

## Exploring the Cardioprotective Effects of *Pterolobium Hexapetalum* Roth Extract Against Isoproterenol-Induced Myocardial Infarction in Rats: A Focus on Beta1-Adrenergic Agonism

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### ABSTRACT

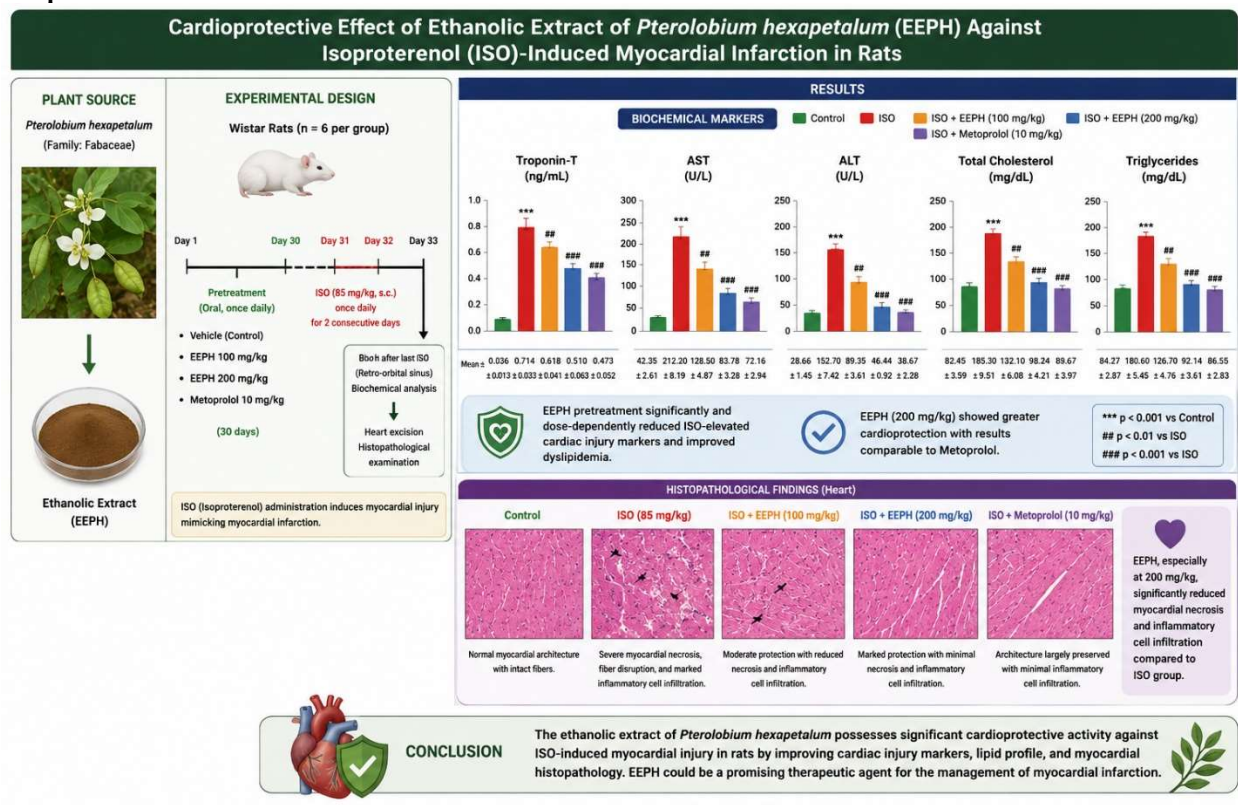
**Objective:** The present study aimed to evaluate the cardioprotective effect of the ethanolic extract of *Pterolobium hexapetalum* (EEPH) against ISO-induced myocardial infarction in Wistar rats and to investigate its possible role in preserving myocardial integrity.

**Methods:** Rats were pretreated orally with EEPH at doses of 100 or 200 mg/kg/day for 30 days. MI was induced by subcutaneous administration of ISO (85 mg/kg body weight) at 24-hour intervals for two consecutive days (days 31 and 32). Twenty-four hours after the final ISO injection, blood was collected from the retro-orbital sinus for biochemical analysis of cardiac injury markers. Hearts were excised for histopathological examination. Metoprolol served as the standard reference drug.

**Results:** ISO administration significantly elevated serum Troponin-T ( $0.714 \pm 0.033$  ng/mL), AST ( $212.2 \pm 8.19$  U/L), ALT ( $152.7 \pm 7.42$  U/L), total cholesterol ( $185.3 \pm 9.51$  mg/dL), and triglycerides ( $180.6 \pm 5.45$  mg/dL), confirming severe myocardial injury. Pretreatment with EEPH significantly and dose-dependently reduced these elevated biochemical markers. The higher dose of EEPH (200 mg/kg) demonstrated greater cardioprotection, with Troponin-T reduced to  $0.510 \pm 0.063$  ng/mL, AST to  $83.78 \pm 3.28$  U/L, and ALT to  $46.44 \pm 0.92$  U/L, showing results comparable to metoprolol. Lipid profile abnormalities were also significantly improved. Histopathological findings further supported these results by showing marked reduction in myocardial necrosis, inflammatory cell infiltration.

