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ORIGINAL ARTICLE

DOI: 10.69723/njms.04.02.0613

CARDIOPROTECTIVE POTENTIAL OF CONVOLVULUS ARVENSIS AGAINST ISOPROTERENOL-INDUCED CARDIOTOXICITY

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Received- 21st July 2025; Revisions received- 6th Sept 2025; Accepted- 10th Sept 2025

ABSTRACT

BACKGROUND: Myocardial infarction is largely driven by oxidative stress-mediated cellular and mitochondrial dysfunction. Isoproterenol-based experimental models closely mimic these pathological mechanisms, while plant-derived antioxidants have gained recognition as potential cardioprotective agents against oxidative injury.

OBJECTIVE : This study aimed to investigate the cardioprotective effects of methanolic extract from Convolvulus arvensis against Isoproterenol-induced cardiotoxicity in rats, focusing on myocyte injury markers and histopathological changes.

METHODOLOGY The experimental study was carried out in the Department of Pharmacology at Khyber Medical College and Khyber Medical University, Peshawar, Pakistan, between August 2022 and April 2023. Female Sprague Dawley rats were randomly allocated into three main groups: a positive control, a negative control, and treatment groups receiving Convolvulus arvensis extract at doses of 50 mg/kg, 150 mg/kg, and 300 mg/kg orally for 14 days. Myocardial infarction was induced in rats by administering Isoproterenol (100mg/kg SC) on the 13th and 14th days. Biochemical and histopathological assessments were conducted on the 15th day.

RESULTS :Administration of Isoproterenol led to changes in serum levels of cardiac injury markers (CK-MB and LDH) and histopathological alterations. Pre-treatment with Convolvulus arvensis extract prevented all parameters of Isoproterenol-induced myocardial infarction in rats, as confirmed by histopathological examination. The study findings suggest that Convolvulus arvensis exerts significant protective effects on the heart against Isoproterenol-induced myocardial infarction by maintaining endogenous antioxidant enzyme activities.

CONCLUSION: Convolvulus arvensis extract significantly lowered serum CK-MB levels and mitigated histopathological damage in isoproterenol-treated rats, refelecting its potential as a cardioprotective agent.

KEYWORDS : Cardiotoxicity, Cardioprotection, Convolvulus arvensis, Isoproterenol, Myocardial infarction, Oxidative stress

HOW TO CITE THIS ARTICLE: Ahmad M, Ali N, Faisal MS, Ahmad S, Qadir H. Cardioprotective Potential of Convolvulus Arvensis against Isoproterenol-Induced Cardiotoxicity. Northwest J Med Sci. 2025; 4(3): 37-43

INTRODUCTION

Myocardial infarction is a prevalent medical emergency associated with high morbidity and mortality. It results from ischemia-induced necrosis of the cardiac muscle, ultimately leading to impaired cardiac function.[1] Reactive oxygen species (ROS), chemically unstable molecules with an unpaired electron,[2] are produced as byproducts of normal cellular metabolism.[3] At elevated levels, ROS play a central role in the pathogenesis of various age-related degenerative diseases. They actively trigger biological processes such as cellular injury, energy depletion, and functional impairment, while also promoting apoptosis and necrosis, ultimately leading to cell death.[4]

Several pharmaceutical agents are known to induce ROS formation and oxidative stress during different stages of drug metabolism. Among them, isoproterenol (ISO) has been identified as a potent inducer of highly cytotoxic ROS.[5] ISO is a synthetic catecholamine with non-selective β-adrenergic agonist activity. At low doses, it is clinically utilized in conditions such as heart block and cardiac arrest. In contrast, chronic exposure or administration of high doses of ISO results in irreversible myocardial membrane injury, ultimately leading to infarct-like necrosis of cardiac muscle.[6] This phenomenon occurs because the oxidative metabolism of catecholamines generates quinones, which subsequently react with oxygen to produce ROS. The excessive ROS burden initiates a cascade of alterations in myocardial structure, function, and biochemical parameters.[7]

Counteracting such oxidative stress is therefore fundamental to preventing cardiac injury. This can be accomplished either by suppressing ROS production or by enhancing endogenous antioxidant defenses. Antioxidants, in particular, play a vital role by delaying or preventing oxidative processes, neutralizing stress, and scavenging ROS, thereby mitigating their harmful effects.[8] Although isoproterenol serves as a valuable experimental tool for investigating cardiac dysfunction, its pronounced cardiotoxic effects underscore the importance of cautious dosing and the exploration of protective strategies in clinical practice.

