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The effect of carvacrol on kidney injury caused by isopreterenol-induced myocardial infarction

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Abstract

Background Myocardial infarction is a major cause of morbidity and mortality, often leading to heart and kidney dysfunction. Despite advancements in treatment, the link between heart and kidney damage is poorly understood. This study aims to evaluate the potential protective effect of Carvacrol, a natural bioactive compound, on kidney injury induced by myocardial infarction.

Methods In this experimental study, 32 male Wistar rats were divided into four groups: Control, Carvacrol (50 mg/kg), Myocardial Infarction (85 mg/kg isoproterenol), and Myocardial Infarction + Carvacrol (50 mg/kg Carvacrol + 85 mg/kg isoproterenol). Carvacrol was administered for six weeks, and myocardial infarction was induced with isoproterenol. Blood pressure, biochemical parametres (creatinin kinase, lactate dehydrogenase, urea, creatinine, GDF-15, IL-6), and kidney tissue histopathology were evaluated.

Results Biochemical analysis showed increased Creatinin Kinase and Lactate Dehydrogenase levels in the Myocardial Infarction group compared to controls($p = 0.023$, $p = 0.020$), with carvacrol reducing these markers. IL-6 and GDF-15 levels were elevated in both the Myocardial Infarction and Myocardial Infarction + Carvacrol groups ($p = 0.009$, $p < 0.001$). Blood pressure was significantly reduced in the Myocardial Infarction group. Histopathological examination revealed severe kidney damage in the Myocardial Infarction group, while Carvacrol treatment showed less kidney damage, with only mild tubular dilation and rare necrosis.

Conclusion Carvacrol appears to have protective effects against kidney injury in myocardial infarction. It reduced myocardial injury markers and kidney damage, suggesting its potential therapeutic use in cardiorenal syndrome. Further studies are needed to understand its mechanisms and clinical applications in cardiovascular and renal diseases.

Keywords Myocardial infarction, Carvacrol, Isopreterenol, Rat, Kidneys

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Introduction

Ischemic heart diseases are among the leading causes of morbidity and mortality both in our country and globally every year [1]. Myocardial infarction (MI) leads to heart failure due to the inability to supply enough blood to the periphery and meet the oxygen demands of the heart tissue [2]. Today, although interventional cardiology techniques and pharmacological treatments have been developed to reduce the risk of MI, morbidity and mortality rates due to MI remain high due to the limitations of current treatment methods. Therefore, the development of new approaches to the prevention and effective treatment of MI is urgently needed.

Different organs of the body maintain healthy physiological balance by working together. Interactions between organs are essential elements for the healthy physiological functioning of the body; pathological damage to one organ can lead to acute or chronic dysfunction of another organ. The heart and kidney mutually influence each other through various hemodynamic and non-hemodynamic pathways necessary for the maintenance of cardiovascular homeostasis. Physiological dysfunction between the heart and kidney has been described as cardiorenal syndrome (CRS) [3]. It is not well known how the pathophysiological mechanisms between kidney failure and heart failure affect each other, many of which may contribute to a vicious cyclic heart/kidney cycle. In this case, hypotension and renal hypoperfusion due to falling cardiac output lead to increased sympathetic activity. In addition, renin-angiotensin-aldosterone and arginine-vasopressin increase the release of peripheral vasoconstriction, organ conjugation and increase the workload of the heart again [4]. One of the complications of having undergone MI is heart failure. Therefore, a better understanding of the changes that occur in kidney function after MI is of great importance in terms of identifying new therapeutic targets that will improve the prognosis of the disease.

Isoproterenol(ISO) is a synthetic β-adrenergic receptor agonist that stimulates β 1 and β 2 receptors and is used to treat bradycardia, atrioventricular block, and cardiac arrest due to its positive chronotropic and inotropic effects [5, 6]. However, giving high doses of ISO may increase myocardial oxygen consumption, leading to the development of myocardial damage and infarction-like changes [7–9]. In experimental animals, ISO causes multiple pathological changes associated with oxidative damage to the heart and the formation of inflammatory and apoptotic responses similar to those observed in acute myocardial infarction in humans [10–13]. Because of these, it is used as a model for myocardial infarction in experimental animals.

