Cardio-Protective Effects of *Ipomea Biloba* Against the Myocardial Infarction in Rats

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ABSTRACT

Background: The myocardial infarction is commonly known as the heart attack and it occurs during the decline of blood and oxygen supply to the cardiac tissues due to the occlusion of atherosclerotic plaques in the coronary artery. The ischemic heart diseases were remaining the prime most cause of death in both developed and developing nations, accounting for nearly 20% of all deaths per year worldwide. **Materials and methods:** The myocardial infarction was induced to the rats by injecting subcutaneously with 85mg/kg/b.wt of Isoproterenol. The heart and body weight was measured and tabulated. The levels of creatine kinase, creatine kinase-MB, and the cardiac troponins (cTnT and cTnI) in the serum experimental animals were investigated by using ELISA assay kits. The level of TBARS and antioxidant enzymes i.e. superoxide dismutase, catalase, and glutathione was determined by the standard methods. **Results:**The treatment with the 150mg/kg of ethanolic extract of *I.biloba* leaves was showed increased the body weight and decreased the heart weight in myocardial infarction induced experimental animals. The extract treatment significantly increased the antioxidant enzymes i.e. superoxide dismutase, catalase and glutathione levels in the heart tissues of myocardial infarction induced rats. The extract treated experimental animals also showed the decreased levels of CK, CK-MB, cTnT and cTnI in the serum of Isoproterenol challenged experimental animals. **Conclusion:** The findings of this present research work were proved that the ethanolic extract of *Ipomea Biloba* leaves has the therapeutic potential against the Isoproterenol induced myocardial infarction in experimental rats. Though, further research was needed in the future to recognize the precise curative mechanisms of *Ipomea Biloba* leaves against the myocardial infarction.

Key Words: Myocardial infarction, *Ipomea Biloba,* Isoproterenol, cardiotoxins, antioxidant enzymes, and cardio-protection.

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INTRODUCTION

The ischemic heart diseases were remaining the prime most cause of death in both developed and developing nations, accounting for nearly 20% of all deaths per year worldwide. Myocardial infarction is the foremost form of ischemic heart disease and it is distinguished by a disproportion of coronary blood supply and myocardial demand that often leads to ischemia and myocardial death [1]. Cardiovascular ailments are a group of disorders of the heart and blood vessels that includes coronary heart disease, cerebrovascular disease, peripheral arterial disease, rheumatic heart disease, congenital heart disease, deep vein thrombosis and pulmonary embolism [2]. The experimental and clinical investigations were revealed that during the ischemic injury, oxidative stress developed via the accumulation of reactive oxygen species that plays a vital function in the progression of myocardial

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infarction. The results of the Animal study conducted by inducing coronary artery stenosis, elevation of ST segment in the electrocardiogram was related to a reduced heart creatinine kinase activity and we discovered that there was a myocardial tissue necrosis in histological evaluation [3]. In ischemic heart tissues, the free radicals and reactive oxygen species were influenced in oxidative chain reactions that injure the cell membrane and then induce the structural and metabolic alterations, which resulting in the cardiac dysfunction and ultimately myocardial cell death.

The myocardial infarction is generally termed as a heart attack. It occurs while the reduction in the blood and oxygen supply to the cardiac muscles due to the occlusion of atherosclerotic plaques in the coronary artery that leads to the heart cell necrosis [4]. The numerous processes offered that the accumulation of free radicals was influenced by the pathological processes of myocardial infarction [5]. The myocardial infarction is distinguished by the imbalance between the coronary blood supply and demand that often leads to myocardial ischemic damage and injuries to the cardiomyocytes [6]. The numerous preclinical investigations, as well as many clinical examinations, revealed that during ischemic damage, the increased oxidative stress generated via the accretion of reactive oxygen species takes a central function in the pathological mechanisms and the progression of myocardial infarction. The ischemia surpasses is a severe level in the protracted period in myocardial infarction and leads to the everlasting myocardial cell damage or even cell necrosis [7].

