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Protective Effect of Mangiferin an active Phytochemical and Cardiotonic from *Mangifera Indica* Linn on Isoproterenol induced myocardial infarcted Rats- An Electrocardiographic, Electrophoretic and Biochemical Evidences

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ABSTRACT - The protective role of mangiferin an active phyto-chemical extracted from *Mangifera indica* Linn was tested on isoproterenol (ISPH) administered experimental myocardial infarction in rats and was confirmed by ECG study in rat heart, electrophoresis analysis of serum protein, serum A/G ratio, biochemical studies such as heart tissue protein, glycogen, nucleic acids and blood glucose. Subcutaneous injection of ISPH (20 mg / 100g body weight in 0.1 ml saline) to rats for 2 consecutive days caused myocardial damage and was confirmed by elevation of ST segments in rat heart ECG pattern, reduction in serum electrophoresis protein bands and serum A/G ratio, increase in heart tissue protein and nucleic acids, increase in blood glucose and decrease in heart tissue glycogen. Pretreatment with mangiferin (10 mg / 100 g body weight in 0.2 ml of dimethyl sulphoxide) for 28 days through intraperitonial injection in ISPH administered rats protected the above-mentioned parameters from alterations as compared with myocardial infarcted rats. This confirmed the myocardial protective role of mangiferin on ISPH-induced myocardial infarction in rats.

KEYWORDS - ECG, Isoproterenol, Mangiferin, Myocardial infarction, Electrophoresis, Nucleic acids, Glycogen, Glucose, Proteins, A/G ratio

INTRODUCTION

In the practice of modern medicine, it is recognized that high blood pressure, atherosclerosis, easy blood clotting, and heart enlargement can lead to catastrophic events such as heart attack and stroke, which are the principal causes of death in persons over 40 years of age. As a result, millions of adults are taking one or more of the drugs to lower blood pressure, lower cholesterol, and/or to reduce platelet aggregation. Presently, the medical fraternity and the patients have increasingly started using plants to overcome various illnesses and sufferings mainly to obviate the profound side effects encountered in usage of modern drugs (1,2). They safely interact with free radicals and terminate the chain reaction before vital molecules are damaged (3). The prophylactic and therapeutic effect of many plant foods and extracts in reducing cardiovascular disease has been reviewed (4).

Recently, pharmacological functions of mangiferin an active phytochemical and natural polyphenolic antioxidant and glucosyl xanthone derivative present in different plants such as in the bark and leaves of *Mangifera Indica* Linn (5) in altering the oxidative mechanisms have received much attention (6). Mangiferin has cardiotonic (7,8) diuretic properties and strong antioxidant activity in the biological peroxidation system and their capacities might result from their action of scavenging free radicals e.g. OH^- and O_2^- associated with initiation of lipid peroxidation rather than terminating radical chain reaction in lipid peroxidation (9).

Several methods have been used to study the beneficial effects of many drugs and cardiac function (10). Administration of isoproterenol is known to produce electrocardiography and enzymatic changes suggestive of myocardial ischemia in experimental animals (11) and the present study is in continuation of our previous report.

The current study is aimed at providing further mechanistic insights into the mangiferin's cardio-protective effects in maintaining the myocardial integrity on ISPH induced cardiac damage with reference to ECG analysis, electrophoretic separation of serum protein, A/G ratio and biochemical studies on blood glucose, heart tissue protein, nucleic acids and glycogen.

MATERIALS AND METHODS

Mangiferin

The mangiferin powder extracted from the leaves of *Manifera indica* Linn (12) was compared with reference mangiferin. The purity of the compound was confirmed by HPLC method as described by Geodakyan *et al* (13), which closely matched to its specified purity of isolated mangiferin. Dimethyl disulphoxide (DMSO) was used as a dissolving solvent (14).

