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Original Article

# Osthenol Shows Cardioprotective Activity Against Isoproterenol-Induced Myocardial Infarction in Rats via Inhibiting Oxidative Stress and Inflammation

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## ABSTRACT

**Background:** Myocardial Infarction (MI) is a devastating cardiovascular complication that develops when blood flow to a region of the myocardium is obstructed, resulting in cardiomyocyte necrosis and loss of contractile function. **Objectives:** This study was intended to assess the cardioprotective activity of the osthenol against Isoproterenol (ISO)-induced MI in rat model. **Materials and Methods:** The Sprague-Dawley rats were subjected to ISO administration to develop MI and were pre- and co-treated with osthenol for 20 days. The standard drug amlodipine was pre-treatment for 20 days. Upon completion, the Systolic Blood Pressure (SBP) and heart rate was analyzed utilizing rat tail-cuff plethysmography. The concentrations of cardiac injury biomarkers, oxidative stress markers, and inflammatory biomarkers were examined utilizing the commercial kits. The cardiac tissues were collected and subjected to histopathological investigation to assess histological alterations. **Results:** The current findings demonstrated that osthenol treatment significantly reduced both SBP and heart rate levels in ISO-treated rats. The cardiac injury biomarkers, pro-inflammatory biomarkers, and lipid peroxidation marker were significantly reduced by osthenol treatment in ISO-treated rats. Furthermore, osthenol treatment considerably elevated the antioxidants in the rats with MI. Moreover, the administration of osthenol significantly mitigated the histological changes in the heart of MI rats. **Conclusion:** The present findings demonstrate that osthenol treatment can mitigate and protect against the biochemical and histological alterations in rat cardiac tissues caused by ISO, because of its antioxidant and anti-inflammatory activities. Thus, osthenol may represent a novel therapeutic option to treat MI.

**Keywords:** Creatine kinase-MB, Myocardial infarction, Osthenol, Interleukin-6, Heart rate.

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## INTRODUCTION

Cardiovascular diseases include a group of disorders impacting the heart and blood arteries, demonstrating a substantial global public health issue. These diseases constitute the primary cause of mortality globally, representing almost one-third of all deaths worldwide. The burden of cardiovascular diseases is substantial, both in terms of mortality and morbidity.[1] The Global Burden of Disease study indicates that the age-standardized rate of cardiovascular disease is increasing in certain high-income countries, where it was previously decreasing, highlighting an urgent necessity for the implementation of effective policies and interventions to tackle this issue.[2] Myocardial Infarction (MI) is one of the most prevalent and lethal cardiovascular disorders. MI emerges when the blood flow to a segment of the heart is obstructed, frequently due to the plaque accumulation in the arteries. The causes of MI are multifactorial, involving a complex interplay of genetic, lifestyle, and environmental causes. Modifiable risk factors for MI include smoking, less physical activity, unhealthy diet, and obesity, while non-modifiable risk causes are age, gender, and family history.[3] The burden of MI is significant, both in terms of mortality and morbidity. Globally, it is estimated that ischemic heart disease, which encompasses MI, accounted for over 17.9 million deaths in 2017, representing 85% of all cardiovascular disease deaths. Timely intervention is essential for reducing mortality during a heart attack, since it can mitigate damage to the cardiac muscle and enhance long-term prognoses.[4]

The pathogenesis of MI is a complex cascade of events, beginning with the rupture of an atherosclerotic plaque, which initiates the activation of the inflammatory response and a cascade of detrimental cellular and molecular processes. The human

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heart has a limited capacity for regeneration, and the healing process following a MI is characterized by the development of a collagen-based wound, which can ultimately lead to severe cardiac remodeling.[5] Current treatment strategies for MI aim to reestablish blood flow to the ischemic region, limit the extent of myocardial damage, and support the healing process. Timely reperfusion therapy, such as thrombolysis, percutaneous coronary intervention, or coronary artery bypass, has significantly developed survival percentages for patients experiencing a MI. However, despite these advancements, a substantial proportion of patients go on to develop heart failure, highlighting the need for the development of novel therapeutic approaches.[6]

One promising area of research is the exploration of plant-derived bioactive compounds and their potential applications to treat MI. Several plant-based compounds have demonstrated cardioprotective effects in animal models, highlighting that they may play a key role to prevent disease advancement and supporting cardiac remodeling after an infarction.[7] These phytochemicals have been shown to modulate various pathways involved in the pathogenesis of MI, including inflammation, oxidative stress, and apoptosis, providing a multifaceted technique to treat this condition.[8] Osthenol is one such bioactive compound extracted from the roots of *Angelica koreana* and *Angelica dahurica*, which belongs to the prenylated coumarin. Previous investigations have demonstrated that osthenol exhibits numerous biological properties, including antitumor, antimicrobial and anti-inflammatory properties. Osthenol exhibited the inhibitory action with minimal cytotoxicity on Raji cells.[9] Moreover, osthenol exhibits potent antimicrobial properties against several pathogens.[10,11] Osthenol demonstrated the capacity to inhibit cyclooxygenase and 5-lipoxygenase, contributing to its anti-inflammatory actions.[12] Furthermore, it effectively inhibited the monoamine oxidase A.[13] However, there no much reports to claim the cardioprotective properties of the osthenol. Therefore, this study was planned to assess the cardioprotective activity of the osthenol against ISO-induced MI in rats.

