

RESEARCH ARTICLE

Cardioprotective effect of ethanol extract of stem-bark and stem-wood of *Premna serratifolia* Lin., (Verbenaceae)

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ABSTRACT

Cardioprotective effect of ethanol extract of *Premna serratifolia* Lin., was tested on Isoproterenol 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 proteins, glycogen, nucleic acids and blood glucose. Subcutaneous injection of Isoproterenol (20mg/100g body weight in 0.1ml 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 proteins and nucleic acids, increase in blood glucose and decrease in heart tissue glycogen. Pretreatment with ethanol extract (100mg/100g body weight in 0.2ml of 5% gum acacia) for 28 days through intraperitoneal injection in Isoproterenol administered rats produced these parameters from alteration as compared with myocardial infarcted rats. This confirmed the cardioprotective effect of ethanol extract of *Premna serratifolia* Lin., on Isoproterenol induced myocardial infarction in rats and the protective myocardial effect may be due to the phytoconstituents like iridoid glycosides, alkaloids, flavonoids and phenolic compounds present in it.

KEY WORDS

Premna serratifolia Lin., ethanol extract, ECG, Isoproterenol, myocardial infarction, serum A/G ratio, proteins.

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 principle 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 plant to overcome various illnesses and suffering mainly to obviate the profound side effects encountered in usage of modern drugs¹. They safely interact with free radicals and terminate the chain reaction before vital molecules are damaged². The prophylactic and therapeutic effect of many plant foods and extracts in reducing cardiovascular disease has been reviewed³.

They are relatively safe, easily available and affordable to masses. Traditional drugs have important load in drug search, resulting in the discovery of novel molecules, Artemisinin for the cure of multi-drug resistant malaria, Silymarin for hepatoprotection and Vincristine and Vinblastin for certain types of cancers, have already been isolated from plants. The world health organization (WHO, 1980) has also recommended the evaluation of the effectiveness of plants in conditions where there is lack of safe synthetic drugs⁴.

Premna serratifolia Lin., (Verbenaceae) has cardiotoxic⁵, anti-coagulant⁶, anti-arthritis⁷ and anti-hyperglycaemic properties⁸. Most of the plant parts of *Premna serratifolia* Lin., are used in the traditional system of medicine in India. It is popularly known as "Agnimantha" in Ayurvedic system of medicine and "Munnai" in Tamil. As per ayurvedic system, agnimantha root forms an important ingredient of Dasamula, which is used for variety of affections⁹. Several methods have been used to study the beneficial effects of many drugs and cardiac functions. Administration of Isoproterenol is known to produce electrocardiography and

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enzymatic changes suggestive to cause myocardial ischemia in experimental animals¹⁰ and the present study will possibly help to confirm the traditional claims of *Premna serratifolia* Lin., and the study is aimed to evaluate the cardioprotective effect of ethanol extract in maintaining the myocardial integrity on Isoproterenol induced cardiac damage with reference to ECG analysis, electrophoretic separation of serum protein, A/G ration and biochemical studies in blood glucose, heart tissue proteins, nucleic acids and glycogen.

MATERIAL AND METHODS:

Plant Collection and Authentication:

Fresh stem-bark and stem-wood of *Premna serratifolia* Lin., were collected from, The Indian Medical Practitioners Co-operative Pharmacy and Stores (IMPCOPS) garden, Thiruvanniyur, Chennai - 41, Tamil Nadu. The plant was identified¹¹, authenticated by Botanist, Dr. P. Jayaraman, Plant Anatomical Research Centre (PARC), Tambaram, Chennai and the voucher specimen (PARC / 2007 / 71) have been kept in the Department of Pharmacognosy, Madras Medical College, Chennai - 600 003, for future reference. Care was taken to select the healthy plants and for normal organs.

Preparation of Extract:

The freshly collected stem-bark and stem-wood was chopped, shade dried and coarsely powdered. The powder was defatted with petroleum ether (60-80°C) and then extracted with 90% ethanol in a soxhlet extractor. The extract was dried under reduced pressure using a rotary vacuum evaporator and the percentage yield was 7.90% w/w.