**Conclusions:** The ethanolic extract of *Pterolobium hexapetalum* possesses significant cardioprotective activity against ISO-induced myocardial injury in rats. These findings suggest that EEPH could be a promising therapeutic agent for the management of myocardial infarction.

Graphical Abstract:



**Keywords:** Myocardial Infarction, *Pterolobium Hexapetalum*, Isoproterenol, Troponin and Lipids.

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**Conflict of interest:** None

**I. INTRODUCTION**

Although many countries are currently attempting to deal with the double liability of infectious and non-communicable diseases, the latter, including cardiovascular diseases (CVD), instantly outcompeting traditional foes such as infectious diseases and malnutrition as the leading causes of premature mortality and disability, accounting for roughly 20% of all worldwide deaths per year. Other major factors involved, Changes in dietary habits over the past few decades, are one of the other key elements at play [1]. People become more sensitive to CVD as their diets vary, often containing a smaller proportion of complex carbohydrates and more sugar and animal fat. More people become obese, which increases the risk of morbidity and early death, especially from CVD and diabetes, when combined with decreased physical activity. High salt consumption elevates blood pressure, which in turn increases the risk of stroke [2] and coronary heart disease (CHD). Myocardial infarction is often referred to as a heart attack

or ischemic cardiac disease. The imbalance between the coronary blood supply and myocardial demand causes acute myocardial cell injury is known as MI, which is what causes it to happen [3]. For Acute coronary syndrome, chest discomfort, flushing, palpitations, and anxiety are signs of MI. Smoking, hypercholesterolemia, high low-density lipoprotein, low high-density lipoprotein, hyperlipoproteinemia, diabetes, high blood pressure, and obesity are major risk factors for MI. Arrhythmias, congestive heart failure, cardiogenic shock, ventricular aneurysm, and pericarditis are among the myocardial infarction complications [4]. MI remains a substantial public health concern that contributes significantly to mortality statistics, not only in developed nations but also in developing ones [5].

Experimental induction of Isoproterenol [1-(3, 4-dihydroxyphenyl)-2-isopropylamino ethanol hydrochloride] (ISO), a synthetic catecholamine and adrenergic agonist, produces severe oxidative stress in the myocardium, resulting in infarct-like necrosis of the heart

muscle [6]. Along with an increase in heart rate, isoproterenol enhanced myocardial VO<sub>2</sub>. However, both oxygen supply and myocardial blood flow increased. The myocardial oxygen extraction was reduced because of this increase outweighing the increase in myocardial VO<sub>2</sub> [7]. Isoproterenol induces cardiac necrosis through different mechanisms, including increased oxygen consumption, poor utilization of oxygen, increased overload and accumulation of calcium, altered metabolism of the myocardium, increased levels of cAMP in the myocardium, alteration in membrane permeability, cellular acidosis, and increased lipid peroxides [8].

*Pterolobium Hexapetalum*, belonging to the family *Fabaceae*, is a tropical and subtropical plant that is distributed in some hills of India and other regions of the world [9]. Different parts of *Pterolobium hexapetalum* are traditionally used for the treatment of fever, chest pain, cough, dog bites, ulcers, diarrhoea, constipation, jaundice, labour pain, and skin infections [10]. *Pterolobium hexapetalum* possesses antimicrobial, antifungal, antiulcer, antipyretic, and antidiarrheal properties [11]. *Pterolobium Hexapetalum* contains several pharmacologically active components such as Amino Acids, Steroids, Phenols, Alkaloids, Glycosides, Flavonoids, and 12 flavonoids in Leaf: Myricetin, Quercetin, Vitexin, Stem Bark contains Luteolin, Vitexin, and Anthocyanidins [12].

## 2. MATERIALS AND METHODS

### 2.1. Plant material

Fresh leaves and stem bark of *Pterolobium hexapetalum* (*roth*) *santapau* & *wagh*, were collected from Yercaud Hill Station-salem (T.N.) India. During September 2021, and was authenticated by SMPG, Mettur. Reference Letter no. 9-1/2020-21/SMPG/Mettur Dam/Authentication/259.

### 2.2 Extraction of *Pterolobium Hexapetalum*

Leaves and stems were collected, dried under shade & coarsely powdered using a mechanical grinder. The powder was then passed through a No.60 sieve. It was extracted by a continuous hot percolation process with petroleum ether, Chloroform, Acetone, Ethanol 99%v/v, and cold maceration using distilled water [13].

### Preliminary phytochemical screening

The ethanolic extract of *Pterolobium hexapetalum* was screened for the presence of various phytochemicals, such as Alkaloids, Phenolic compounds, sterols, Glycosides, and Flavonoids are present [12].

### 2.4 Drugs and Chemicals

Isoproterenol hydrochloride (Sigma Aldrich, USA), metoprolol (Pfizer), and ethanol (Sigma-Aldrich, St. Louis, Mumbai). All the chemicals and reagents used in this study were of analytical grade [14].