Extensive research has focused on the cardioprotective potential of medicinal plants and plant-derived compounds against isoproterenol-induced toxicity. Several agents, including *Ferulic acid, Emblica officinalis,* and *Fumaria indica* have shown

DOI: 10.69723/njms.04.02.0613

protective effects by restoring cardiac biomarkers and alleviating oxidative stress.[9-11] Polyherbal formulations such as Arogh, DHC-1, and Marutham have likewise demonstrated protective effects against isoproterenol-induced myocardial injury in rat models. Their cardioprotective action is attributed to favorable modulation of key enzymatic systems, including cardiac biomarkers (CK-MB, LDH, AST) and antioxidant defense mechanisms.[12]

Convolvulus arvensis, a member of the Convolvulaceae family and the genus Convolvulus, has been phytochemically characterized to contain flavonoids, saponins, caffeic acid derivatives, lipids, alkaloids, and δ-aminolevulinic acid. Several studies have highlighted a direct correlation between its phenolic constituents and notable antioxidant activity.[13,14]

Isoproterenol is widely used to induce myocardial necrosis in rats, serving as a well-established experimental model for investigating various types of cardiac dysfunction. In this context, various approaches have been reported, such as inducing cardiac fibrosis with a single high-dose ISO injection or using lower doses administered repeatedly over several days. These variations in dosing regimens highlight the flexibility of the ISO model and its adaptability to different research objectives.[15]

The current study aimed to evaluate the cardio-protective potential of *C. arvensis* extract in Isoproterenol-induced cardiotoxicity, leveraging its experimentally proven antioxidant properties and scavenging activities as demonstrated through a well-designed study protocol.[16,17]

METHODOLOGY

Preparation of plant extract and extract solutions

The experimental study was carried out in the Department of Pharmacology at Khyber Medical College and Khyber Medical University, Peshawar, Pakistan, between August 2022 and April 2023. *Convolvulus arvensis* was collected, washed, air-dried, crushed, and macerated in 80% methanol with continuous shaking, followed by filtration. The filtrate was concentrated under reduced pressure and at a high temperature (approximately 42°C) using a rotary evaporator, resulting in a dark, chocolate-brown paste, which was subsequently stored in a refrigerator. From this plant extract, three different concentrations were prepared: 50 mg/mL, 150 mg/mL, and 300 mg/mL.

The ethical approval number 441/DME/KMC was obtained from the Institutional Review Board of Khyber Medical College on 30/06/2022.

Chemicals and drugs

The experimental ingredients were sourced according to international standards and were of analytical grade, prepared on the day the research commenced. Isoproterenol was obtained from TCI Chemicals, an Indian company. The planned dosage of the drug for the experiment was 100 mg/kg of body weight, administered via subcutaneous injection. The storage conditions for the drug were strictly adhered to as specified in the brochure included with the drug packaging.

Procurement and placement of Animals

Healthy Sprague Dawley rats, aged 8-9 weeks with normal activity and stable weight, were acclimatized to ambient conditions for 7 to 10 days before the experiment. Animals showing illness, pregnancy, abnormal behavior, or significant weight changes during acclimatization were excluded. They were kept in a regulated room where temperature and air pressure were carefully monitored and maintained at designated levels. The rats were fed approved Rodent Chow Purina and had access to water as per normal requirements. The research protocol received approval from the institute, and animal care procedures followed the 1996 ILAR Guide for the Care and Use of Laboratory Animals (National Research Council, 1996).

Grouping of rats and dosing of isoproterenol with and without plant extract

The rats were divided into three main groups (the third group had three further divisions), with four animals in each subgroup, making a total of 20 rats used in the study. Sample size was determined using the resource equation method (E = N–G), where N represents the total number of animals and G the number of groups. This yielded E = 15, which lies within the recommended range of 10–20, ensuring statistical reliability while minimizing animal use.

Group 1 (Negative control) rats received distilled water (1ml/kg PO) daily for 14 days. Additionally, on the 13th and 14th days, they received distilled water (1ml/kg SC) with a 24-hour interval between doses.

Group 2 (Positive control) rats received distilled water (1ml/kg PO) daily for 14 days. On the 13th and 14th days, they received Isoproterenol (100mg/kg SC) with a 24-hour interval between doses to induce cardiotoxicity[18].

Group 3 rats were treated with *Convolvulus arvensis* extract in three sub-groups, each receiving the plant extract at doses of 50mg/kg, 150mg/kg, and 300mg/kg SC daily for 14 days. Additionally, on the 13th and 14th days, Isoproterenol (100mg/kg SC) was administered. The administration of the extract was scheduled before the start of the research, and a strict timetable was followed throughout the study period.