## MATERIALS AND METHODS

### Chemicals

Osthenol (CAS No: 484-14-0, Purity: >=98%), Isoproterenol (CAS No: 7683-59-2, Purity 99.0%) and reagents utilized in this work were procured from Sigma Aldrich, USA. To estimate the cardiac injury marker, oxidative stress markers and inflammatory cytokine kits were purchased from MyBioSource, Abcam USA and Elabscience, USA, respectively.

### Animals

The Sprague-Dawley rats were utilized in this work. The rats were housed in sterile polypropylene enclosures under controlled air conditions of 22-24ºC and a 12-hr light/dark sequence. Throughout the duration of studies, rats were granted full access to pellet food and drinking water. Rats were acclimatized to the laboratory condition for one week before the commencement of the experiments.

### Experimental design and treatment groups

The rats were categorized into five groups as follows: group I: control rats administered alone with a NaCl (0.1%) solution; group II: rats administered ISO (85 mg/kg; i.p.) on days 19 and 20 to induce MI. groups III and IV: received oral pre- and co-treatment of 20 mg/kg of osthenol for 20 days, with ISO delivered on the 19$^{th}$ and 20$^{th}$ days; group V: received oral pre-treatment of 5 mg/kg of amlodipine (standard drug) for 20 days, with ISO delivered on the 19$^{th}$ and 20$^{th}$ days. Heart rate and Systolic Blood Pressure (SBP) was assessed using a rat tail-cuff plethysmography. Following the end of the treatments, the rats were euthanized, and a blood sample was then collected for serum preparation. The cardiac tissues were removed and washed with saline solution. The removed heart was weighed to assess any changes in weight. The heart tissues were subjected to histological investigation, while the remaining portions were used to prepare homogenates for subsequent biochemical evaluations.

### Analysis of cardiac injury marker levels

The Lactate Dehydrogenase (LDH) and Creatine Kinase-MB (CK-MB) concentrations in the serum was evaluated using the commercial diagnostic kits (Elabscience, USA). The experiments were done in triplicate as per the manufacturer's indicated protocols.

### Analysis of oxidative stress markers

The excised cardiac tissues were homogenized in iced saline and subsequently centrifuged for 6000 rpm 10 min. The resultant supernatant was utilized to evaluate lipid peroxidation marker Malondialdehyde (MDA) employing commercial assay kits (Abcam, USA). The concentrations of Glutathione (GSH), Catalase (CAT), and Superoxide Dismutase (SOD) in the heart tissue homogenates was examined utilizing kits (Elabscience, USA). The assays were performed using three replicates in accordance with the manufacturer's recommendations.

### Analysis of inflammatory cytokine levels

Commercial diagnostic kits were used to assess the quantities of TNF-α and IL-6 in the serum of the experimental rats. The manufacturer's specified methods were followed to conduct the assays in triplicate (MyBioSource, USA).

### Histological analysis

The hearts were excised from the rats and treated with a 10% formalin solution. The hearts were dehydrated with ethanol and subjected to paraffin embedding. Following deparaffinization, tissues were sectioned to 6 µm. The slides were then stained with

eosin and hematoxylin. The stained slides were later investigated using a microscope at 40× magnification.

### Statistical analysis

The data are revealed as Mean±SD of triplicates. The data are analyzed using GraphPad Prism. The data changes among experimental groups were evaluated using a one-way ANOVA and Tukey's *post hoc* assay. A significance at $p<0.05$ was used for comparisons among experimental groups.

## RESULTS

### Effect of osthenol on SBP and heart rate in experimental rats

The effects of osthenol on the SBP and heart rate levels were evaluated in the experimental rats, with findings depicted in Figure 1. The ISO-treated rats exhibited increase in both SBP and heart rate. Nonetheless, the co- and pre-treatments of osthenol (20 mg/kg) decreased the SBP and heart rate in the ISO-treated rats. The standard drug amlodipine treatment also considerably reduced both SBP and heart rate, which is similar to the results of osthenol treatment.