Preliminary Phytochemical Analysis:

Ethanol extract was then treated with various reagents, which revealed the presence of various phytoconstituents¹² namely alkaloids, steroids, flavonoids, phenolic compounds and glycosides specifically iridoid glycosides. The fluorescence analysis with different reagents, TLC and HPTLC profile for different active constituents were also studied with different solvent system.

Animals:

Adult male albino rats of wistar strain weighing 150-200g housed in cages at 270 ± 20°C on a 12 h light / dark cycle were used for the studies. The animals were fed with standard diet and water ad libitum. The animals were maintained as per the norms of CPCSEA (991/C/06/CPCSEA) and the experiments were cleared by CPCSEA and the institutional ethics committee (Mohamed Sathak A. J. College of Pharmacy, Chennai).

Chemicals:

All chemicals were obtained from Sigma chemical Co.,

Toxicity studies:

Ethanol extract was suspended in 5% gum acacia and administered i. p. to wistar strain rats at the doses of 100, 250, 500 and 1000mg/kg 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 behaviors.

Table – 1- HPTLC Finger Print Data for Ethanol Extract of *Premna serratifolia* Lin.,

S. No.	Extracts	Wave length (nm)	No. of Peaks	Total Height	Total Area
1.	Ethanol	260	10	586.9	16264.7
		366	6	1046.8	27474.0
		550	9	1817.4	80892.3

Experimental design:

Animals were divided into four groups of six animals each. Group I animals received 0.2mg/100g of 5% gum acacia for 28 days. Group II animals received 20mg/100g body weight Isoproterenol in 0.1ml of 0.9% saline, s. c. once daily at an interval of 24 hours for 2 days and referred as Isoproterenol myocardial infarcted rats. Group III animals received ethanol extract at the dose of 100mg/100g body weight i. p. suspended in 5% gum acacia for 28 days and referred as drug control animal. Group IV animals were treated with ethanol extract at the dose of 100mg/100g body weight in 5% gum acacia given i. p. for 28 days and Isoproterenol was administered as in Group II and this group animals were referred as ethanol pretreatment group.

To find out the interference of gum acacia, a separate group of animals (Group V) fed with only standard diet and water ad libitum monitored for the same period of duration was compared with group I positive control rats and no significant changes were observed in serum marker enzyme parameters between these groups of rats and hence group V was dropped from the experimental design. Similarly, to find out the interference of gum acacia with Isoproterenol, another separate group of rats (Group VI) was administered with both gum acacia and Isoproterenol for the same period of duration and compared with group II (Isoproterenol myocardial infarcted rats) and no significant changes were observed in serum marker enzyme parameters and hence group VI was dropped from the experimental design. From this, it could be possible to find out the role of gum acacia as a suspending agent and not as an inducer either for ethanol or for Isoproterenol. As well as ethanol extract is soluble only in gum acacia and Isoproterenol is easily soluble in 0.9% saline, gum acacia was not provided for Group II rats.

After 30 days of experimental period, all the animals were anaesthetized with Phenobarbitol sodium (35mg/kg, i. p.). Blood was drawn from the external jugular vein and used for the estimation of blood glucose. Serum was separated from the remaining blood by centrifugation after allowing the blood to clot for few minutes. The heart tissue was dissected out immediately and washed in ice-cold saline;

100mg of wet tissue was weighed accurately and homogenized in 5ml of 0.1M Tris-HCl buffer (pH 7.4) in ice-cold condition. The homogenate was centrifuged at 2500g and the clear supernatant solution was taken for the assay of tissue protein, nucleic acids and glycogen. The serum was applied for electrophoresis separation of serum protein and estimation of A/G ratio. ECG on rats were performed under sodium thiopentone anesthesia (30mg/kg i. p.) 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 25mm/sec sensitivity of 4mV on a physiograph was measured. The nucleic acids such as DNA and RNA in tissue homogenate were estimated¹³ & ¹⁴ after the extraction of nucleic acids¹⁵. Tissue glycogen was extracted and estimated¹⁶. Serum and heart tissue proteins were estimated¹⁷ and electrophoretic analysis of serum protein along with A/G ratio was determined¹⁸.

