



## Curative role of modified Arjunarishta on isoproterenol-induced myocardial infarction in rats

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### ABSTRACT

World health organization estimates 16.7 million people globally die every year due to cardiovascular diseases. Huge attention is required towards CVD as it is causing quick health impact and lacking a better therapeutic solution. The present study was undertaken to evaluate the therapeutic effect of modified arjunarishta on isoproterenol-induced myocardial infarction in rats. In the experiment, animals were randomly divided into four groups (n = 6 rats per group). Group 1 served as normal control. Group 2 (Induced group) received Isoproterenol 85mg/kg body weight subcutaneously for the first two days (24 hrs interval) to induce myocardial infarction. Group 3 (Therapeutic model) received Isoproterenol as per group 2 followed by the administration of Modified Arjunarishta orally from 3<sup>rd</sup> day to end of the experiment (16<sup>th</sup> day). The effective dose of 400mg/kg body weight was fixed by dose fixation study. Group 4 (Arjunarishta model) received Isoproterenol as per group 2 followed by the administration of Standard Arjunarishta orally 2ml/kg body weight daily from 3<sup>rd</sup> day to rest of the experiment period. At the end of the two-week experiment, Isoproterenol induced rats showed a significant increase in the levels of LDH, CPK, CK-MB, Troponin, SGOT, SGPT, Cholesterol, TGL, LDL and a significant decrease in the levels of HDL. The therapeutic activity estimated through biochemical parameters, cardiac markers and lipid profile.



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### INTRODUCTION

Myocardial infarction is an acute cardiovascular disease causing heart attack due to narrowing blood vessel which is supplying blood to the heart.

So, it leads to cardiac muscle injury. This is the condition of necrosis of the myocardium that occurs as a result of an imbalance between

coronary blood supply and myocardial demand (De Bono and Boon, 1992). The generation of toxic reactive oxygen species induces superoxide radicals, hydrogen peroxide and hydroxyl radical (Vaage and Valen, 1993). The primary symptom is chest pain and discomfort which may migrate into shoulder, arm, back, neck and even jaw. Often a severe pain in the centre slight left last more than few minutes. Such kind of discomfort feels like heartburn. Secondary symptoms include shortness of breath, nausea, feeling faint, cold sweat and tiredness (Signs and symptoms of coronary heart diseases, 2015). Generally, 5% of 75-year-old people have myocardial infarction with little or no

history of symptoms (Conventry. LL *et al.*, 2011). The actual cause of Myocardial infarction is heart failure, irregular heartbeat and cardiac arrest.

It is an ongoing demand to bring specific remedy without any side effects to other clinical functions. In this aspect phytomedicine is an irreplaceable resource which brings the research attention to study the preventive and therapeutic effect of phytochemicals. In this aspect, Ayurveda provides an important platform to treat several long-term challenging diseases and disorders.

The isoproterenol is core responsible for severe stress in myocardium resulting in infarct like necrosis of the cardiac muscle (Wexler, 1978). However, due to the generation of reactive oxygen species, these compounds may contribute to oxidative stress. Production of free radical and accumulation of lipid peroxide have been recognized as one of the possible mechanism for isoproterenol-induced cardiac damage (Kumari *et al.*, 1989). Isoproterenol-induced myocardial infarction in experimental rats is analysed by an increase in cardiac markers (Sathish *et al.*, 2003). Following the myocardial ischemia, intracellular release of the lysosomal enzyme may directly or through activation of the complement pathway result in cell injury.

