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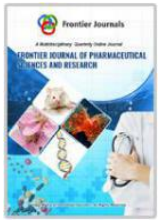

Original Research Paper

CARDIOPROTECTIVE ACTIVITY OF POLYALTHIA SUBEROSA AGAINST ISOPROTERENOL INDUCED MYOCARDIAL INFARCTION IN ALBINO WISTAR RATS

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ABSTRACT

The present study was carried out to evaluate the Cardio protective activity of leaf extract of *Polyalthia suberosa* against Isoproterenol (ISO) induced Myocardial Infarction (MI). ISO-induced myocardial ischemia is considered as one of the most widely used experimental model to study the beneficial effects of many drugs on cardiac function. *Polyalthia suberosa* is used in the indigenous system of medicine as an antioxidant. However, there are no reports available in literature on its traditional use in MI. In the present study, an increase in LDH1 isoenzyme band in ISO myocardial infarcted rats was observed. The results showed a significant increase of serum CK-MB and LDH levels in ischemic control when compared with normal group. Different doses (200 mg/kg and 400 mg/kg) of plant extract treated groups have shown significant and dose dependent decrease in serum CK-MB and LDH levels when compared with ischemic control group. The increased activities of these enzymes following injection of ISO as observed in this study confirmed the onset of myocardial necrosis. Pretreatment with leaf extract of *Polyalthia suberosa* lowered the elevated levels of enzymes compared to the control. This is an indication of the protective action of the extract in reversing cardiac damage due to isoproterenol. ISO induced MI had been shown to elevate plasma TC, TG, LDL and decrease HDL levels. Also higher level of LDL has a positive correlation whereas, high level of HDL has a negative correlation with MI. Histopathological studies of cardiac tissue in ISO group showed the presence of focal myo necrosis with myo phagocytosis and lymphocytic infiltration in sub-endocardial region indicative of infract like lesions. Scrutiny of cardiac tissue of ISO + MEPS group shows significant and dose dependent reduction in myonecrosis and lymphocyte infiltration than ISO group. Moreover as the plant possesses flavonoids the cardio protective activity may be due to presence of flavonoids. Hence, it can be summarized that MEPS pre-treatment to ISO treated rats provide cardio protection by inhibiting the formation of free radicals generated during oxidation of catecholamine thus inhibiting peroxidation of membrane lipids and preventing subsequent leakage of soluble enzymes. Also, *Polyalthia suberosa* pre-treatment appears to be instrumental in preventing oxidation of -SH group of cardiac ATP ases and improvement in status of enzymatic and non-enzymatic antioxidants that further contributes to its overall cardio protective property.

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1. INTRODUCTION

Cardiovascular diseases have become very common worldwide and have been one of the major reasons of high mortality rate. Among the cardiovascular diseases epidemiologic studies have shown that myocardial infarction is the most common disease which is increasing the mortality rate. It is estimated that by 2020 MI will be the major disease worldwide. Myocardial infarction (MI), commonly known as "heart attack," occurs due to an interruption in the supply of blood to heart tissue. As a result of coronary artery occlusion, necrosis of part of the myocardium occurs[1]. In fact, an imbalance between coronary blood supply and myocardial demand is the main cause of myocardium necrosis resulting from MI. MI is a common presentation of ischemic heart disease (IHD) and is followed by numerous pathophysiological and biochemical changes, including lipid peroxidation (LPO), hyperglycemia, and hyperlipidemia[2].

In the developed world and most developing countries, MI is one of the main causes of mortality and morbidity. At low concentration, catecholamines exert a positive ionotropic effect and are beneficial in regulating heart function. However, when present in high doses (administered or released in excess from the endogenous stores), catecholamines can deplete the reserved energy of cardiomyocytes, resulting in structural and biochemical changes leading to irreversible damage. Isoproterenol 4-[1-hydroxy-2-(isopropylamino) ethyl] benzene-1,2-diol hydrochloride (ISO) is a synthetic catecholamine and adrenergic agonist that causes severe stress to the myocardium, resulting in an infarct like necrosis of the heart muscle[3]. Free radicals thus produced may attack polyunsaturated fatty acids (PUFAs) within membranes, forming peroxyl radicals. These radicals then attack adjacent fatty acids, causing a chain reaction of LPO. Lipid hydroperoxide end products are harmful and may be responsible for the disruption of the integrity of the myocardial membrane.

