Research Article

Cardioprotective Effects of *Troxerutin* Against Isoproterenol-Induced Myocardial Infarction: Experimental Evaluation and Mechanistic Insights

Pettem Ashwitha, Chikram Vigneshwar, Namburi Bramarambika Anoohya, Maduri Akhila, Yellu Narasimha Reddy*
*Department of Pharmacology, University College of Pharmaceutical Sciences, Kakatiya University, Warangal – 506009, TS, India.
***Corresponding author's E-mail:** ynrku@kakatiya.ac.in

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ABSTRACT

Myocardial infarction (MI) continues to be among the top causes of morbidity and mortality globally, largely due to an imbalance of oxygen supply and myocardial demand. Experimental MI models caused by isoproterenol, a synthetic catecholamine, closely replicate human cardiac damage and are excellent tools for examining therapeutic intervention. Troxerutin, a rutin-derived natural flavonoid, has various pharmacological effects that include antioxidant, anti-inflammatory, anti-apoptotic, and cardioprotective effects. The current research sought to assess the cardioprotective efficacy of troxerutin against isoproterenol-induced myocardial infarction in Wistar albino rats. Methodologically, rats were pre-treated with troxerutin at certain doses before isoproterenol injection. Biochemical markers like creatine kinase-MB (CK-MB), lactate dehydrogenase (LDH), and troponin-I were determined together with markers of oxidative stress like malondialdehyde (MDA), superoxide dismutase (SOD), and glutathione (GSH). Electrocardiographic (ECG) alterations and histopathological changes in cardiac tissues were also determined. The results proved that troxerutin effectively attenuated the elevation of serum cardiac markers and lipid peroxidation induced by isoproterenol and restored antioxidant defense mechanisms. ECG showed the blockade of ST-segment elevation, whereas histopathology proved the maintenance of the architecture of the myocardium. The cardioprotective effects can be assigned to the modulation of oxidative stress, inflammation, and apoptotic signaling pathways. In summary, troxerutin showed significant cardioprotective effect against isoproterenol-induced myocardial damage, warranting its therapeutic use as an adjunct to cardiovascular disease treatment. Additional studies such as clinical trials are needed to ascertain its translational significance in human myocardial infarction.

Keywords: Troxerutin, Myocardial infarction, Isoproterenol, Cardioprotection, Antioxidant activity, Wistar rats.

1. INTRODUCTION

Myocardial infarction (MI), more popularly known as a heart attack, is a potentially fatal condition that arises when coronary blood supply is blocked, causing ischemia and necrosis of the cardiac tissue[1]. It continues to be one of the top causes of morbidity and mortality globally, with cardiovascular diseases causing almost one-third of annual deaths worldwide [2]. The mechanisms underlying MI are multifactorial and include oxidative stress, inflammatory reactions, mitochondrial damage, and apoptosis that together augment myocardial damage and compromise cardiac function[3, 4]. In vitro models based on synthetic catecholamines like isoproterenol (ISO) are generally used to simulate myocardial injury in experimental animals. ISO causes biochemical and morphological changes that resemble those occurring in human myocardial infarction, such as increases in cardiac biomarkers, typical electrocardiographic (ECG) changes, and myocardial structure injury [5, 6]. The model has been useful in investigating new therapeutic agents that have the potential for reducing cardiac injury.

In the past few years, flavonoids of natural origin have received a lot of attention because of their antioxidant, anti-inflammatory, and anti-apoptotic properties, which combined contribute to cardiovascular well-being. Troxerutin, a naturally occurring bioflavonoid that is a derivative of rutin, occurs in tea, coffee, and many fruits and vegetables. Troxerutin has been described to possess various pharmacological activities such as cardioprotective, hepatoprotective, nephroprotective, neuroprotective, and antidiabetic effects[7-9]. Mechanistically, troxerutin scavenges reactive oxygen species, strengthens endogenous antioxidant defence mechanisms, modulates inflammatory cytokines, and controls cell survival pathways like PI3K/Akt signaling [10]. Despite advancements in conventional pharmacological therapy, including β-blockers, angiotensin-converting enzyme inhibitors, and statins, the management of myocardial infarction remains challenging due to drug-related adverse effects and incomplete protection against oxidative damage [11, 12]. Therefore, identifying safer and more effective alternatives remains a priority in cardiovascular research. Troxerutin, with its broad-spectrum biological activity, offers a promising natural approach to cardio protection. However, experimental validation of its protective role in isoproterenol-induced myocardial infarction models remains limited.