The isoproterenol is a synthetic β-adrenergic receptor agonist, which causes serious stress to the myocardium and leading to the infarct-like cell necrosis of the heart muscles. The isoproterenol-induced animal models of myocardial necrosis provide the well established and distinguished replica to examine the different cardiac dysfunctions and to investigate the potency of numerous natural and synthetic cardioprotective agents [8]. The myocardial infarction stimulated via isoproterenol was reported to display the numerous metabolic as well as morphological anomalies in the heart tissues of the experimental animals that are quite similar to those noted in the human myocardial infarction. The isoproterenol stimulated tissue necrosis is multifaceted processes that involved in relative hypoxia, coronary insufficiency, alternations in the metabolic process, reduced levels of high energy phosphate stores, intracellular Ca2± overload, changes in electrolyte content, and oxidative stress [9]. The isoproterenol induction often results in the augmented heart rate (tachycardia) that predisposes patients to cardiac dysrhythmias [10].

Ever since the prehistoric period, the uncountable Indian herbal plants were utilized as conventional medicines and these plants were possessed enormous biological and pharmacological benefits and used to the management of widespread diseases in humans that including cardiovascular diseases [11]. The herbal plants play an essential function in the medicinal applications as well as in the pharmaceuticals. Herbal medicine was the oldest form of healthcare known to mankind, much of the medicinal use of plants have been developed through observation of wild animals, and by trial and error method. A wide range of medicinal plant parts is used for extract as raw drugs and they possess varied medicinal properties. The different parts used include roots, stems, flowers, fruits, twigs exudates, and modified plant organs. While some of these raw drugs are collected in smaller quantities and other raw drugs are collected in larger quantities and traded in the market as the raw materials for many herbal industries [12].

The *Ipomea Biloba* is an imperative herbal plant that belonged in the Convolvulaceae family. This plant was found to be a very vital source of bioactive compounds. The biological properties of the *Ipomea* plant are mentioned as antimicrobial, anticancer, anti-inflammatory and other ailments [13, 14]. The plant *I.biloba* is highlighted for its analgesic, antioxidant and anti-inflammatory, antinociceptive, antispasmodic, immunostimulant, antihistaminic, hypoglycaemic, insulinogenic, and antimicrobial properties [15, 16]. However, there were no pieces of evidence for the cardioprotective effects of *Ipomea Biloba* leaves. Hence, the present research was designed to evaluate the cardioprotective effects of the ethanolic extract of *I.biloba* leaves against the isoproterenol-induced myocardial infarction in experimental rats.

MATERIALS AND METHODS

Chemicals and reagents

Isoproterenol was acquired from the Sigma Aldrich (USA). All other additional chemicals and reagents were used in the analytical grade and the same was purchased from the Himedia chemicals, USA.

Ipomea Biloba plant leaf collection and extract preparation

The clean and matured leaves of *Ipomea Biloba* was collected from the Kolli Hills, Namakkal district, Tamilnadu, India. The collected leaves were thoroughly washed with running tap water shade-dried. Then the dried leaves were finely powdered by using a mechanical grinder and then the powder was utilized for the preparation of various extracts. The 10g of powder was weighed and extracted with 100ml of ethanol by the cold percolation method. Finally, the resulting extract was filtered with the Whatman No.1 filter paper and stored at 4°C for further use.

Experimental animals

The healthy and matured Wistar albino rats (male breeds) that weighing about 150-180g have opted for this current investigation and the same were acquired from the Institutional Animal House and all these experimental animals were acclimatized for one week in a standard laboratory conditions with the 12h light and dark sequences, about 60% air humidity and 25±3°C temperature. All animals were maintained in infection-free plastic cages and fed with standard pellet diet and water *ad libitum*. In this investigation, all the experiments were done by strictly following the rules stated by the Institutional Animal Ethical Committee.