In recent years, studies on the pharmacological effects of natural compounds have been drawing attention to the therapeutic potential of bioactive molecules such as Carvacrol (CRV). CRV is a monoterpenic phenol found in the essential oil of Origanum, Satureja, Thymbra, Thymus and Corydothymus species of the family Labiatae (Lamiaceae) [14]. Commercially, CRV is synthesized by both chemical and biotechnological methods [15]. Research has shown that CRV has a broad pharmacological profile of action. In particular, its antibacterial and antifungal [16, 17], antiviral [18, 19], antioxidant [20] and anticancerogenic [21] properties suggest that this compound may be evaluated as a potential therapeutic agent in various diseases. There is also some evidence that CRV supports kidney health. The antioxidant property of CRV protects kidney cells against free radicals and may help prevent kidney damage [22]. Furthermore, the anti-inflammatory properties of CRV may reduce kidney inflammation and preserve kidney function [23]. It has been shown that CRV can prevent the onset and progression of Parkinson's disease by downregulating inflammation and other inflammatory mediators [24]. It is known that CRV has protective effects due to its application before ischemia or during reperfusion periods [25, 26]. Carvacrol has been shown to reduce oxidative stress-related inflammatory processes and NLRP3-mediated pyroptosis in isoproterenol-induced myocardial infarction, possibly through the activation of Nrf2/HO-1 and PPARγ [27]. However, the mechanisms that are effective in protection are not fully understood. Therefore, it is thought that CRV may have protective effects against kidney damage in the model of myocardial infarction formed by ISO.

The aim of this study was to examine the effects of CRV on kidney ischemia in the MI model created with ISO. Our study aims to assess the potential of CRV to prevent the development and progression of kidney function disorders associated with MI. Accordingly, the effects of CRV on kidney function will be investigated through biochemical analyses and histopathological evaluations. Based on the data obtained, it will be evaluated whether CRV can be used as a potential protective agent against MI-induced kidney ischemia.

Material and method

This study was carried out at Kirsehir Ahi Evran University Experimental Research Center. All animals used in this study were obtained from the Kirsehir Ahi Evran University Experimental Animal Laboratory in Experimental Research Center. The supply, care, and experimental modeling of the animals used in the study will be conducted at the Kirsehir Ahi Evran University Experimental Animal Laboratory. Before starting experimental studies, approval was obtained from Kirsehir Ahi Evran University Local Ethics Committee for Animal Experiments (Aprroval number: 2024-08-7) in Kirsehir Ahi

Evran University Experimental Research Center. The experiments were conducted in accordance with the revised Animals (Scientific Procedures) Act 1986 in the UK and Directive 2010/63/EU in Europe. In the study, 32 male rats of the Wistar albino breed weighing 200–250 were used. Before and during the experiment, all animals were housed in rooms with 12 h of light, 12 h of darkness, and a constant temperature of 22–24 ° C. In the feeding of animals, pellet feed and fountain water were used, and there were no restrictions on feed and water consumption.

Our study was conducted on 4 groups, each of which was formed to have 8 per rat. Groups are designated as follows;

Control group: The rats in this group were given standard rat feed and tap water for 6 weeks. No action has been taken.

CRV group: The rats in this group were given standard rat feed and tap water for 6 weeks and administered 50 mg/kg of CRV (Lot: 282197-10G- Sigma Aldrich) through oral gavage for 6 weeks [28]. The administration of CRV at 50 mg/kg was based on previous studies [29, 30]. CRV was dissolved in corn oil and given at a dose of 1 ml/kg/day [31].