The current study intends to determine the cardioprotective action of troxerutin in protecting against isoproterenol-induced myocardial infarction in Wistar albino rats by analyzing biochemical markers, electrocardiographic changes, and histopathological changes. With this methodology, the research aims to clarify the mechanisms by which troxerutin's cardioprotective action occurs and determine its

importance as an adjunct treatment in preventing and managing myocardial infarction.

2. METHODOLOGY

2.1 Experimental Animals

Healthy Wistar albino rats of either sex, weighing 180-220 g, were utilised for the study. The animals were kept in standard polypropylene cages under controlled laboratory conditions (temperature 25 ± 2°C, relative humidity 50–60%, and a 12-hour light/dark cycle). They received free access to a standard pellet diet and water ad libitum. All experimental procedures were conducted in compliance with the guidelines of the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA, Government of India), and the study protocol was approved by the Institutional Animal Ethics Committee (IAEC), University College of Pharmaceutical Sciences, Kakatiya University, Warangal, Telangana, India.

2.2 Experimental Design

The animals were randomly divided into four groups (n = 6 per group):

Group I (Normal Control): Underwent normal saline during the study. Group II (Disease Control): Was administered isoproterenol (ISO) at 85 mg/kg subcutaneously on day 14 and 15 in order to create myocardial infarction[5] Group III (Troxerutin Control): Was administered troxerutin alone for 14 days in order to assess its baseline effect. Group IV (Troxerutin + ISO): Pretreated with troxerutin for 14 days, then isoproterenol was administered on the last two days.

The dose of troxerutin was chosen based on earlier reports pointing towards its antioxidant and cardioprotective activities in experimental models [10, 13, 14].

2.3 Induction of Myocardial Infarction

Myocardial infarction was induced through subcutaneous injection of isoproterenol (ISO) at the dose of 85 mg/kg for two consecutive days. This procedure is well documented for inducing biochemical, electrocardiographic, and histological changes like human myocardial infarction[5, 15, 16].

2.4 Biochemical Analysis

Twenty-four hours following the final ISO treatment, retro-orbital plexus blood was taken under light anesthesia. Serum was separated and assayed for markers of cardiac injury such as lactate dehydrogenase (LDH), creatine kinase-MB (CK-MB), aspartate transaminase (AST), and cardiac troponin-I (cTnI). Oxidative stress indices like malondialdehyde (MDA), superoxide dismutase (SOD), catalase (CAT), and reduced glutathione (GSH) were estimated using spectrophotometric assays[17, 18].

2.5 Histopathological Examination

Following biochemical and ECG analyses, rats were euthanized, and hearts were removed. The tissues were fixed in 10% buffered formalin and processed to paraffin, sectioned, and stained with hematoxylin and eosin (H&E). Microscopy involved the detection of histological changes such as myofibrillar degeneration, necrosis, inflammatory infiltration, and interstitial edema among various experimental groups.

2.6 Statistical Analysis

Values were presented as mean ± standard error of mean (SEM). Statistical comparison was done by using one-way analysis of variance (ANOVA), and if the ANOVA showed significance, it was post hoc tested with Tukey's post hoc test to compare groups. A p-value less than 0.05 was used to declare statistical significance.

3. RESULTS

3.1 Estimation of parameters:

Creatine kinase (CK-MB):

Table 1: *Depicting Creatine kinase (CK-MB) levels of Blood in the rats of different groups*

Groups	Control	Induction	Test-1	Test-2	Test-3
1	644	1454.8	1380	1286	1080
2	656.1	1490	1358	1295	1100
3	658	1450	1352.1	1305.1	1075
4	649.3	1460	1364.3	1283.6	1095
5	660	1480	1350	1302	1070
6	653	1475	1372	1297.3	1155.2
Mean	**653.4**	**1468.3**	**1362.73**	**1294.83**	**1095.86**
SD	**5.95**	**15.73**	**11.69**	**8.56**	**7.62**

Data was expressed as Mean ± SD values (n=6) P-values were significant at **p<0.01, *p<0.05, compared between control, induction and treated groups analysed by one way ANOVA followed by multiple comparison t-test.