Experimental design

Later than the one week acclimatization period, all rats have grouped arbitrarily into four with the 6 rats in each. The group-I rats were considered as control and supplemented with the standard pellet diet for 30 days, whereas the group-II rats were disease control rats that injected subcutaneously treated with 85mg/kg /b.wt of Isoproterenol to stimulate the myocardial infarction. Group-III rats were pretreated with the 150mg/kg of ethanolic extract of *Ipomea Biloba* leaves and the myocardial infarction was stimulated as mentioned in group-II. The group-IV rats were supplemented with the 150mg/kg of ethanolic extract of *Ipomea Biloba* leaves excluding the myocardial infarction induction. After the experimental period, all rats were anesthetized and sacrificed via cervical displacement and then the heart tissue was surgically excised from the rats and washed with ice-cold saline, dried using tissue paper. The heart tissue was weighed and stored immediately at -80°C for further analysis. The blood samples were collected in clean and anticoagulant coated bags and then serum was separated and used for further biochemical estimations.

Biochemical investigations

Estimations of myocardial enzymes

Measurement of serum creatine kinase and cardiac tropins levels

The serum creatine kinase activity in the experimental animals was examined by using the colorimetric method suggested by Wagner *et al*. (1973) [17]. The creatine phosphate and adenosine phosphate that developed because of the catalytic activity of creatine enzyme was measured colorimetrically and expressed as IU/L. The levels of creatine kinase MB and the cardiac troponins in the serum of both control and experimental animals were investigated via the commercially procured ELISA assay kits (Sigma Aldrich, USA).

Oxidative stress estimation

Assay of thiobarbituric acid reactive substances

The levels of lipid peroxidation were investigated through the TBARS assay by using the procedure described by Yagi (1978) [18].The levels of oxidative stress-induced in control and experimental rats were examined via investigating the malondialdehyde levels present in the serum of rats. The secondary product of lipid peroxidation malondialdehyde reacts with the thiobarbituric acid reactive substance to produce pink chromogen which estimated at 532nm using the microplate reader.

Preparation of heart tissue homogenate

After the animal sacrifice, the heart was instantly separated from the nearby tissues and was washed twice with the ice-cold phosphate-buffered saline solution. Then the heart tissues were homogenized on phosphate buffer to get an about 10% w/v homogenate. The resultant homogenate was centrifuged at 1500rpm for 10min then the supernatant was collected and stored at -20°C until the usage. To improve the heart rate detection, many algorithms have been investigated [19].

Estimation of antioxidant enzyme levels

Determination of superoxide dismutase

The level of superoxide dismutase enzyme level in the heart tissue homogenate of both control and experimental animals have examined via the Kakkar et al. (1984) procedure [20]. The 0.1ml of cell lysate was diluted to 0.2ml with the double-distilled water subsequently to the addition of 1ml of ethanol and 0.6ml of ice-cold chloroform. Then this reaction mixture was shaken well and included with 480µl of sodium pyrophosphate buffer, 40µl of phenazine methosulphate, 120µl of nitroblue tetrazolium. The reaction was initiated by the addition of NADH (80µl) and then incubated for 2mins at 30°C. Finally, the absorbance was taken 520nm.

Determination of catalase enzyme level

The catalase enzyme level in the heart tissue homogenate of both control and experimental animals were examined by the method of Beers and Sizer, (1952). 0.1ml of cell lysate was mixed with a 1.9ml phosphate buffer [21]. Then the 1ml of hydrogen peroxide was mixed. Finally, the absorbance was taken at the 240nm in a one-minute interval for three minutes. The control solution was placed on the reference containing 0.1ml of cell lysate & 2.9ml of the phosphate buffer.

Assay of glutathione level

The glutathione level in the heart cell lysate was assayed by the method of Sedlak and Lindsay (1968) [22]. The portion of the tissue homogenate was weighed and mixed with the EDTA solution. The distilled water and trichloroacetic acid were added with the tissue homogenate then this suspension was centrifuged at 6000rpm for 6 minutes. Then the upper layer was

collected and mixed to the tris buffer and DTNB (Ellman's reagent) and shaken vigorously. Finally, the absorbance was taken at 412nm.