### Osthenol prevents on cardiac injury biomarkers in the experimental rats

A notable elevation in the concentrations of both CK-MB and LDH, in the serum of ISO-treated rats, contrasting with the values recorded in the control group (Figure 2). Interestingly, both co- and pre-treatment of 20 mg/kg of osthenol considerably diminished the concentrations of both LDH and CK-MB in the ISO-treated rats. Moreover, the standard drug amlodipine treatment also resulted in a reduction in LDH and CK-MB concentrations in the ISO-induced rats (Figure 2).

### Osthenol attenuates oxidative stress and enhances antioxidants in heart of ISO-injected rats

The lipid peroxidation and antioxidant biomarkers were measured in the heart of the experimental rats. The MDA level was increased considerably while the concentrations GSH, CAT, and SOD were significantly decreased in the heart tissues of ISO-induced rats. Captivatingly, the co- and pre-treatments of osthenol at 20 mg/kg dose effectively elevated the antioxidant levels and reduced MDA content in the cardiac tissues of ISO-treated rats (Figure 3). These findings also corroborated by the findings of amlodipine, which proves the antioxidant properties of osthenol.

### Osthenol mitigates myocardial inflammation in ISO-Injected rats

Figure 4 demonstrates the inflammatory cytokine concentrations assessed in the serum of rats. The present findings exhibited that ISO-treated rats had a remarkable elevation in the IL-6 and TNF-α concentrations relative to the control group. Interestingly, the co- and pre-treatments of osthenol at 20 mg/kg concentration showed substantial reduction in the IL-6 and TNF-α levels in the ISO-induced rats. The standard drug amlodipine treatment also reduced these cytokines in the ISO-induced rats, which evidences the anti-inflammatory properties of osthenol.

### Osthenol prevents the ISO-induced histopathological damage in the heart

The microscopic images of cardiac tissue from control rats (Group I) depict the usual arrangement of cardiomyocytes and tissues patterns (Figure 5). However, the current findings demonstrate that ISO treatment (Group II) resulted in myophagocytosis, localized necrosis, inflammatory cell infiltrations, and edema compared to the control group. Whereas, the osthenol at 20 mg/kg concentration in both co-and pre-treatments (Group III&IV) shown a significant decrease in myocardial damage, encompassing decreased inflammation, myonecrosis, and edema. These findings further validated by the results of amlodipine treatment (Group V) which demonstrates the cardioprotective properties of osthenol (Figure 5).

## DISCUSSION

MI is a devastating cardiovascular complication that can have severe complications for an individual's health and well-being. When the blood flow to a region of the myocardium, or heart muscle, is clogged, it leads to the necrosis of cardiomyocytes in that area. This ischemic or infarcted region, loses its capacity to contract, developing a mechanical difficulty for the heart and compromising its overall function. The loss of cardiomyocytes during a MI is a significant burden, as the adult heart lacks the capacity to replace them effectively.[14] To better comprehend the complex pathophysiology of MI and explore novel salutary interventions, researchers have developed animal models that mimic the disease process.[15] The ISO-treated MI in rats is an extensively utilized experimental model to assess the effects of myocardial ischemia and the potential for pharmacological interventions to ameliorate the associated cardiac damage. ISO is a synthetic catecholamine that, when administered at high doses, can induce myocardial necrosis and mimic the clinical presentation of a MI. The advantages of this model include its relative simplicity, reproducibility, and the ability to study the mechanisms of myocardial damage and the potential for salutary interventions.[16] Numerous studies have utilized the ISO-treated MI model in rats to evaluate the efficacy of various plant-based compounds and phytochemicals in reducing the burden of cardiac injury.[17,18] These investigations have provided useful insights into the mechanisms of myocardial protection, such as the modulation of inflammatory pathways, the enhancement of antioxidant defenses, and the preservation of mitochondrial function.[19]

The analysis of SBP and heart rate in animal models of cardiovascular disease has become increasingly crucial in understanding the pathophysiology and potential therapeutic interventions. Furthermore, analyzing SBP and heart rate can offer useful insights into the cardiovascular responses and the extent of myocardial injury. Examining the changes in SBP and heart rate in these drug-treated rats can offer useful insights into the mechanisms of action and the impact of these interventions on cardiac function.[20] ISO, a beta-adrenergic agonist, can trigger myocardial ischemia and fibrosis, leading to cardiac dysfunction and remodeling. ISO treatment has been revealed to induce a significant elevation in heart rate due to the stimulation of beta-adrenergic receptors and the resulting vasodilation. These changes in cardiovascular parameters can be utilized as biomarkers of the level of myocardial damage and the effectiveness of therapeutic interventions.[21] Monitoring the SBP and heart rate in these animal models can help researchers understand the cardiovascular responses to different therapeutic interventions. The assessment of SBP and heart rate can also aid in the evaluation of potential therapeutic interventions, as changes in these parameters can serve as indicators of the overall cardiovascular function and the effectiveness of the treatment. Furthermore, the analysis of these parameters can help identify potential adverse effects of the drugs on the cardiovascular system.[22] In this work, the results illustrated that the ISO-treated rats displayed substantial elevation in both SBP and heart rate levels. Interestingly, the osthenol treatment considerably decreased the SBP and heart rate levels in the ISO rats, which evidences the beneficial effects of osthenol in cardiovascular system.