MI Group: The rats in this group were given standard rat feed and tap water for 6 weeks. The rats were given 85 mg/kg of ISO (Lot: 4122564, Merck, Germany) as subcutaneous for the last 2 days to induce a myocardial infarction.

MI + CRV group: The rats in this group were given standard rat feed and tap water for 6 weeks. At the same time, 50 mg/kg of CRV was administered through oral gavage for 6 weeks, the last two days 85 mg/kg of ISO was made subcutaneous.

CRV application

There are different doses of CRV administered in different studies. 5, 10, 15, 25, 50 and 100 mg/kg [26, 32, 33] have been reported. CRV has been administered by oral gavage at 50 mg/kg for 6 weeks.

Myocardial infarction induction

In order to create the myocardial infactus, 85 mg/kg of ISO was applied to the rats in the last two days of the experiment as subcutaneous [34–36]. After the administration of isoproterenol at a dose of 85 mg/kg, Two rats died in the MI group. At the end of the experiment, the rats were anesthetized by giving 50 mg/kg of sodium thiopental intraperitoneally. Thoracotomy was performed under thiopental anesthesia, blood was taken from the heart of the animals. The kidney tissue was then quickly removed for histological studies. After tissue samples and blood samples were taken under general anesthesia, the animals were sacrificed by cervical dislocation.

Serum and kidney tissue analysis

The blood collected in tubes was allowed to stand upright for 40 min and then centrifuged at 3000 rpm for 10 min. Serum was obtained after centrifuge and levels of creatine kinase (CK) (lot: OTTOBC137), lactate dehydrogenase (LDH) (lot: OTTOBC129) [37], urea (lot: OTTOBC157), and creatinine (lot: OTTOBC139) were measured using the Mindray BS-400 biochemistry analyzer. Kidney tissue was analyzed for growth differentiotion factor (GDF-15)(Lot: 202310, Sunred) and interleukin-6 (IL-6) (Lot: 202310, Sunred) levels using the ELISA kit method.

Blood pressure measurement

To confirm myocardial infarction, blood pressures were measured using tail cuff plethysmography (MAY NIBP250, Turkey) before and at the end of the experiment. All the animals were placed in restraints for 20 min, cuffs were attached to their tails, and blood pressures were recorded. For each animal, a total of five measurements were made at 1-minute intervals. The highest and lowest measurements were excluded and systolic pressure, diastolic pressure, heart rate and average arterial pressure data were obtained with the remaining three measurement averages [38].

The Mean Arterial Pressure = Diastolic Pressure + (Systolic pressure-Diastolic pressure) was obtained by the formula/3.

Histopathological analysis

Left kidney tissue samples from all rats were first detected for light microscopic examination in a 10% formaldehyde solution for 72 hours. After detection, tissue samples were placed on cassettes and washed under the stream for 24 hours. For the removal of water, tissues have undergone increased alcohol series (50%, 70%, 80%, 90%, 100%). The tissues were then passed through xylol for transparency and then buried in molten paraffin. Sections 5–6 µm thick from the prepared paraffin blocks were painted with Hematoxylene-Eosin (H&E) (Bio-Optica 05-06004/L Harris "Hematoxylin & Bio-Optica 05-10002/L, Eosin Y 1%) and PAS dye (Lot: C9002, GBL Lab). Changes in kidney tissue histology have been shown with H&E staining. PAS staining has been used to show glycogen accumulation, especially in tubule epithelium and mesengial cells, and connective tissue accumulation in basement membranes.

Kidney histopathological scoring method

Degeneration and necrosis of tubule epithelium in cross-sections stained with hematoxylene-Eosin were evaluated as hyperemia semicantitative in interstitial vessels.