Measurement of heart and body weight ratio

The heart weight and body weight ratio of both control and experimental animals were determined. The body weight of each animal on the day of sacrifice was measured by using the sensitive electronic balance. The heart weight was measured after washing it in an ice-cold buffered saline solution after removal from the animals, and squeezing out the blood and blotted on the filter paper.

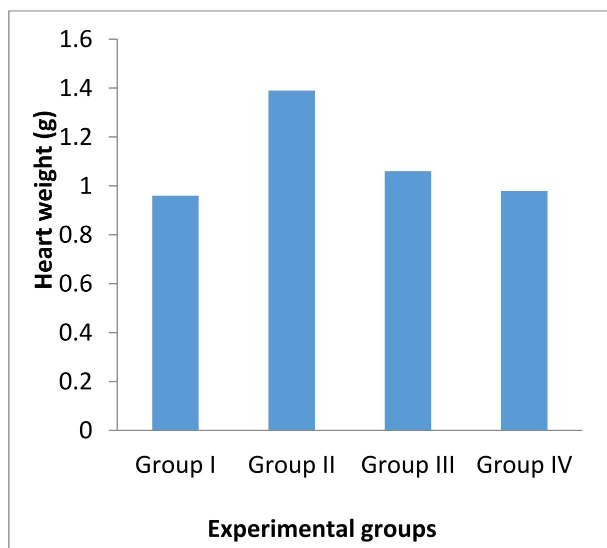
Statistical analysis

The results were described as mean±standard deviation. The differences among the groups were analyzed with one-way analysis of variance (ANOVA) followed by Duncan multiple range test by SPSS (version 19). The significance level was set as $p<0.05$.

RESULTS

Effect of ethanolic extract of *Ipomea Biloba* leaves on heart and bodyweight of experimental rats

The significant elevation in the heart weight and decrease in the body weight was observed in the myocardial infarction stimulated experimental rats when compared to the control and 150mg/kg of ethanolic extract of *I.biloba* leaves alone treated animals (Figure 1). The treatment with the 150mg/kg of ethanolic extract of *I.biloba* leaves to the myocardial infarction induced experimental rats was showed an appreciable increase in the body weight and decrease in the whole heart weight of experimental animals when compared to the Isoproterenol treated rats. The control animals and ethanolic extract of *I.biloba* leaves alone treated animals were showed a similar kind of results.



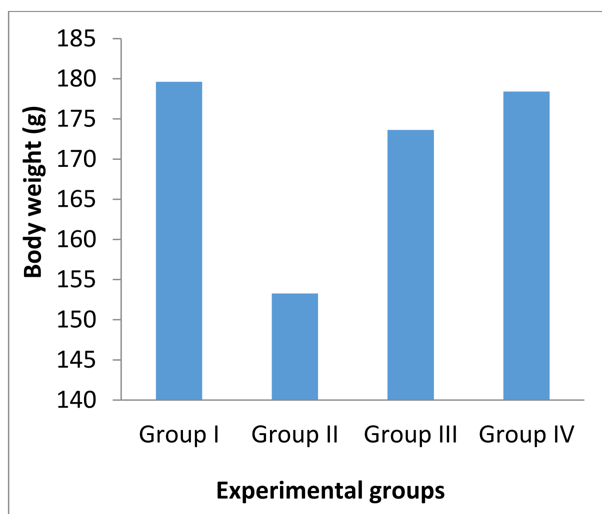
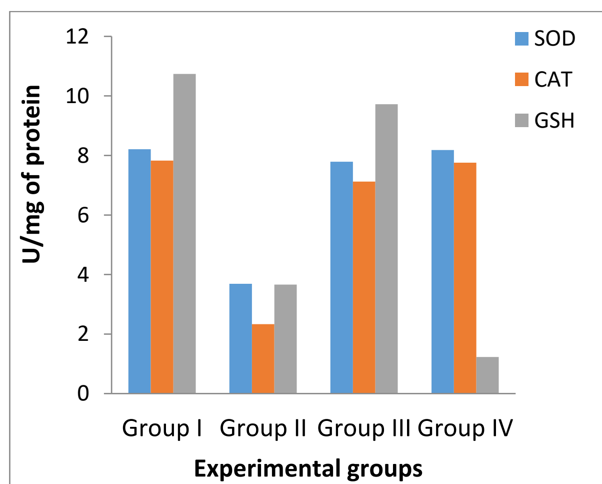


