

## Original Article

# *Evaluation of the Effects of p-Coumaric Acid on Oxidative Stress, Electrocardiographic Parameters, and Cardiac Arrhythmias in a CaCl<sub>2</sub>-Induced Arrhythmia Model in Rats*

Mohammadreza Naderi<sup>1</sup>, MS; Mahin Dianat<sup>1\*</sup>, PhD; Mohammad Badavi<sup>1</sup>, PhD; Zahra Mansouri<sup>1</sup>, PhD

### ABSTRACT

**Background:** Cardiovascular diseases remain a leading global cause of mortality, with sudden cardiac death—primarily resulting from arrhythmias—accounting for nearly half of these fatalities. Limited research has explored the impact of p-coumaric acid (P-co) on chemically induced arrhythmias. Given the cardioprotective role of antioxidants, this study aimed to investigate the effects of P-co on oxidative stress, electrocardiographic (ECG) parameters, and cardiac arrhythmias in Wistar rats using a calcium chloride (CaCl<sub>2</sub>)-induced arrhythmia model.

**Methods:** Forty-eight Wistar rats were divided into 6 groups: (1) Control (normal saline); (2) CaCl<sub>2</sub> (normal saline + CaCl<sub>2</sub> 140 mg/kg); (3–5) CaCl<sub>2</sub> + P-co 25, 50, and 100 mg/kg, respectively; and (6) P-co 100 mg/kg. P-co was administered orally for 10 consecutive days, followed by an intravenous injection of CaCl<sub>2</sub> via the femoral vein on the final day. Electrophysiological assessment and arrhythmia evaluation were conducted using lead II ECG. Furthermore, biochemical analyses measured oxidative stress and cardiac injury markers, including MDA, CK-MB, LDH, SOD, CAT, and GPx, across all groups.

**Results:** Intravenous injection of CaCl<sub>2</sub> led to significant changes in ECG parameters and the development of arrhythmias. Pretreatment with P-co significantly improved the observed changes. Compared with the CaCl<sub>2</sub> group, P-co pretreatment reduced cardiac damage markers and lipid peroxidation and enhanced antioxidant enzymes.

**Conclusions:** The results of this study suggest that the intravenous administration of CaCl<sub>2</sub> induces cardiac arrhythmias and oxidative stress in heart tissue. As a natural polyphenol and antioxidant, P-co exhibited a protective effect against CaCl<sub>2</sub>-induced cardiac damage. (*Iranian Heart Journal 2026; 27(2): 65-80*)

**KEYWORDS:** CaCl<sub>2</sub>; p-coumaric acid; arrhythmia; oxidative stress

<sup>1</sup> Department of Physiology, Faculty of Medicine, Persian Gulf Physiology Research Center, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, IR Iran.

\*Corresponding Author: Mahin Dianat, PhD; Department of Physiology, Faculty of Medicine, Persian Gulf Physiology Research Center, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, IR Iran.

Email: dianatmah@yahoo.com

Tel: +989163110437

Received: May 28, 2025

Accepted: February 12, 2026

Cardiovascular diseases (CVDs) represent a major global burden, contributing extensively to mortality, morbidity, and diminished quality of life. In 2008, CVDs accounted for approximately 17 million deaths worldwide. According to the World Health Organization (WHO), by 2030, around 23.6 million people are expected to have died from CVDs, with the condition remaining one of the leading causes of mortality. Research from the MONICA project, conducted across 21 countries on 4 continents (excluding Iran), indicated that the average 28-day mortality rate from coronary artery disease was 49% in men and 51% in women. This finding means that nearly half of the patients who suffered a heart attack died within the first month. Nonetheless, a more recent study conducted in Iran found that the 1-month survival rate after a heart attack was 85%, and the 1-year survival rate was 80%.<sup>1,2</sup> According to the WHO, over 80% of CVDs occur in low- and middle-income countries. CVDs encompass a wide range of conditions, including coronary artery disease, myocardial infarction, angina pectoris, heart failure, and various arrhythmias. Arrhythmias refer to abnormal heartbeats, causing either tachycardia or bradycardia, reflecting irregular impulse generation, conduction irregularities, or a combination of both. The major causes of arrhythmias include myocardial ischemia, exposure to high levels of catecholamines, autonomic nervous system influences, drug toxicity, and increased production of free radicals.<sup>1-3</sup> Studies have shown that about half of deaths caused by CVDs are due to sudden cardiac arrest, predominantly associated with arrhythmias. Cardiac arrhythmias involve disturbances in heart rhythm, manifesting as irregular, accelerated (tachycardia), or slowed (bradycardia) heart rates. Arrhythmias can generally be classified into 2 categories: ventricular and atrial. They can occur in various heart

conditions, such as acute coronary syndromes or cardiomyopathies, and can lead to heart failure or sudden death.<sup>4-6</sup>

The most significant ventricular arrhythmias include premature ventricular contractions (PVCs), ventricular tachycardia (V-tach), and ventricular fibrillation (VF). The most common supraventricular arrhythmias include atrial flutter and atrial fibrillation. Other notable arrhythmias are torsades de pointes, Wolff-Parkinson-White syndrome, and Stokes-Adams syndrome.<sup>7, 8</sup> Untreated arrhythmias can lead to high mortality, with certain types necessitating urgent intervention as cardiac emergencies. Nevertheless, antiarrhythmic medications pose inherent risks, often related to dosage or high plasma concentrations of the drugs. Moreover, the severity of adverse effects is frequently influenced by underlying cardiac conditions and concurrent drug therapies.<sup>9, 10</sup> Intracellular free radicals are small molecules with an unpaired electron, often derived from oxygen. The terms “free radicals” and “reactive oxygen species” (ROS) are frequently used interchangeably. ROS readily reacts with most biomolecules, initiating a reaction chain that propagates free radical production. Oxidative stress, induced by free radicals and ROS, contributes significantly to the pathogenesis of various diseases, including CVDs, cancers, and diabetes. Neutralization of free radicals through interactions with other radicals or antioxidants is essential to interrupt this damaging cascade.<sup>11, 12</sup>

According to the Vaughan-Williams classification system, antiarrhythmic drugs are grouped based on their inhibition of specific ion channels. These categories include blockers of fast sodium channels,  $\beta$  receptors, potassium channels, and calcium channels.<sup>13, 14</sup> Amiodarone is effective in treating most types of arrhythmias and is considered the most effective antiarrhythmic drug. It inhibits potassium, calcium, sodium

channels, and  $\beta$  receptors, prolonging the action potential duration, increasing the refractory period, and lengthening the Q-T interval. Still, it can cause significant side effects, such as pulmonary fibrosis, corneal microdeposits, tremors, and thyroid dysfunction.<sup>15, 16</sup>

In experimental settings, arrhythmias can be induced by either electrical or chemical methods. Calcium chloride ( $\text{CaCl}_2$ ) is a commonly used agent for chemically inducing arrhythmias. It causes arrhythmias directly by acting on the myocardium and possibly indirectly through the sympathetic nervous system.<sup>17</sup>

Polyphenolic compounds, the largest group of phytochemicals, are commonly found in plant-based foods, and numerous studies have demonstrated their beneficial effects on health. Polyphenols exhibit antioxidant properties that support the body's antioxidant defense system against oxidative stress caused by free radicals. The protective mechanism of these compounds may be linked to their involvement in intracellular signaling pathways.<sup>18-20</sup> In this regard, p-coumaric acid (P-co) is a phenolic acid that exhibits a range of biological activities, including antioxidant, anti-inflammatory, analgesic, and antimicrobial effects. It is widely present in plants and constitutes part of the human diet.<sup>21, 22</sup>

Given that the effects of P-co on chemically-induced arrhythmias have not yet been investigated, and considering the importance of antioxidants in protecting against heart diseases, a protocol was designed to evaluate the effects of P-co on oxidative stress, electrocardiographic (ECG) parameters, and cardiac arrhythmias in a  $\text{CaCl}_2$ -induced arrhythmia model in Wistar rats.