The Sanskrit terminology of Ayurveda refers to 'Knowledge of Life' which provides a rich, comprehensive outlook to a healthy life, and its origin goes back nearly 5000 years. The art of Ayurveda had spread around in the 6<sup>th</sup> century BC to China, Mongolia, Korea, Tibet and Srilanka, carried over by the Buddhist monks travelling in those lands. The Ayurveda form a lifestyle adopted to maintain perfect balance and harmony within human existence. The AFI (Ayurvedic formulation of India) lists 37 asavas and arishtas (Ayurvedic Formulary of India, 2003). Arishta and Asava have been used as medicine for around 3000 years to treat various disorders and also taken as appetisers and stimulants. People are prone to consume a higher dose of these drugs for longer periods due to their medicinal value and easy availability (Damodaran S and Yenamandra S., 1987). In the official Ayurveda pharmacopoeia of Sri Lanka, the preparation and scale of 34 varieties of Arishta and 25 varieties of Asava has been legalised and listed (Ommachan, 1977). Arista is an important group of formulations used in Ayurveda. Arjunarishta also said as parthdyarishta is one of the ancient liquid oral formulation prescribed for cardiovascular diseases (Dwivedi S, and Jauhari R., 1997). The polyphenolic compounds of flavonoids with antioxidant properties are widely distributed in plant origin food such as vegetables, fruits and tea (Hertog *et al.*, 1993). The antioxidant capacity

of flavonoids is much stronger than vitamins C and E (Prior and Cao., 2000). The novel ayurvedic drug Modified arjunarishta is cardiotoxic which nourishes and strengthens myocardial muscle and promotes cardiac function. It was primarily derived from *Terminalia arjuna* tree bark which has essential nutrients that extensively support cardiac function. As the formulation of arjunarishta prepared through fermentation method, it contains a certain quantity of alcohol which is lethal to the liver. To make an alcohol free extract, the arjunarishta was prepared in an alternative way and named as modified arjunarishta. It is a tri-herbal formulation of *Terminalia arjuna*, *Mudhuca longifolia* and *Vitis vinifera* prepared directly without any fermentation process. Time-saving and easy preparation of modified arjunarishta is jaggery free. Thereby it is recommendable to cardiac patients with diabetes also. We already reported that modified arjunarishta have enriched phytochemicals through the characterisation studies (Santhosh kumar.B *et al.*, 2017). To bring evidence that modified arjunarishta have cardiotherapeutic activity, the following experiment was conducted along with arjunarishta which serves as a standard.

## MATERIALS AND METHODS

**Chemicals:** The inducing chemical isoproterenol purchased from Sigma Aldrich Pvt. Ltd. For sample analysis, analytical grade chemicals like ferric chloride, aluminium oxide, perchloric acid were all purchased from Merck.

**Drug Preparation:** The selected plant parts for the proposed study are *Terminalia arjuna* bark, *Vitis vinifera* fruit, and *Mudhuca longifolia* flower were collected from Villivakkam-Chennai, K.G. Kandigai-Tiruttani and from Ayurvedic shop-Chennai respectively during September 2015. It was identified and authenticated by K.N. Sunilkumar, Research Officer (Pharmacognosy) from Siddha Central Research Institute, Chennai. The identified plant powders were mixed with 32 part of sterile water and allowed to boil. The boiling was continued till the liquid level was reduced to one part through evaporation. The extract is filtered through filter paper. The filtrate is transferred into an airtight sterile container and stored in refrigerator 2-8°C. Standardisation of the formulation was done as per AYUSH Guidelines

**Experiment:** Institutional Animal Ethical Committee (IAEC) at Nandha College of Pharmacy, Erode has approved the experimental protocol of this study (NCP/IAEC/2015-16-11). Male albino Wistar rats of weight 160-180gms were obtained from central animal house, Nandha Pharma college, Erode, Tamil Nadu, India were used for this study. They were housed in polypropylene cages