Blood sampling

At the end of the experiment, blood was collected from the rats, and serum samples were stored at –20 °C. The levels of CK-MB and LDH were measured 48 hours after isoproterenol administration to provide an accurate assessment of myocardial injury.[19] CK-MB is recognized as a gold standard marker for assessing the degree of cardiac muscle injury due to oxidative

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stress.

Histo-pathological examination

Whole rat heart tissues obtained through dissection were sliced and processed by dehydration with alcohol to remove any residual moisture, followed by treatment with xylene. These tissue sections were embedded in paraffin wax and cut into 5-micrometer-thick blocks. Subsequently, the sections were stained with hematoxylin and eosin dye. The obtained slices were thoroughly examined under light microscopy to assess histo-morphological changes. These included gross features such as color and texture of the heart, histological features of muscle fibers (such as disruption of branching pattern, necrotic changes like swelling, nuclear changes, and vacuoles in the cytoplasm), histological features of the interstitium (such as cellular infiltration and fibrosis), and histological features of blood vessels (including congestion and extravasation of blood).

RESULTS

Effects of Isoproterenol and *Convolvulus arvensis* extract on cardiac markers

In the current study, the effects of *C. arvensis* extract on serum levels of LDH (Lactate dehydrogenase) and CK-MB (Creatine Kinase-MB) in rats were investigated and compared to a positive control using t-tests. The findings did not show significant evidence that any of the tested doses of *C. arvensis* extract had a notable impact on serum LDH levels compared to the positive control group (p-value 0.18). However, there was a significant difference in CK-MB levels between the positive control group, which received only isoproterenol, and the groups treated with various doses of *C. arvensis* extract (p-value 0.0003). This suggests that the extract, at the tested doses, may exert a protective or mitigating effect against the rise in CK-MB levels induced by isoproterenol.

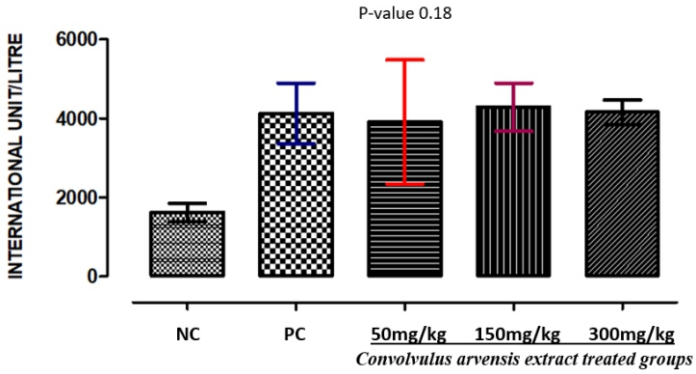

Figure 1: Effects of Negative control (NC), Positive control (PC), and *Convolvulus arvensis* extract on serum levels of LDH

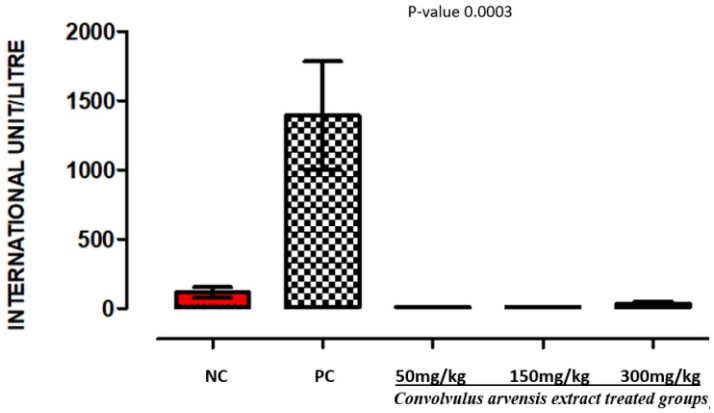

Figure 2: Effects of Negative control (NC), Positive control (PC), and *Convolvulus arvensis* extract on serum levels of CK-MB

Effects of Isoproterenol and *Convolvulus arvensis* extract on cardiac muscles

According to Table 1 and Figure 3, neither the control groups nor the group treated with the extract showed any gross morphological abnormalities in the color and texture of the heart. Similarly, the histological examination of cardiac muscle in the negative control group did not reveal any abnormalities. The architecture of muscle fibers, interstitium, and blood vessels appeared normal. In contrast, microscopic examination of heart tissue from the Isoproterenol-only group showed abnormal architecture of muscle fibers, cellular infiltration of the interstitium, as well as vessel congestion and extravasation of blood.