The analysis of cardiac damage biomarkers in the animal models of MI holds great importance for understanding the pathophysiology and potential therapeutic interventions for this devastating cardiovascular condition.[23] Two key biomarkers that play a pivotal role in the diagnosis and understanding of the pathophysiology of MI are CK-MB and LDH. CK-MB is an

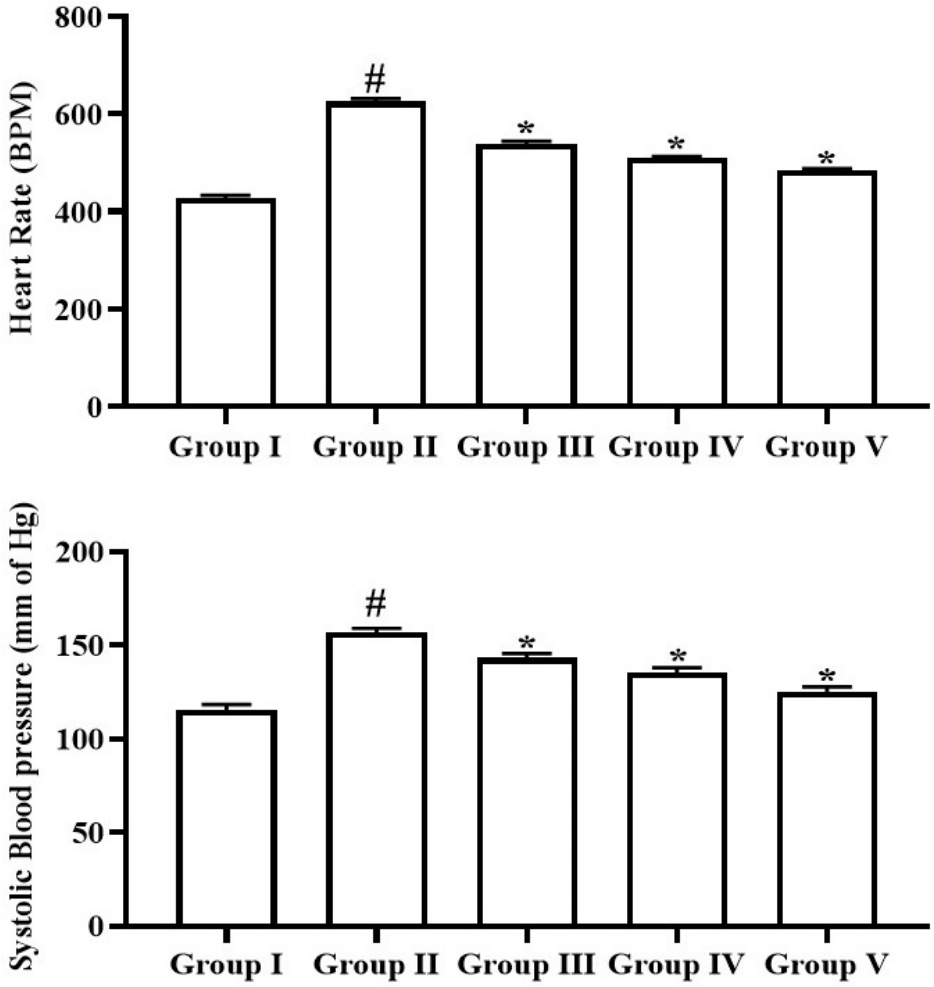


**Figure 1:** Effect of osthenol on the heart rate and SBP levels in the experimental rats. The results were presented as a Mean±SD of triple experiments. A one-way ANOVA and Tukey's *post hoc* test were utilized to evaluate the statistical significance among treatment groups. '#' denotes statistical significance at $p<0.01$ compared to the control group; '*' indicates statistical significance at $p<0.05$ relative to the ISO-induced group.