Animals

Adult male albino rats of Wistar strain weighing 150-200 g were obtained from Tamil Nadu Veterinary and Animal Sciences University, Chennai. They were fed with standard diet and water *ad libitum* and housed under standard environmental conditions. All experiments were carried out according to the guidelines of Institutional Animal Ethics Committee (IAEC No: 01/046/04).

Chemicals

Isoproterenol, Dimethyl sulphoxide, standard biochemicals such as Glucose, Glycogen, Deoxy ribonucleic acid, Ribonucleic acid, Bovine serum albumin, and synthetic mangiferin were purchased from Sigma Chemical Co, St. Louis, USA. All other chemicals were obtained from Loba Chemie Co., Bombay, India.

Toxicity studies

Keeping 5% as a standard dilution and concentration ratio, mangiferin was dissolved in appropriate volume of DMSO and administered ip to *Wistar* strain rats at the doses of 100, 250, 500 and 1000 mg / kg bodyweight / day. 5% DMSO was given to another group of animals, which served as control. The dosing schedule was used once a day for 60 days for chronic toxicity study. Rats were weighed daily for the observation of any change in morphological behavior.

Experimental design

Animals were grouped into following 4 of each six animals.

Group 1: Control rats received DMSO (0.2 ml/ 100 g body weight) as a vehicle, ip, for 28 days. Group1 rats were referred as positive control rats.

Group 2: Rats were administered with ISPH (20 mg/100 g body weight suspended in 0.1 ml of 0.9% saline), sc, once daily at an interval of 24 hr (12) for 2 days. Group 2 rats were referred as ISPH myocardial infarcted rats.

Group 3: Rats treated with mangiferin alone (10 mg/100 g body weight, ip suspended in 0.2 ml of DMSO) for 28 days (13). Group 3 rats were referred as drug control rats.

Group 4: Rats pretreated with mangiferin (10 mg/100 g body weight suspended in 0.2 ml of DMSO) given ip for 28 days and ISPH was administered as in Group 2. Group 4 rats were referred as mangiferin pretreated rats.

To find out the interference of DMSO a separate group of animals (Group 5) fed with only standard diet and water *ad libitum* monitored for the same period of duration was compared with Group 1 positive control rats and no significant change was observed in serum marker enzyme parameters between these groups of rats and hence Group 5 rats was dropped from the experimental design. Similarly to find out the interference of DMSO with ISPH, an another separate group of rats (Group 6) administered with both DMSO and ISPH for the same period of duration was compared with Group 2 ISPH myocardial infarcted rats and no significant change was observed in serum marker enzyme parameters and hence Group 6 rats were dropped from experimental design. From this experiment it could be possible to find out the role of DMSO as a dissolving agent and not as an inducer either for mangiferin or for ISPH. As well as mangiferin is soluble only in DMSO and ISPH is easily soluble in 0.9% saline, DMSO was not provided to Group 2 rats.

After the 30 days of experimental period, the Groups of animals depicted in experimental design were anaesthetized with pentobarbital sodium (35 mg / kg, ip). Blood was drawn from the external jugular vein of the rat and used for the estimation of blood glucose. From remaining blood, serum was separated by centrifugation after allowing the blood to clot for few minutes. The heart tissues were dissected out immediately and washed in ice-cold saline. 100 mg of wet tissue was weighed accurately and homogenized in 5 ml of 0.1 M Tris-HCl buffer (pH 7.4) in ice-cold condition. The homogenate was centrifuged at 2500 g and the clear supernatant solution was taken for the assay of tissue protein, nucleic acids and glycogen. The collected serum was applied for electrophoresis separation of serum protein and estimation of A/G ratio. ECG on rats was performed under sodium thiopentone anesthesia (30 mg/kg ip) and alligator clips were placed in the front left arm, right arm and back left arm of the rat. The standard record ECG at paper speed of 25 mm / second sensitivity of 4 mV on a physiograph (Physio Control, USA) was measured. The nucleic acids such as DNA and RNA in tissue homogenate were estimated by Burton (15) and Rawal *et al* (16) method after the extraction of nucleic acids by Schneider method (17). Tissue glycogen was