## METHODS

### Animals

Forty-eight male healthy Wistar rats (200–250 g) were obtained from the Animal

Laboratory of Ahvaz Jundishapur University of Medical Sciences. The animals were housed in controlled temperatures (20–24 °C) under a 12-hour light/dark cycle with unlimited access to food and water. Then, they were randomly assigned to the target groups. Animals were treated in accordance with animal care guidelines. The study protocol received approval from the Animal Ethics Committee of Ahvaz Jundishapur University of Medical Sciences (IR.AJUMS.ABHC.REC.1402.019).

### Experimental Groups

Animals were randomly divided into 6 groups, each containing 8 rats:

1. Control group: Normal saline (10 consecutive days, gavage) followed by intravenous injection of normal saline.<sup>23</sup>
2.  $\text{CaCl}_2$  group: Normal saline (10 consecutive days, gavage) followed by intravenous injection of  $\text{CaCl}_2$  (140 mg/kg).<sup>23</sup>
3.  $\text{CaCl}_2$  + P-co-25 group: P-co (25 mg/kg, 10 consecutive days, gavage) followed by intravenous injection of  $\text{CaCl}_2$  (140 mg/kg).<sup>23, 24</sup>
4.  $\text{CaCl}_2$  + P-co-50 group: P-co (50 mg/kg, 10 consecutive days, gavage) followed by intravenous injection of  $\text{CaCl}_2$  (140 mg/kg).<sup>24</sup>
5.  $\text{CaCl}_2$  + P-co-100 group: P-co (100 mg/kg, 10 consecutive days, gavage) followed by intravenous injection of  $\text{CaCl}_2$  (140 mg/kg).<sup>23, 24</sup>
6. P-co100 group: P-co (100 mg/kg, 10 consecutive days, gavage) followed by intravenous injection of normal saline.<sup>23, 24</sup>

### Induction of Cardiac Arrhythmia Model

The animals were orally administered P-co for 10 days. After that, the rats were anesthetized with a mixture of ketamine (50 mg/kg) and xylazine (5 mg/kg). Based on

the group assignments, 140 mg/kg of CaCl<sub>2</sub> was injected via the femoral vein to induce arrhythmia. Animals in the control and P-co100 groups received normal saline (the solvent for CaCl<sub>2</sub>).<sup>24</sup>

### P-co Administration

P-co was administered orally at doses of 25, 50, and 100 mg/kg daily for 10 consecutive days prior to CaCl<sub>2</sub> injection.<sup>24</sup>

### ECG Parameters Assessment

Following anesthesia, lead II ECG was recorded for all groups to assess heart rate, P-R interval, Q-T interval, QRS complex voltage, PVCs, and the number of VF and V-tach cases. The Q-T interval was corrected for heart rate (QTc) utilizing the Bazett formula<sup>25</sup>:

$$QTc = QT/\sqrt{RR}$$

### Measurement of Lactate Dehydrogenase (LDH) and CK-MB Enzyme Activities in Plasma

Following the ECG recordings, blood samples were obtained directly from the animals' hearts. Plasma was isolated by centrifugation, and the parameters were quantified using validated assay kits in accordance with the manufacturers' protocols.<sup>26</sup>

### Assessment of Antioxidant Markers (catalase [CAT], superoxide dismutase [SOD], and glutathione peroxidase [GPx]) and Lipid Peroxidation (malondialdehyde [MDA]) in Cardiac Tissue

At the end of the experiment, heart tissues were excised and immediately frozen in liquid nitrogen before being stored at -80 °C. On the day of analysis, the frozen samples were carefully weighed and homogenized in phosphate-buffered saline at a ratio of 1:10. The homogenates were subsequently centrifuged at 12,000 rpm for

15 minutes at 4 °C. The resulting supernatants were utilized to assess biochemical parameters following the instructions provided with the respective assay kits using spectrophotometry at the specified wavelengths.<sup>27</sup>

## RESULTS

### ECG parameters analysis

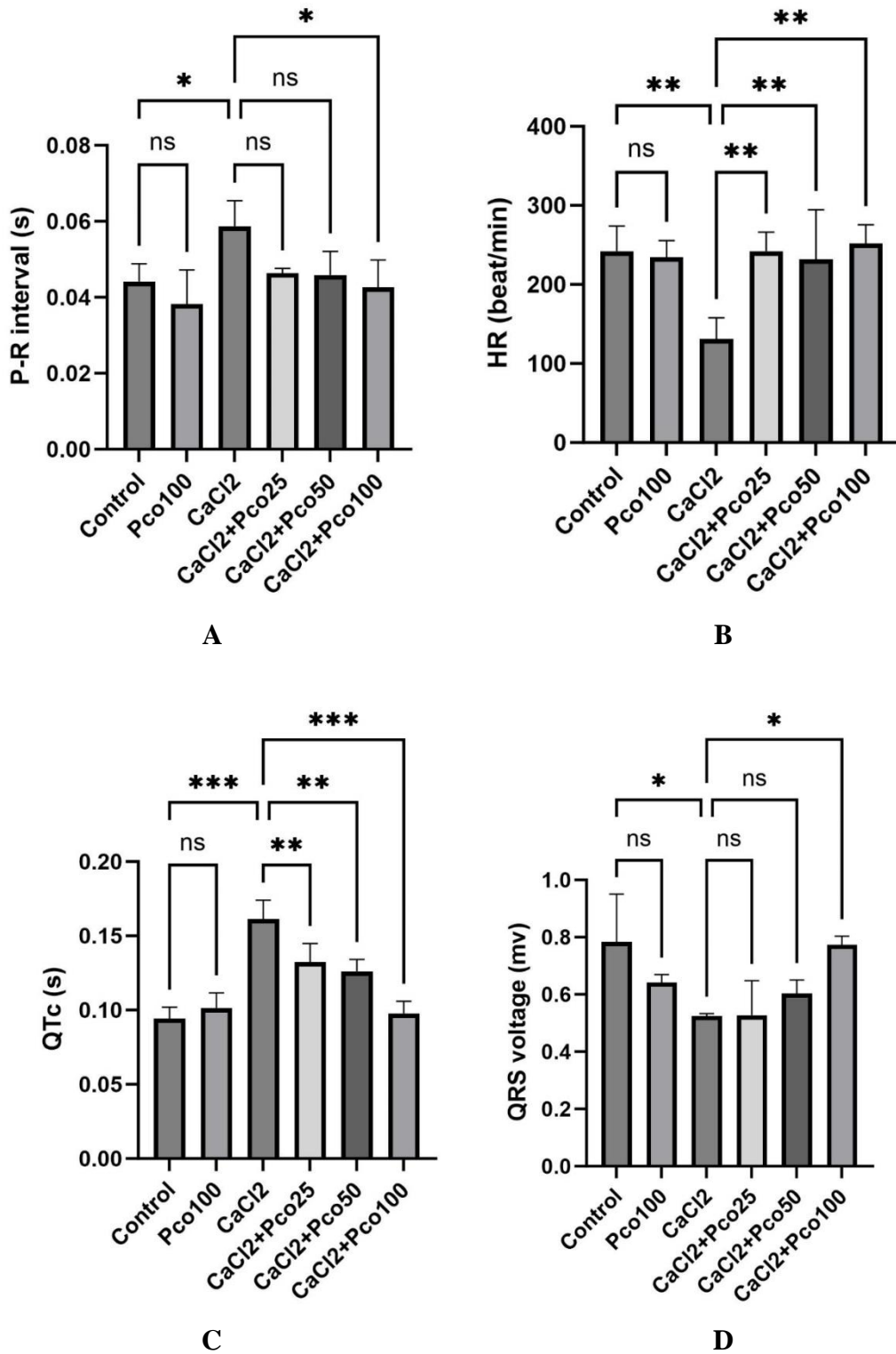
The heart rate examination across different groups revealed that CaCl<sub>2</sub> injection decreased heart rate ( $P < 0.01$ ) compared with the control group. Pretreatment with P-co significantly increased heart rate ( $P < 0.01$ ) compared with the CaCl<sub>2</sub> group (Figure 1.A).