Histological analysis of heart tissue from the group treated with *C. arvensis* extract at a dose of 50mg/kg showed a noticeable reduction in focal disruptions of muscle fibers and slight

DOI: 10.69723/njms.04.02.0613

mitigation of necrotic changes. However, there were no significant protective effects observed in terms of interstitial cellular infiltrations or vessel congestion and extravasation of blood. Heart tissue from the groups treated with *C. arvensis* extract at doses of 150mg/kg and 300mg/kg demonstrated the most pronounced cardioprotective effects. These groups showed diminished damage to muscle fiber architecture, fewer inflammatory cells spreading in the interstitium, and reduced necrotic and congestive changes in blood vessels (Table 1).

Table 1: Histomorphological changes in the respective group of experimental animals

Characteristics	Negative control group n(%)	Isoproterenol only group n(%)	Plant extract group		
			50mg/kg n(%)	150mg/kg n(%)	300mg/kg n(%)
	n=4	*n*=2*	*n*=4	*n*=4	*n*=4
Gross features of heart					
Color					
Normal	4(100%)	2(100%)	4(100%)	4(100%)	4(100%)
Abnormal	None	None	None	None	None
Texture					
Normal	4(100%)	2(100%)	4(100%)	4(100%)	4(100%)
Hard	None	None	None	None	None
Histological features of muscle fibers					
Disruption of branching pattern					
Yes	None	2(100%)	None	None	None
No	4(100%)	None	4(100%)	4(100%)	4(100%)
Necrotic changes (Swelling)					
Yes	None	2(100%)	3(75%)	1(25%)	None
No	4(100%)	None	1(25%)	3(75%)	4(100%)
Necrotic changes (Nuclear changes)					
Yes	None	2(100%)	3(75%)	1(25%)	1(25%)
No	4(100%)	None	1(25%)	3(75%)	3(75%)
Vacuoles in cytoplasm					
Yes	Nil	2(100%)	2(50%)	1(25%)	None
No	4(100%)	None	2(50%)	3(75%)	4(100%)
Histological feature of the interstitium					
Cellular infiltration					
Yes	None	2(100%)	4(100%)	4(100%)	4(100%)
No	4(100%)	None	None	None	None
Fibrosis					
Yes	None	2(100%)	1(25%)	4(100%)	None
No	4(100%)	None	3(75%)	None	4(100%)
Histological features of blood vessels					
Congestion					
Yes	None	2(100%)	4(100%)	4(100%)	2(50%)
No	4(100%)	None	None	None	2(50%)
Extravasation of blood					
Yes	2(50%)	2(100%)	1(25%)	1(25%)	None
No	2(50%)	None	3(75%)	3(75%)	4(100%)

***Two rats in the isoproterenol-only group died prior to sampling (likely from severe ISO-induced cardiotoxicity) and were excluded from the analyses.**

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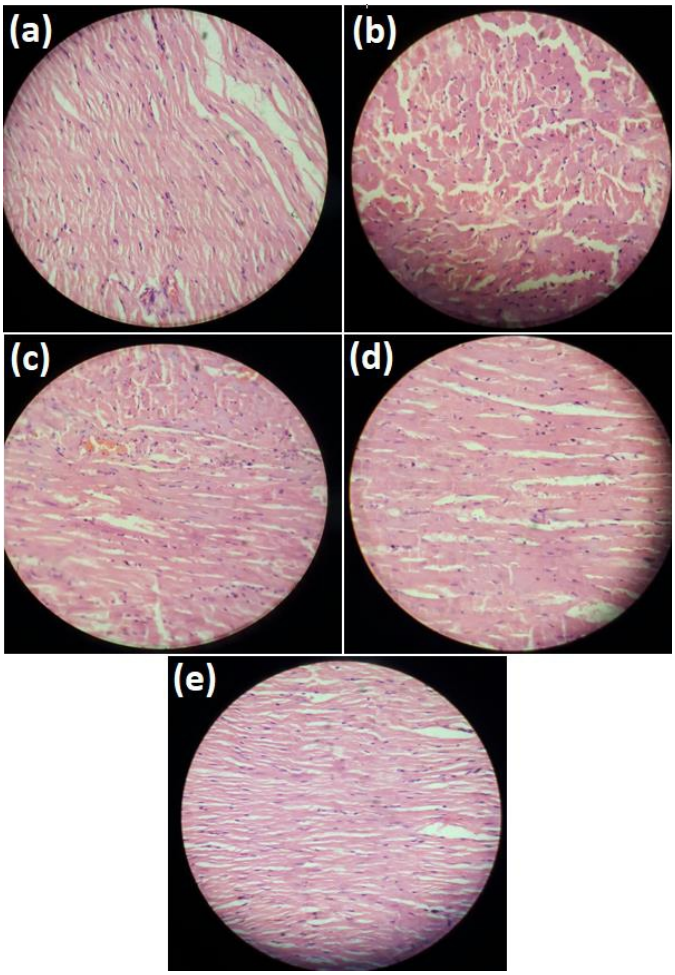