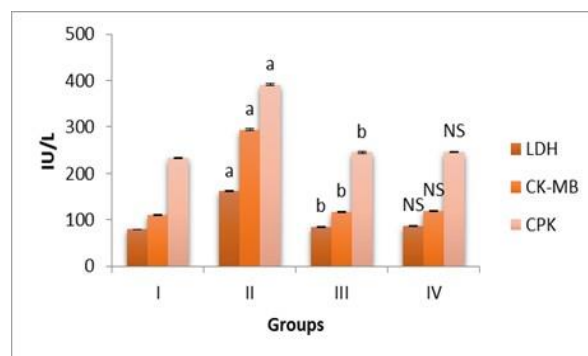
(three rats per cage) of size 47X34X20cm bedded with paddy husk which was renewed every 24hrs under 12:12 hrs dark and light cycle at around 22°C. Rats had free access to tap water and food of standard pellet diet which was obtained from M/s. Hindustan Lever Ltd, Mumbai, India. According to the guidelines of the committee, the control and supervision of experimental animals, New Delhi, India, the experiment was carried out. An acute toxicity study was carried out according to OECD guidelines after administration animals were regularly observed for behaviour and morphological changes.

Animals were randomly divided into four groups (n = 6 rats per group). Group 1 (Normal control) received free access to pure drinking water and normal pellet diet. Group 2 (Induced group) received Isoproterenol 85mg/kg body weight subcutaneously for first two days (24 hrs interval) to induce myocardial infarction (Panda and naik 2008; Rajadurai and prince, 2007b). Group 3 (Modified Arjunarishta model) received Isoproterenol as per group 2 followed by the administration of Modified Arjunarishta orally 400mg/kg body weight daily from 3<sup>rd</sup> day to end of the experiment. The effective dose of 400mg/kg body weight was fixed by dose fixation study. Group 4 (Arjunarishta model) received Isoproterenol as per group 2 followed by the administration of Standard Arjunarishta orally 2ml/kg body weight daily from 3<sup>rd</sup> day to end of the experiment. The dose was selected according to AFI. At the end of the experiment (16<sup>th</sup> day), the animals were anaesthetised, and blood samples were collected in the plane and EDTA blood collection tubes. Plane tubes collected blood was allowed to clot for serum separation.

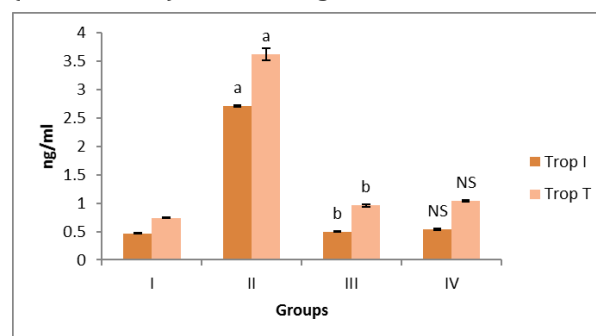
The collected serum sample was used for the estimation of following cardiac markers: Cardiac phosphokinase (CPK) by the method of Okinaka et al (1961), lactate dehydrogenase (LDH) by the method of King (1965), aspartate transaminase (AST) and alanine transaminase (ALT) by the method of Berg Meyer and Bernt (1974). CK-MB (creatinine kinase - MB) was analysed using the commercially available standard enzymatic kit (Tulip diagnostics Pvt, Ltd, India). The level of serum Troponin I and Troponin T was estimated by chemiluminescence immunoassay using standard kits (Roche Diagnostics Pvt. Ltd.). Lipids in serum were estimated by the method of Floch et al. (1957). Fluids of the organic extracts were evaporated to dryness and used for the estimation of cholesterol (Parekh and Jung 1970), triglyceride (TGL) (Rice, 1970), LDL (Friede wald formula; Friedwald et al., 1972), serum HDL (Lopes - Virella et al, 1977) and PLP (phospholipids) through the method described by Fiski and subbarow (1925).

## RESULTS

Figure 1 shows the effect of modified arjunarishta on cardiac markers including CPK, CK-MB and LDH. Figure 2 depicts the level of Troponin I and Troponin T in normal and experimental rats. Figure 3 shows the effect of MA on AST and ALT. The activities of these marker enzymes were increased significantly ( $p < 0.05$ ) in isoproterenol-treated rats as compared to normal. Both Arjunarishta and modified Arjunarishta administered rats after isoproterenol treatment showed significantly decreased the markers levels.