Analysis of the P-R interval among various groups demonstrated a notable increase ( $P < 0.05$ ) in the P-R interval of the CaCl<sub>2</sub> group in comparison to the control group. Furthermore, pretreatment with P-co (100 mg/kg) significantly decreased the P-R interval relative to the CaCl<sub>2</sub> group ( $P < 0.05$ ) (Figure 1.B).

The analysis of the Q-T interval, reported as QTc, demonstrated a significant prolongation ( $P < 0.001$ ) in the CaCl<sub>2</sub> group compared with the control group. Moreover, pretreatment with P-co resulted in a statistically significant decrease in the Q-T interval ( $P < 0.01$ ,  $P < 0.01$ , and  $P < 0.001$ , respectively) by comparison with the CaCl<sub>2</sub> group (Figure 1.C).

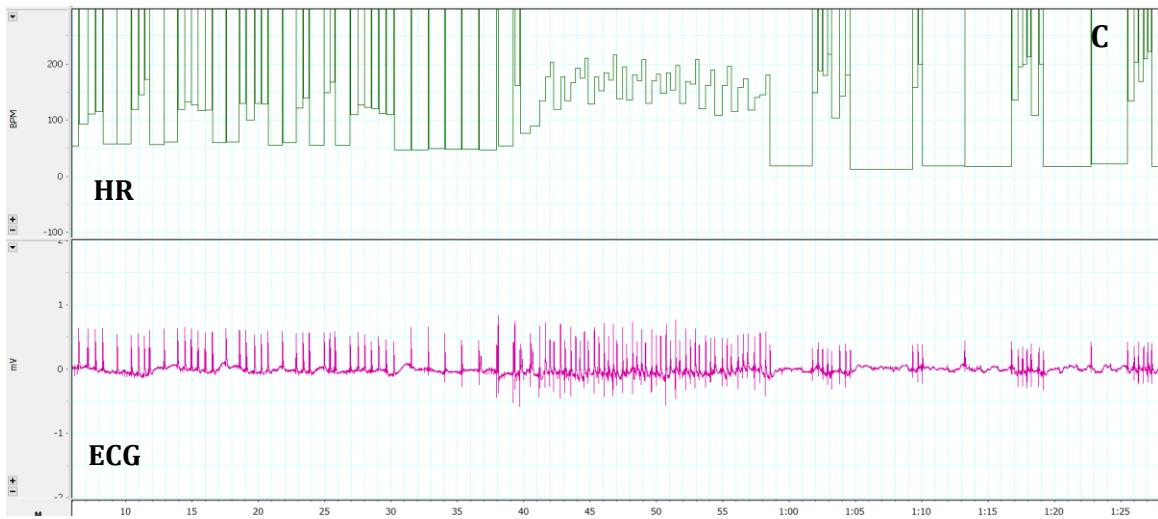
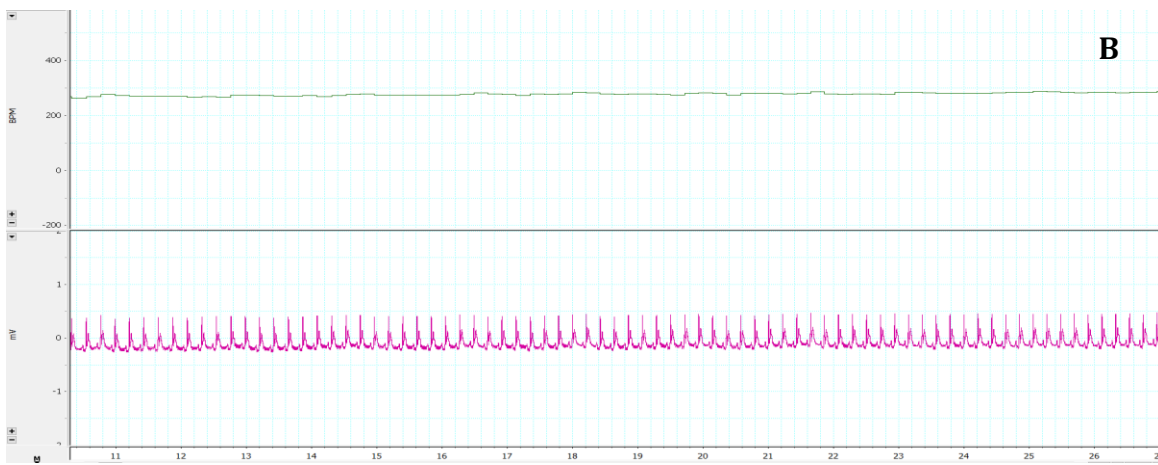
The analysis of QRS complex voltage indicated a significant reduction ( $P < 0.05$ ) in the CaCl<sub>2</sub> group compared with the control group. Notably, pretreatment with P-co (100 mg/kg) elicited a significant increase in QRS voltage ( $P < 0.05$ ) relative to the CaCl<sub>2</sub> group (Figure 1.D).