### 2.5 Experimental Animals.

Albino Wistar rats (120-150 g) of either sex or albino mice (20-25 g), female mice of approximately the same age, procured from the listed suppliers of Mass Biotech Chennai, were used for the study. They were housed in propylene cages in an air-conditioned room, maintained at standard humidity (40 ± 5%) and temperature (23 ± 2°C), and fed a standard commercial pellet diet (Hindustan Lever Limited, Bangalore) with ad libitum water [15]. The animals were exposed to alternating cycles of 12 hours of darkness and light. Before each test, the animals were fasted for at least 12 hours. The experimental protocol was reviewed and approved by the institutional Animal Ethics Committee. Bedding materials in the cages were changed daily [16]. Standard orogastric cannulae and syringes were used for drug administration. The protocols were approved by the Institutional Animal Ethical Committee [IAEC NO.-P.COL 34/2021/IAEC/VMCP].

### 2.6 Acute Toxicity Studies

The Organisation for Economic Co-operation and Development (OECD) regulates the guidelines for oral acute toxicity studies. This organisation minimises both the number of animals and the level of pain associated with acute toxicity testing. An acute Oral toxicity study was conducted, and the LD<sub>50</sub> values were calculated according to the OECD guidelines 423. An acute toxicity study aims to establish the therapeutic index is the ratio between the pharmacologically effective dose and the lethal dose, as well as to perform the primary screening [17]. The ethanolic extract of *Pterolobium hexapetalum* was administered orally once. Immediately after dosing, the mice were observed continuously for 4h for symptoms of toxicity such as tremors, convulsions, tonic extension, muscle spasm, loss of righting reflex, ataxia, lacrimation, and writing. The mice were then kept under observation for up to 14 days for any mortality.

### 2.7 Induction of Myocardial Infarction

Isoproterenol (ISO) 85 mg/kg was dissolved in physiological saline solution and injected subcutaneously into rats daily for two consecutive days to induce experimental myocardial infarction.

### 2.8 Experimental Design

The animals were acclimatized into five groups. Each group consisted of six rats [17].

Group 1 Control rats received distilled water (1ml/kg *p.o*).

Group 2 ISO control rats received Isoproterenol (85mg/kg,s.c)

Group 3 Standard group rats received Metoprolol(20mg/kg)

Group 4 Test 1 rats received a lower dose of EEPH (100mg/kg/day)

Group 5 Test 2 rats received a higher dose of EEPH (200mg/kg/day) for 30 days.

Isoproterenol(ISO)was injected on the 31st and 32nd day, and on the next day, blood was collected through the retroorbital vein under mild ether anesthesia. Plasma was obtained by cold centrifugation of the sample set at 3000rpm for 10min. Later, animals were sacrificed by cervical dislocation, and heart tissues were excised immediately, rinsed in ice-cold saline, and stored at 80 °C till further use the biochemical estimation and histopathological analysis. The initial and final body and heart weights of the rats were measured [18].

### 2.9 Biochemical assay

The collected serums were through estimate of the cardiac marker enzyme Troponin. The troponin-T levels were estimated by the ROCHE TROP T kit method. Alanine aminotransferase (ALT), Aspartate aminotransferase (AST), and serum levels were also estimated for the lipid profile, including Cholesterol (C), Triglycerides (TG) were estimated by the CHOD-PAP method [19].

### 2.10 Histopathological Assessment of Myocardial Damage

At the end of each scheduled duration, the control and treated rats were sacrificed by using cervical dislocation, and the heart was dissected. The heart was fixed in Bouin's fluid for 24 hrs and washed with water to remove the colour of Bouin's fluid and dehydrated in alcohol in ascending and descending orders, embedded in paraffin, and cut at 5µm (Automatic tissue processor, Lipshaw) in a rotary microtome. The sections were then deparaffinized in xylene and stained with hematoxylin-eosin using a routine method [18]. The section was then stained with haematoxilin-eosin dye (Merck) and mounted with Canada balsam. Histopathological slides

were examined, and photographs were taken using a digital stereomicroscope.

### 2.11. Statistical analysis

The results of all the above estimations are indicated in terms of means + SEM. Differences between the groups were statistically determined by analysis of variance, one-way ANOVA with Tukey post-test using GraphPad Prism version 8.00. The level of significance was set at  $p < 0.05$ .

## 3. RESULTS

### 3.1 Preliminary Phytochemical Screening

Preliminary phytochemical analysis of *P.hexapetalum* revealed the presence of the following active constituents: amino acids, Alkaloids, Phenolic compounds, Glycosides, and Flavonoids.

### 3.2 Effect of Acute Toxicity Study of EEPH

The observation indicated that EEPH showed no changes in behaviour up to 4 h, and no mortality was observed up to 24 hrs at the maximum dose level LD50 2000mg/kg b/w. Therefore, further studies were performed at doses of 100 & 200mg/kg.b/w. Therefore, the ED50 was determined to be 200mg/kg.