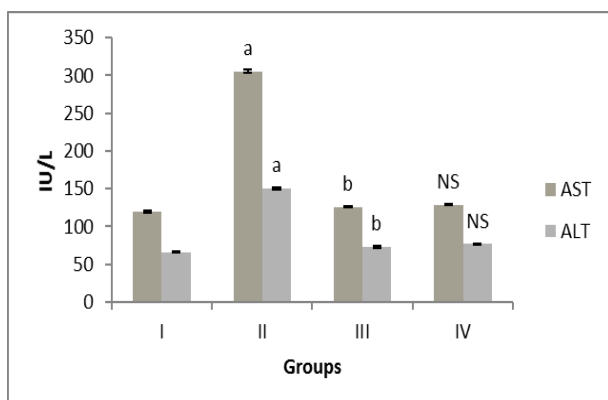
**Figure 1: Effect of MA on Cardiac Markers in Experimental rat;** Results are expressed as mean  $\pm$  S.D. (n = 6). One way ANOVA followed by Duncan's multiple test range post hoc.  $P < 0.05$ ; a: Group II (ISO Induced) compared with Group I (Control); b: Group III (MA-treated) compared with Group II (ISO-induced); NS: Non-significant



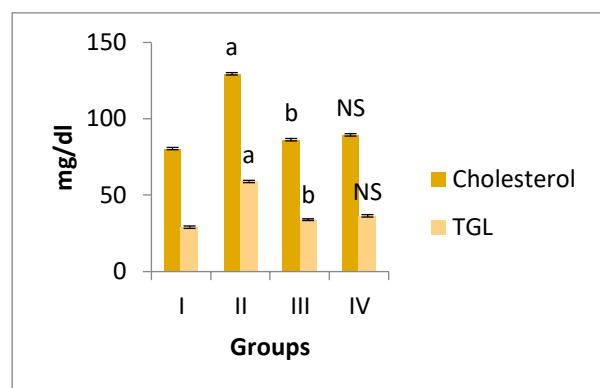
**Figure 2: Effect of MA on Troponin in Experimental rats;** Results are expressed as mean  $\pm$  S.D. (n = 6). One way ANOVA followed by Duncan's multiple test range post hoc.  $P < 0.05$ ; a: Group II (ISO Induced) compared with Group I (Control); b: Group III (MA-treated) compared with Group II (ISO-induced); NS: Non-significant

The level of serum total cholesterol and TGL in the normal and experimental group of rats are represented in figure 4. Figure 5 & 6 shows the effect of modified arjunarishta on lipoproteins and Cholesterol HDL ratio respectively. Figure 7 represents the level of Free fatty acid and phospholipids in the serum of normal and experimental group of rats. Total cholesterol, TGL, and FFA level in serum showed a significant

increase in group II isoproterenol induced Myocardial infarcted rats when compared with group I control rats. In modified arjunarishta treated group III rats, the level of serum cholesterol, TGL, and FFA showed a significant decrease when compared with group II. Similarly, in group IV, Arjunarishta standard treated rats showed a non-significant change for the above parameter in serum when compared with group I rats. Group II Isoproterenol-induced myocardial infarcted rats showed a significant decrease in serum phospholipid level when compared to normal group I control rats whereas a significant increase in serum phospholipids was observed in group III modified arjunarishta treated rats when compared with group II.



**Figure 3: Effect of MA on Transaminases in Experimental rat;** Results are expressed as mean  $\pm$  S.D. (n = 6). One way ANOVA followed by Duncan's multiple test range post hoc. P < 0.05; a: Group II (ISO Induced) compared with Group I (Control); b: Group III (MA-treated) compared with Group II (ISO-induced); NS: Non-significant