Myocardial infarction occurs when there is an obstruction in the blood supply to the heart due to the fat deposits in the coronary arteries. These fat deposits are usually the result of high cholesterol levels in the body or they are the waste products of the cell. Commonly it is called as heart attack. Efforts are being made to include alternative medicine along with the conventional medications to improve the chances of obtaining cure for these diseases. Most of the world population is getting attracted towards the natural drugs as they will have fewer side effects when compared with the synthetic ones. The non-nutrient phytochemicals and polyphenols are being considered for the prevention and management of cardiac diseases which include flavonoids, alkaloids and xanthones etc. they are having anti-oxidant nature. Flavonoids present in the plants show strong anti-oxidant properties which can be used to treat heart ailments[4].

The plant *Polyalthia suberosa* used in the present study is found all over India and its genus *Polyalthia* has been phytochemically investigated and was found to contain alkaloids, flavonoids, anthocyanins, triterpenoids and mucilage of the plant contains polysaccharides. The ethno pharmacological studies have shown that the plant *Polyalthia suberosa* has strong antioxidant property[5]. Oxidative stress is the most important cause of MI, hence we are trying to prove the cardio protective activity of *Polyalthia suberosa* on isoproterenol induced MI in wistar rats. A synthetic catecholamine called isoproterenol causes myocardial damage when ingested in large doses. It increases the c-AMP levels, intracellular calcium overload and exhaustion of high energy phosphates, thus inducing necrosis. Catecholamines are held responsible as they can easily undergo oxidation and cause myocardial changes. They can also undergo auto oxidation resulting in the formation of highly toxic free radicals. Thus, these free radicals play a lead role in catecholamine induced cytotoxicity. They can cause cell necrosis and contractile failure of the heart in rats. Isoproterenol significantly increases the activity of acute myocardial injury markers and thus it serves as one of the best models to study the beneficial effects of many drugs[6].

2. MATERIAL AND METHODS

PLANT MATERIAL

Preparation of the Extract

About 1.5 Kg. leaves of *Polyalthia suberosa* were collected by handpicking method to avoid rusty, discoloured and mottled leaves. They were cleaned, dried

and coarsely grinded in a mixer grinder to obtain a powder of course texture, which was then passed through 40 mesh sieve to obtain about 1300 gm of powdered drug. The powdered drug obtained was extracted using distilled water (1:30). The extraction was done until the plant material was exhausted. The extract was concentrated to obtain a brownish coloured viscous liquid. The extract was air dried and after the experimental use, was stored in a dessicator for further use[7].

Drugs and Chemicals

Isoproterenol, Sodium dihydrogen phosphate, potassium dihydrogen phosphate, Tris buffer, Distilled water and all others were of analytical grade and were obtained from Sigma-Aldrich, Bangalore. The parameters evaluated in the present study were estimated using their respective kits obtained from Erba Diagnostics Ltd. India i.e., CK-MB, LDH, AST, ALT, ALP, Total cholesterol, HDL, and Triglyceride estimation kits.

3.BIOLOGICAL ACTIVITY

Experimental Animals

In the present study healthy wistar rats of either sex ranging between 150 gm-200 gm were taken. The animals were housed in group of six and standard conditions i.e., 27±2ºC, relative humidity 44 - 56% and light and dark cycles of 10 hours and 14 hours respectively were maintained. They were given standard rat diet and drinking water for 1 week before and through the experiments.The experiments and protocols performed in this study were approved by the Institutional Animal Ethical Committee (IAEC).

Experimental Design - Cardio Protective Activity

All the experimental animals were divided into four groups, each containing 6 animals (n=6). The treatment to the respective group of animals was carried out for a period of 14 days. Isoproterenol (100 mg/kg body weight) was administered subcutaneously to induce myocardial infarction in animals. The prepared leaf extract of *Polyalthia suberosa* was freshly suspended in Tween 80. It is administered by using an oral feeding needle to the animals. MI was induced in rats by subcutaneous injection of 100 mg/kg isoproterenol dissolved in saline once daily for two successive days as per the procedure[8-9].

BIOCHEMICAL ESTIMATIONS

Collection of Blood Samples

Blood samples from al animals was done at regular intervals during the treatment. It was collected from the retro orbital puncture method. After collection the blood serum was carried out by centrifugation at 2000 rpm for 15 min and was stored for estimation of various biochemical parameters.

Parameters Measured

Cardiac Markers and Lipid Profile Estimation

Biochemical kits were used to measure the Cardiac and Lipid profile. The levels of marker enzymes like LDH, AST, ALT & ALP were measured as an index of cardiac markers, whereas the estimation of Total Cholesterol, HDL and Triglycerides was done to obtain the lipid profile[10].