### 3.3 Effect of EEPH on Cardiac Enzyme Marker-Troponin-T

In our study, control rats exhibited a Troponin-T level of 0.33 ng/ml, while the ISO-induced groups showed a higher level of 0.77 ng/ml. This difference was statistically significant ( $p < 0.05$ ), indicating a marked increase in Troponin-T activity in the ISO-induced group. Furthermore, the standard treatment groups demonstrated significantly lower Troponin-T values compared to the ISO-induced group. Notably, rats in the EEPH group showed a reduction in Troponin-T levels compared to those in the ISO-induced group, as illustrated in Table 1 & Figure 1.

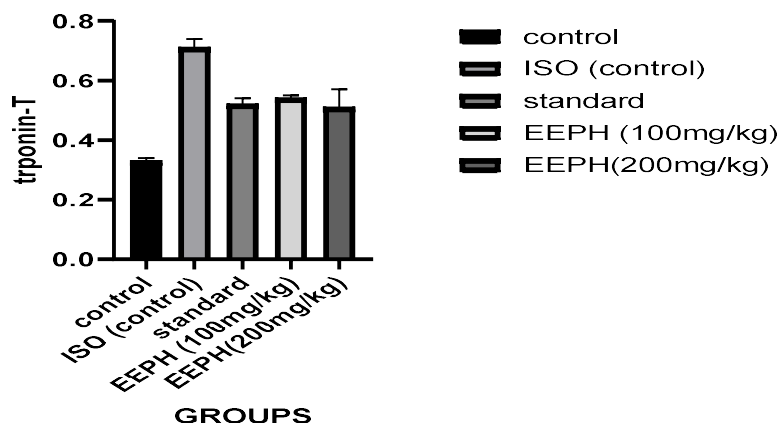
**Table 1**

**Effects on Ethanolic Extracts of *Pterolobium Hexapetalum* in Cardio Marker Enzymes**

S.NO	GROUPS	TROPONIN-T (ng/ml)
1	Control (p.o)	0.331 ± 0.017
2	Isoproterenol (85mg/Kg) s.c	0.714 ± 0.033
3	Standard -Metoprolol (20mg/Kg) (p.o)	0.522 ± 0.028***
4	EEPH (100mg/kg) + ISO. (p.o)	0.542 ± 0.015***
5	EEPH (200mg/kg) + ISO. (p.o)	0.510 ± 0.063***

*N=6, the data values are expressed as mean ± SEM; \*\*\*<0.001, \*\*<0.01 vs control. Data were analyzed by one-way ANOVA followed by Tukey's post multiple comparison test. Units:ng/ml.*

**Effect of EEPH on Cardio Marker enzymes**



**Figure 1. Effect on Cardio Marker Enzyme**

**3.4 Effects on Ethanolic Extracts of *Pterolobium Hexapetalum* in Serum Marker Enzymes**

In the Control group, the rats recorded AST levels of 41.46 U/L and ALT levels of 69.81 U/L. In contrast, rats from the ISO-induction group exhibited a significant increase in serum AST and ALT levels compared to the

Control group. Notably, the AST and ALT levels in the standard treatment group were not significantly different from those observed in the ISO-induction group. In contrast, the EEPH group demonstrated a significant decrease in serum enzyme levels. These findings are illustrated in Table 2 & Figures 2 and 3.

**Table 2**

**Effects on Ethanolic Extracts of *Pterolobium Hexapetalum* in Serum Marker Enzymes**

S.NO	GROUPS	AST(u/l)	ALT(u/l)
1	Control (p.o)	41.46 ± 0.72	69.81 ± 1.10
2	Isoproterenol (85mg/kg) S.c	212.2 ± 8.19	152.7 ± 7.42
3	Standard-Metoprolol (20mg/kg) (p.o)	75.08 ± 4.17***	52.02 ± 2.19***
4	EEPH (100mg/kg) + ISO. (p.o)	91.58 ± 6.19***	52.02 ± 2.19***
5	EEPH (200mg/kg) + ISO. (p.o)	83.78 ± 3.28***	46.44 ± 0.92***

*N=6, the data values are expressed as mean ± SEM, \*\*\*<0.001, \*\*<0.01 vs. control. Data were analyzed using one-way ANOVA followed by Tukey's Post multiple comparison test. Units:u/l*