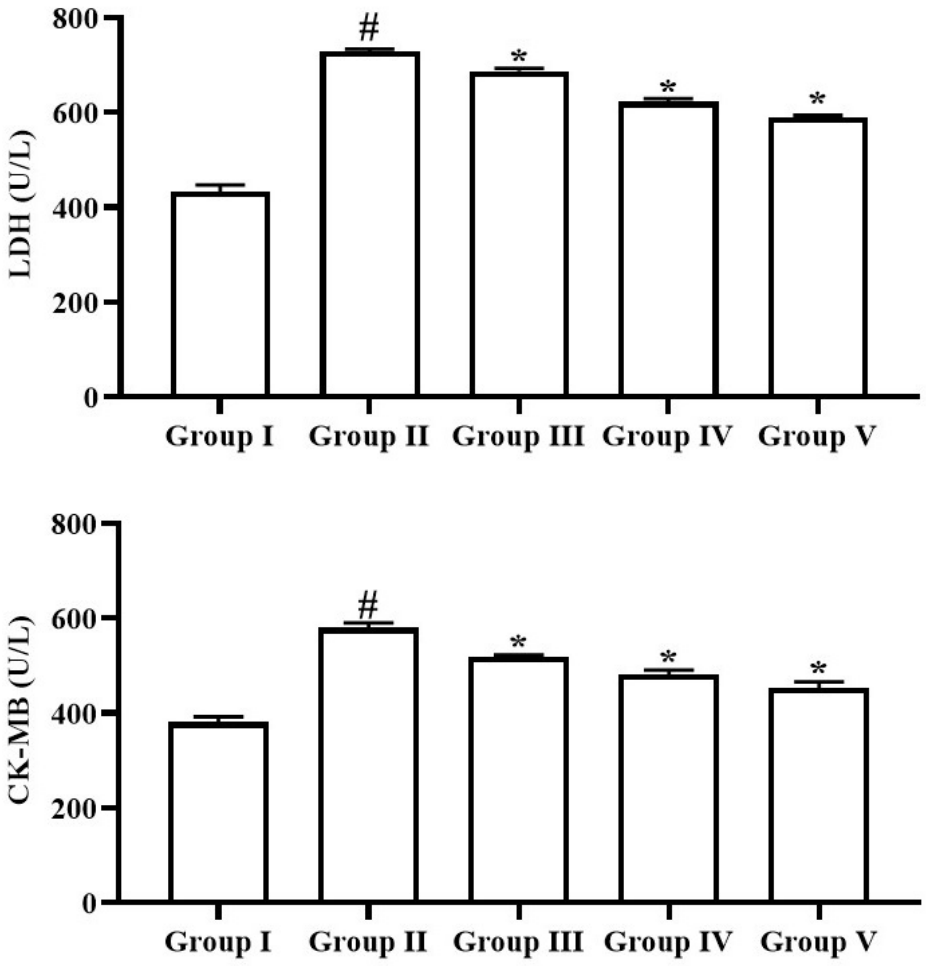


**Figure 2:** Effect of osthenol on the cardiac injury marker levels in the experimental rats. The results were presented as a Mean±SD of triple experiments. A one-way ANOVA and Tukey's *post hoc* test were utilized to evaluate the statistical significance among treatment groups. '#' denotes statistical significance at $p<0.01$ compared to the control group; '*' indicates statistical significance at $p<0.05$ relative to the ISO-induced group.

isoenzyme of the creatine kinase enzyme that is predominantly occur in the myocardium, the muscular wall of the heart.[24] When cardiac cells are injured or die because of the heart attack, CK-MB is released into the bloodstream, and its elevated levels can be detected. The CK-MB remains an extensively used marker for the initial diagnosis of MI, as it is more specific to the heart compared to the total creatine kinase enzyme.[25] A significant biomarker in evaluating MI is LDH, an enzyme that facilitates the conversion of lactate to pyruvate, an essential process in energy metabolism. Increased LDH level can be noted in patients with MI, as the damaged myocardial cells release this enzyme into the bloodstream.[26] CK-MB and LDH still play an imperative role in the assessment and understanding of the pathophysiology of MI. The measurement of these biomarkers can offer valuable information about the level of myocardial injury and the progression of the disease.[27] Elevated CK-MB and LDH concentrations in the serum of ISO-treated MI models can serve as early indicators of myocardial damage, allowing for timely intervention and potential therapeutic strategies to be evaluated.[28] The present findings indicated the substantial elevation in the CK-MB and LDH concentrations in the ISO-induced rats. However, the osthenol treatment considerably decreased both LDH and CK-MB concentrations in the ISO-treated rats, which highlight that osthenol alleviated the detrimental effects of ISO in the experimental rats.

