# Piceatannol Protects Against Isoproterenol-Induced Myocardial Injury in Rats

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## ABSTRACT

**Myocardial infarction (MI) is a critical medical emergency and an advanced stage of coronary artery disease. The disease's pathophysiology includes oxidative stress, inflammation, and cellular apoptosis. Isoproterenol (ISO), is a synthetic adrenergic agonist that mainly acts on adrenergic (β) receptors. Its administration in rats instigates significant myocardial strain, resulting in myocardial damage that resembles myocardial infarction. Piceatannol (PIC), a natural stilbene compound, exhibits free radical-scavenging, tumor-inhibiting, and chemo-preventive activities. This investigation intended to evaluate the cardioprotective benefits of piceatannol in mitigating cardiac damage provoked by ISO in rats. After 28 days of PIC treatment (5 or 10 mg kg-1), rats received two doses of ISO (85 mg kg-1) 24 hours apart to induce myocardial damage. The administration of ISO resulted in significant changes to ECG parameters, elevated blood levels of cardiac enzymes, and histological alterations linked to myocardial damage. It also caused oxidative damage, as evidenced by elevated malondialdehyde (MDA) levels, alongside a decline in glutathione (GSH) concentration and superoxide dismutase (SOD) function. Furthermore, ISO stimulated the synthesis of inflammatory markers such as interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and nuclear factor-kappa B (NF-κB) in the myocardium, concurrently elevating the Bax/Bcl-2 ratio. Conversely, pretreatment with PIC significantly normalized ECG measurements, mitigated the increase of cardiac enzyme levels in the serum, and maintained the normal histological characteristics of the heart. PIC elevated cardiac antioxidant enzyme levels and activity, diminished lipid peroxidation products, and inhibited the expression of inflammatory markers as well as the Bax/Bcl-2 ratio. These results suggest that PIC had a cardio-protective effect in this model.**

***Keywords: Piceatannol; Isoproterenol; Myocardial injury; Oxidative damage; Inflammation; Apoptosis***

## INTRODUCTION

For many decades, it has been recognized that heart disease, particularly myocardial infarction (MI), remains the foremost global contributor to mortality, even in the face of advancements in clinical management, increased public awareness, and innovations in medical technologies that have significantly reduced associated mortality and morbidity[1,2]. MI is a life-threatening medical emergency and represents a serious complication of coronary heart disease. It is the ultimate consequence of either acute or chronic myocardial ischemia, resulting from a disturbed balance between oxygen supply and demand. MI involves myocardial necrosis, which is indicated by elevated myocardial enzymes and abnormal electrocardiogram (ECG) changes[3]. Investigations from both animal and clinical research have demonstrated that the etiology of myocardial infarction (MI) entails the overproduction of reactive oxygen species (ROS), compromised antioxidant defenses, and ensuing lipid peroxidation and cellular membrane damage[4,5]. Therefore, treatment modalities that augment the antioxidant mechanisms and reduce the generation of ROS are expected to halt the progression of the disease.

Isoproterenol is a synthetic catecholamine that acts on β-adrenergic receptors. Its administration generates substantial cardiac stress by activating the adrenergic system and neurohumoral processes, including the enhanced inflow of calcium through L-type calcium channels[6]. As a consequence of cardiac β-receptor activation by isoproterenol, multiple signal transduction pathways are triggered, including those involving kinases, adenosine nucleotides, and G proteins[7-9], renin-angiotensin-aldosterone system activation[5,10], generation of oxidative insult[11], alterations in nitric oxide (NO) production (Ribeiro et al. 2009), and increased levels of fibrogenic factors[12]. Acute exposure to isoproterenol has been shown to induce myocardial ischemia, as evidenced by ECG changes in patients[13]. Similarly, one or two high-dose administrations of isoproterenol in rats have been found to induce myocardial injury resembling that observed in clinical MI[14].

Piceatannol or 3,4′,3′,5-*trans*-trihydroxystilbene is an analog of resveratrol with an extra phenolic group. It is recognized for its potent antioxidant, anticancer, and chemo-preventive activities[15]. The natural stilbene-based compound is found to be abundant in grapes, sugar cane, berries (blue berries, cranberries) peanuts, passion fruit (*Passiflora edulis*) seeds, and white tea[16,17]. Previous pharmacological studies revealed that piceatannol has potent antioxidant, anti-inflammatory, and cardioprotective effects[18]. It has been reported that piceatannol mitigated acute cardiac injury by regulating phosphoinositide 3-kinases/protein kinase B/endothelium nitric oxide synthase (PI3K/Akt/eNOS) signaling *in vitro*[19,20]. Piceatannol, by suppressing oxidative insult, has demonstrated strong protective action against hypoxia-induced injury in H9c2 cardiomyocytes[21].

Since the pathogenesis of MI involves a disturbance in oxidative balance, along with the activation of inflammatory pathways, and given that piceatannol is a potent antioxidant, the current research was carried out to evaluate its potential cardioprotective effects in mitigating myocardial injury caused by isoproterenol in rats.

