase, reduced glutathione and membrane bound enzymes and decreased significantly the level of lipid peroxidation in heart (Bafna and Balaraman, 2005). Similarly, Abana, a polyherbal formulation containing a mixture of *Terminalia arjuna*, *Withania somnifera*, *Terminalia chebula*, *Phyllanthus emblica*, *Nardostachys jatamansi*, *Tinosporia cordifolia*, *Glycyrrhiza glabra*, *Zingiber officinale* and *Nepeta hindostana* was evaluated for activity against isoprenaline induced myocardial infarction in rats. The authors found that in the animals treated with Abana the cardiac marker enzymes were found to be normal. The enzymes were estimated in the serum as well as heart homogenate. They have attributed the positive effect to various compounds present in the formulation, which have previously demonstrated antioxidant activity (Shashikumar and Shyamaladevi, 2000).

CONCLUSIONS

In context of the aforementioned studies, it is apparent that any given natural product extends its protective effect through assorted mechanisms. Several natural products, taken as fruits, extracts, crude formulations or in any other form have been reported to have a protective role against isoprenaline induced myocardial infarction. It has been found that most of these products act through one or the other of their antioxidant potentials. Free radical scavenging and stabilization of ROS is their chief action. They may show antioxidant activity by themselves or may even the augment the myocardial antioxidants. Besides, the diverse cluster of beneficial chemical compounds present in the natural products is the main reason for these compounds being active against isoprenaline induced myocardial infarction. The flavonoids, polyphenols, alkaloids, etc. are a few classes of compounds which lend their antioxidative capability to the natural products. The herbal preparations prevent the products of lipid peroxidation from damaging the myocardium. The cardiac marker enzymes and antioxidant enzyme levels are maintained. Likewise, apart from maintaining the biochemical parameters towards normal, the natural products also wield their protective role in maintaining the normal cardiac histopathology. The natural products, as reviewed, have been found to normalize the electrocardiographic changes occurring after isoprenaline intoxication. Several authors have reported that ST segment elevation, prolongation of QT interval, reduction of P-wave and R-R interval, etc. have returned to conventional values

after treatment with natural products. To add a feather to the cap, natural products have also been able to reduce or even prevent the inflammation that arises due to myocardial necrosis that arises after isoprenaline intoxication. The herbal products prevent degeneration of myofibrillar tissue and also leucocyte infiltration. These herbals also prevent myocardial hypoxia and even fibroblastic hyperplasia. These effects may be ascribed to some chemical constituents that are able to normalize the calcium influx following induction of infarction. The natural products not only reduce the infarct size but prevent DNA damage due to necrosis also. A few authors have shown that smearing of DNA during gel electrophoresis decreased when the DNAs were isolated from hearts of animals treated with natural products. Some natural products may also prevent excessive NO production, which may injure the myocardium.

Still several problems remain inherent with the natural products. Requirement of a high dose, characterization of chemical constituents and the difficulty to extrapolate the findings to clinical research are the prime bottlenecks that prevent natural products from being brought into the market. Nevertheless, much remains to be done and the studies mentioned above need to be supplemented with molecular and clinical studies. These natural products hold great potential amongst them as a first-line therapy for myocardial infarction provided the bottlenecks are met with.

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ABBREVIATIONS

AST: aspartate aminotransferase, LDH: lactate dehydrogenase, CPK: creatine phosphokinase, CK-MB: creatin kinase-MB,LPO: lipid peroxides, MDA: Malondialdehyde, GSH: reduced glutathione, GPx: glutathione peroxidase, GST: glutathione-*S*-transferase, CAT: catalase ,SOD: superoxide dismutase, TC: total cholesterol, TG: triglyceride, PL: phospholipids, FFA: free fatty acids, LDL: low density lipoproteins, VLDL: very low density lipoproteins HDL: high density lipoproteins, LCAT: Lecithin Cholesterol acyl transferase, LPL: Lipoprotein lipase, CES: Cholesterol ester synthetase, TTC: triphenyl tetrazolium chloride, ECG: electrocardiograph, ALP: alkaline phosphatase, SGOT: serum glutamate oxaloacetate transaminase, SGPT: serum glutamate pyruvate transaminase, ROS: reactive oxygen species, NO: nitric oxide, ALT: alanine transaminase, TCA: tricarboxylic acid, NADH: Nicotinamide adenine dinucleotides, CRP:C reactive protein, iNOS: inducible nitric oxide synthatase, βAR: beta adrenergic receptor, ISO: isoproterenol, TEM: Transmission electron microscopy.

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