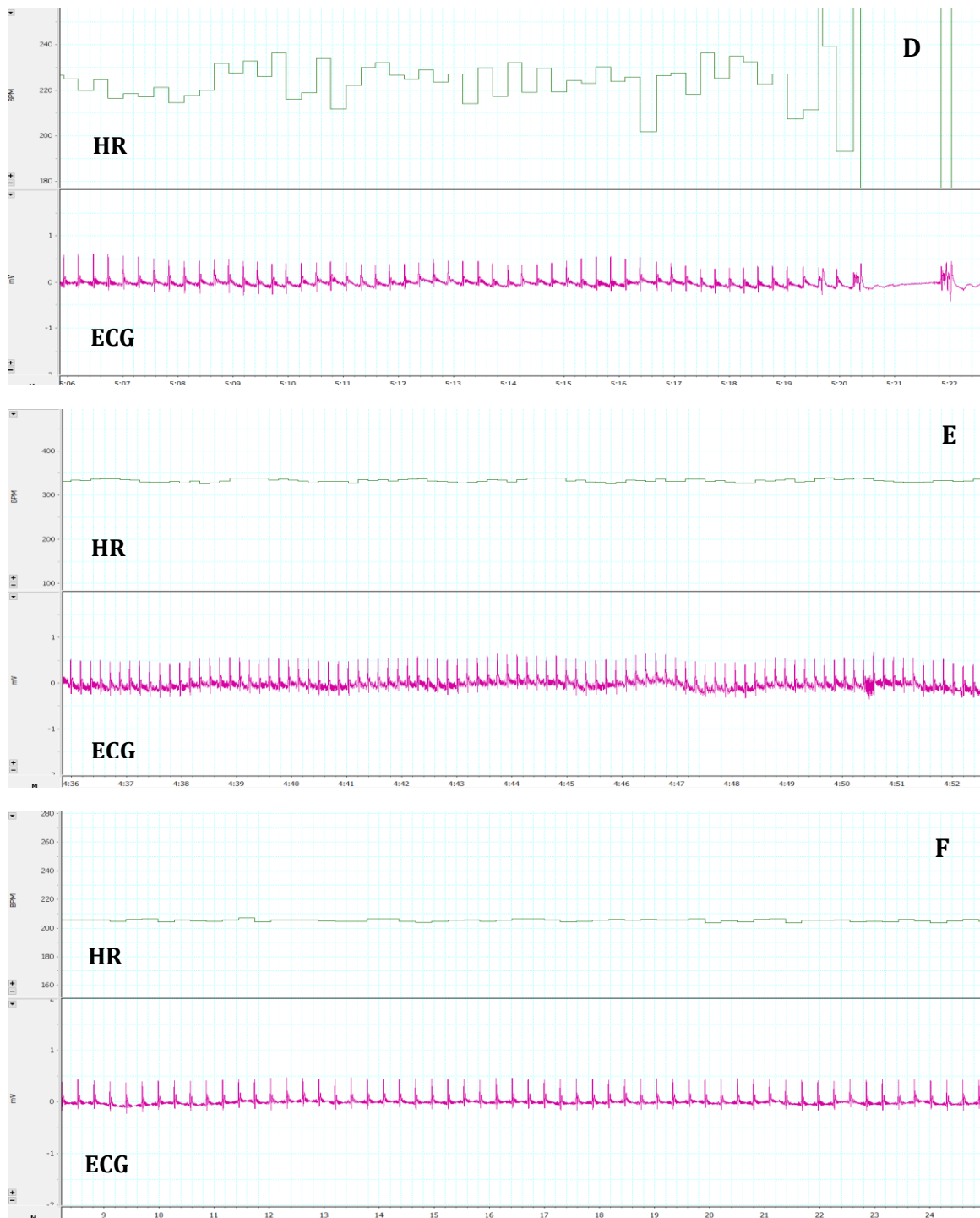
The ECG recording from lead II is illustrated in Figure 2.



**Figure 1.** Effect of P-co on ECG parameters in different groups. A: HR, B: P-R interval, C: QTc, D: QRS voltage ( $^*P < 0.05$ ,  $^{**}P < 0.01$ , and  $^{***}P < 0.001$ ). Data are expressed as mean  $\pm$  SEM (n = 8).

P-co: p-coumaric acid; HR: heart rate





**Figure 2.** Effect of P-co on ECG patterns in different groups. A: Control, B: P-co100, C: CaCl<sub>2</sub>, D: CaCl<sub>2</sub>+P-co25, E: CaCl<sub>2</sub>+P-co50, F: CaCl<sub>2</sub>+P-co100.

P-co: p-coumaric acid; ECG: electrocardiography; HR: heart rate; CaCl<sub>2</sub>: calcium chloride

### Cardiac arrhythmia analysis

As demonstrated in Figure 3, the administration of CaCl<sub>2</sub> significantly

increased the incidence of arrhythmias, including V-tach, VF, and PVC, compared with the control group ( $P < 0.001$ ).

Additionally, pretreatment with P-co significantly reduced the occurrence of these arrhythmias in comparison with the CaCl<sub>2</sub> group ( $P < 0.001$ ).

Figure 4 depicts the effect of CaCl<sub>2</sub> (140 mg/kg) on cardiac arrhythmias, clearly demonstrating the incidence of V-tach, VF, and PVC.

### CK-MB analysis

In this experiment, CaCl<sub>2</sub> injection significantly increased CK-MB levels ( $P < 0.05$ ) in the CaCl<sub>2</sub> group compared with the control group. Pretreatment with P-co (100 mg/kg) significantly decreased ( $P < 0.05$ ) CK-MB levels compared with the CaCl<sub>2</sub> group (Figure 5).

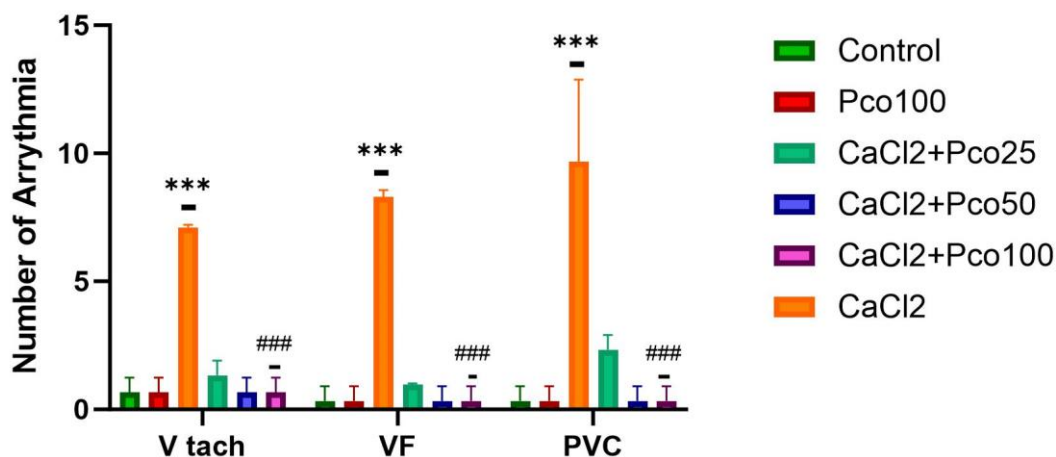
### LDH analysis

The levels of LDH exhibited a significant increase ( $P < 0.001$ ) in the CaCl<sub>2</sub> group

compared with the control group. In addition, pretreatment with P-co resulted in a notable reduction in LDH levels ( $P < 0.05$ ,  $P < 0.05$ , and  $P < 0.001$  respectively) in comparison with the CaCl<sub>2</sub> group (Figure 6).