Statistical analysis:

Results were 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 < 0.0001 .

RESULT:

The result of the study assessing the toxicological effect of ethanol extract have shown that a small increase in body weight may be considered as variation that is within the normal range and appeared survival outcome. Ethanol extract showed no lethal effect up to an i. p. dose of 1000mg/kg body weight for 60 days for chronic toxicity, indicating that LD₅₀, if any, should be higher than this dose.

Group II (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 I (Control animals) is shown in table - 2. Group III (Ethanol extract - control group) rats showed a non-significant change in all these parameters as compared to Group I (Control rats). Group IV rats (Ethanol extract pretreated group) 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 II rats (Isoproterenol administered rats).

Group I and III rats showed normal ECG pattern and an elevation of ST segment were observed in Group II rats. Ethanol extract pretreated and Isoproterenol induced Group IV 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 shown in table-3.

Fluorescence analysis indicated the presence of chromophore in this plant, which may help in identification from other species. Thin layer chromatography also confirmed the presence of phytoconstituents like alkaloids, steroids, flavonoids, phenolic compounds and glycosides. HPTLC peaks for the ethanol extracts have been shown in the Table - 1. With the solvent system of Hexane: Ethylacetate (3:1), Ethanol extract showed 10 peaks when scanned at 260nm with a maximum peak area of 19.24% at Rf value 0.51, 9 peaks when scanned at 550nm with a maximum peak area of 37.90% at Rf value 0.33 and 6 peaks when scanned at 366nm with a maximum peak area of 75.47% at Rf value 0.49, which indicates the number of constituents present in it.

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-cardiographic abnormalities¹⁹. Administration of isoproterenol is known to produce electrocardiograph and enzymatic changes suggestive of myocardial ischemia in experimental animals²⁰ & ²¹. An elevation of ST segment observed in Group II Isoproterenol Myocardial infarcted rats is coincidence with the already obtained report²². This could be due to myocardial necrosis accelerated by isoproterenol. This is supported by other scientist stating the acute ischemic tissue injury manifests as ST segment elevation in the regions of injured myocardium²³.

Ethanol extract pretreated group (Group IV) has exhibited a near normal ECG pattern with a slight elevation in ST segment. Serum protein electrophoresis (SPEP) is a screening test that measures the major blood proteins by separating them into five distinct fractions: albumin, alpha, alpha 2, beta and gamma proteins²⁴. The fractions form a characteristic band on electrophoretogram. Alterations in these patterns are associated with the manifestation of chronic disease. The serum total protein fractions and albumin: globulin ratio's were found to be significantly reduced in Group II (Isoproterenol Myocardial infarcted rats) when compared to Group I (Control group). The electrophoresis separation of serum total protein of Group II (Isoproterenol 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 myocardial infarcted rats²⁵. A decrease in serum protein is usually as a result of a fall in albumin or sometimes gamma globulin²⁶. 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 attack²⁷. Isoproterenol induced myocardial infarction is a free radical mediated tissue damage and may lead to the production of more oxygen and hydrogen peroxide ions which in turn could bind with albumin and thus destroy it. Similar results also reported with another

Table – 2- Effect of ethanol extract on level of blood glucose, heart tissue proteins and glycogen, nucleic acids in Isoproterenol induced Myocardial infarction in rats

Groups	Protein (mg/g tissue)	DNA (mg/g tissue)	RNA (mg/g tissue)	Glycogen (mg/g tissue)	Blood glucose (mg/dl)
I (Control)	152.66±8.64	19.50±0.83	9.50±0.83	26.04±1.85	50.09±4.24
II (Isoproterenol)	239.16±17.61 ^{a***}	47.93±3.28 ^{a***}	23.99±1.62 ^{a***}	12.36±0.96 ^{a***}	69.91±5.2 ^{a***}
III (Ethanol extract)	149.50±9.77 ^{aNS}	18.86±1.10 ^{aNS}	8.98±0.63 ^{aNS}	26.9±1.98 ^{aNS}	48.85±3.51 ^{aNS}
IV (Ethanol extract + Isoproterenol)	171.33±6.56 ^{b***}	22.03±1.14 ^{b***}	10.82±0.83 ^{b***}	23.57±1.54 ^{b***}	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 – I, ^{aNS} statistically non-significant when compared with group – I and ^{b***}<0.001, statistically significant when compared with group – III.