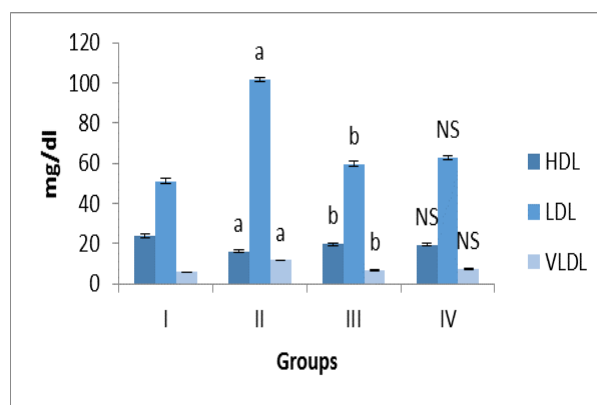


**Figure 4: Effect of MA on Lipids in Experimental rat;** Results are expressed as mean  $\pm$  S.D. (n = 6). One way ANOVA followed by Duncan's multiple test range post hoc. P < 0.05; a: Group II (ISO Induced) compared with Group I (Control); b: Group III (MA-treated) compared with Group II (ISO-induced); NS: Non-significant

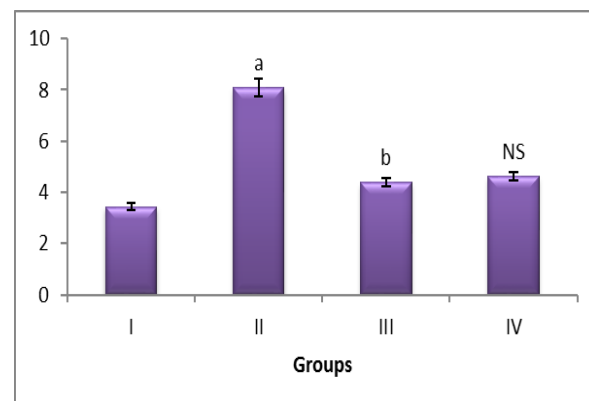
**DISCUSSION**

Isoproterenol is a synthetic catecholamine and non-selective  $\beta$ -adrenergic agonist which

produces myocardial infarction in a submaximal dose (Rona G et al., 1959). Isoproterenol induces myocardial infarction in a non-invasive and well-established method in rodents. Calcium overload, elevated production of highly cytotoxic free radicals from auto-oxidation, inflammatory cytokines and activation of proteolytic enzymes were reported as a possible mechanism of isoproterenol-induced myocardial infarction. Highly reactive free radicals react with lipids, proteins and nucleic acids causing lipid peroxidation, change in membrane permeability and integrity leading to damage of the myocardiocyte (Yates JC et al., 1981). The myocardial infarction is manifested by increased release of cardiac enzymes and lipids (Rajadurai M et al., 2006). These manifestation and pathological alterations are similar to human myocardial infarction.

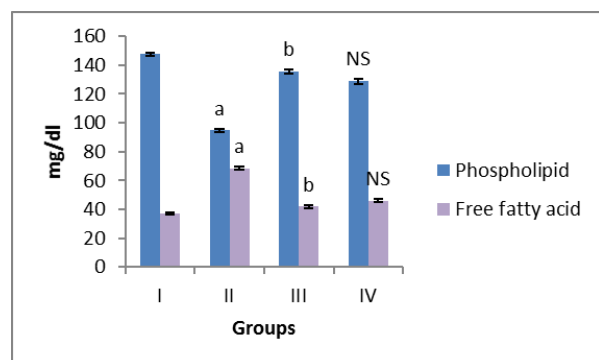


**Figure 5: Effect of MA on Lipoproteins in Experimental rat;** Results are expressed as mean  $\pm$  S.D. (n = 6). One way ANOVA followed by Duncan's multiple test range post hoc. P < 0.05; a: Group II (ISO Induced) compared with Group I (Control); b: Group III (MA-treated) compared with Group II (ISO-induced); NS: Non-significant



**Figure 6: Effect of MA on Cholesterol and HDL ratio in Experimental rat;** Results are expressed as mean  $\pm$  S.D. (n = 6). One way ANOVA followed by Duncan's multiple test range post hoc. P < 0.05; a: Group II (ISO Induced) compared with Group I (Control); b: Group III (MA-treated) compared with Group II (ISO-induced); NS: Non-significant