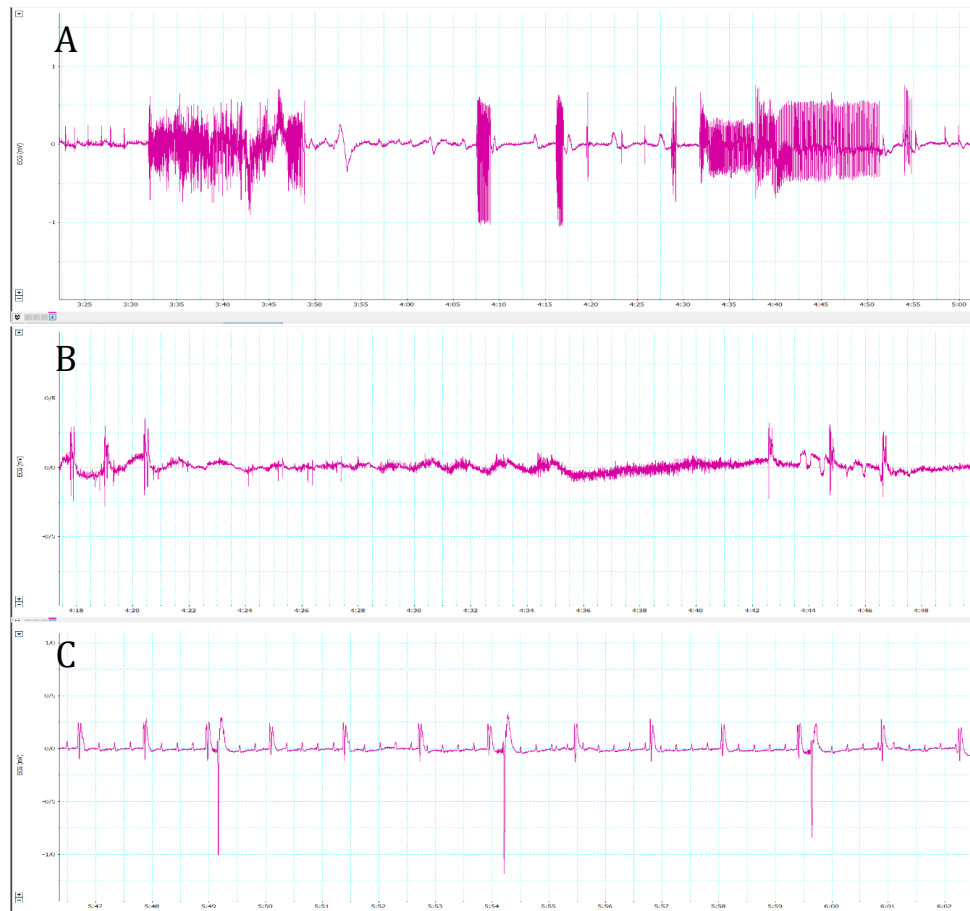
### Antioxidant level analysis

Oxidative stress markers showed that the levels of SOD ( $P < 0.01$ ), CAT, and GPx ( $P < 0.001$ ) were considerably reduced in the CaCl<sub>2</sub> group relative to the control group. Further, CaCl<sub>2</sub>-treated rats demonstrated a significant increase in MDA levels ( $P < 0.05$ ) compared with the control group. Pretreatment with P-co (100 mg/kg) significantly increased the level of antioxidant enzyme concentrations ( $P < 0.05$  and  $P < 0.01$ ) and also decreased the level of MDA ( $P < 0.05$ ) compared with the CaCl<sub>2</sub> group (Figure 7).



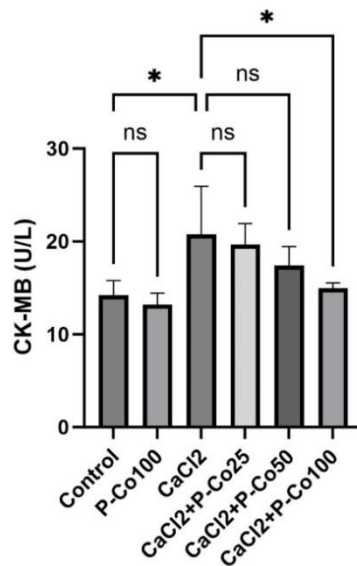
**Figure 3.** Effect of P-co on cardiac arrhythmias in different groups. V-tach, VF, and PVC were evaluated ( $***P < 0.001$  vs the control group and  $###P < 0.001$  vs the CaCl<sub>2</sub> group). Data are expressed as mean  $\pm$  SEM ( $n = 8$ ).

P-co: p-coumaric acid; V-tach: ventricular tachycardia; VF: ventricular fibrillation; PVC: premature ventricular contractions; CaCl<sub>2</sub>: calcium chloride



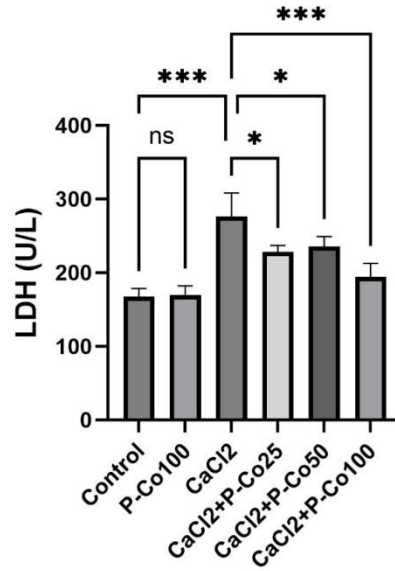
**Figure 4.** Effect of CaCl<sub>2</sub> (140 mg/kg) on cardiac arrhythmia. A: V-tach, B: VF, and C: PVC

CaCl<sub>2</sub>: calcium chloride; V-tach: ventricular tachycardia; VF: ventricular fibrillation; PVC: premature ventricular contractions



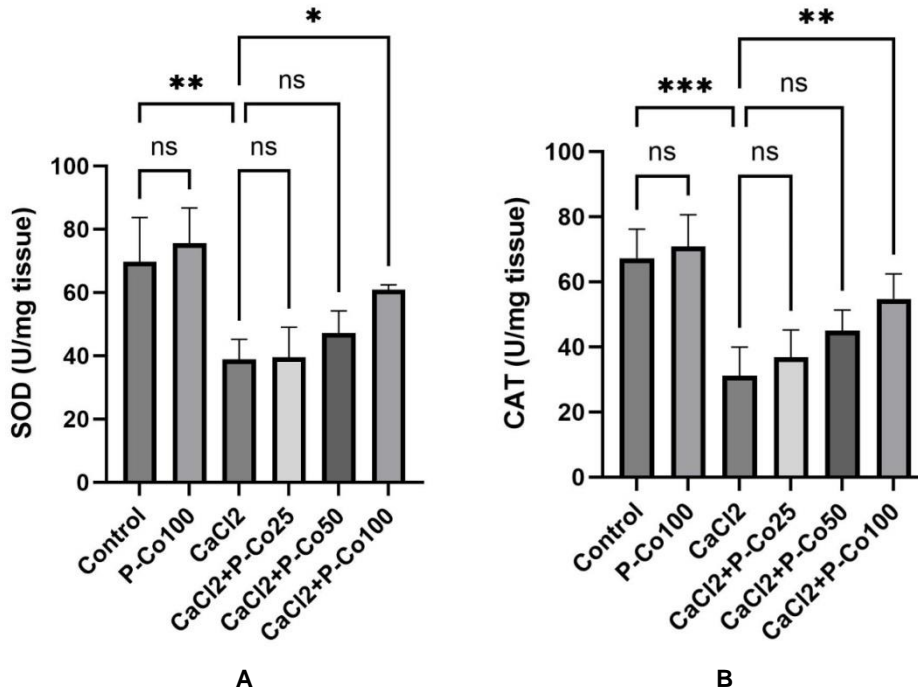
**Figure 5.** Effect of P-co on the CK-MB level in different groups ( $P < 0.05$ ). Data are expressed as mean  $\pm$  SEM (n = 8).

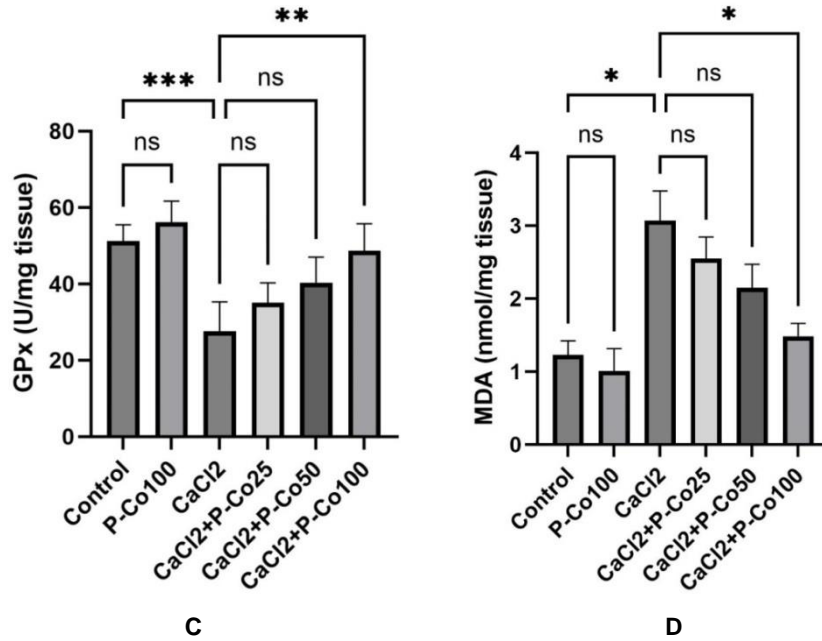
P-co: p-coumaric acid; CaCl<sub>2</sub>: calcium chloride



**Figure 6.** Effect of P-co on the LDH level in different groups ( $P < 0.05$  and  $***P < 0.001$ ). Data are expressed as mean  $\pm$  SEM (n = 8).

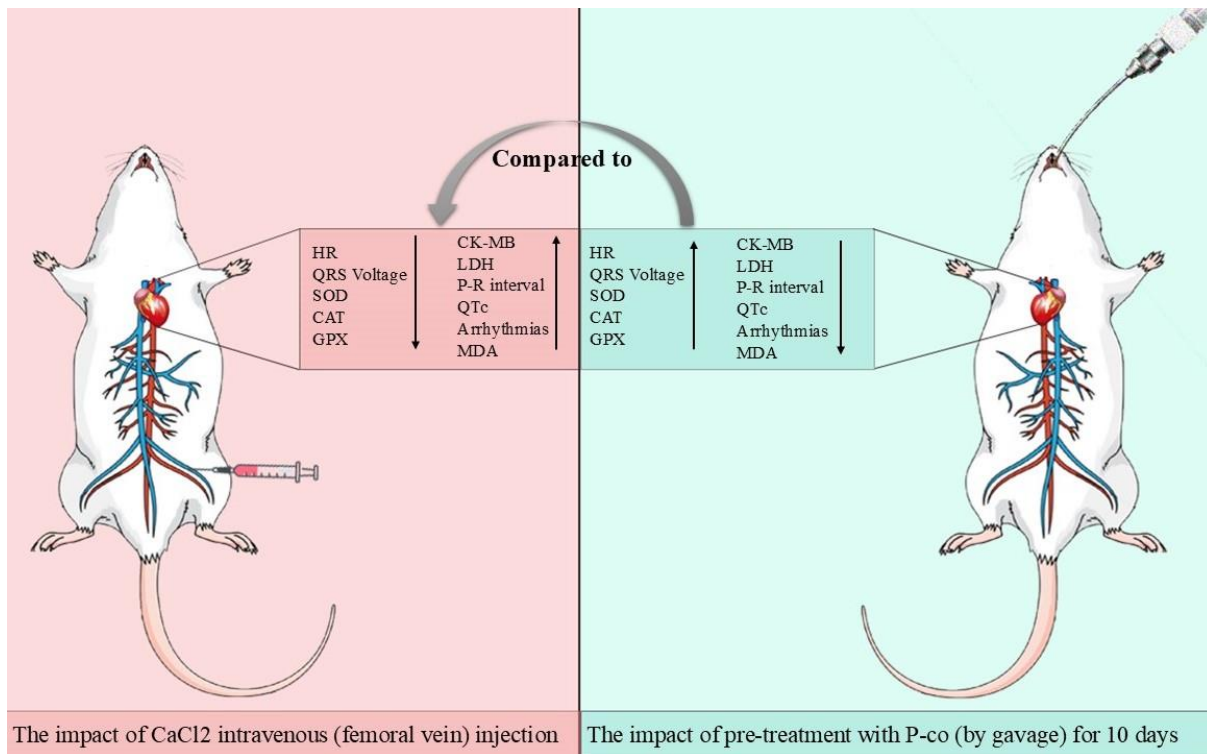
P-co: p-coumaric acid; CaCl<sub>2</sub>: calcium chloride; LDH: lactate dehydrogenase





**Figure 7.** Effect of P-co on the heart tissue antioxidant content in different groups. A: SOD, B: CAT, C: GPx, D: MDA ( $P < 0.05$ ,  $**P < 0.01$ , and  $***P < 0.001$ ).

P-co: p-coumaric acid; CaCl<sub>2</sub>: calcium chloride; SOD: superoxide dismutase; CAT: catalase; GPx: glutathione peroxidase; MDA: malondialdehyde



**Figure 8.** Schematic representation showing the impact of CaCl<sub>2</sub>-induced cardiac arrhythmia via oxidative stress pathway and the protective role of pretreatment with P-co

P-co: p-coumaric acid; CaCl<sub>2</sub>: calcium chloride

## DISCUSSION

CVDs, including cardiac arrhythmias, remain the leading cause of mortality and morbidity worldwide. Arrhythmias are disorders of the heart's rhythm resulting from structural or functional abnormalities, oxidative stress, or electrolyte imbalances. These conditions can lead to severe complications such as heart failure or sudden cardiac death. Understanding arrhythmias' mechanisms and identifying potential therapeutic interventions are crucial for improving patient outcomes.<sup>28</sup>

The current study demonstrates that P-co, a natural antioxidant, effectively protects the heart from injury due to CaCl<sub>2</sub>-induced arrhythmia in rat models.

An ECG is one of the main tools in diagnosing and evaluating cardiac function, which provides valuable information about heart rhythm, electrical conduction, and heart muscle health by recording the electrical activity of the heart. This noninvasive method allows the identification of various cardiac disorders, including arrhythmias, ischemia, myocardial infarction, and structural heart problems.<sup>29</sup>

Additionally, detailed analysis of ECG components such as P-R, Q-T intervals, and ST-segment changes provides detailed information about the heart's electrical function and the extent of cardiac tissue damage, which is used in research and clinical practice as one of the key tools for cardiac evaluation.<sup>30, 31</sup> Detailed ECG analysis in the present study revealed significant alterations in cardiac electrical activity induced by CaCl<sub>2</sub> injection. A dramatic reduction in heart rate and QRS voltage was observed, indicating a compromised ability of the heart to generate and conduct electrical impulses efficiently. This was further accompanied by a marked increase in the QTc and the P-R interval, suggesting prolonged ventricular repolarization and impaired atrioventricular

conduction. These findings highlight the extent of cardiac dysfunction and underscore the utility of ECG parameters in identifying and quantifying the severity of cardiac injury and associated electrophysiological disturbances.

Cardiac arrhythmias are disturbances in the heart's normal rhythm caused by problems producing or conducting electrical impulses. These disturbances may cause the heart rate to increase, decrease, or become irregular. Arrhythmias can be mild and non-existent or severe and life-threatening.<sup>32</sup> V-tach is an arrhythmia in which the ventricles contract abnormally at a high rate. This leads to low blood pressure, reduced blood flow to the extremities, and VF or cardiac arrest in more severe cases.<sup>33, 34</sup> PVCs are abnormal beats that start in the ventricles and disrupt the heart's normal rhythm; these beats are usually felt as skips or extra beats and, if repeated, can lead to more serious arrhythmias. VF is a dangerous and life-threatening arrhythmia in which the ventricles contract rapidly and irregularly, causing a sudden stop in blood pumping; this condition can lead to cardiac arrest and death without immediate intervention, such as defibrillation.<sup>35-37</sup> The findings of our study are consistent with previous research. For instance, Khaksar et al<sup>38</sup> reported that intravenous administration of CaCl<sub>2</sub> induced cardiac arrhythmias, including V-tach, VF, and premature ventricular beats. Similarly, Kheradmandpour et al<sup>39</sup> demonstrated that CaCl<sub>2</sub> administration in rats resulted in alterations of ECG parameters, subsequent development of cardiac arrhythmias, and heightened oxidative stress.