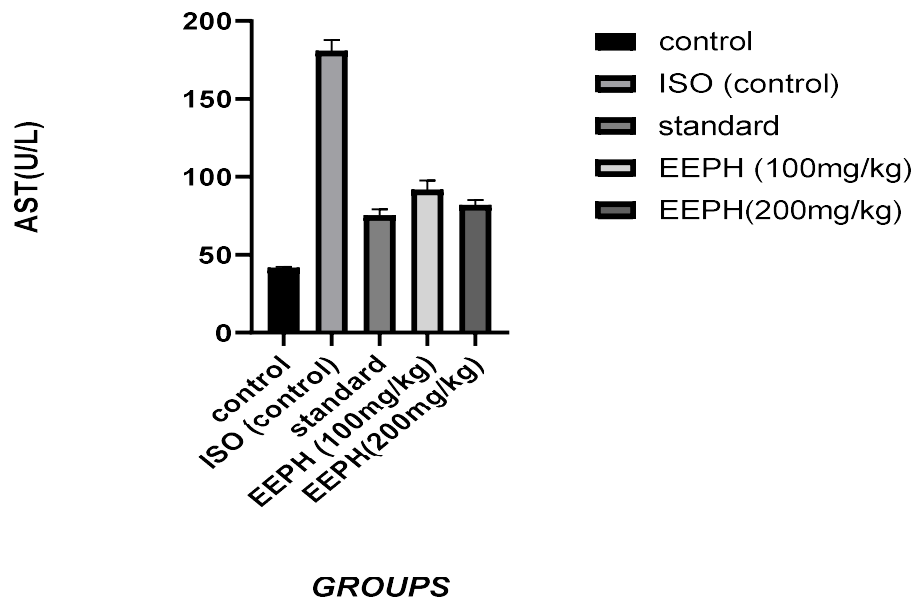


Figure 2. Effect of EEPH on Aspartate Aminotransferase.

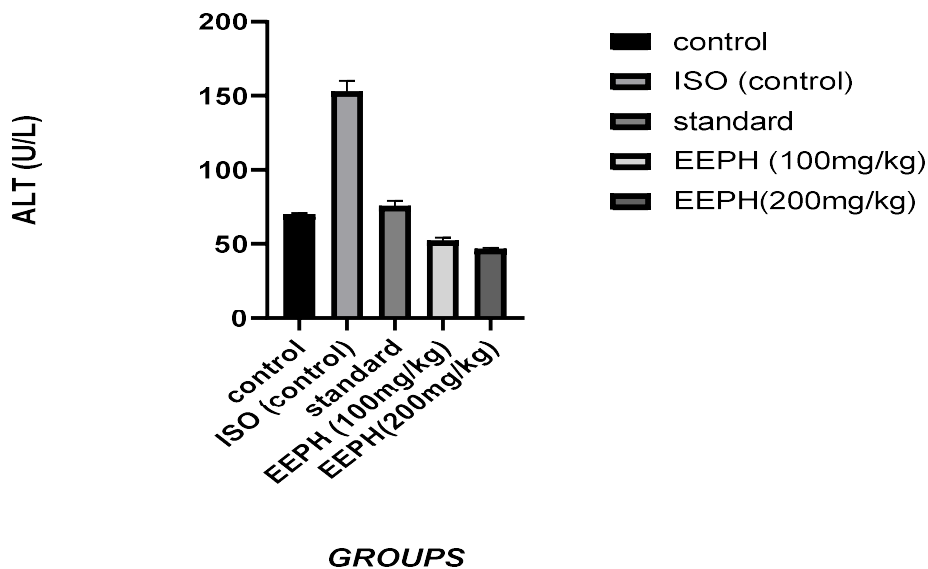


Figure 3. Effect of EEPH on Alanine Aminotransferase

### 3.5 Effects on Ethanolic Extracts of *Pterolobium Hexapetalum* in Lipid Profile

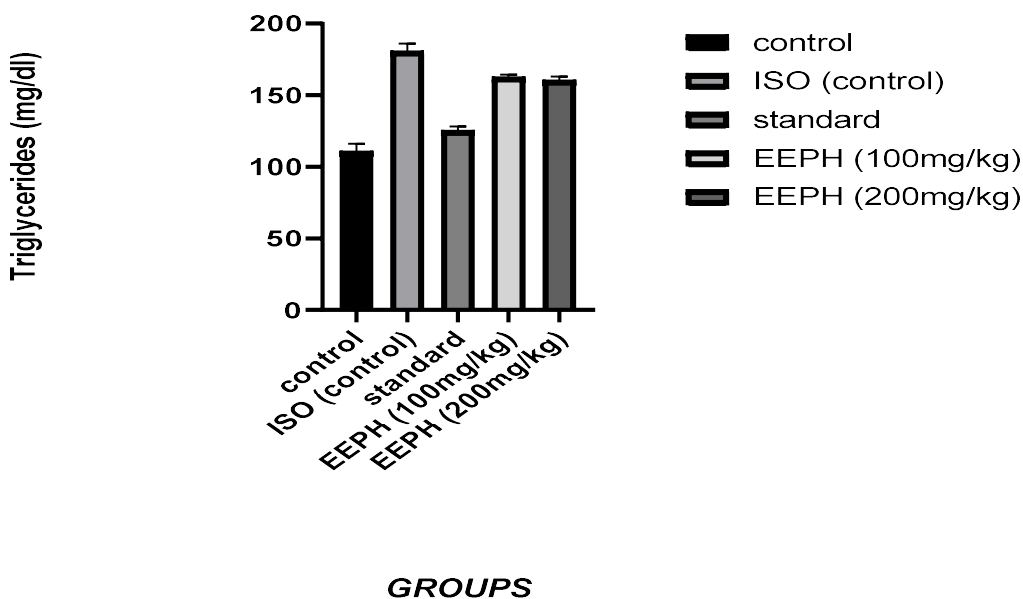
Total cholesterol and triglyceride levels in the serum of group I rats were 110 mg/dl and 130 mg/dl, respectively. Rats administered with isoproterenol showed a significant ( $p < 0.05$ ) increase in the levels of total cholesterol and triglycerides, while the standard group rats showed a