The pathogenesis of MI is complex, including various factors, including oxidative stress. It has been indicated that oxidative stress is integral to the onset and advancement of MI. Oxidative stress denotes the disparity between the generation of ROS and the body's capacity to neutralize these reactive intermediates or to repair the resultant injury. During a MI, the interruption of the electron transport chain in the mitochondria results in the excessive generation of superoxide anions, which are the precursors of various ROS.[29] Increased oxidative stress can induce a cascade of events that ultimately contribute to the pathogenesis of MI. One of the critical markers of oxidative stress is MDA, a byproduct of lipid peroxidation. The high MDA level have been observed in the MI patients and are connected with greater

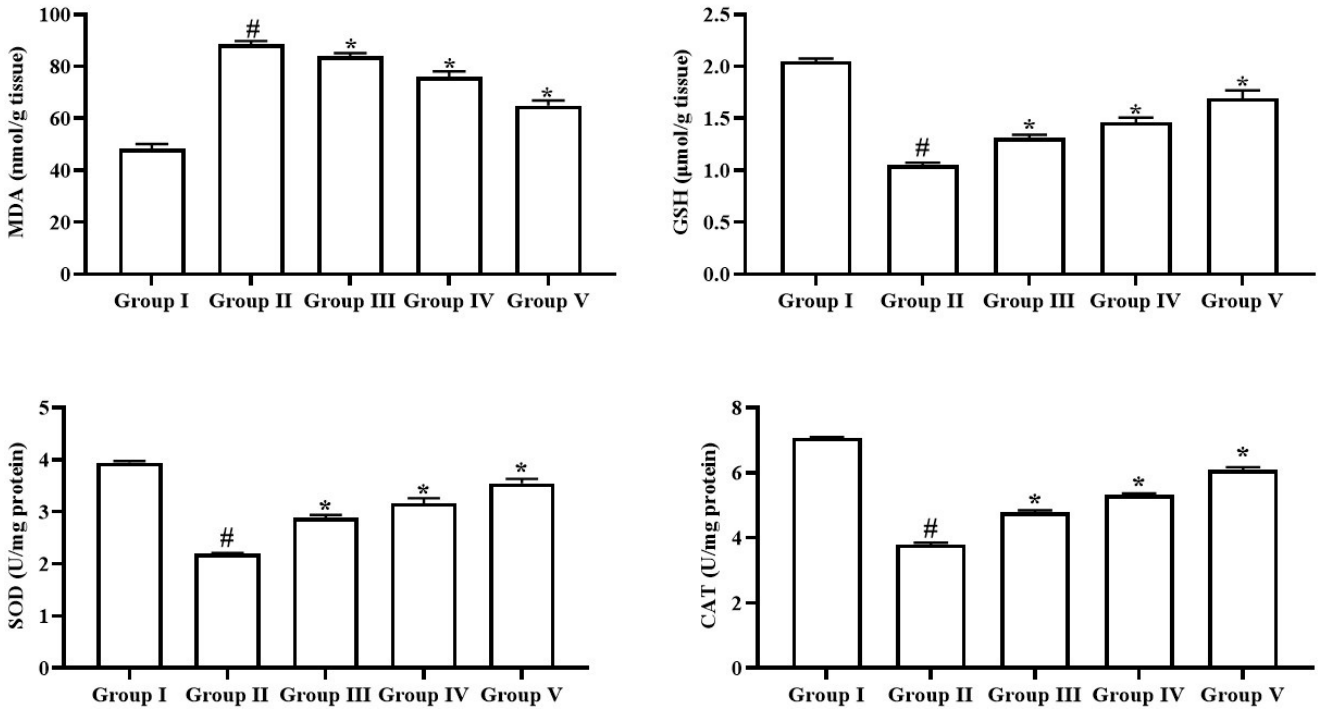


**Figure 3:** Effect of osthenol on the oxidative stress in the experimental rats. The results were presented as a mean±SD of triple experiments. A one-way ANOVA and Tukey's *post hoc* test were utilized to evaluate the statistical significance among treatment groups. '#' denotes statistical significance at $p<0.01$ compared to the control group; '*' indicates statistical significance at $p<0.05$ relative to the ISO-induced group.

myocardial injury. Oxidative stress can also lead to cardiomyocyte damage, apoptosis, and necrosis, as well as impair endothelial function and promote the development of atherosclerosis.[30] To counteract the deleterious effects of oxidative stress, the body relies on the upregulation of antioxidants like SOD, CAT, and GSH. SOD is responsible for the conversion of $O_2\bullet^-$ radicals into less reactive $H_2O_2$, which is subsequently metabolized by CAT and GPx. Decreased concentrations of these antioxidants have been observed in the heart of animals with ISO-treated MI, suggesting an impairment of the body's defensive mechanisms against oxidative stress.[31] Several reports have highlighted that the capacity of these antioxidants is often impaired in patients with MI, further exacerbating the oxidative damage.[32,33] For example, decreased SOD activity has been connected to elevated oxidative stress and poorer outcomes in individuals with acute MI.[34] The excessive of ROS and the impairment of the body's natural defense mechanisms contribute to cardiomyocyte injury, endothelial dysfunction, and the progression of cardiovascular disease. Therefore, oxidative stress and the dysregulation of antioxidant mechanisms play a critical role in the onset of MI. Understanding the role of oxidative stress and the changes in these biomarkers can participate in the advancement of targeted therapeutic interventions aimed at reducing the burden of MI.[35] The results of this work indicated that the MDA level was elevated while the concentrations antioxidants like GSH, CAT, and SOD was substantially reduced in the hearts of ISO-treated rats. Interestingly, the treatment of osthenol effectively increased the antioxidant levels and reduced MDA content in the hearts of ISO-treated rats, which highlights the antioxidant effects of osthenol.