Cardiac biomarkers are crucial in diagnosing and monitoring heart diseases, as they reflect the extent of myocardial injury and stress. Among these, CK-MB and LDH are widely used indicators of cardiac damage. CK-MB is an isoenzyme predominantly found in the myocardium, and its elevation in serum is a

hallmark of myocardial infarction or injury. LDH, an enzyme in cellular energy metabolism, is released into the bloodstream when myocardial cells are damaged or lysed. Elevated levels of these biomarkers signify cellular necrosis and provide valuable insights into the severity and progression of cardiac pathology.<sup>40</sup> Similarly, Liu et al<sup>41</sup> demonstrated that dexmedetomidine-induced cardiac injury through ischemia/reperfusion leads to increased cardiac biomarkers, including CK-MB, troponin I, and LDH levels. The results of this study demonstrated that intravenous injection of CaCl<sub>2</sub> caused cardiac damage, leading to increased levels of LDH and CK-MB markers, which, in turn, affected cardiac function. Conversely, pretreatment with P-co by decreasing the leakage of CK-MB and LDH leads to improved cardiac function. A study by Ponnian et al<sup>42</sup> indicated that pretreatment with P-co in isoproterenol-induced myocardial infarction in a rat model reduced the level of cardiac biomarkers and confirmed the cardioprotective effect of this polyphenol.

Oxidative stress occurs when there is an imbalance between oxidation and antioxidant processes. During cardiac injury, superoxide and hydrogen peroxide radicals can inactivate SOD and CAT. This inactivation leads to superoxide and hydrogen peroxide accumulation, which can damage myocardial cells. Previous studies have shown that infarcted mice treated with coumaric acid significantly increased antioxidant activity and levels.<sup>43, 44</sup> In the present study, we evaluated lipid peroxidation and antioxidant enzyme levels. The results indicated increased lipid peroxidation, as evidenced by elevated MDA levels, accompanied by a significant decrease in the levels of SOD, CAT, and GPx. Pretreatment with P-co has been shown to improve the levels of SOD, CAT, and GPx in the heart while reducing MDA

levels. In the same regard, Shen et al<sup>45</sup> reported that P-co supplementation could slightly reduce body weight in mice and decrease total cholesterol levels, atherosclerosis index, and serum CAT levels. P-co administration also improved lipid peroxidation and antioxidant defense. It is a potent natural antioxidant with potential therapeutic efficacy for treating cardiac arrhythmia.

Although this study examined the effects of P-co on oxidative stress, ECG parameters, and cardiac arrhythmias, it is recommended that future research elucidate the precise mechanisms underlying the influence of P-co on cellular signaling pathways, as well as explore potential analogous or synergistic effects of P-co.

## CONCLUSIONS

In conclusion, this study demonstrates that CaCl<sub>2</sub> injection in Wistar rats causes significant cardiac dysfunction, including elevated LDH and CK-MB markers, arrhythmias, and reduced antioxidant activity due to oxidative stress. P-co, as a natural antioxidant, effectively mitigated these effects by improving ECG parameters, reducing lipid peroxidation, and enhancing antioxidant enzyme activity. These findings suggest that P-co may offer protective benefits against CaCl<sub>2</sub>-induced cardiac damage, providing potential therapeutic value in managing oxidative stress and arrhythmias.

## Conflict of Interest

There are no conflicts of interest.

## Acknowledgments

The source of data used in this paper was from the MS thesis of Mr Mohammadreza Naderi a student of Ahvaz Jundishapur University of Medical Sciences. The authors gratefully acknowledge the help and financial support of the Persian Gulf Physiology

Research Center, Basic Sciences Research Institute, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran. (No. APRC-0112). The protocol was approved by the Research Ethics Committee of Ahvaz Jundishapur University of Medical Sciences [IR.AJUMS.ABHC.REC.1401.091].

## REFERENCES

- Hung MY, Kounis NG, Lu MY, Hu P. Myocardial Ischemic Syndromes, Heart Failure Syndromes, Electrocardiographic Abnormalities, Arrhythmic Syndromes and Angiographic Diagnosis of Coronary Artery Spasm: Literature Review. *Int J Med Sci.* 2020; 17(8):1071-82.
- Xu M, Yang X. Double hazards of ischemia and reperfusion arrhythmias in a patient with variant angina pectoris. *J Electrocardiol.* 2015;48(4):739-43.
- Yesin M, Kalcik M, Gursoy MO, Karakoyun S, Cagdas M, Ozkan M. Acute myocardial infarction in a patient suffering from penicillin-induced laryngeal edema : Kounis syndrome aggravated by adrenaline. *Wien Klin Wochenschr.* 2017; 129(13-14):509-11.
- Chiwane A, Pradeep. Study of Rhythm Disturbances in Acute Myocardial Infarction. *J Assoc Physicians India.* 2018; 66(1):54-8.
- Riad O, Russell C, Garfield B, Behar JM. Atrial pacing to suppress ventricular arrhythmias in the critically ill patients: a case report. *Eur Heart J Case Rep.* 2022; 6(5):ytac163.
- Salinas P, Lopez-de-Sa E, Pena-Conde L, Viana-Tejedor A, Rey-Blas JR, Armada E, et al. Electrocardiographic changes during induced therapeutic hypothermia in comatose survivors after cardiac arrest. *World J Cardiol.* 2015; 7(7):423-30.
- Bhandari A, Woodruff R, 3rd, Murthy A. A large hiatal hernia causing frequent premature ventricular contractions with bigeminy: A case report and review of literature. *J Cardiol Cases.* 2023; 28(1):36-9.
- Hu D, Li J. Rapid wide QRS tachycardia with an unknown cause. *Ann Noninvasive Electrocardiol.* 2022; 27(5):e12959.
- Erath JW, Hohnloser SH. Drugs to prevent sudden cardiac death. *Int J Cardiol.* 2017; 237:22-4.
- Kasper S. Choosing among second-generation antidepressant treatments for depressed patients with cardiac diseases. *Int J Psychiatry Clin Pract.* 2019; 23(2):134-48.
- Jakubczyk K, Dec K, Kaldunska J, Kawczuga D, Kochman J, Janda K. Reactive oxygen species - sources, functions, oxidative damage. *Pol Merkur Lekarski.* 2020; 48(284):124-7.
- Khramtsov VV. In Vivo Electron Paramagnetic Resonance: Radical Concepts for Translation to the Clinical Setting. *Antioxid Redox Signal.* 2018;28(15):1341-4.
- Kotoda M, Ino H, Kumakura Y, Iijima T, Ishiyama T, Matsukawa T. Analgesic effects of amiodarone in mouse models of pain. *J Pain Res.* 2019; 12:1825-32.
- Williams EA, Russo V, Ceraso S, Gupta D, Barrett-Jolley R. Anti-arrhythmic properties of non-antiarrhythmic medications. *Pharmacol Res.* 2020; 156:104762.
- Ermakov S, Scheinman M. Arrhythmogenic Right Ventricular Cardiomyopathy - Antiarrhythmic Therapy. *Arrhythm Electrophysiol Rev.* 2015; 4(2):86-9.
- Mujovic N, Dobrev D, Marinkovic M, Russo V, Potpara TS. The role of amiodarone in contemporary management of complex cardiac arrhythmias. *Pharmacol Res.* 2020; 151:104521.
- Cao Z-P, Zhang Y, Mi L, Luo X-Y, Tian M-H, Zhu B-L. The expression of B-type natriuretic peptide after CaCl<sub>2</sub>-induced arrhythmias in rats. *The American Journal of Forensic Medicine and Pathology.* 2016; 37(3):133-40.
- Abdelsalam SA, Renu K, Zahra HA, Abdallah BM, Ali EM, Veeraraghavan VP, et al. Polyphenols Mediate Neuroprotection in Cerebral Ischemic Stroke-An Update. *Nutrients.* 2023; 15(5).