Figure 1: Effect of ethanolic extract of *Ipomea Biloba* leaves on heart and body weight

Effect of ethanolic extract of *Ipomea Biloba* leaves on lipid peroxidation and antioxidant enzymes level in experimental rats

The Isoproterenol administered rats were showed a remarkable reduction in the levels of the antioxidant enzyme like superoxide dismutase, glutathione, and catalase and increased the lipid peroxidation in the heart tissues of myocardial infarction induced experimental rats when compared to the control animals. Interestingly, the treatment with the 150mg/kg of ethanolic extract of *Ipomea Biloba* leaves was significantly increased the antioxidant enzymes level in the heart tissues of myocardial infarction induced experimental animals (Figure 2). The Isoproterenol challenged rats were showed the drastic elevation in the lipid peroxidation (TBARS) level than the normal control animals. While the ethanolic extract of *I.biloba* leaves treatment was significantly attenuates the Isoproterenol induced oxidative stress in experimental rats. A completely similar kind of result was observed between the control and 150mg/kg of ethanolic extract of *I.biloba* leaves alone treated groups.



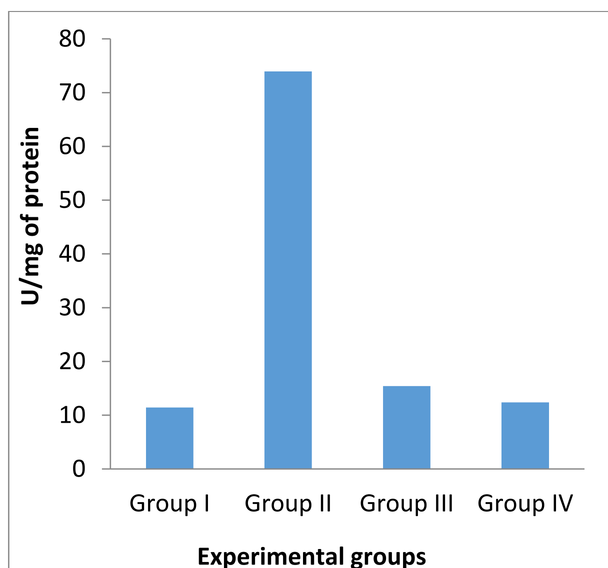


Figure 2: Effect of ethanolic extract of *Ipomea Biloba* leaves on lipid peroxidation and antioxidant enzymes level

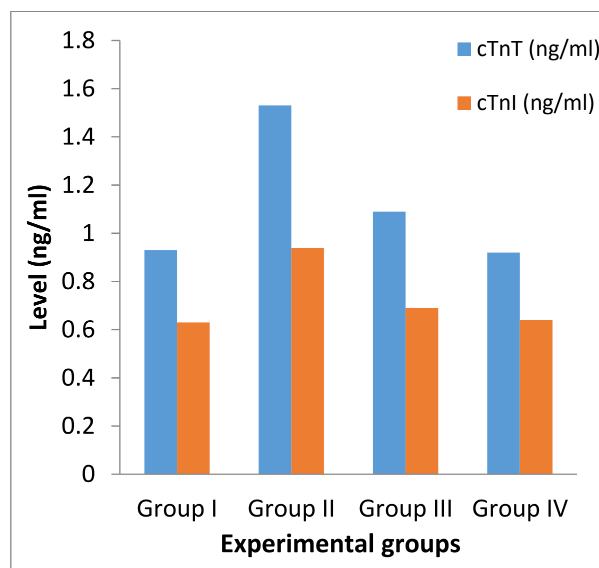
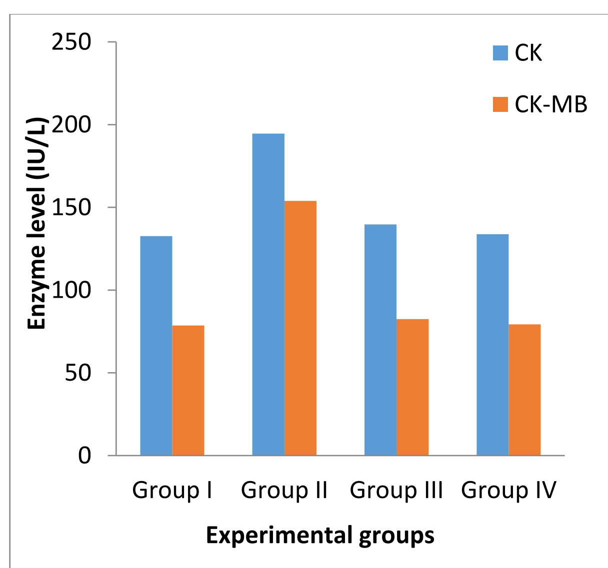


Figure 3: Effect of ethanolic extract of *Ipomea Biloba* leaves oncreatine kinase and cardiotoxins

Effect of ethanolic extract of *Ipomea Biloba* leaves oncreatine kinase and cardiotoxins in the experimental rats

As mentioned in Figure 3, the level of creatine kinase (CK), creatine kinase-MB, cardiotoxins (cTnT and cTnI) was notably increased in the serum of myocardial infarction induced experimental animals. However, the treatment with the 150mg/kg of ethanolic extract of *Ipomea Biloba* leaves amazingly decreased the levels of CK, CK-MB, cTnT and cTnI in the serum of Isoproterenol challenged experimental animals (Figure 3). The control animals and the 150mg/kg of ethanolic extract of *I.biloba* leaves alone treated animals were showed a similar kind of results.



DISCUSSION

The findings of this current investigation were revealed that the ethanolic extract of *Ipomea Biloba* leaves was possessed the appreciable cardioprotection against the isoprenaline stimulated myocardial infarction by attenuating the alterations in heart and body weight, increasing antioxidant enzymes and decreasing the leakage of myocytes injury marker enzymes. The Isoproterenol stimulated myocardial infarction is a widely utilized *in vivo* animal replica for the experimental investigation of cardioprotective functions of sample agents as it possessing the clinical pertinent in recapitulating the features of human myocardial infarction [23]. The subcutaneous injection of Isoproterenol results in the disproportion between the supply of oxygen and demand by the cardiomyocytes via elevating the chronotropic and inotropic important to the overt myocardial function and increase in the calcium overload in the myocardium [24]. Also, the metabolic mechanisms and auto-oxidation of Isoproterenol participated in the pathological processes and disease progression of myocardial infarction via accumulating the free radicals [25]. After the challenge with Isoproterenol, the drastic reduction in the protective functions of endogenous antioxidants of the heart tissues results in the steady loss of antioxidant balance that accretes in the cardiomyocytes and apparent as oxidative tissue injuries. The endogenous antioxidant enzymes like superoxide dismutase, catalase, and glutathione peroxidase are the first line cellular defense against the oxidative stress and work against the generation of numerous reactive oxygen species that includes superoxide anions and hydroxyl radicals [26]. The noticeable decrease in the enzymatic functions of superoxide dismutase, catalase, and glutathione, after the

Isoproterenol challenge, denotes the increased generation and functions of free radicals that lead to the oxidative damage to the myocardial tissues. Many clinical researches revealed that higher OPG levels which is related to cardiovascular complications is involved with vascular calcification, advanced atherosclerosis, heart failure, abdominal aortic aneurysm, other diabetic complications and fatality [27].