Table – 3- Effect of ethanol extract of stem-bark and stem-wood of *Premna serratifolia* Lin., on ECG pattern

Groups	QRS peak (in sec)	P-wave intensity (in sec)	QT interval (in sec)
I (Control)	0.02050±0.0010	0.0416±0.0002	0.0705±0.0004
II (Isoproterenol)	0.0262±0.0016 ^{a***}	0.0376±0.0008 ^{a***}	0.0734±0.0032 ^{a***}
III (Ethanol extract)	0.0202±0.0008 ^{aNS}	0.0419±0.0004 ^{aNS}	0.0700±0.0002 ^{aNS}
IV (Ethanol extract + Isoproterenol)	0.0220±0.0007 ^{b***}	0.0419±0.0004 ^{b***}	0.0717±0.0016 ^{b***}

Values are expressed as mean±SD for 6 animals in each group, P values: ^{a***}<0.001, statistically significant when compared with group – I, ^{aNS} statistically non-significant when compared with group – I and ^{b***}<0.001, statistically significant when compared with group – III.

studies²⁸. In an in vivo experimental model of wounded rat heart have reported that the wound sections of heart myocyte had contained only 25% of cytosolic serum albumin²⁹. Group V ethanol extract pretreated rats exhibited a significant increase in these levels when compared to group II (Isoproterenol Myocardial infarcted rats).

Isoproterenol Myocardial infarcted rats (group II) showed a significant increase in protein, DNA and RNA content in heart tissue when compared to Group I control rats. Amount of DNA increased during the Myocardial infarction have already reported^{30 & 31}. 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 division³². Increase protein synthesis following experimental myocardial infarction as a part of repair process may be stimulated after cellular necrosis was reported by one study³³. The reports of Ravichandran and Puvanakrishnan, 1993 also support the present study. It has been reported that protein synthesis is preceded and accompanied by enhanced RNA synthesis³⁴.

Wood et al.,³⁵ have also suggested that the early rise in RNA synthesis could be a primary event and leads to hypertrophy at a later phase.

Venugopal et al.,³⁶ have reported that the adrenergic agent's adrenaline and Isoproterenol exert effects on cardiovascular cells and induces mRNA hybridization signals in the vascular cells of the heart and also in cardiocytes. Ethanol extract pretreatment reduced the myocardial tissue DNA, RNA and tissue protein levels in the present study. Ethanol extract could have protected the myocardium by reducing the cellular

DNA and RNA generation thereby reducing the release of protein.

In Isoproterenol induced Myocardial Infarcted rats, (Group II) blood glucose level was found to be increase whereas heart tissue glycogen level was found to be decreased when compared to Group I (Control animals). Surabhi and Kapoor³⁷, Zakirov et al.,³⁸ have reported the decreased level of glycogen in Isoproterenol induced myocardial infarcted rats. The observed decrease in 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 lipolysis³⁹. Isoproterenol administration in rats is associated with pronounced metabolic abnormalities such as elevation of blood glucose⁴⁰ and total hexose in heart when compared to normal rats at peak period of infarction⁴¹.

The observed increase in blood glucose could be due to enhanced glycogen break down and less utilization of peripheral tissues. The Group IV ethanol pretreated rats showed a significant decrease in blood glucose level with a significant increase in tissue glycogen level when compared with group II Isoproterenol Myocardial Infarcted rats.

The therapeutic efficacy of ethanol extract may be due to its anti-coagulation, anti-oxidant, free radical scavenging and cardio-tonic properties that could have prevented Isoproterenol induced tissue injury. Thus it could be concluded that ethanol extract of stem-bark and stem-wood of *Premna serratifolia* Lin., protects experimental myocardial infarction as revealed by histological changes and biochemical markers of cardiac tissue damage without any adverse effects which merits further detailed studies to develop it as a cardioprotective drug.

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