significant ( $p < 0.05$ ) reduction in these levels. Meanwhile, pretreatment with the EEPH-treated group significantly decreased the levels of total cholesterol and triglycerides compared to isoproterenol-induced rats, which helped protect the cardiac muscle from injury. As shown in Tables 3 & Figures 4 and 5.

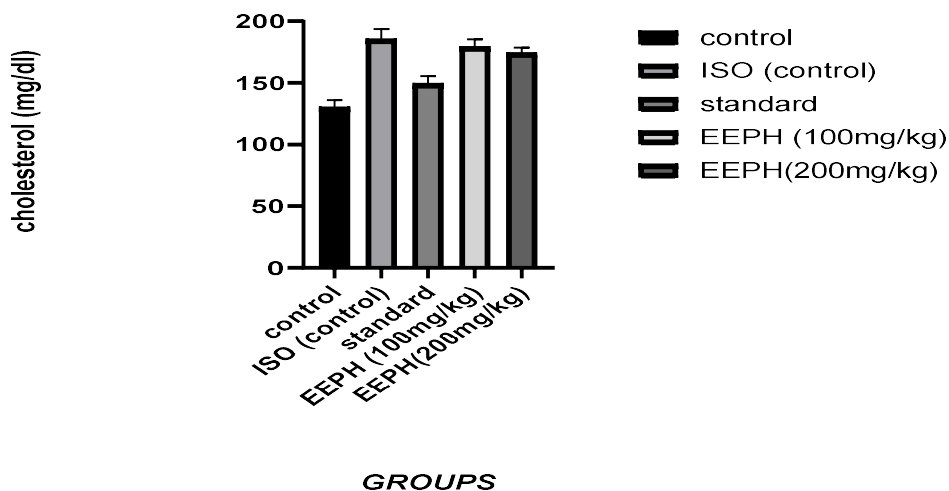
**Table 3. Effects of Ethanolic Extracts of Pterolobium Hexapetalum on Lipid Profile**

S.NO	GROUPS	TGL (mg/dl)	CHOLESTEROL (mg/dl)
1	Control (p.o)	110.53 ± 5.43	130.2 ± 6.03
2	Isoproterenol (85mg/kg) sc	180.6 ± 5.45	185.3 ± 9.51
3	Standard-Metoprolol (20mg/kg) (p.o)	125.8 ± 3.02**	149.2 ± 6.36**
4	EEPH (100mg/kg) + ISO (p.o)	162.3 ± 2.09**	179.1 ± 6.36**
5	EEPH (200mg/kg) + ISO (p.o)	160.2 ± 2.94**	174.1 ± 4.75**

*N=6 the data values are expressed as mean ± SEM ;\*\*\*<0.001, \*\*<0.01 vs. control. Data was analyzed using one-way ANOVA followed by Tukey's Posts multiple comparison test. Units:mg/dl*