Later than the Isoproterenol challenge, the immense quantity of various reactive oxygen species was developed that owing to the auto-oxidation, which reacts with the polyunsaturated fatty acids present within the cell membrane thereby initiating the processes lipid peroxidation. The myocardium consists of the plentiful amount of diagnostic marker enzymes and once it was metabolically injured, they released its contents into the extracellular fluids [28]. The lipid peroxidation is an imperative pathological process in myocardial infarction and the generated lipid peroxides imitate the numerous phases of the ailment and its difficulties [29]. The superoxide dismutase enzymes catalyzed the dismutation of the superoxide anions (O_2^-) into the hydrogen peroxide and molecular oxygen [30]. The overexpression of the superoxide dismutase guards against the apoptosis and stimulates cell differentiation [31]. The measurement of superoxide dismutase provides knowledge about cell oxidative stress levels. The catalase enzymes usually catalyze the decomposition of hydrogen peroxide to water and oxygen molecules and assist in the disposal of hydrogen peroxide molecules [32]. The catalase assay is performed to determine the level of oxidative stress of the cells. The thiobarbituric reactive substances measurement was utilized to the viewing and examining the lipid peroxidation levels that is a very important indicator of the intracellular oxidative stress level [33]. This measurement was providing imperative information about the free radical activities in the disease conditions.

In this present study, we observed that the levels of antioxidant enzymes like superoxide dismutase, catalase and glutathione were notably reduced and level of TBARS, a lipid peroxidation marker was drastically increased in the Isoproterenol challenged myocardial infarction induced animals that denotes the increased oxidative stress. Interestingly, the treatment with the 150mg/kg of ethanolic extract of *Ipomea Biloba* leaves to the myocardial infarction induced rats were showed increased antioxidant enzymes like superoxide dismutase, catalase, and glutathione levels and also decreased the lipid peroxidation marker i.e. TBARS level in the myocardial infarction induced animals.

The lipid peroxidation is a receptive index of oxidative stress, but also it is an imperative pathological process in the myocardial cell death, and the generation of lipid hydroperoxides that imitates the injury of cardiac constituents [24]. The reduction in the level of glutathione enzyme may lead to increased lipid peroxidation that can able to increased the consumption of glutathione enzyme in the number of chronic diseases such as cardiovascular diseases, cancer and neurodegenerative [34]. The myocardial tissues contain numerous cardiac enzymes like creatinine kinase, lactate dehydrogenase, and aspartate transaminase. At the time of Isoproterenol's challenge to the animals, the oxygen demand of the heart drastically increased with elevation in the ionotropic activity in the heart tissues that lead to prolonged ischemia and glucose reduction. The myocardial cells were injured with the elevated muscle contractility that leads to the increased permeability of the cell membranes that permitting the cardiac enzymes to leak out into the bloodstream [35]. The creatine kinase is an enzyme that able to reversibly transfer the phosphate group from the energy storage form of creatine phosphate to a molecule of ADP, producing ATP. The CK-MB was restricted primarily in the heart tissues and this makes it an important analytical tool for myocardial infarction since injure specific to the myocardium may lead to the increase of CK-MB levels [36]. In this current investigation, the levels of creatine kinase, creatine kinase-MB, cardiotoxins i.e. cTnT and cTnI were drastically elevated in the serum of Isoproterenol challenged myocardial infarction induced experimental animals. Interestingly, the treatment with the 150mg/kg of ethanolic extract of *Ipomea Biloba* leaves was appreciably decreased the CK, CK-MB, cTnT and cTnI levels in the serum of Isoproterenol induced experimental rats (Figure 3). The overall results of this present research work were proved that the ethanolic extract of *Ipomea Biloba* leaves has the therapeutic potential against the Isoproterenol induced myocardial infarction in experimental rats.

CONCLUSION

The findings of this present research work were showed that the ethanolic extract of *Ipomea Biloba* leaves was possessed the potential cardioprotective activity against the Isoproterenol induced myocardial infarction in experimental rats. The extract treated experimental animals were noticeably decreased the heart weight, increased the body weight, elevated the antioxidant enzymes level and significantly reduced the creatine kinase and cardiotoxins level in the myocardial infarction induced experimental rats. These findings were proved that the plant *Ipomea Biloba* leaves may use for the treatment of myocardial infarction. However, further research works still needed in the future to understand the exact therapeutic mechanisms of *I.biloba* leaves against the myocardial infarction.

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