Histopathological Studies

The myocardial tissue was isolated from the excised heart and it was immediately fixed in 10% buffered neutral formalin solution. These fixed tissues were embedded in paraffin and cut into serial sections and stained with Hemtoxylin and eosin stains (H & E stain) . The stained sections were then examined using light microscope and photo micrographs were taken. The photomicrographs were observed for histo pathological findings.

Statistical Analysis

The data thus obtained was expressed as Mean ± S.E.M. The Statistical significance observed between more than two groups was analysed using one way ANOVA followed by the Tukey's test.

4.RESULTS & DISCUSSION

Preliminary Phytochemical Investigations

Leaves extract of plant possesses phytoconstituents such as flavonoids, phenolic acids, anthocyanins, alkaloids, tannins and saponins which were found to be positive upon phytochemical screening using standard methods. Studies suggest that increase in the formation of free radicals and consequent oxidative stress is associated with the imbalance between the oxygen demand and supply which results in the necrosis of myocardial tissue causing myocardial infarction. In the present study myocardial infarction is caused by the use of Isoproterenol which causes severe oxidative stress.

Serum Cardiac Markers

Effect of creatinephosphokinase -MB

Serum CK-MB levels were estimated by using commercial Erba CK-MB kit and the results were shown in Table No. 1. The level of CK-MB was found to be 87.33±1.145 in group 1 normal rats which increased to 183.2±0.980### when the rats were treated with isoproterenol (100mg/kg). When they were continuously treated with the leaf extract of *Polyalthia suberosa* (200mg/kg and 400mg/kg respectively) for 14 days, there was a decrease in the values comparable to that of control group rats, which were found to be 164.3±0.749***and 91.67±0.843*** respectively. The values indicate that high dose of the leaves extract of the plant showed similar result to that of normal[11-12].

Effect of Lactate dehydrogenase (LDH)

Serum LDH levels were estimated by using commercial Erba LDH kit and the results were shown in Table.1. The level of LDH was found to be 161.3±1.174 in group 1 normal rats which increased to 192.3±0.881### when the rats were treated with isoproterenol (100mg/kg). When they were continuously treated with the leaf extract of *Polyalthia suberosa* (200mg/kg and 400mg/kg respectively) for 14 days, there was decrease in the values comparable to that of control group rats, which were found to be 182.5±1.384*** and 170.3±0.988*** respectively. The values indicate that high dose of the leaves extract of the plant showed similar result to that of normal.

Effect on Aspartase transaminase (AST)

Serum AST levels were estimated by using commercial Erba AST kit and the results were shown in Table No.1. The level of AST was found to be 81.00±0.577 in group 1 normal rats which increased to 114.5±1.335### when the rats were treated with isoproterenol (100mg/kg). When they were continuously treated with the leaves extract of *Polyalthia suberosa* (200mg/kg and 400mg/kg respectively) for 14 days, there was decrease in the values comparable 98.3±1.022***and 87.2±0.980*** respectively. The values indicate that high dose of the leaves extract of the plant showed similar result to that of normal.to that of control group rats, which were found to be 98.3±1.022***and 87.2±0.980*** respectively. The values indicate that high dose of the leaves extract of the plant showed similar result to that of normal.

Effect on Alanine transaminase (ALT)

Serum ALT levels were estimated by using commercial Erba ALT kit and the results were shown in Table No.1.The level of ALT was found to be 98.67±0.988 in group 1 normal rats which increased to 151.00±0.730### when the rats were treated with isoproterenol (100mg/kg). When they were continuously treated with the leaves extract of *Polyalthia suberosa* (200mg/kg and 400mg/kg respectively) for 14 days, there was decrease in the values comparable to that of control group rats, which were found to be 119.50±0.619***and 102.00±0.774*** respectively. The values indicate that high dose of the leaves extract of the plant showed similar result to that of normal.

Effect on Alkaline Phosphate (AlkP)

Serum AlkP levels were estimated by using commercial Erba AlkP kit and the results were shown in table No.1. The level of AlkP was found to be 183.17±0.980 in group 1 normal rats which increased to 280.4±1.033### when the rats were treated with isoproterenol (100mg/kg). When they were continuously treated with the leaves extract of *Polyalthia suberosa* (200mg/kg and 400mg/kg respectively) for 14 days, there was decrease in the values comparable to that of control group rats, which were found to be 240.00±0.683***and 210.83±0.749* respectively.The values indicate that high dose of the leaves extract of the plant showed similar result to that of normal.

Lipid Profiles

Effect on serum cholesterol

Serum cholesterol levels were estimated and the results are shown in Table No.2.The level of cholesterol was found to be 52.0±0.774 in group 1 normal rats which increased to 58±0.980### when the rats were treated with

Effect on serum HDL-cholesterol

Serum HDL-cholesterol levels were estimated and the results are shown in table No.2.The level of HDL-cholesterol was found to be 24.5±1.45 in group 1 normal rats which increased to 20.82±1.16### when the rats were treated with isoproterenol (100mg/kg). When they were continuously treated with the leaves extract of *Polyalthia suberosa* (200mg/kg and 400mg/kg respectively) for 14 days, there was decrease in the values comparable to that of control group rats, which were found to be 26.64±1.25***and 23.32±1.42*** respectively[13]. The values indicate that high dose of the leaves extract of the plant showed similar result to that of normal.

Table 1 Effect of drugs and leaves extract of Polyalthia suberosa on serum cardiac markers

GROUPS	TREATMENT	On 14th Day				
		CK-MB (IU/L)	LDH (IU/L)	AST (IU/L)	ALT (IU/L)	AlkP (IU/L)
I	Animals received distilled water (2 ml/kg) for 14 days	87.33±1.145	161.3±1.174	81.00±0.577	98.67±0.988	183.17±0.980
II	Animals received distilled water (2 ml/kg) for 14 days + isoproterenol 100 mg/kg, s.c. injection on the 13th & 14th day.	183.2±0.980###	192.3±0.881###	114.5±1.335###	151.00±0.730###	280.4±1.033###
III	Animals received leave extract (200 mg/kg, p.o.) for 14 days + isoproterenol 100 mg/kg, s.c. injection on the 13th & 14th day.	164.3±0.749***	182.5±1.384***	98.3±1.022***	119.50±0.619***	240.00±0.683***
IV	Animals received leave extract (400 mg/kg, p.o.) for 14 days + isoproterenol 100 mg/kg, s.c. injection on the 13th & 14th day.	91.67±0.843***	170.3±0.988***	87.2±0.980***	102.00±0.774***	210.83±0.749*

CK-MB: Creatine phosphokinase - MB, LDH: Lactate dehydrogenase, AST: Aspartate transaminase, ALT: Alanine transaminase, AlkP:Alkaline phosphate

Note: The above values are expressed in mean ±SEM and n=6. ###p<0.001 when compared with normal group.*Indicates p<0.05, ***indicates p<0.001 when compared with ischemic control group

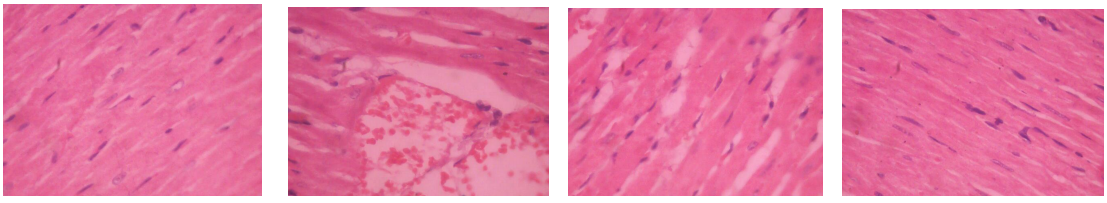
Table 2 Effect of drugs and leaves extract of Polyalthia suberosa on serum lipid profiles

GROUPS	TREATMENT	On 14th Day			
		CH (mg/dl)	HDL (mg/dl)	LDL (mg/dl)	TG (mg/dl)
I	Animals received distilled water (2 ml/kg) for 14.	52.0±0.774	24.5±1.45	19.3±0.879	38.67±0.614
II	Animals received distilled water (2 m/kg) for 14 + isoproterenol 100 mg/kg, s.c. injection on the 13th & 14 th day.	58±0.980###	20.82±1.16###	28.3±1.453###	52.0±1.125###
III	Animals received leave extract (200 mg/kg, p.o.) for 14 + isoproterenol 100 mg/kg, s.c. injection on the 13th & 14 th day.	55±0.980***	26.64±1.25***	24.3±0.881***	42.17±1.302***
IV	Animals received leave extract (400 mg/kg, p.o.) for 14 + isoproterenol 100 mg/kg, s.c. injection on the 13th & 14 th day.	51.0±1.125***	23.32±1.42***	21.0±1.000***	41.00±0.619***