19. Miranda AR, Albrecht C, Cortez MV, Soria EA. Pharmacology and Toxicology of Polyphenols with Potential As Neurotropic Agents in Non-communicable Diseases. *Curr Drug Targets*. 2018; 19(2):97-110.
20. Kazemzadeh R, Khorsandi L, Radan M, Ghafouri S, Mard SA. Pretreatment with p-coumaric acid protect rat's liver against ischemia-reperfusion injury. *Physiology and Pharmacology*. 2021; 25(1):69-75.
21. Malik N, Dhiman P. New Approaches and Advancements in Drug Development from Phenolic P-coumaric Acid. *Curr Top Med Chem*. 2022; 22(18):1515-29.
22. Pei K, Ou J, Huang J, Ou S. p-Coumaric acid and its conjugates: dietary sources, pharmacokinetic properties and biological activities. *J Sci Food Agric*. 2016; 96(9):2952-62.
23. Dianat M, Akbari G. Protective effect of hydroalcoholic extract of hawthorn fruit on CaCl<sub>2</sub>-induced arrhythmias in rat. *Jundishapur Scientific Medical Journal*. 2014; 12(6):693-703.
24. Kheiry M, Dianat M, Badavi M, Mard SA, Bayati V. p-Coumaric acid protects cardiac function against lipopolysaccharide-induced acute lung injury by attenuation of oxidative stress. *Iranian Journal of Basic Medical Sciences*. 2019; 22(8):949.
25. Dianat M, Amini N, Badavi M, Farbood Y. Ellagic acid improved arrhythmias induced by CaCl<sub>2</sub> in the rat stress model. *Avicenna Journal of Phytomedicine*. 2015; 5(2):120.
26. Cheng D, Xi Y, Cao J, Cao D, Ma Y, Jiang W. Protective effect of apple (Ralls) polyphenol extract against aluminum-induced cognitive impairment and oxidative damage in rat. *Neurotoxicology*. 2014; 45:111-20.
27. Dianat M, Radan M, Badavi M, Mard SA, Bayati V, Ahmadizadeh M. Crocin attenuates cigarette smoke-induced lung injury and cardiac dysfunction by anti-oxidative effects: the role of Nrf2 antioxidant system in preventing oxidative stress. *Respiratory research*. 2018; 19:1-20.
28. Gaur U, Gadkari C, Pundkar A, Gaur Jr U. Associated factors and mortality of arrhythmia in emergency department: A narrative review. *Cureus*. 2024; 16(9).
29. Klabunde RE. Cardiac electrophysiology: normal and ischemic ionic currents and the ECG. *Adv Physiol Educ*. 2017; 41(1):29-37.
30. Kramer J, Nordbeck P, Stork S, Ritter C, Ertl G, Wanner C, et al. Electrical Changes in Resting, Exercise, and Holter Electrocardiography in Fabry Cardiomyopathy. *JIMD Rep*. 2015; 28:19-28.
31. Vazquez-Gonzalez KI, Ochoa-Brust A, Rodriguez-Hernandez A, Ventura-Cisneros H, Lino-Lopez GJ, Barbosa-Valdovinos R, et al. Cardiac alterations induced by *Heloderma horridum horridum* venom in rats: An experimental study with ECG analysis using a linear regression algorithm. *Toxicon*. 2024; 249:108062.
32. Kingma J, Simard C, Drolet B. Overview of Cardiac Arrhythmias and Treatment Strategies. *Pharmaceuticals (Basel)*. 2023; 16(6).
33. Chen SM, Sun C, Wang XY, Zhang Y, Liu SW. [Arrhythmogenic right ventricular cardiomyopathy associated with arrhythmia-induced cardiomyopathy: A case report]. *Beijing Da Xue Xue Bao Yi Xue Ban*. 2021; 53(5):1002-6.
34. Pelter MM, Suba S, Sandoval C, Zegre-Hemsey JK, Berger S, Larsen A, et al. Actionable Ventricular Tachycardia During In-Hospital ECG Monitoring and Its Impact on Alarm Fatigue. *Crit Pathw Cardiol*. 2020; 19(2):79-86.
35. Campos FO, Shiferaw Y, Vigmond EJ, Plank G. Stochastic spontaneous calcium release events and sodium channelopathies promote ventricular arrhythmias. *Chaos*. 2017; 27(9):093910.
36. Cluitmans MJM, Bear LR, Nguyen UC, van Rees B, Stoks J, Ter Bekke RMA, et al. Noninvasive detection of spatiotemporal activation-repolarization interactions that prime idiopathic ventricular fibrillation. *Sci Transl Med*. 2021; 13(620):eabi9317.

37. Yozgat CY, Yesilbas O, Iscan A, Yurtsever I, Temur HO, Bayramova N, et al. Development of Antiarrhythmic Therapy-Resistant Ventricular Tachycardia, Ventricular Fibrillation, and Premature Ventricular Contractions in a 15-Year-Old Patient. *J Pediatr Intensive Care*. 2022; 11(1):72-6.
38. Khaksar MA, Purchini P, Radan M, Dianat M. Protective effects of the combination of exercise and gallic acid supplementation on cardiac system in CaCl<sub>2</sub>-induced arrhythmias model in rats. *Jundishapur Journal of Physiology*. 2018; 1(1):12-6.
39. Kheradmandpour M, Aminifar SA, Dianat M. The effect of hydro-alcoholic extract of *Ocimum basilicum* on CaCl<sub>2</sub>-induced cardiac arrhythmias in rats. *Jentashapir Journal of Cellular and Molecular Biology*. 2020; 11(4).
40. Amini N, Sarkaki A, Dianat M, Mard SA, Ahangarpour A, Badavi M. Protective effects of naringin and trimetazidine on remote effect of acute renal injury on oxidative stress and myocardial injury through Nrf-2 regulation. *Pharmacological Reports*. 2019; 71(6):1059-66.
41. Liu Y, Qu X, Zhang J, Wang X, Wang J. Effects of dexmedetomidine on the degree of myocardial ischemia-reperfusion injury, oxidative stress and TLR4/NF- $\kappa$ B signaling pathway in rats. *Pakistan Journal of Pharmaceutical Sciences*. 2021; 34.
42. Ponnian SMP, Stanely SP, Roy AJ. Cardioprotective effects of p-coumaric acid on tachycardia, inflammation, ion pump dysfunction, and electrolyte imbalance in isoproterenol-induced experimental myocardial infarction. *J Biochem Mol Toxicol*. 2024; 38(3):e23668.
43. Douiri S, Bahdoudi S, Hamdi Y, Cubi R, Basille M, Fournier A, et al. Involvement of endogenous antioxidant systems in the protective activity of pituitary adenylate cyclase-activating polypeptide against hydrogen peroxide-induced oxidative damages in cultured rat astrocytes. *J Neurochem*. 2016; 137(6):913-30.
44. Liu D, Yue Y, Ping L, Sun C, Zheng T, Cheng Y, et al. *Lactobacillus delbrueckii* subsp. *bulgaricus* 1.0207 Exopolysaccharides Attenuate Hydrogen Peroxide-Induced Oxidative Stress Damage in IPEC-J2 Cells through the Keap1/Nrf2 Pathway. *Antioxidants (Basel)*. 2024; 13(9).
45. Shen Y, Song X, Li L, Sun J, Jaiswal Y, Huang J, et al. Protective effects of p-coumaric acid against oxidant and hyperlipidemia-an in vitro and in vivo evaluation. *Biomed Pharmacother*. 2019; 111:579-87.