**Figure 4. Effect on EEPH in Triglyceride**

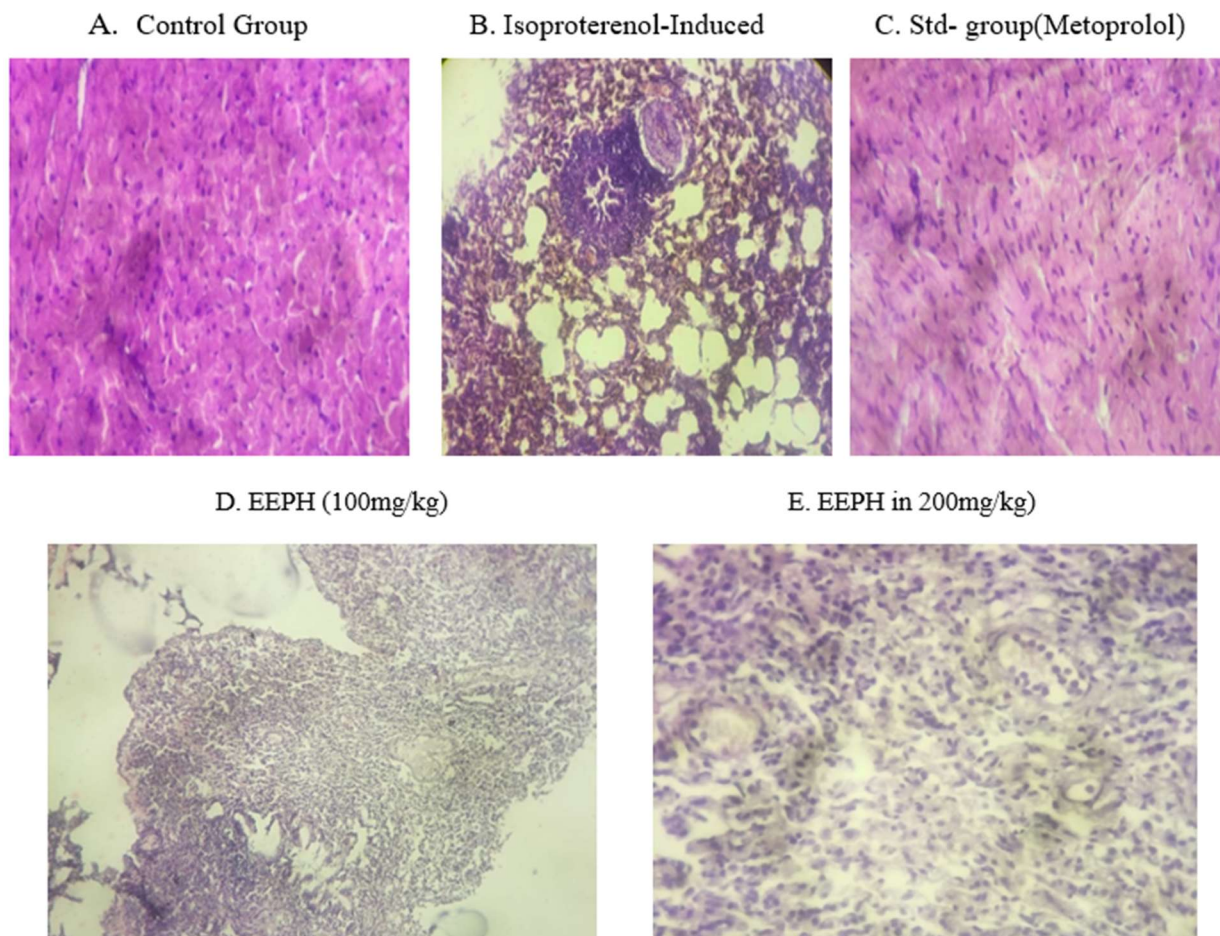


**Figure 5. Effect on EEPH in Cholesterol**

### 3.6 Histopathological studies

In control rats, the myocardial membrane exhibited adequate cellularity and normal morphology [20]. The myocytes appeared healthy, with no signs of myocyte necrosis, vascular proliferation, macrophage activity, or muscle hypertrophy [21]. In the isoproterenol (85 mg/kg) control group (group II), the observed morphological changes strongly indicated isoproterenol-induced myocardial injury. Large regions of coagulative necrosis were seen, accompanied by neutrophilic infiltration, diffuse interstitial edema, and myocytes appearing pale with fading nuclei and reduced striations. The standard group displayed myocardial architecture similar to that of the control group, with adequate cellularity and normal

morphology. No evidence of necrosis, vascular proliferation, macrophage activity, or muscle hypertrophy was observed. In the pretreatment group with *Pterolobium hexapetalum* (group VI), many areas of myocyte debris were disintegrated in the presence of macrophages, suggesting removal of myocytes by macrophage activity. In the pretreatment group with *Pterolobium hexapetalum* (group V), fewer areas of myocyte debris were disintegrated with macrophage presence, indicating similar removal activity as represented in figure 6. Macrophage activity was prominent in some areas of injury, which was also evident in regions of vascular proliferation found throughout the myocardium.



**Figure 6. Effect of *P.Hexapetalum* on Morphology: (A)control, (B) Iso control, (C) Standard: (D) Test 1: (E) Test 2.**

### 4. DISCUSSION

Myocardial infarction (MI) is one of the main causes of death due to cardiovascular disease (CVD). Myocardial infarction, a highly prevalent ischemic condition characterized by tissue necrosis, [22] develops due to an imbalance between oxygen requirement and actual supply. The present study was designed to investigate the protective effect of *P.hexapetalum* against isoproterenol-

induced myocardial functional and structural damage by reducing lipid peroxidation.

The Administration of isoproterenol (85 mg/kg, s.c.) for two consecutive days caused significant myocardial injury, as evidenced by a marked elevation in serum cardiac Troponin-T level to  $0.714 \pm 0.033$  ng/mL compared to the control group ( $0.331 \pm 0.017$  ng/mL,  $p <$

0.001). This confirms ISO-induced cardiomyocyte membrane damage and leakage of cardiac-specific biomarkers [23].

Pretreatment with ethanolic extract of *Pterolobium hexapetalum* (EEPH) for 30 days produced a significant and dose-dependent reduction in Troponin-T levels. The 100 mg/kg dose reduced Troponin-T to **0.542 ± 0.015 ng/mL** ( $p < 0.001$  vs ISO group), while the 200 mg/kg dose further lowered it to **0.510 ± 0.063 ng/mL** ( $p < 0.001$  vs ISO group). The higher dose of EEPH showed cardioprotective efficacy comparable to the standard drug metoprolol (**0.522 ± 0.028 ng/mL**). These findings indicate that EEPH effectively preserves myocardial membrane integrity and limits the release of cardiac troponin-T, a highly sensitive and specific marker of myocardial necrosis [24].