The pathophysiology of MI is complex, involving a cascade of inflammatory and reparative processes that play a crucial role in the advancement of the disease. The initial stage of MI is characterized by the rapid necrosis of cardiomyocytes because of the shortage of oxygen and nutrients caused by the blockage of a coronary artery.[36] This sudden loss of cardiac tissue initiates the severe inflammatory reaction, which is orchestrated by the activation of immune system. The inflammatory phase is marked by the release of inflammatory mediators like IL-6 and TNF-α, which play a central role in the pathophysiology of MI.[37] TNF-α is a potent inflammatory cytokine that is rapidly upregulated in response to myocardial injury. This cytokine can induce cardiomyocyte apoptosis, enhance the inflammatory cell influx, and participate in the onset of cardiac remodeling and dysfunction.[38] Similarly, IL-6 is another inflammatory marker that is elevated in the incidence of MI. IL-6 can activate the acute phase response, stimulate the other inflammatory cytokine accumulations, and participate in the advancement of cardiac hypertrophy and fibrosis.[39] The inflammatory response following MI is a double-edged sword. The initial inflammatory response is essential for eliminating dead cells and initiating repair processes; however, prolonged and over accumulation of pro-inflammatory cytokines can result in additional tissue injury and adverse cardiac remodeling.[40] The inflammatory response and the increased inflammatory cytokine accumulations, like IL-6 and TNF-α, play a central role in the pathophysiology of

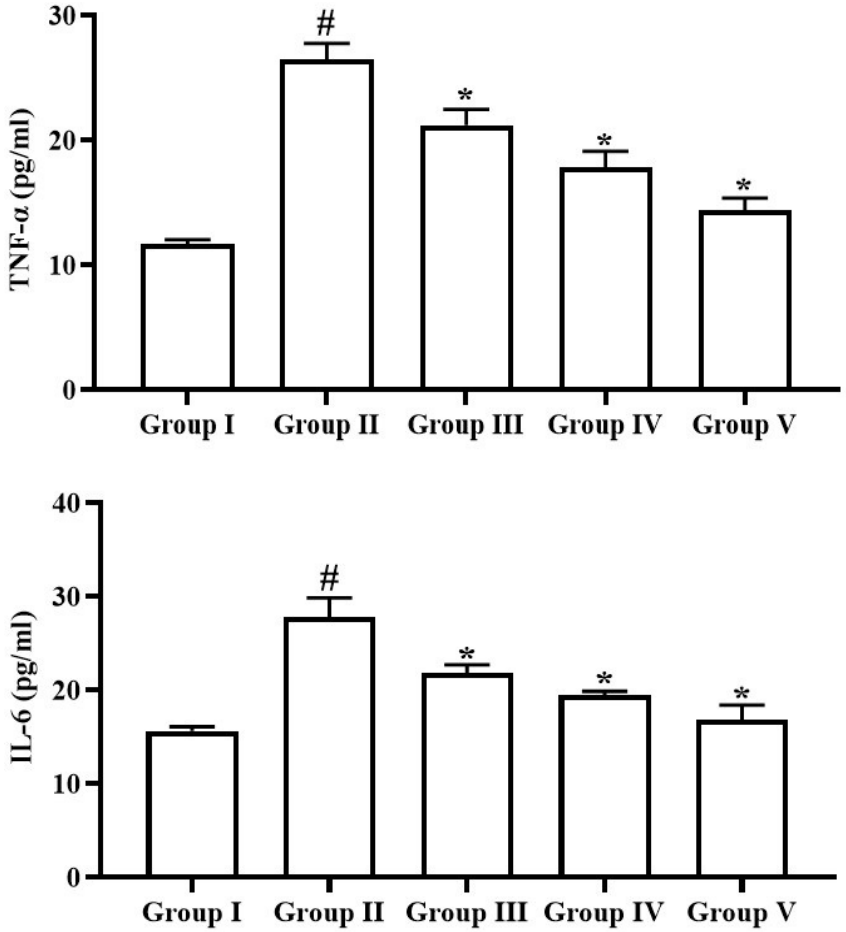


**Figure 4:** Effect of osthenol on the pro-inflammatory cytokines in the experimental rats. The results were presented as a Mean±SD of triple experiments. A one-way ANOVA and Tukey's *post hoc* test were utilized to evaluate the statistical significance among treatment groups. '#' denotes statistical significance at $p<0.01$ compared to the control group; '*' indicates statistical significance at $p<0.05$ relative to the ISO-induced group.