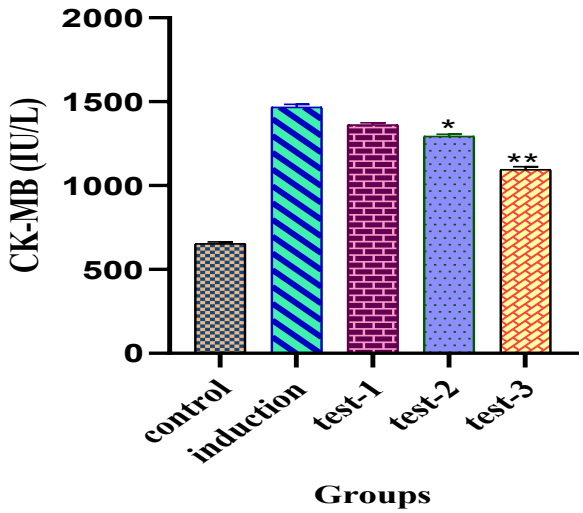

Figure 1: Graph depicting Creatine kinase (CK-MB) levels of Blood in the rats of different groups

From table 1 and Figure 1, The control group (653.4 ± 5.95) represents normal physiological conditions where no myocardial injury was induced, and therefore the CK-MB level remained within the normal range. In contrast, the induction group (1468.3 ± 15.73) showed a marked elevation in CK-MB levels, almost double that of the control

group, clearly indicating myocardial damage and confirming the successful induction of cardiac injury. In the Test-1 group (1362.73 ± 11.69), CK-MB levels were slightly reduced when compared with the induction group, suggesting a mild protective effect; however, the decrease was comparatively less pronounced than in the other treatment groups. The Test-2 group (1294.83 ± 8.56) demonstrated a further reduction in CK-MB levels relative to the induction group, and the associated statistical value ($p < 0.05$) indicates that this decrease is significant and reflects a meaningful improvement. A more notable decline in CK-MB levels was observed in the Test-3 group (1095.86 ± 7.62), where the reduction was statistically highly significant ($p < 0.01$). This substantial decrease suggests a stronger cardioprotective effect of the treatment, indicating that the Test-3 group exhibited the most effective response in lowering CK-MB levels among the tested treatments.

3.2 Aspartate Aminotransferase (AST):

Table 2: depicting Aspartate aminotransferase (AST) levels of Blood in the rats of different groups

Groups	Control	Induction	Test-1	Test-2	Test-3
1	70	256	177	168	115
2	71	263	182	150	120
3	75	269	185	163	125
4	74	258	175	154	116
5	73	254	186	151	122
6	81	271	189	160	128
Mean	**74**	**261.83**	**182.33**	**157.66**	**121**
SD	**3.90**	**7.02**	**5.42**	**5.25**	**5.05**

Data was expressed as Mean ± SD values (n=6) P-values were significant at **p<0.01, *p<0.05, compared between control, induction and treated groups analysed by one way ANOVA followed by multiple comparison t-test using MS Excel 2021.

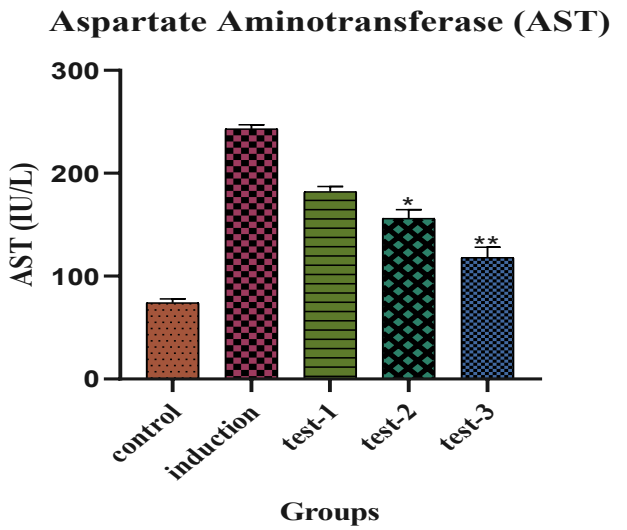

Figure 2: Graph depicting Aspartate aminotransferase (AST) levels of Blood in the rats of different groups