Table No. 1 - Effect of mangiferin on the level of blood glucose, heart tissue protein, nucleic acids and heart tissue glycogen in isoproterenol (ISPH) induced MI rats

Parameters	*Control (Group1)*	*ISPH (Group2)*	*Mangiferin (Group3)*	*Mangiferin + ISPH (Group4)*
Protein (mg/g tissue)	152.66 ± 8.64	239.16 ± 17.61^{a***}	149.50 ± 9.77^{aNS}	171.33 ± 6.56^{c**}
DNA (mg/g tissue)	19.50 ± 0.83	47.98 ± 3.28^{a***}	18.86 ± 1.10^{aNS}	22.03 ± 1.47^{b***}
RNA (mg/g tissue)	9.50 ± 0.83	23.99 ± 1.62^{a***}	8.98 ± 0.63^{aNS}	10.82 ± 0.83^{b***}
Glycogen (mg/g tissue)	26.04 ± 1.85	12.36 ± 0.96^{a***}	26.9 ± 1.98^{aNS}	23.57 ± 1.54^{b***}
Blood glucose (mg/dl)	50.09 ± 4.24	69.91 ± 5.2^{a***}	48.85 ± 3.51^{aNS}	56.16 ± 4.31^{b***}

Values are expressed as mean ± SD for 6 animals in each group. P values: ^{a***} <0.001 statistically significant when compared with Group 1; ^{aNS} statistically non-significant when compared with Group 1; ^{b***} <0.001, ^{C**} <0.001 statistically significant when compared with Group 2.

Table No.2 - Effect of mangiferin on ECG pattern of the control and experimental group of animals

ECG Changes	*Control (Group1)*	*ISPH (Group2)*	*Mangiferin (Group3)*	*Mangiferin + ISPH (Group4)*
QRS Peak in sec	0.0205 ± 0.0010	0.0262± 0.0016 ^{a***}	0.0202± 0.0008^{aNS}	0.0220± 0.0007^{b***}
P-wave intensity in sec	0.0416±0.0002	0.0379 ± 0.0008^{a***}	0.0419 ± 0.0004^{aNS}	0.0409 ± 0.0007^{b***}
QT interval in sec	0.0705± 0.0004	0.0734 ± 0.0032^{a***}	0.0700 ± 0.0002^{aNS}	0.0717 ± 0.0016^{b***}

Values are expressed as mean ± SD for six animals in each group. ; P values: ^{a***}<0. 001, statistically significant when compared with Group 1; ^{aNS}, statistically non-significant when compared with Group 1; ^{b***} <0. 001, statistically significant when compared with Group 2.

extracted and estimated by the method of Morales *et al* (18). Serum and heart tissue proteins were estimated by Lowry *et al* (19) method and electrophoretic analysis of serum protein along with A/G ratio was determined by Varley and Varley standard (20) procedure.

Statistical analysis

Results are presented as mean ± SD. The significance of difference among the groups was assessed using one way analysis of variance (ANOVA) followed by Least Significant Difference (LSD) multiple comparison test. Significance was set at *P<0.05, <0.01 and <0.001.*

Results

The results of the study assessing the toxicological effect of mangiferin have shown that a small increase in body weight may be considered as variation that is within the normal range and appeared to be non-toxic as monitored by survival outcome. Mangiferin showed no lethal effect at least up to an i.p dose of 1000 mg/kg bodyweight day for 60 days for chronic toxicity indicating that LD_{50} if any, should be higher than this dose.

The Group 2 isoproterenol induced rats showed a significant increase (*P*<0.001) in blood glucose, heart tissue protein and nucleic acids with a significant decrease (*P*<0.001) in myocardial glycogen as compared to Group 1 control animals (Table 1). Mangiferin pretreated Group 4 rats showed a significant decrease in blood glucose (*P*<0.001), heart tissue protein (*P*<0.01) and heart tissue nucleic acids level and a significant increase (*P*<0.001) in myocardial glycogen level as compared with Group 2 isoproterenol administrated rats. Group 3 drug control rats showed a non-significant change (NS) in all these parameters as compared to Group 1 control rats.