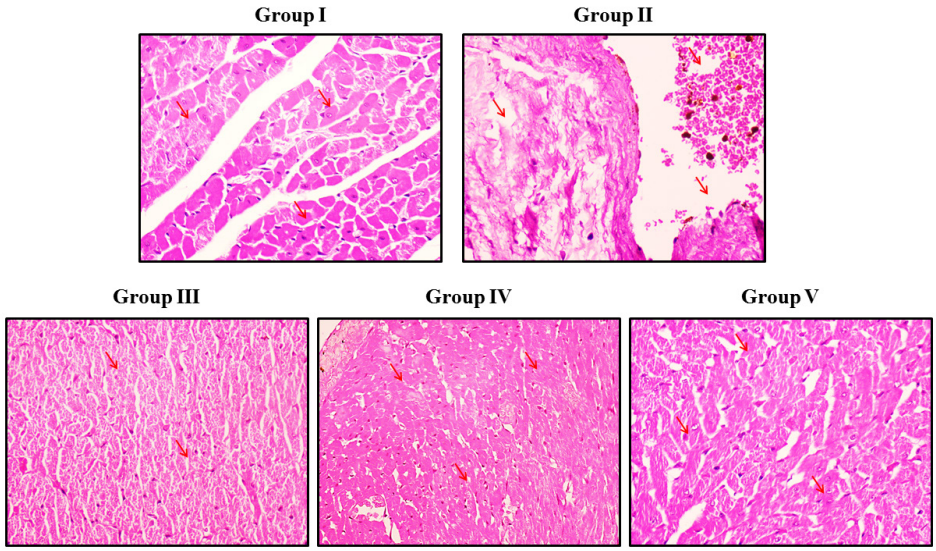


**Figure 5:** Effect of osthenol on the heart histology of the experimental rats. Group I: The cardiac tissue from control rats demonstrate the normal cardiomyocyte arrangements and tissues patterns. Group II: The ISO-induced rats showed myophagocytosis, localized necrosis, and inflammatory cell infiltrations. Group III-IV: The co- and pre-treatments of osthenol at 20 mg/kg concentration showed decrease in myocardial damage, inflammation, and myonecrosis. Group V: The standard drug amlodipine treatment also reduced the histopathological changes in the heart tissue of ISO-induced rats.

MI. The orchestrated and timely resolution of the inflammatory mechanism is crucial for the successful repair and healing of the infarcted myocardium.[41] The findings of this work illustrated the increased TNF-α and IL-6 concentrations in the ISO-treated rats. Whereas, the treatment with osthenol considerably diminished the TNF-α and IL-6 concentrations serum of in the ISO-treated rats. These findings evidence the anti-inflammatory properties of osthenol.

## CONCLUSION

The present findings demonstrate that osthenol treatment can mitigate and protect against the biochemical and histological alterations in rat cardiac tissues caused by ISO. The advantageous effect of osthenol may be due to its notable anti-inflammatory and antioxidant activities. Thus, osthenol may represent a new therapeutic option to treat MI. Further research is strongly suggested to enhance our understanding of the antioxidant, anti-inflammatory, and cardioprotective properties of osthenol in alleviating MI.

## CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

## ETHICAL STATEMENTS

Xi'an Qin Huang Hospital (REC-46/03/1200).

## ABBREVIATIONS

**ISO:** Isoproterenol; **SBP:** Systolic blood pressure; **MI:** Myocardial infarction; **LDH:** Lactate dehydrogenase; **CK-MB:** Creatine kinase; **MDA:** Malondialdehyde; **GSH:** Glutathione; **CAT:** Catalase; **SOD:** Superoxide dismutase.

## SUMMARY

This study was intended to assess the cardioprotective activity of the osthenol against ISO-induced MI in animal model. Our findings indicate that Osthenol protects against myocardial injury caused by isoproterenol. Reduced pro-inflammatory biomarkers, lipid peroxidation marker and elevated antioxidant levels also decreased activity of cardiac injury biomarkers are characteristics of this type of protection. Moreover, the administration of osthenol significantly mitigated the histological changes in the heart of MI rats. Therefore, our data confirm that Osthenol has the potential to be an effective treatment for isoproterenol-induced cardiotoxicity.

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