Figure 3: Microscopic appearance of heart tissue from (a) Negative control group; (b) Isoproterenol only group; (c) Plant extract (50mg/Kg) treated group; (d) Plant extract (150mg/Kg) treated group; (e) Plant extract (300mg/Kg) treated group

DISCUSSION

Heart muscle metabolism and contractility are intricately regulated by various catecholamines. Excessive levels of catecholamines, such as those induced by Isoproterenol, can lead to myocardial tissue damage, resulting in a spectrum of heart-related pathologies (e.g., anginal episodes, acute coronary insufficiency, and myocardial infarction) and transient myocardial hypoxia.[20] Isoproterenol, a potent synthetic catecholamine, is known to cause tissue damage and necrotic lesions upon injection into experimental rats.

Histomorphological lesions observed in heart tissue following Isoproterenol injection resemble myofibrillar degeneration and disruption of specialized cardiac cellular networks, which are among the pathophysiological bases described for acute myocardial infarction and cardiac arrest in humans.[21] Various pathways contributing to Isoproterenol-induced toxic damage include non-selective beta agonism, resulting in potent chronotropic and inotropic actions. Isoproterenol also induces moderate ischemia due to coronary hypotension from increased heart muscle activity. Other proposed mechanisms include calcium overload, increased cAMP levels, depletion of cellular energy, and oxidative stress from toxic free radicals.[22] The auto-oxidation of isoproterenol generates intermediate compounds that, upon interacting with oxygen, produce highly reactive oxygen species such as hydroxyl radicals (OH) and hydrogen peroxide (H_2O_2). These reactive species play a pivotal role in myocardial injury by causing extensive cellular damage and promoting the release of myocardial enzymes, which serve as key

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biomarkers of cardiac damage.[23]

In this study, rats treated with Isoproterenol exhibited significant elevations in CK-MB and LDH levels, indicating myocardial necrotic damage and increased membrane permeability. Pre-treatment with *Convolvulus arvensis* extract effectively prevented the rise in cardiac enzyme activity. Histomorphological evaluation of heart tissue from rats treated with distilled water showed normal cellular architecture with intact membranes and basement structures, without signs of inflammation. Conversely, rats treated with Isoproterenol showed typical signs of cellular and tissue damage, including necrosis, disrupted interstitial branching patterns, and inflammatory cell infiltration. However, rats pre-treated with *Convolvulus arvensis* extract demonstrated reduced inflammatory cell infiltration and preserved structural integrity of cardiac muscle fibers, suggesting potential cardioprotective effects of the extract. This aligns with previous research on plant extracts like Ginkgo Biloba and mangiferin, which have also shown cardioprotective properties.[24]

Histologically, vacuolation of cardiomyocytes, characterized by the accumulation of small, clear vacuoles, is indicative of degenerative processes associated with cardiotoxicity. Additional features of cardiotoxicity include loss of myocardial basement membranes in necrotic areas and hypercontraction bands in affected myocytes.[25] The levels of CK-MB and LDH enzymes correlate with the degree of histomorphological changes observed in heart tissue slides. In this study, CK-MB levels showed a stronger correlation with histomorphological parameters of cardiotoxicity compared to LDH levels. The positive control group treated exclusively with Isoproterenol exhibited typical signs of cardiotoxicity at both histomorphological and biochemical levels. In contrast, the group treated with *Convolvulus arvensis* extract showed attenuated signs of Isoproterenol-induced damage, further supporting the extract's potential as an antioxidant and cardioprotective agent.

CONCLUSION

The current study demonstrates that *Convolvulus arvensis* extract may protect against isoproterenol-induced cardiotoxicity in rats by reducing serum CK-MB levels and improving histopathological outcomes. Further studies with larger cohorts and additional biomarkers, including cardiac troponins, are warranted to validate its cardioprotective potential.

Conflict of Interest

The authors declare no conflict of interest related to this publication

Financial Disclosure Statement

No dedicated financial support or external funding was received for the completion of this work

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B.Acquisition, Analysis, or Interpretation of Data
C.Manuscript writing
D.Critical Review and approval
All the authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved