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Cardioprotective effect of *Curcuma longa* (turmeric) on serum cardiac marker enzymes in isoproterenol induced myocardial infarction in rats

Qazi Shamima Akhter [1] and Sharmin Nahar [2,*]

[1] *Qazi Shamima Akhter, Department of Physiology, Dhaka Medical College, Dhaka, Bangladesh.*
[2] *Sharmin Nahar, Department of Physiology, National Institute of Cardiovascular diseases and Hospital, Dhaka, Bangladesh.*

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Abstract

Myocardial infarction is one of the major causes of global premature mortality and morbidity. As a traditional medicine, *Curcuma longa* have been used to reduce risk of cardiovascular disease. This study was designed to evaluate the cardioprotective effect of *Curcuma longa* in isoproterenol induced myocardial infarction in rats. Total 28 Wistar albino male rats were divided into BC (base line control group), ISP (isoproterenol treated control group), CLP-ISPT (*Curcuma longa* pretreated and isoproterenol treated group) and AP-ISPT (amlodipine pretreated and isoproterenol treated group). At the end of experiment, all the rats were sacrificed. Blood samples were collected from the heart. Serum Aspartate Aminotransferase (AST), Lactate Dehydrogenase (LDH) and Creatine Kinase-MB (CK-MB) levels were estimated to assess myocardial injury. The statistical analysis was done by one-way ANOVA, followed by Bonferroni test. In this study, mean serum AST, LDH and CK-MB levels were significantly ($P<0.001$) higher in ISP than those of BC. Again, mean serum AST ($P<0.001$), LDH ($P<0.01$), CK-MB ($P<0.05$) levels were significantly lower in CLP-ISPT and AP-ISPT than those of ISP group. From the results, it can be concluded that *Curcuma longa* has cardioprotective effect on isoproterenol induced myocardial infarction in rats.

Keywords: *Curcuma longa*; Cardioprotective; Myocardial infarction; Isoproterenol; Amlodipine

1. Introduction

Cardiovascular diseases representing 31% of all global death in 2012 [1]. Among these, myocardial infarction causes majority of mortality and morbidity in both developed and developing countries [2]. In developing countries cardiovascular diseases emerging as a major disease burden due to increase prevalence of cardiovascular risk factors [3].

Myocardial infarction (MI) is characterized by an inequality of coronary blood supply and myocardial demand, resulting ischemic injury and necrosis of myocardial cells [4]. In myocardial ischemia, oxidative stress occurs due to generation of reactive oxygen species (ROS) which play a major role in the development of MI [5].

Isoproterenol (ISP) is a potent, synthetic, non- selective β adrenoceptor agonist [6]. It is used to produce myocardial injury in experimental animals to evaluate beneficial effects of cardioprotective agents on cardiac dysfunction [7]. Subcutaneous injection of ISP in experimental animals causes severe oxidative stress in myocardium resulting infarct like lesion in the heart muscles [8]. It generates free radicals and stimulates lipid peroxidation that causes irreversible

* Corresponding author: Sharmin Nahar
Sharmin Nahar, Department of Physiology, National Institute of Cardiovascular diseases and Hospital, Dhaka, Bangladesh.

damage to the myocardial membrane in experimental myocardial infarction [9]. Thus, elevates different cardiac biomarker enzymes in serum e.g. - AST, LDH and CK-MB due to cell necrosis [10, 11].

Curcuma longa (Turmeric) belongs to the Zingiberaceae family, is commonly used as spice. It is a medicinal plant extensively used in Ayurveda, Unani and Siddha system of medicine as home remedy for various diseases. The various beneficial effects of *Curcuma longa* include antioxidant, anticancer, anti-inflammatory, antidiabetic, hypolipidemic and wound healing activities among many others [12]. The rhizomes of *Curcuma longa* are cheap and easily available in our country and play an important role in primary health care. The main active compound of *Curcuma longa* is curcumin which have a wide range of biological effects including anti-inflammatory, antioxidant, antitumor, antibacterial, and antiviral activities [13].

Amlodipine is the third generation dihydropyridine type of calcium channel blocker. It prevents chest pain (angina). It inhibits the transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle. It has most potent antioxidant activity that provides protection against the ischemic myocardial injury by decreasing myocardial oxygen demand [14, 15].

Some researchers observed that serum AST, LDH and CPK levels were significantly increased in rats treated with doxorubicin (2.5 mg/kg body weight, i.p.) for two weeks. Curcumin, the active component of *Curcuma longa* significantly decreased the levels of these cardiac marker enzymes. These findings suggested that curcumin maintained the normal structural and architectural integrity of cardiomyocytes [16].

Some other investigators demonstrated the cardioprotective effect of amlodipine in oxidative stress induced by experimental myocardial infarction in rats. Here, amlodipine significantly decreased serum AST and LDH levels and protected the myocardium from adrenalin induced myocardial injury [17].

Therefore, the present study has been aimed to observe the cardioprotective effect of *Curcuma longa* on isoproterenol induced myocardial infarction in Wistar albino rats. Moreover, the findings of this study might be helpful to make the *Curcuma longa* acceptable among the people to prevent myocardial diseases.

2. Material and methods

This experimental study was carried out in the Department of Physiology, Dhaka Medical College, in 2015.

2.1. Purchase, preparation and animals' protocol

Table 1 Experimental groups

Experimental groups	Number of animals	Application
BC	7	Normal saline was given (1ml/kg body weight, orally) for 9 consecutive days.
ISP	7	Isoproterenol was administered (150 mg/kg body weight/day, subcutaneously) on 8th and 9th day.
CLP-ISPT	7	Ethanolic extract of *Curcuma longa* was given (200 mg/kg body weight, orally) for 9 consecutive days and isoproterenol (150 mg/kg body weight/day, subcutaneously) on 8th and 9th day.
AP-ISPT	7	Amlodipine was administered (5 mg/kg body weight, orally) for 9 consecutive days and isoproterenol (150 mg/kg body weight, subcutaneously) on 8th and 9th day.

Twenty-eight (28) Wistar albino male rats with aged 85 to 100 days and weighing 100 to 150 gm were selected for the study. The animals were purchased from the animal house of Department of Pharmacy, Jahangirnagar University, Savar, Dhaka. The animals were kept in metallic case in the animal house of Institute of Nutrition and Food Science, University of Dhaka. Before conducting the study, they were kept in a standard laboratory condition on a 12/12 hour light/dark cycle for acclimatization. Total study period was 23 consecutive days. During this period all the rats had free access to

food and water. After acclimatization, they were divided into 4 experimental groups (Table-1). After grouping, initial body weight of all the rats were measured on 1st day.

2.2. Preparation of blood sample

On the 10th day, after taking final body weight all the rats were anaesthetized by 30% chloroform and sacrificed. About 5ml of blood were collected from the heart of each rat and centrifuged at a rate of 4000 rpm for 5 minutes. Supernatant serum was collected and preserved in a refrigerator at -20°C for biochemical analysis.

2.3. Serum biochemical assay

Serum Aspartate Aminotransferase (AST) level was estimated by Colorimetric method [18]. Serum Lactate Dehydrogenase (LDH) [19] and Creatine Kinase-MB (CK-MB) [20] levels were estimated by ELISA method to assess myocardial injury.

2.4. Statistical analysis

Statistical analysis was done by one way ANOVA and Bonferroni test to compare all the parameters between the groups as applicable. p value <0.05 was accepted as level of significance. Statistical analysis was performed by using SPSS (Statistical package for social science) Version 22.

3. Results

3.1. Effect on body weight

The initial and final body weights of all the rats were almost similar and showed no statistically significant difference among the groups. (Table-2).

Table 2 Initial and final body weight in different groups of rats (N=28)

Groups	Initial body weight (gm)	Final body weight (gm)
BC	127.14 ± 14.96	122.85 ± 11.12
ISP	127.14 ± 11.12	112.85 ± 11.12
CLP-ISPT	115.71 ± 13.97	111.71 ± 10.67
AP-ISPT	118.57 ± 3.77	114.42 ± 4.23

Values are means ± SD. Statistical analysis was done by one-way ANOVA and then Bonferroni test. N = Number of rats. BC= Baseline control group, ISP= Isoproterenol treated control group, CLP-ISPT= *Curcuma longa* pre-treated and isoproterenol treated group & AP-ISPT= Amlodipine pre-treated and isoproterenol treated group

3.2. Effects on serum cardiac marker enzymes

Table 3 Serum cardiac marker enzymes level in different groups of rats (N=28)

Parameter (U/L)	Groups			
	BC	ISP	CLP-ISPT	AP-ISPT
AST	35.70 ± 2.71	614.92 ± 73.39***	42.41 ± 3.02^^^	35.21 ± 3.37###
LDH	206.7 ± 73.61	731.59 ± 124.41***	452.87 ± 105.87^^	411.50 ± 111.43###
CK- MB	12.84 ± 2.80	51.47 ± 10.65***	33.87 ± 6.81^	33.28 ± 8.66#

Values are means ± SD. Statistical analysis was done by one-way ANOVA and then Bonferroni test. N = Number of rats. For AST, LDH & CK-MB (***P<0.001, BC vs ISP). For AST (^^^P<0.001, ISP vs CLP-ISPT, ###P<0.001, ISP vs AP-ISPT). For LDH (^^P<0.01, ISP vs CLP-ISPT; ###P<0.001, ISP vs AP-ISPT). For CK-MB (^P<0.05, ISP vs CLP-ISPT; ##P<0.01, ISP vs AP-ISPT). BC= Baseline control group, ISP= Isoproterenol treated control group, CLP-ISPT= *Curcuma longa* pre-treated and isoproterenol treated group & AP-ISPT= Amlodipine pre-treated and isoproterenol treated group.

Mean serum AST, LDH and CK-MB levels were significantly (P<0.001) higher in ISP in comparison to those of BC. Again, mean serum levels of AST (P<0.001), LDH (P<0.01) and CK-MB (P<0.05) were significantly lower in CLP-ISPT and AP-ISPT in comparison to those of ISP. Moreover, mean serum LDH level were significantly higher in CLP-ISPT (P<0.01)

and AP-ISPT ($P<0.05$) compared to BC. Mean serum CK-MB levels were also significantly ($P<0.01$) higher in CLP-ISPT and AP-ISPT compared to BC. But there was no significant difference in mean serum AST, LDH and CK-MB levels between CLP-ISPT and AP-ISPT. (Table-3).

4. Discussion

In the present study, the body weight of the rats in all experimental groups was relatively unchanged. Similar type of observation was found by different research worker [21].

Again, this study reveals serum AST, LDH and CK-MB levels were significantly higher in ISP in comparison to those of BC but these changes were significantly lower in CLP-ISPT and AP-ISPT when compare with ISP. Similar findings were also observed by some other researchers of different countries [17, 22, 23]. Again, non-significant difference in these enzymes level was observed when compare with CLP-ISPT and AP-ISPT. Further evaluation of the study can be done to support these findings.

It has been suggested that high doses of isoproterenol injection have the ability to destroy myocardial cells by increasing ionotropic effect of the heart that increase oxygen demand of the myocardium. As a result, cytosolic enzymes are released into the bloodstream due to increased cell membrane permeability [24]. Again, several studies have been demonstrated that alteration of membrane permeability, integrity and fluidity also occurs due to lipid peroxidation [25]. It has also been suggested that, alteration in the membrane bound enzymes affect the function of the heart [26]. High doses of injection ISP causes decrease in Na^{+}-K^{+} ATPase and Mg^{2+} ATPase activity and correspondingly increase in Ca^{2+}ATPase activity of the myocardial cell membrane. These enzymes are responsible for maintaining normal ion levels inside the myocyte and play an important role in the contraction and relaxation of the cardiac muscle. Again, this membrane bound ATPases are lipid dependent enzymes which initiate lipid peroxidation and destroy membrane phospholipid resulting in myocardial cell injury. Moreover, enhanced activity of Ca^{2+}ATPase causes increased formation of cAMP and depletes high energy phosphate stores [27]. As a result, complex biochemical and structural changes occur in the cardiac muscle cells leading to cell damage and necrosis [28].

In this study, isoproterenol induced myocardial injury in rats was assessed by serum AST, LDH and CK-MB levels. These changes may be due to increased production of free radicals which initiate lipid peroxidation and subsequent myocardial cell damage. Whereas, decreased serum AST, LDH and CK-MB levels observed in CLP-ISPT suggested that the *Curcuma longa* extract may be responsible for cardioprotection against ISP induced myocardial injury. According to the suggestions made by different investigators, this effect is due to antioxidant and free radical scavenging activity of *Curcuma longa* which inhibits lipid peroxidation.

5. Conclusion

The result of the present study reveals that *Curcuma longa* has cardioprotective effect on isoproterenol induced myocardial infarction in rats. Therefore, *Curcuma longa* may be used as a good source of cost- effective medicine for the prevention of myocardial infarction.

Compliance with ethical standards

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Disclosure of conflict of interest

The authors hereby disclose no conflicts of interest regarding the publication of this paper.

Statement of ethical approval

The animals were maintained throughout of experiment in accordance with the recommendations of the guide for the care and use of laboratory animals. Ethical clearance of this study was obtained from Research review committee and Ethical review committee of Dhaka Medical College, Dhaka.

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