Figure 1 presents the electrocardiographic pattern of normal and experimental group of animals. Group 1 and Group 3 rats showed normal ECG pattern and an elevation of ST segment were observed in Group 2 ISPH administered rats. Mangiferin pretreated and isoproterenol induced Group 4 rats exhibited a near normal ECG pattern with a slight elevation in ST segment. The ECG data of the experimental animals, including the QRS peak, p wave intensity, QT interval are represented in Table 2. The electrophoretic separation of serum total proteins and protein fractions such as albumin and globulins (alpha (1, 2), beta and gamma globulins) of control and experimental rats are provided in Figs 2.a to 2.d. The densitometer readings of these separated serum protein level and albumin globulin ratio values are provided in Fig 3.

DISCUSSION

The diagnosis of myocardial infarction is dependent on documentation that cardiac necrosis has taken place. The main criteria generally used for the definite diagnosis of myocardial infarction is evolving pattern of electro-cardio graphic abnormalities (21). Administration of isoproterenol is known to produce electrocardiograph and enzymatic changes suggestive of myocardial ischemia in experimental animals (22), (23). An elevation of ST segment observed in Group 2 ISPH myocardial infarcted rats is co incidence with the report of Ran *et al* (24). This could be due to myocardial necrosis accelerated by isoproterenol. This is supported by other scientists stating that acute ischemic tissue injury manifests an ST segment elevation in the region of injured myocardium (25), when tissue damage has occured. Mangiferin pretreated (Group4) rats exhibited a near normal ECG pattern-with a slight elevation in ST segment. Marona *et al* (26) have explained an observed pattern of ECG test on the cardio protective effect of derivatives of xanthones and reported that these compounds are potential anti arrhythmic agents. Since mangiferin is one type of glucosyl xanthone derivative the maintenance of normal ECG pattern might be attributed to the protective effect of mangiferin in preventing free radical mediated myocardial damage and thereby eliminating the acute fatal complications by protecting the membrane damage against isoproterenol mediated infarction.

Serum protein electrophoresis (SPEP) is a screening test that measures the major blood proteins by separating them into five distinct fractions: albumin, $alpha_1$, $alpha_2$, beta, and gamma proteins (27). The fractions form a characteristic band on electrophorotogram. Alterations in these patterns are associated with manifestation of chronic diseases. The serum total protein fractions and albumin: globulin ratios were found to be significantly reduced in Group 2 ISPH myocardial infarcted rats when compared to Group 1 control rats. The electrophoresis separation of serum total protein of Group 2 ISPH myocardial infarcted rats showed low bands of protein and albumin fraction zones. During active necrosis, changes in serum protein levels were reported in isoproterenol induced MI rats (28). A decrease in serum protein is usually as a result of a fall in albumin or some times gamma globulin (29). A decrease in albumin with a rise in the $alpha_2$ globulin usually indicates an acute

reaction of the type that occurs in infections, burns, stress or heart attack (30). Isoproterenol induced myocardial infarction is a free radical mediated tissue damage and may lead to production of more 0_2 and H_2O_2 ions which in turn could bind with albumin and thus destroy it. Similar results reported by Halliwell and Gutteridge (31) in earlier study. Since proteins are SH group moieties they are easily affected by free radicals. Clarke *et al* (32) in an *in-vivo* experiment model of wounded rat heart have reported that the wound sections of heart myocyte had contained only 25% of the cytosolic serum albumin. Group 4 mangiferin pretreated rats exhibited a significant increase in these values when compared to ISPH myocardial infarcted Group 2 rats. Martinez *et al* (33) has reported that the stem bark extract of *mangifera indica* linn is effective in reducing the hydroxyl mediated oxidation of BSA with antioxidant activity exhibited by its polyphenolic component, mangiferin. Misra *et al* (34) have reported that the polyphenol prevented the cigarette smoke (CS) induced oxidative damage of microsomal proteins and BSA in heart both *invivo* and *invitro* condition. Since mangiferin is a potent poly phenolic antioxidant, it could have neutralized 0_2 and H_2O_2 ions generated by isoproterenol and in turn could have protected the "SH group" and prevented the albumin and total protein damage.