From the table 2 and figure 2, The control group showed an AST level of 74 ± 3.90, which reflects normal physiological conditions and indicates the absence of tissue injury. In contrast, the induction group exhibited a markedly elevated AST level of 261.83 ± 7.02, demonstrating a substantial increase compared to the control group. This sharp rise in AST suggests significant myocardial tissue damage and confirms the successful induction of tissue injury in the experimental model. In the Test-1 group, the AST level decreased to 182.33 ± 5.42 when compared with the induction group, although it remained higher than that of the control group. This reduction indicates that the treatment produced a moderate protective effect against tissue damage; however, the enzyme level still suggests the presence of some degree of myocardial injury. The Test-2 group showed a further decline in AST levels to 157.66 ± 5.25 compared with Test-1. The observed reduction was statistically significant ($p < 0.05$), indicating that the treatment in this group provided a more pronounced protective effect and meaningfully reduced tissue damage. A more substantial improvement was observed in the Test-3 group, where the AST level decreased to 121.00 ± 5.05. This value is considerably lower than that of the induction group and approaches the level observed in the control group. The reduction was highly significant ($p < 0.01$), suggesting a strong protective action of the treatment. Overall, these findings indicate that while all treatment groups demonstrated some degree of protection against myocardial tissue injury, the Test-3 group showed the most effective reduction in AST levels and therefore provided the greatest protection.

3.3 Lactate dehydrogenase (LDH):

Table 3: Depicting Lactate dehydrogenase (LDH) levels of Blood in the rats of different groups

Groups	Control	Induction	Test-1	Test-2	Test-3
1	152	620	515	464	328
2	160	625	523	469	321
3	158	642	535	453	335
4	163	635	509	450	315
5	150	633	538	461	342
6	155	611	511	448	326
Mean	**156.33**	**627.66**	**521.83**	**457.5**	**327.83**
SD	**4.92**	**11.23**	**9.66**	**8.40**	**6.32**

Data was expressed as Mean ± SD values (n=6) P-values were significant at **p<0.01, *p<0.05, compared between control, induction and treated groups analysed by one way ANOVA followed by multiple comparison t-test using MS Excel 2021.

From the table 3 and figure 3, The control group recorded an LDH level of 156.33 ± 4.92, which represents normal physiological conditions without any myocardial injury. In contrast, the induction group showed a markedly elevated LDH value of 627.66 ± 11.23, indicating severe myocardial tissue damage. This substantial increase compared with the control group confirms that the experimental induction of cardiac injury was successfully established.

In the Test-1 group, the LDH level decreased to 521.83 ± 9.66 when compared with the induction group; however, the value remained relatively high, suggesting that although

some reduction in tissue damage occurred, the protective effect was limited. The Test-2 group demonstrated a further decrease in LDH levels to 457.50 ± 8.40, showing a more pronounced reduction than that observed in Test-1. The statistical significance indicated by $p < 0.05$ suggests a moderate protective influence in reducing myocardial tissue damage.

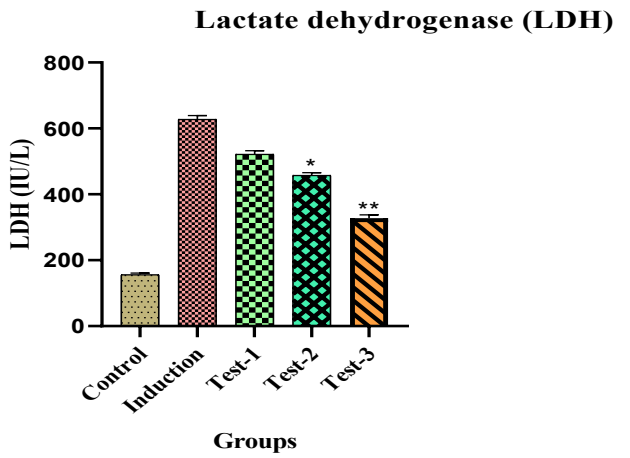

Figure 3: Graph depicting Lactate dehydrogenase (LDH) levels of Blood in the rats of different groups

Notably, the Test-3 group exhibited the greatest improvement, with LDH levels reduced to 327.83 ± 6.32. This marked decline compared with the induction group, along with a higher level of statistical significance ($p < 0.01$), indicates that Test-3 produced the strongest protective effect and was most effective in limiting myocardial tissue injury.