***CH:** Cholesterol, **HDL:** High density lipoproteins, **LDL:** Low density lipoproteins, **TG:** Triglyceride*

The above values are expressed in mean ±SEM and n=6. ### p<0.001 when compared with normal group. *** p<0.001 when compared with control group

Fig. 1 Photomicrographs of sections of rat cardiac apexes



I) Normal **II)Control** **III) Test-I** **IV) Test-II**

Effect on serum HDL-cholesterol

Serum HDL-cholesterol levels were estimated and the results are shown in table No.2.The level of HDL-cholesterol was found to be 24.5±1.45 in group 1 normal rats which increased to 20.82±1.16### when the rats were treated with isoproterenol (100mg/kg). When they were continuously treated with the leaves extract of *Polyalthia suberosa* (200mg/kg and 400mg/kg respectively) for 14 days, there was decrease in the values comparable to that of control group rats, which were found to be 26.64±1.25***and 23.32±1.42*** respectively. The values indicate that high dose of the leaves extract of the plant showed similar result to that of normal.

Effect on serum LDL- cholesterol

Serum LDL-cholesterol levels were estimated and the results are shown in table 2. The level of LDL-cholesterol was found to be 19.3±0.879 in group 1 normal rats which increased to 28.3±1.453### when the rats were treated with isoproterenol (100mg/kg). When they were continuously treated with the leaves extract of *Polyalthia suberosa* (200mg/kg and 400mg/kg respectively) for 14 days, there was decrease in the values comparable to that of control group rats, which were found to be 24.3±0.881*** and 21.0±1.000**** respectively.The values indicate that high dose of the leaves extract of the plant showed similar result to that of normal[14].

When they were continuously treated with the leaves extract of *Polyalthia suberosa* (200mg/kg and 400mg/kg respectively) for 14 days, there was decrease in the values comparable to that of control group rats, which were found to be 55±0.980***and 51.0±1.125*** respectively. The values indicate that high dose of the leaves extract of the plant showed similar result to that of normal[15].

Effect on serum triglycerides (TG)

Serum triglycerides levels were estimated and the results are shown in Table No.2.The level of triglycerides was found to be 38.67±0.614 in group 1 normal rats which increased to 52.0±1.125### when the rats were treated with isoproterenol (100mg/kg). When they were continuously treated with the leaves extract of *Polyalthia suberosa* (200mg/kg and 400mg/kg respectively) for 14 days, there was decrease in the values comparable to that of control group rats, which were found to be 42.17±1.302***and 41.00±0.619*** respectively. The values indicate that high dose of the leaves extract of the plant showed similar result to that of normal.

5.DISCUSSION

Microscopic examination of the section of heart from different groups was carried out to assess the impact of isoproterenol injection on cardiac cytoarchitecture and its modulation by test drug administration. Sections of heart from normal control rats exhibited normal cyto architecture. The myofibrillar structure was normal with striations, branching and continuity with adjacent myofibrils[16].

Examination of the sections of heart from isoproterenol group (100 mg/kg.) exhibited remarkable changes in the cytoarchitecture. In most of the rats moderate to severe necrotic lesions were found especially in the apical region. The basal region was not affected to great extent. In the area surrounding this region myocarditis, interstitial edema and focal cell infiltration were observed. Loss of myocardial fibres was observed in some areas. Heamorrhage and fatty changes were observed in some sections.Severe necrotic lesions were observed in all the rats in this group.Whereas in *Polyalthea suberosa* Leaf Aqueous extract treated and isoproterenol injected groups, at a dose of 200 and 400mg/kg, the severity of the degenerative changes was found to be moderate and less in comparison to the control isoproterenol treated group. Moderate necrosis with cell infiltration was observed in sections from two rats. Mild to moderate necrosis and degenerative changes in the form myocarditis and fatty changes were observed in sections from the remaining cardiac tissue of rats[17-18].

6.CONCLUSION

In the present study the Cardio protective activity of leaf extract of *Polyalthia suberosa* against Isoproterenol (ISO) induced Myocardial Infarction (MI) was carried out in Albino Wistar Rats. The results of our study it can be concluded that the cardioprotective effect exhibited by Polyalthea suberosa leaf extract may be due to the antioxidant mechanism of phytoconstituents, mostly flavonoids present in the Leaf Aqueous Extract[19]. The results of the biochemical estimations and histopathological findings were further in support of the study. Further studies are required to isolate the constituents and explore the mechanism of action responsible for the cardioprotective activity of the plant.

7.CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest

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