ISPH myocardial infarcted (Group2) rats showed a significant increase in protein, DNA and RNA content in heart tissues when compared to Group 1 control rats. Kizer *et al* have reported that the amount of DNA is increased during myocardial infarction (35). Ravichandran and Puvanakrishnan (36) have also reported similar result. The increased DNA content in isoproterenol treated rats has been reported to be probably attributable to fibroblast cells since, cardiac muscle cells do not undergo mitotic division (37). Lochner *et al* (38) have reported that the increased protein synthesis following experimental myocardial infarction as a part of repair process may be stimulated after cellular necrosis. The reports of Ravichandran and Puvanakrishnan (36) support the present study. It has been reported that protein synthesis is preceded and accompanied by enhanced RNA synthesis (39). Wood *et al* have also suggested that the early rise in RNA synthesis could be a primary event and leads to hypertrophy at a later phase (40).

Venugopal *et al* (41) have reported that the adrenergic agents adrenaline and isoproterenol exert effects on cardiovascular cells and induces mRNA hybridization signals in the vascular cells of the heart and also in cardiocytes. Mangiferin pretreatment reduced the myocardial tissue DNA level in the present study. Mangiferin has been reported to inhibit DNA and protein metabolism in animal study. This could be due to antitumor, immunomodulatory and anticancer activity exhibited by mangiferin (42). Leiro *et al* (43) have also suggested that mangiferin may protect cells against oxidative damage and mutagenesis. Mangiferin pretreatment reduced RNA and tissue protein levels in the present study. Leiro *et al* (43) have reported that mangiferin possesses inhibiting activity on mRNA. Mangiferin could have protected the myocardium by reducing the cellular DNA and RNA generation thereby reducing the release of protein.

In isoproterenol induced myocardial infarcted Group 2 rats, blood glucose level was found to be increased where as heart tissue glycogen level was found to be decreased when compared to Group 1 control animals. Surabhi, Kapoor (44) and Zakirov *et al* (45) have reported the decreased level of glycogen in isoproterenol induced myocardial infarcted rats. The observed decrease in the glycogen content of heart could be due to enhanced glycogenolysis and lipolysis. Isoproterenol administration followed by beta-receptor binding activates phosphorylase kinase leading to glycogenolysis and lipolysis (46). Isoproterenol administration in rats is associated with pronounced metabolic abnormalities such as elevation of blood glucose (47), (48) and total hexose in heart when compared to normal rats at peak period of infarction (49). The observed increase in blood glucose could be due to enhanced glycogen break down and less utilization of peripheral tissues. The Group 4 mangiferin pretreated rats showed a significant decrease in blood glucose level with a significant increase in tissue glycogen level as compared with Group 2 ISPH MI rats. Miura *et al* (50) & Ichiki *et al* (51) have also reported the decreased level of blood glucose in mangiferin treated rats. The decreased glucose content in blood could be due to anti diabetic activity of mangiferin.

The therapeutic efficacy of mangiferin may be due to its antioxidant, antilipidperoxidative, free radical scavenging, immunomodulatory and cardiotonic property that could have prevented ISPH-induced tissue injury. Thus it could be concluded that mangiferin protects experimental myocardial infarction as revealed by the amelioration of histological changes and biochemical markers of cardiac tissue damage without any adverse effect

which merit further detailed studies to develop it as a cardio protective drug.

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