Isoproterenol induction resulted in a sharp rise in serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels, reaching **212.2 ± 8.19 U/L** and **152.7 ± 7.42 U/L**, respectively, compared to control values of **41.46 ± 0.72 U/L** (AST) and **69.81 ± 1.10 U/L** (ALT) ( $p < 0.001$ ). This elevation reflects ISO-mediated leakage of cytosolic enzymes due to extensive myocardial cell damage.

Pretreatment with EEPH significantly attenuated these elevations in a dose-dependent manner. At 100 mg/kg, AST and ALT levels were reduced to **91.58 ± 6.19 U/L** and **52.02 ± 2.19 U/L**, respectively. The 200 mg/kg dose produced even greater protection, bringing AST down to **83.78 ± 3.28 U/L** and ALT to **46.44 ± 0.92 U/L** (both  $p < 0.001$  vs ISO group). These reductions were comparable to or better than the metoprolol-treated group (**75.08 ± 4.17 U/L** for AST and **52.02 ± 2.19 U/L** for ALT). The restoration of AST and ALT levels strongly suggests that EEPH stabilizes cardiomyocyte membranes and mitigates ISO-induced cellular injury [25].

ISO administration significantly altered the lipid profile, elevating serum triglycerides (TGL) to **180.6 ± 5.45 mg/dL** and total cholesterol (CHO) to **185.3 ± 9.51 mg/dL** from control values of **110.53 ± 5.43 mg/dL** and **130.2 ± 6.03 mg/dL**, respectively ( $p < 0.01$ ). Such dyslipidemia exacerbates myocardial damage by promoting oxidative stress and membrane lipid peroxidation.

Pretreatment with EEPH significantly improved the lipid profile in a dose-dependent fashion. The 100 mg/kg dose reduced TGL to **162.3 ± 2.09 mg/dL** and CHO to **179.1 ± 6.36 mg/dL**, while the 200 mg/kg dose further lowered them to **160.2 ± 2.94 mg/dL** (TGL) and **174.1 ± 4.75 mg/dL** (CHO) ( $p < 0.01$  vs ISO group). These improvements, though slightly less pronounced than metoprolol, indicate that EEPH possesses hypolipidemic activity that may contribute to its overall cardioprotective

effect by reducing lipid-mediated oxidative damage to the myocardium [26-27].

The ISO-treated rats showed a significant reduction in final body weight and an increase in heart weight-to-body weight ratio compared to the control group, indicating cardiac hypertrophy and deemed due to myocardial injury. Pretreatment with EEPH (200 mg/kg) significantly prevented body weight loss and normalized the heart weight-to-body weight ratio, suggesting prevention of myocardial edema and hypertrophy. These changes further support the cardioprotective potential of EEPH. The Histopathological analysis of heart sections provided morphological confirmation of the biochemical findings. Control group hearts exhibited normal myocardial architecture with intact myocytes, clear striations, and absence of necrosis or inflammatory infiltration.

In contrast, the ISO-control group displayed extensive myocardial damage characterized by widespread coagulative necrosis, neutrophilic infiltration, interstitial edema, pale myocytes with faded nuclei, and loss of striations. Pretreatment with EEPH markedly reduced these pathological changes in a dose-dependent manner. The 100 mg/kg dose showed moderate protection with reduced necrotic areas and fewer inflammatory cells, while the 200 mg/kg dose exhibited near-normal myocardial architecture with minimal necrosis, significantly less edema, and limited inflammatory cell infiltration, comparable to the metoprolol-treated group. These histopathological improvements corroborate the biochemical data and confirm the ability of EEPH to preserve myocardial structural integrity against ISO-induced necrotic damage [28-29].

## 5. CONCLUSION

This study demonstrates that *Pterolobium hexapetalum* extract exhibits significant cardioprotective effects against *isoproterenol*-induced myocardial infarction in rat models. The findings suggest that these protective effects may be attributed to the modulation of *beta1-adrenergic receptor* activity, which is crucial in regulating cardiovascular responses under stress conditions. Administration of the extract led to notable improvements in cardiac function, reduced myocardial injury markers, and enhanced antioxidant status, highlighting its potential as a therapeutic agent for preventing cardiac damage associated with chronic stress and ischemic events. Moreover, our research underscores the importance of exploring natural compounds like *Pterolobium hexapetalum* as valuable alternatives or adjuncts to conventional therapies, particularly in the context of cardiac diseases characterized by excessive *adrenergic stimulation*. Future studies should further investigate the underlying molecular mechanisms and the potential clinical applications of *Pterolobium hexapetalum* in cardioprotection, paving the way for novel strategies in

the management of myocardial infarction and other related disorders.

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## 8. Conflict of Interest

The author declared none

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