3.4 Histopathological Examination:

From the Histopathological Examination Figure 4, the control group showed normal tissue architecture with well-preserved and intact muscle fibers. The arrangement of the fibers appeared compact and regular, with minimal cellular infiltration. No signs of structural damage, necrosis, or inflammatory changes were observed, indicating healthy tissue morphology. In contrast, the induction group demonstrated pronounced pathological alterations. The tissue section exhibited focal areas of vacuolation along with large gaps between the muscle fibers, suggesting degeneration of the tissue. Muscle fibers appeared disorganized and fragmented, and extensive inflammatory infiltration was present, involving approximately 80–90% of the examined section. Edematous changes were also visible, and some areas suggested possible necrotic damage. These alterations clearly confirm the successful induction of tissue injury and inflammatory response in this group.

The Test-1 treated group showed partial restoration of tissue structure when compared with the induction group. Although improvement was evident, the tissue still displayed multiple foci of inflammatory cell infiltration, mainly composed of lymphocytes. Spaces between muscle fibers were observed along with the presence of vacuoles and some fatty deposition. However, the severity of these alterations was less pronounced than in the induction group, suggesting a limited protective or restorative effect of the treatment. Further improvement was observed in the Test-2 group. The tissue architecture appeared more organized, and the degree of inflammatory infiltration was reduced compared with Test-1.

Inflammatory cells, primarily lymphocytes, were still present but involved approximately 60–70% of the tissue section. The muscle fibers showed relatively better alignment and integrity, although minor structural disturbances were still noticeable. These findings indicate that the treatment in this group exerted a stronger protective effect against tissue damage compared with Test-1.

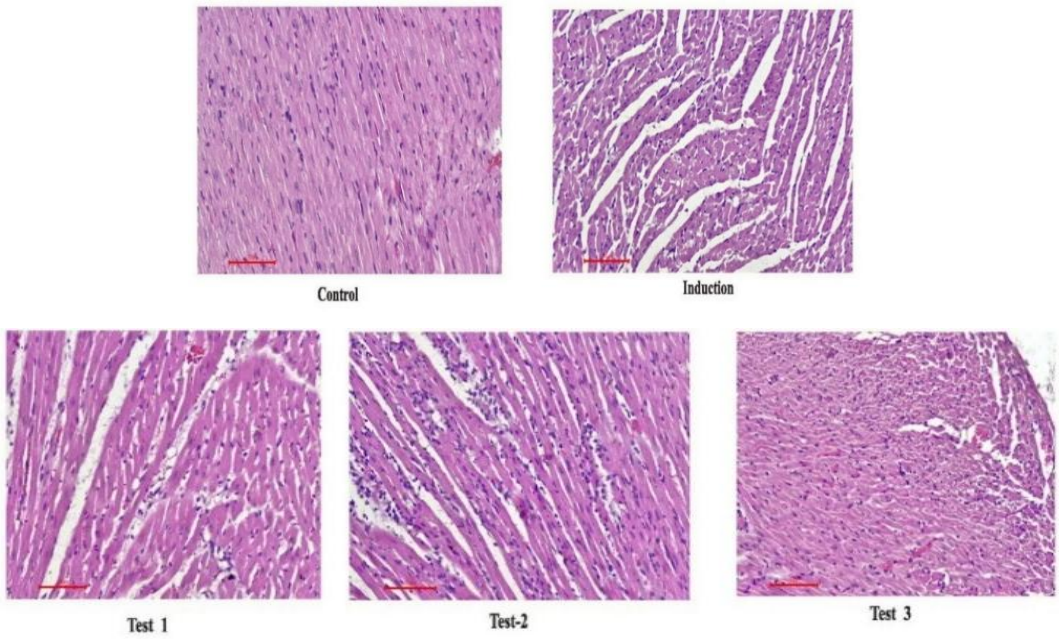

Figure 4: Histopathological observations of Heart in Wistar rats

Among the experimental groups, the Test-3 group exhibited the most notable recovery in tissue morphology. The inflammatory response was comparatively lower, with lymphocytic infiltration involving about 40–50% of the tissue section. The muscle fibers appeared more closely arranged with fewer gaps between them, and only minimal inflammatory cell presence was detected. Edema and necrotic changes were markedly reduced, suggesting improved tissue repair and restoration. Overall, the histological findings indicate that the Test-3 treatment provided the most effective protection against tissue injury among the tested groups.

3.5 Immunohistochemical (IL-6) examination:

From Table 4, Figures 5 and 6, The quantitative analysis of IL-6 expression demonstrated clear differences among the experimental groups, reflecting the level of inflammatory response in the tissue.