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## MATERIALS AND METHODS

**Drugs and Chemicals:** The research employed isoproterenol from LKT Labs (St. Paul, MN, USA) and piceatannol from Beijing Yibai Biotechnology (Beijing, China). The study utilized only analytical-grade chemicals for all other substances.

**Animals:** Forty mature male Wistar rats (ages of two and three months and weighing between 150 and 180 grams) were bought from King Abdulaziz University, Kingdom of Saudi Arabia. They were housed under a climate-controlled atmosphere with 22 ± 2°C temperature and a comparative humidity of (50–60%). A 12-hour cycle of light and dark was employed to replicate the circadian rhythms that exist in nature. The animals had an unrestricted approach to conventional food and drinking water. A one-week acclimatization phase was implemented prior to the commencement of the experiment to facilitate adaptation and mitigate stress. The study procedures were evaluated and authorized by the Research and Ethics Committee of the Faculty of Pharmacy (Approval No: PH-134-41).

**Experimental Design:** The animals were allotted to five classes randomly (n=8), and received treatments for 28 days as follows:

Group 1: The control group was given the corresponding vehicles for piceatannol (0.5% carboxymethylcellulose (CMC), p.o.) and isoproterenol. (saline, s.c.).

Group 2: The piceatannol group received 10 mg/kg piceatannol (p.o., in 0.5% CMC) daily for 28 days, with saline (s.c.) on days 26 and 27, 24 hours apart.

Group 3: The isoproterenol group received 0.5% CMC (p.o.) daily over a 28-day period and 85 mg/kg isoproterenol (s.c.) on days 26 and 27, with a 24-hour gap.

Group 4: The piceatannol (5 mg/kg) and isoproterenol group that received 5 mg/kg piceatannol daily over a 28-day period and 85 mg/kg isoproterenol (s.c.) on days 26 and 27, with a 24-hour gap.

Group 5: The piceatannol (10 mg/kg) and isoproterenol group that received 10 mg/kg piceatannol daily over a 28-day period and 85 mg/kg isoproterenol (s.c.) on days 26 and 27, with a 24-hour gap.

**Electrocardiography:** Twenty-four hours post-final dose, the rats received intraperitoneal injections of ketamine (65 mg/kg) and xylazine (10 mg/kg) for anesthesia in preparation for electrocardiogram (ECG) tracing. A thermostatically regulated heating blanket was used to keep the rectal temperatures at 37.5 °C during assessments. The electrodes were placed into the skin of the right hind, front, and left hind limbs. The ECG was recorded using PowerLab model 8/35. The parameters of the ECG were measured and documented.

**Blood and Sample Collection:** After ECG recordings, with the animals remaining under anesthesia, blood was drawn from the retro-orbital plexus, permitted to stand for 15 minutes, and subsequently centrifuged for 10 minutes at 3000 rpm at 4°C to isolate serum. Decapitation then took place, the hearts tissues were' been extracted, meticulously rinsed with chilled saline, and positioned between filter paper. Histopathological and immunohistochemical evaluations were conducted on cardiac sections preserved in 10% formalin. Additional portions of cardiac tissue were preserved in RNA Later Reagent (Cat. #76106, Qiagen, MD, USA). The residual cardiac tissues were promptly frozen in liquid nitrogen and preserved at -80°C alongside the serum for future analyses.

**Assessment of the markers for Cardiac Injury:** Following the manufacturer's instructions, serum cardiac enzyme concentrations were determined using ELISA kits. Sandwich enzyme immunoassays were used to quantify creatine kinase myocardial band (CK-MB), lactate dehydrogenase (LDH), and troponin levels. The kits, sourced from Cloud-Clone Corp in Houston, TX, USA, were identified by catalog numbers SEA479Ra, SEB370Ra, and SEA478Ra.

**Histopathological Examination:** Following fixation in formalin, cardiac tissues were dehydrated by washing with tap water and then progressively treated with methyl alcohol, ethyl alcohol, 100% ethyl alcohol, and xylene. After that, the specimens were cleaned with xylene and set in paraffin blocks. A sledge tissue microtome was employed to produce 5 µm thick tissue sections. Hematoxylin and eosin (H&E), Sirius red, and Masson's trichrome (MTC) were used to stain the sections following deparaffinization and rehydration.

**Immunohistochemical Assessment of the Inflammatory Markers:** Following deparaffinization, cardiac tissue specimens were rehydrated through a series of ethanol dilutions. The tissues were heated for 10 minutes in 0.1 M citrate buffer (pH 6) and then incubated for 120 minutes at room temperature in 5% BSA in TBS to block non-specific binding. The slides were incubated at 4°C for 12 hours with primary mouse antibodies specific to interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) from Abcam® (Cambridge, UK) (catalog numbers ab9324 and ab220210), along with a nuclear factor-kappa B (NF-κB) antibody from Santa Cruz (CA, USA) (catalog number sc-8414). After rinsing with TBS, the slides were incubated with a biotinylated anti-mouse secondary antibody. The target antigen was stained using the Cell & Tissue Staining Anti-Mouse Kit (R&D Systems, Minneapolis, MN, USA, catalog number CTS002). The slides were examined under a light microscope, and optical density was quantified using ImageJ software (version 1.8.0, NIH, Bethesda, MD, USA).