Isoproterenol administration in rats leads to increased lipid peroxidation and eventually extensive necrosis of the cell membrane. As a result of this selected marker enzymes like serum LDH and CK increase in myocardial infarction. The increased activity of these enzymes in a body fluid with a subsequent decrease in the heart is due to their leakage from cardiac tissue as a result of isoproterenol-induced necrosis. In Modified, Arjunarishta treated group the activity of these enzymes in serum was decreased while it increases in cardiac tissue. Among the several cardiac markers, troponin is the primary one. Cardiac Troponin I and Troponin T have been showed to be highly sensitive and specific markers of myocardial cell injury (Alpert *et al.*, 2000). These markers are normally not found in the blood as they are contractile protein. During myocardial necrosis, they get released into blood (Gupta and De lemos, 2007). The increased levels of Troponin are due to isoproterenol-induced cardiac damage. Isoproterenol followed by modified Arjunarishta post-treated group showed a decrease in the level of Troponin I and Troponin T markers. Thereby it is revealed that modified Arjunarishta have a cardiotherapeutic effect.



**Figure 7: Effect of MA on Free fatty acid and Phospholipids in Experimental rat;** Results are expressed as mean  $\pm$  S.D. (n = 6). One-way ANOVA followed by Duncan's multiple test range post hoc. P < 0.05; a: Group II (ISO Induced) compared with Group I (Control); b: Group III (MA-treated) compared with Group II (ISO-induced); NS: Non-significant

The present study has shown an increase of serum lipids in Isoproterenol induced cardiotoxic group II Myocardial infarcted rats. Lipid peroxidation can play an important role in lipoprotein modifications, which makes them susceptible to atherogenesis, which could be the reason for acute myocardial infarction mediated cardiotoxicity by isoproterenol (Nirmala and Puvanakrishnan, 1996). The studies of Prabhu *et al.* 2006a also correlated that isoproterenol induces lipid peroxidation and accelerates myocardial necrosis. Increased level of TGL and cholesterol is associated with cardiovascular disturbances, and

isoproterenol promotes lipolysis in the myocardium. Enhancement of lipolysis and subsequent elevation of plasma free fatty acids levels may lead to an increase in hepatic Triglyceride synthesis and secretion of increased TGL and cholesterol. In modified arjunarishta treated group of rats, the level of serum lipid was reduced significantly. Modified arjunarishta is a polyphenol possessing antioxidant property which could have inhibited lipid peroxidation due to its scavenging lipid peroxy and alkoxy radicals and thereby treating continued obstruction of hydrogen from cellular lipids. The improvement of hyperlipidemia may also be due to the significant reduction in lipolysis and hence decreased the level of TGL and FFA are observed. The increased levels of phospholipid in group III rats could be due to its anti-lipid peroxidative property, which could have protected tissue membrane phospholipid from isoproterenol mediated peroxidation damage.

An increase in the level of total cholesterol increases the risk of myocardial infarction. The increased concentration of cholesterol in serum could be due to a decrease in HDL cholesterol since HDL cholesterol is known to be involved in the transport of cholesterol from the systematic circulation into the liver for its catabolism. Alteration in lipid composition found in isoproterenol-treated cardiac tissue might have been due to the destruction of cardiomyocytes. Paritha and Devi (1997) reported an increase in lipid levels in isoproterenol-induced rats and this might have been due to enhanced lipid biosynthesis by cardiac cAMP.

## CONCLUSION

In conclusion, the obtained results indicate that the curative role of modified arjunarishta in isoproterenol-induced myocardial infarcted rats could be related to its antioxidant defence system. Our results had shown that modified arjunarishta was safe and highly effective in treating cardiovascular dysfunction in rats, possibly due to both antioxidative and cardiotoxic properties. This study coated that modified arjunarishta is one of the promising herbal drugs for improving defence mechanism in the physiological system against oxidative stress caused by myocardial infarction.

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