Table 4: Table depicting Immunohistochemical (IL-6) levels of heart tissues in the rats of different groups

Groups	Control	Induction	Test-1	Test-2	Test-3
1	3.2	7.9	8.6	6.3	5.8
2	2.3	9.2	7.2	6.1	5.1
3	3.1	9.6	8.1	7	6.2
4	2.6	8.3	7.5	7.2	5.3
5	4.1	8.8	7.9	6.8	4.9
6	2.9	9.7	8.5	6.6	6
Mean	**3.03**	**8.91**	**7.96**	**6.66**	**5.55**
SD	**0.32**	**0.71**	**0.55**	**0.41**	**0.37**

Data was expressed as Mean ± SD values (n=6) P-values were significant at **p<0.01, *p<0.05, compared between control, induction and treated groups analysed by one way ANOVA followed by multiple comparison t-test using MS Excel 2021.

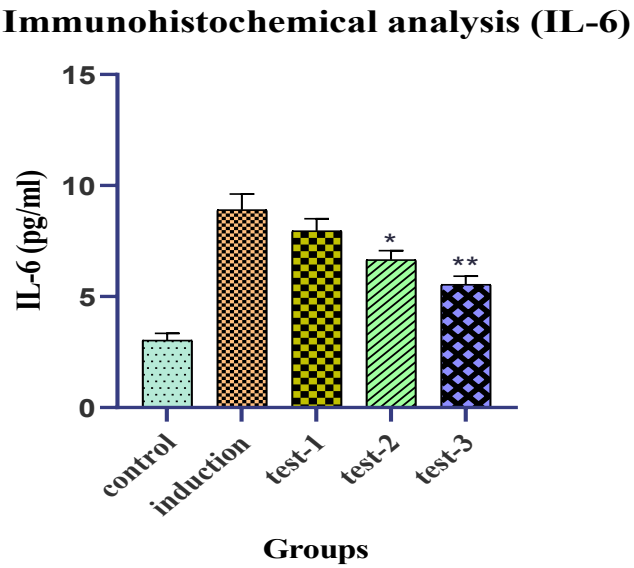

Figure 6: Graph depicting Immunohistochemical (IL-6) levels of heart tissues in the rats of different groups

The control group exhibited a mean IL-6 value of 3.03 ± 0.32, representing the normal physiological baseline in healthy tissue.

This relatively low level indicates minimal inflammatory activity, which is typically expected under normal biological conditions. In contrast, the induction group showed a markedly elevated IL-6 expression of 8.91 ± 0.71, representing the highest value among all groups. Such a substantial increase suggests a strong inflammatory response and significant tissue damage, confirming that the experimental induction of inflammation was successful and effectively created the disease model. In the treatment groups, a gradual reduction in IL-6 expression was observed when compared with the induction group.