**Colorimetric Analysis of Biomarkers of the Oxidative Damage:** The levels of the malondialdehyde (MDA) and reduced glutathione (GSH) were assessed using commercial kits purchased from Biodiagnostics (Cairo, Egypt) with catalog numbers MD 2529 and GR 2511, respectively. The activity of the antioxidant enzyme superoxide dismutase was assessed using a Biodiagnostics kit with catalog number SD 252. The assays were carried out according to the manufacturer's instructions.

**Assessing the mRNA Expression of the Apoptosis-Related Genes:** The real-time reverse transcription polymerase chain reaction (RT-PCR) method was used to analyze the gene expression of Bax and Bcl-2. Total RNA was extracted using TRIzol, and cDNA was synthesized with the Omniscript RT kit (Qiagen, MD, USA, catalog number 205113). SYBR Green Master Mix (Qiagen, MD, USA, catalog number 180830) was used for amplification. The data were analyzed using the ΔΔCt method, with β-actin used as the housekeeping gene for data standardization. Table 1 lists the primer sequences for β-actin, Bax, and Bcl-2.

**Table 1.** Sequence of Bax, Bcl-2, and β-actin primers.

| | Forward | Reverse |
|---|---|---|
| **Bax** | CCTGAGCTGACCTTGGAGCA | GGTGGTTGCCCTTTTCTACT |
| **Bcl-2** | TGATAACCGGGAGATCGTGA | AAAGCACATCCAATAAAAAGC |
| **β-actin** | TCCGTCGCCGGTCCACACCC | TCACCAACTGGGACGATATG |

**Statistical Analyses:** Data were analyzed by one-way ANOVA with Tukey's post hoc test (n=8), expressed as mean ± SD, with significance at $p < 0.05$, using GraphPad Prism 8.1.

## RESULTS

### Effect of Piceatannol on Isoproterenol-Induced ECG Changes in Rats

As shown in Table 2, isoproterenol significantly disrupted the ECG parameters compared to the vehicle-treated group, characterized by an elevated heart rate, reduced R wave amplitude, and enhanced ST segment uplift. The pretreatment with piceatannol followed by isoproterenol significantly attenuated the changes in ECG parameters relative to the isoproterenol-only-treated group, with no notable variation detected between the two doses (5 and 10 mg/kg) of piceatannol.

Effect of Piceatannol on the Serum Levels of the Cardiac Injury Markers

As illustrated in Figure 1, statistical analysis of the serum markers of heart injury showed significantly higher levels of CK-MB (Figure 1A), LDH (Figure 1B), and troponin (Figure 1C) in the sera of rats treated only with isoproterenol compared to the control group. Conversely, piceatannol pretreatment markedly reduced the increase in serum markers. Furthermore, the group of animals that received a higher dose of piceatannol (10 mg/kg) prior to treatment showed significantly lower serum levels of LDH and troponin than those treated with the lower dose.

### Effect of Piceatannol on Isoproterenol-induced Histopathological Abnormalities in the Hearts of the Treated Rats

Figure 2 illustrates that H&E staining of cardiac sections from control and piceatannol-only-treated animals displayed regular and well-maintained histological features. However, photomicrographs of the isoproterenol-only-treated animals showed signs of cardiac injury, including fibrosis with myxomatous degeneration and inflammatory cell infiltration. Pretreatment with 5 mg/kg piceatannol provided moderate protection against isoproterenol-induced histopathological abnormalities, while treatment with 10 mg/kg piceatannol significantly restored normal cardiac tissue features. Staining with MTC and Sirius red revealed high levels of collagen deposition and fibrosis in the cardiac specimens of the isoproterenol-only-treated group. In contrast, pretreatment with piceatannol markedly reduced collagen deposition in a dose-dependent manner

**Table 2.** The effect of piceatannol on isoproterenol-induced changes in the rats ECG parameters

| GROUP | Heart Rate (Beat/min) | P wave amplitude (mv) | QRS complex interval (sec) | QT interval (sec) | RR interval (sec) | R wave amplitude (mV) | ST elevation (mV) |
|---|---|---|---|---|---|---|---|
| **Control** | 368.75±29.54 | 0.01739± 0.0043 | 0.01449±0.0021 | 0.0556±0.0021 | 0.211±0.02234 | 0.6940±0.1003 | 0.02637±0.0070 |
| **PIC 10 mg/kg** | 365±25.82 | 0.02083±0.0024 | 0.01620±0.00147 | 0.0622±0.0085 | 0.20157±0.02774 | 0.6742±0.0368 | 0.02625±0.0086 |
| **ISO** | 531$^{a,b}$±26.57 | 0.01551±0.0061 | 0.01082±0.00126 | 0.0633±0.0184 | 0.2224±0.01668 | 0.3642$^{a,b}$±0.034 | 0.08528$^{a,b}$±0.011 |
| **PIC 5 mg/kg + ISO** | 446.25$^{c}$±29.26 | 0.01702±0.0014 | 0.01270±0.00115 | 0.06414±0.0215 | 0.2455±0.02558 | 0.4980$^{c}$±0.053 | 0.0606$^{c}$±0.011 |
| **PIC 10 mg/kg + ISO** | 388.75$^{c}$±33.75 | 0.01381±0.0025 | 0.01369±0.00215 | 0.08018±0.0059 | 0.23785±0.02340 | 0.5363$^{c}$±0.055 | 0.04892$^{c}$±0.012 |

Data are displayed as mean ± SEM. Groups with different superscripts (a, b, and c) are considerably distinct at $p \leq 0.05$.

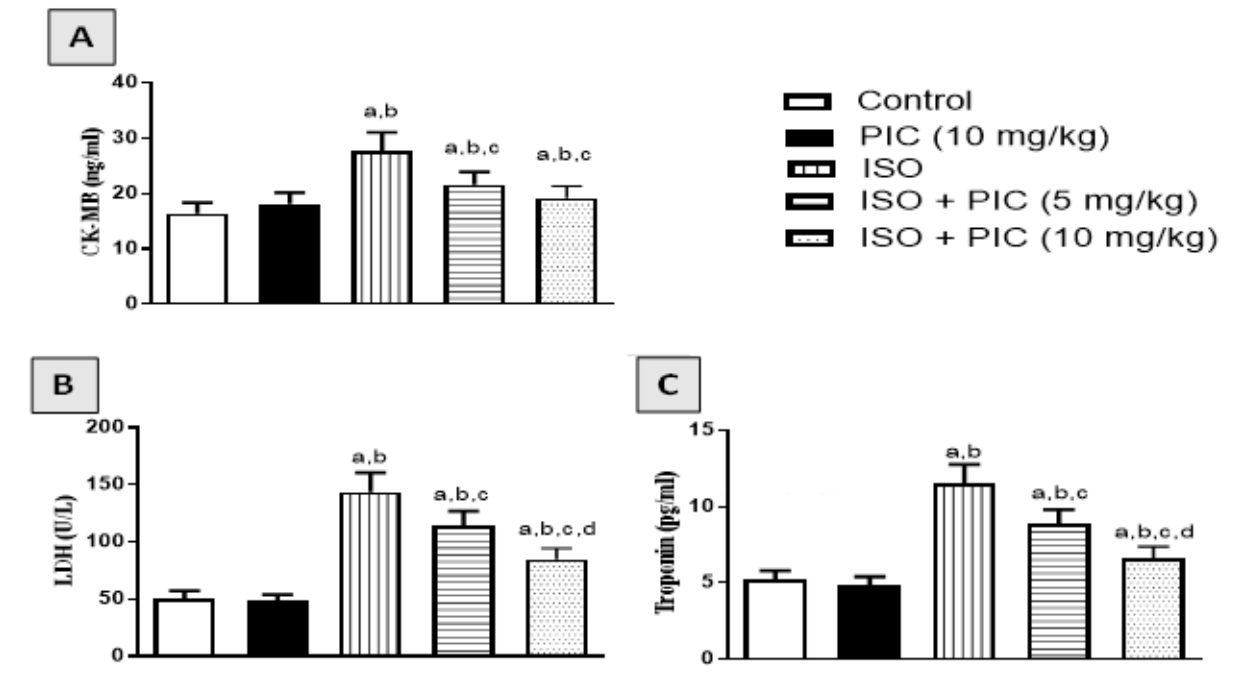


**Figure 1.** The impact of PIC and ISO on serum levels of cardiac damage indicators, including CK-MB, LDH, and troponin. Data are displayed as mean ± SEM. Groups with different superscripts (a, b, c and d) are considerably distinct at $p \leq 0.05$.

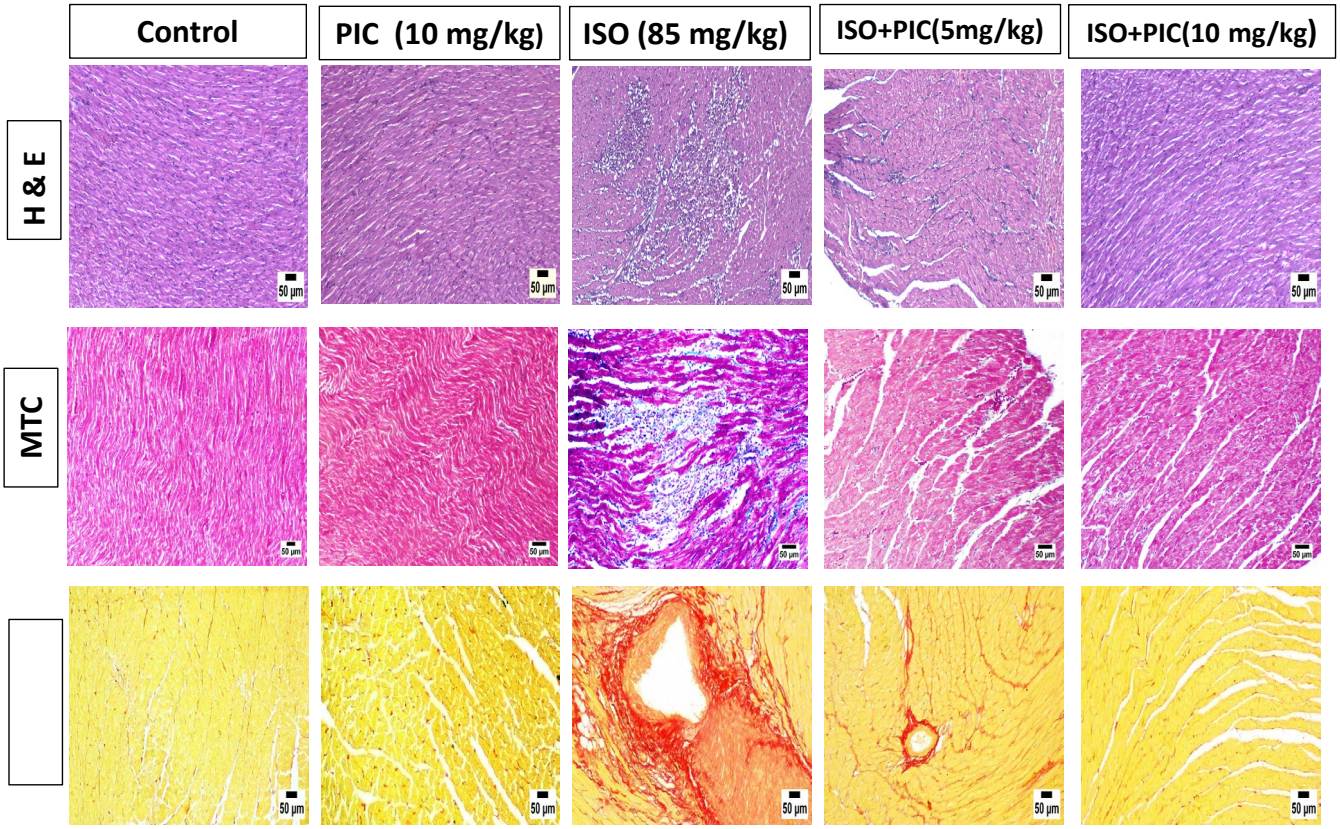


**Figure 2.** Photomicrographs of cardiac tissue sections from rats exposed to ISO and PIC, stained with H&E, MTC, or Sirius red.

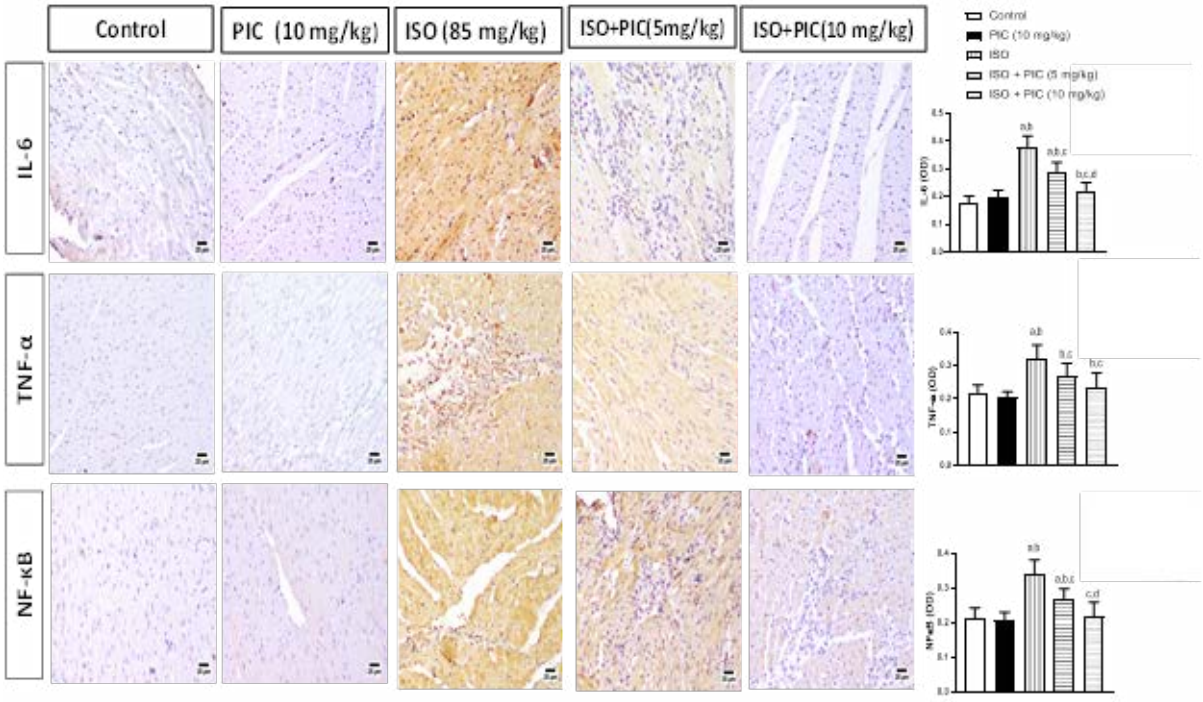


**Figure 3.** The effect of PIC and ISO on the immunohistochemical reactivity of the IL-6, TNF-α, and NF-κB in the cardiac tissue of the treated rats. Data are displayed as mean ± SEM. Groups with different superscripts (a, b, c and d) are considerably distinct at $p \leq 0.05$.

### Effect of Piceatannol on the Inflammatory Biomarkers in rats treated with Isoproterenol

As depicted in Figure 3, isoproterenol administration significantly raised the levels of inflammatory markers IL-6, TNF-α, and NF-κB in comparison to the control group. However, pretreatment with piceatannol (5 or 10 mg/kg) effectively reduced the elevated tissue expression of these inflammatory biomarkers in a dose-dependent manner. Moreover, the higher piceatannol dose (10 mg/kg) led to significantly lower tissue expression of IL-6 and NF-κB compared to the lower dose (5 mg/kg).

### Effect of Piceatannol on the Oxidative Stress Biomarkers in the Cardiac Tissue of Isoproterenol-treated Rats

As illustrated in Figure 4, subcutaneous administration of isoproterenol (85 mg/kg) for two successive days significantly induced oxidative damage in the rat heart. This was evidenced by a marked increase in lipid peroxidation (elevated MDA levels) alongside a reduction in detoxifying GSH levels and a decline in the activity of antioxidant enzyme SOD. On the contrary, the pretreatment of the animals with piceatannol in both doses 5 and 10 mg/kg for 28 days significantly restored the redox balance and decreased the cardiac levels of MDA, increased GSH, and restored the activity of SOD.

### Effect of Piceatannol on the mRNA Expression of the Apoptotic Markers in the Cardiac Tissue of Isoproterenol-treated Rats

Analysis of the RT-PCR results assessing cardiac gene expression of the anti-apoptotic gene Bcl-2 and the proapoptotic gene Bax (Figure 5) showed that ISO administration significantly upregulated Bax expression while downregulating Bcl-2 expression compared to the control groups Moreover, upon calculating the Bax to Bcl-2 ratio, it was noticed that the isoproterenol group showed a significantly higher

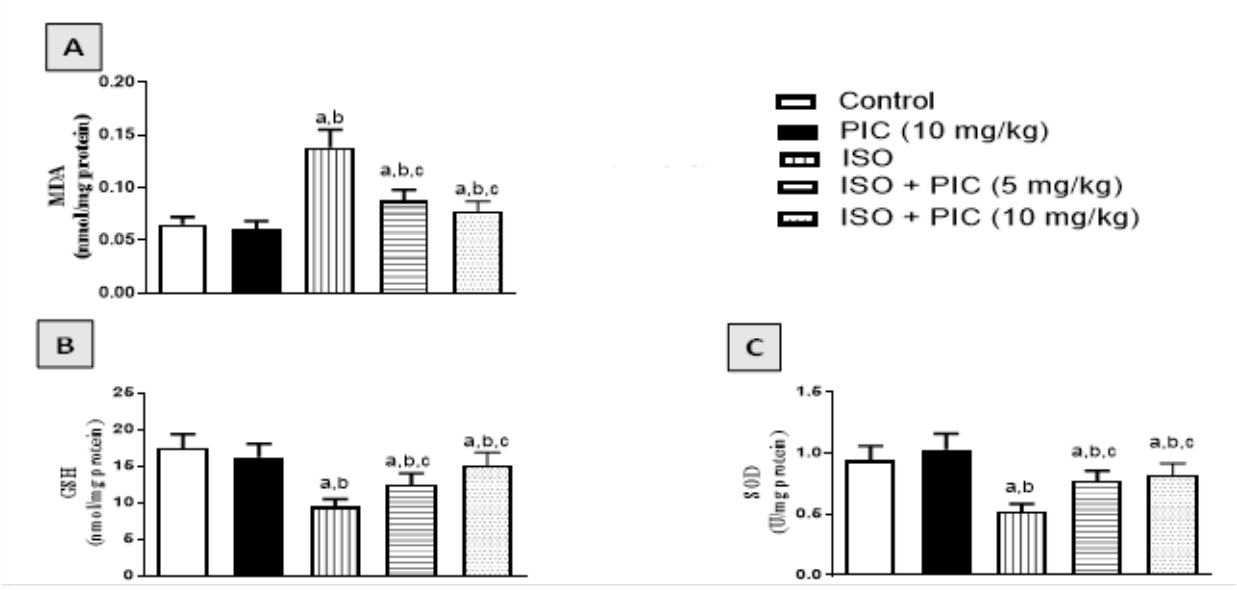


**Figure 4.** The effect of PIC and ISO on the levels of MDA and GSH and the activity of SOD in the cardiac tissue of the treated rats. Data are displayed as mean ± SEM. Groups with different superscripts (a, b, and c) are considerably distinct at p≤0.05.

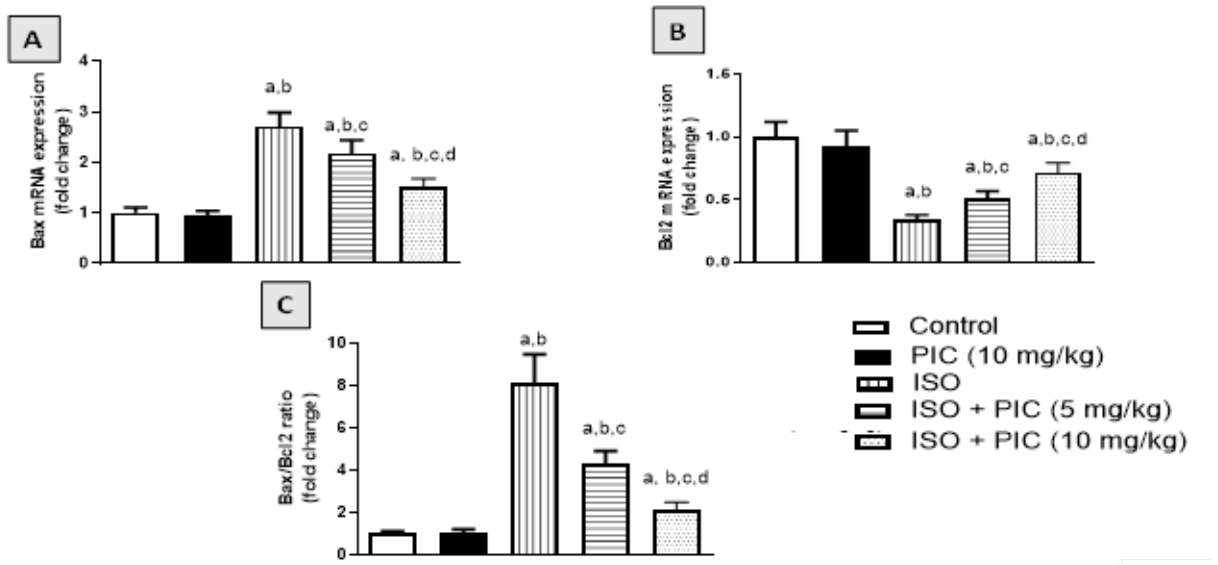


**Figure 5.** The effect of PIC and ISO on the levels of mRNA expression of the cardiac apoptotic markers Bax, Bcl-2, and their ratio. Data are displayed as mean ± SEM. Groups with different superscripts (a, b, c and d) are considerably distinct at p≤0.05.

ratio indicating its effect on inducing apoptosis in the cardiac myocytes. Conversely, prior administration of PIC significantly reduced Bax gene expression while increasing Bcl-2 expression, leading to a restored Bax/Bcl-2 ratio. The higher dose of PIC showed significantly higher Bcl-2 values and lower Bax and Bax/Bcl-2 ratio compared to the lower dose.

## DISCUSSION

Myocardial infarction, a myocardial condition characterized by high prevalence and associated with very high mortality rates, can be defined as a condition of acute myocardial cell death[22]. It occurs due to myocardial hypoxia resulting from the disturbed balance between blood demand and supply which in turn triggers inflammation and apoptosis[23]. MI is associated with lipid peroxidation, and mitochondrial and cell membrane damage due to the overproduction of ROS including hydroxyl radicals and superoxide anion[4,24]. Therefore, prevention of tissue damage and blood supply restoration can be a potential therapy for ischemia-induced injury. Suppression of ROS production and augmentation of the endogenous antioxidant enzyme can reduce the infarct size[25].

Endogenous or exogenous catecholamines augment contractile force and heart rate, resulting in a significant elevation in cardiac output and oxygen consumption. Elevated levels of circulating catecholamines lead to myocardial tissue injury, observable in clinical situations including ischemia, angina, infarction, cardiac arrhythmia, and heart block. They provoke cardiomyocyte and cardiac remodeling at the subcellular level[26,27]. Consequently, catecholamines such as isoproterenol are extensively utilized to create models of cardiac damage[28].

Sugar cane, berries, passion fruit seeds, peanuts, grapes, wine, and white tea are all natural sources of the polyphenolic stilbene piceatannol[16,17]. Pharmacological studies have indicated that piceatannol exhibits potent antioxidant, anti-inflammatory, anti-cancer, and cardioprotective effects[18]. Furthermore, it has been demonstrated to successfully safeguard H9c2 cardiomyocytes from hypoxia-induced injury by mitigating oxidative stress[21].

Since the pathogenesis of MI involves ROS-induced myocardial injury, the activation of inflammatory cytokines, and increased cellular apoptosis, and given that piceatannol is a natural compound recognized for its strong antioxidant, anti-inflammatory, and antiapoptotic properties, this study aimed to explore its potential cardioprotective effects. The investigation focused on assessing ECG parameters, serum markers of cardiac injury, and tissue markers of oxidative stress, inflammation, and apoptosis.

The study's findings indicated that administering isoproterenol (85 mg/kg over a two-day period) efficiently produced heart damage akin to that observed in clinical myocardial infarction. The incidence of myocardial injury was emphasized through the abnormalities in the ECG parameters including the markedly elevated ST-segment which is a hallmark of the occurrence of MI in the clinical practice. There was also an elevation in the serum cardiac enzymes, and histopathological alterations including inflammatory cell infiltration, degeneration, collagen deposition, and signs of fibrosis. It is worth mentioning that heart autopsy samples from patients dying due to MI revealed areas of necrosis, fibrosis, and neutrophil infiltration[29]. Additionally, the study's findings showed that pretreatment with piceatannol corrected the ECG parameters, attenuated the elevation of the serum cardiac enzymes, and maintained the normal histological features of the heart to a considerable extent. Piceatannol was previously proven to attenuate fibrosis and collagen deposition in a study concerning lung injury[30,31].

The onset of myocardial infarction is a complex and multidimensional process, with oxidative stress serving a crucial role in its initiation and progression[32,33]. Under ischemic conditions, the myocardium, owing to insufficient antioxidant defenses, becomes vulnerable to oxidative stress, leading to the overproduction of reactive oxygen species (ROS) that harm cardiomyocytes, provoke membranous lipid peroxidation, impair cell permeability and integrity, and ultimately result in cell death. Besides oxidative stress, inflammation contributes to the pathogenesis of myocardial infarction and influences myocardial damage and cardiomyocyte apoptosis[34,35]. Immune cell infiltration in the hearts of myocardial infarction patients promotes the production of significant amounts of proinflammatory cytokines, including IL-1β, IL-6, and TNF-α, along with the recruitment of inflammatory cells[35]. Moreover, the interplay between these two processes creates a harmful cycle of inflammation and oxidative stress. Inflammation exacerbates oxidative stress by elevating the synthesis of reactive oxygen species (ROS) and diminishing the body's antioxidant defenses, thereby initiating the release of proinflammatory cytokines via redox dependent signaling. Ultimately leading to induced apoptosis and progressive damage to cardiomyocytes[36].

The superoxide radical and hydrogen peroxide react to produce a more reactive free radical, the hydroxyl radical[37]. Furthermore, isoproterenol undergoes autoxidation, resulting in the formation of highly toxic reactive species, including quinones, which, in conjunction with the superoxide anion and hydroxyl radical, compromise cardiac membrane lipids and inflict cellular damage[38]. The research findings demonstrated that isoproterenol administration caused cellular oxidative damage, as revealed by increased lipid breakdown (elevated MDA levels) and a compromised defense mechanism, evidenced by decreased GSH levels and SOD activity. Isoproterenol increased the tissue levels of inflammatory markers (IL-6, TNF-α, and NF-κB), while modifying the gene expression of apoptosis-related markers to facilitate cell death. It enhanced the expression of the pro-apoptotic gene Bax, diminished the expression of the Bcl-2 (anti-apoptotic gene), and elevated the Bax/Bcl-2 ratio, promoting apoptosis in cardiac myocytes. In contrast, previous treatment of piceatannol substantially alleviated the detrimental effects induced by isoproterenol in the heart.

## CONCLUSION

**In conclusion, piceatannol exhibits significant cardioprotective effects against isoproterenol-induced myocardial injury, as evidenced by its restorative impact on ECG parameters, normalization of myocardial histological features, and reduction of elevated serum cardiac enzyme levels. These advantages can be ascribed to its powerful antioxidant, anti-inflammatory, and anti-apoptotic characteristics.**

**Authorship Contribution:** All authors share equal effort contribution towards (1) substantial contributions to conception and design, acquisition, analysis and interpretation of data; (2) drafting the article and revising it critically for important intellectual content; and (3) final approval of the manuscript version to be published. Yes.

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**Potential Conflicts of Interest:** None

**Competing Interest:** None

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