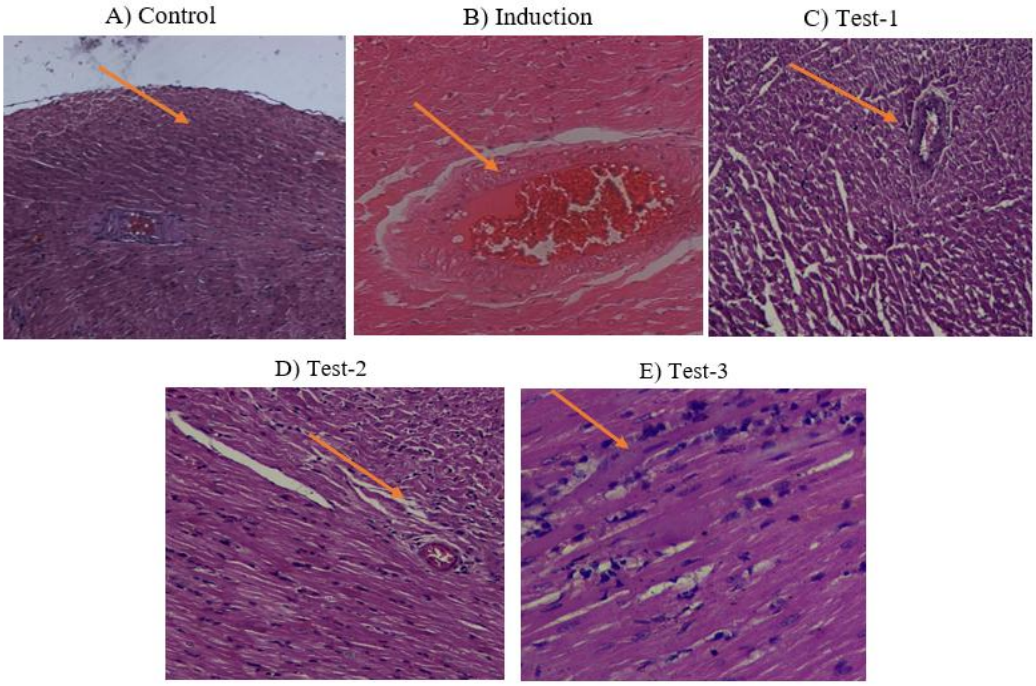

Figure 5: The image shows immunohistochemical staining for Interleukin-6 (IL-6) across different groups: Control (A), Induction 85mg/kg (B), Test-1 75mg/kg (C), Test-2 150mg/kg (D), and Test-3 300mg/kg (E)

The Test-1 group recorded a mean IL-6 level of 7.96 ± 0.55, which, although slightly lower than the induction group, still remained relatively high. This finding suggests that Test-1 treatment provided a limited degree of protection against the inflammatory condition, resulting in only a modest decrease in cytokine expression. A more noticeable reduction was seen in the Test-2 group, which showed an IL-6 level of 6.66 ± 0.41. The lower value indicates improved protective activity compared with Test-1, suggesting that Test-2 has a stronger capacity to reduce inflammatory signaling and associated tissue injury. The Test-3 group demonstrated the most pronounced improvement, with an IL-6 level of 5.55 ± 0.37, representing the lowest value among the treatment groups. This substantial reduction in cytokine expression indicates that Test-3 produced the greatest anti-inflammatory effect, suggesting enhanced protection against tissue damage and a more effective suppression of the inflammatory response. Overall, the pattern of results indicates a progressive improvement in anti-inflammatory activity from Test-1 to Test-3, with Test-3 showing the most promising therapeutic potential.

4. DISCUSSION

The current research proved that troxerutin has profound cardioprotective actions against isoproterenol-induced myocardial infarction in Wistar albino rats. Troxerutin pretreatment reduced biochemical markers of myocardial damage, improved electrocardiographic alterations, restored antioxidant homeostasis, and maintained cardiac histoarchitecture. All these findings together indicate that troxerutin defends the heart by antioxidant, anti-inflammatory, and anti-apoptotic mechanisms. Administration of isoproterenol increased serum biomarkers like LDH, CK-MB, AST, and troponin-I, denoting myocardial necrosis, as previously reported with ISO-induced cardiotoxicity[19-21]. Troxerutin greatly mitigated these increases, indicating membrane stabilization and anti-necrotic protection. Concurrently, markers of oxidative stress indicated that ISO stimulated lipid peroxidation with decreased levels of SOD, CAT, and GSH. Troxerutin pretreatment reversed these alterations, validating its position as a powerful free radical scavenger and antioxidant enhancer(10, 22, 23).

The findings thus underscore the therapeutic benefit of troxerutin as a natural cardioprotective agent. Traditional drugs like β-blockers and ACE inhibitors continue to play a core role in myocardial infarction treatment but are constrained by their side effects and limited efficacy[24, 25]. Troxerutin's pleiotropic action-acting against oxidative stress, inflammation, and apoptosis, would make it an effective adjunct to existing treatments. In addition, its capacity to maintain biochemical and structural myocardial integrity suggests a role in the prevention of long-term myocardial infarction complications like heart failure. However, additional pharmacologic investigations and clinical trials are necessary to prove these experimental results and apply them to clinical use.

5. CONCLUSION

The results of this research reaffirm that troxerutin provides strong protection against isoproterenol-induced myocardial infarction in Wistar albino rats. Through cardiac biomarker reduction, recovery of antioxidant defenses, correction of electrocardiographic alterations, and the maintenance of myocardial histology, troxerutin exhibited robust cardioprotective activity. These are largely due to its anti-apoptotic, anti-inflammatory, and antioxidant mechanisms. Although the findings are encouraging, additional mechanistic research and properly designed clinical trials are required to confirm its potential as an adjuvant therapeutic agent for myocardial infarction in the human.

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Ethics statement:

All Animals used in the research are approved by the institutional animal ethical committee (IAEC) UCPSc, Kakatiya University (06/IAEC/UCPSC/KU/2024).

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