Table 1 Table of histopathological evaluation of kidney tissue (none = 0, mild = 1, moderate = 2, severe = 3, very severe = 4)

Histopathological Evaluation	Control Group	MI Group	MI + CRV Group	CRV Group
Hydropic degeneration in the tubule epithelium	0	4	0	0
Necrosis of coagulation in the tubule epithelium	0	3	1	0
Dilatation in the tubule epithelium	0	2	1	0
Hyperemia of the veins	0	3	0	0
Increase in collagen (fibrosis) and glycogen	0	3	1	0

Table 2 Rat weights

	Rat Weights in the 1st Week (g)	Rat Weights in the 7th Week (g)
Control Group	215.4	307.0
MI Group	219.6	319.6
MI + CRV Group	208.1	326.3
CRV Group	200	289.5

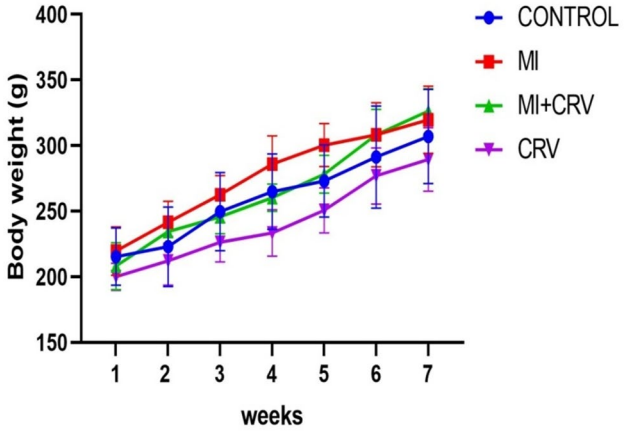

Fig. 1 Body weight in experimental groups

The mean percentile values in the group were calculated by scoring each damage parameter in 10 different areas in each kidney section. Histopathological changes were rated 1 (mild) when observed in less than 25% of tubule epithelium, 2 (moderate) when observed in 25–50%, 3 (severe) when observed in greater than 50–75%, 4 (very severe) when observed in 75–100% (none = 0, mild = 1, moderate = 2, severe = 3, very severe = 4***).*** Histopathological Scoring Method is given in Table 1 [39].

Statistical analyses

Results from biochemical and histological analyses were evaluated using GraphPad Prism 9.0 statistical program. The Shapiro-Wilk test was performed to assess the normality of the data distribution. One-way variance analysis (ANOVA) and the Kruskal-Wallis test were used for comparisons involving multiple groups. Post hoc analyses were performed using the Bonferroni test for ANOVA and the Dunn test for the Kruskal-Wallis test. Numerical measurements were summarized as median and minimum - maximum. The p-value below 0.05 for all analyses was considered statistically significant.

Results

In this study, MI was induced, and the changes in biochemical parameters, histopathological alterations, and hemodynamic effects of MI on kidney tissue were examined.

Evaluation of weight changes in groups

The weights of the experimental animals showed a significant increase over time; however, no statistically significant differences were found in between groups. Average weights of groups 1 and 7 in week are given in Table 2 (Fig. 1).

Evaluation of biochemical parameters

In our study, the biochemical parameters of the groups were evaluated and the effects of myocardial infarction and CRV administration on Urea, CK, LDH, GDF-15 and IL-6 levels were examined. Urea, Creatinine, CK, LDH, GDF-15 and IL-6 values of the groups are given in Table 3.

Table 3 Biochemical parameters assessed in this study (Mean ± SD)

	Control	MI	MI + CRV	CRV
Urea	47.9 ± 8.99	45.38 ± 5.29	45.75 ± 4.80	39.75 ± 5.12
Creatinine	0.41 ± 0.06	0.37 ± 0.04	0.38 ± 0.04	0.43 ± 0.03
CK	481.0 ± 117.6	718.8 ± 153.4	583.9 ± 226.6	497.3 ± 83.13
LDH	506.5 ± 143.3	756.4 ± 237.3	501.1 ± 64.49	485.9 ± 145.1
GDF-15	109.1 ± 3.2	116.6 ± 3.73	137.9 ± 1.49	113.0 ± 4.15
IL-6	59.7 ± 3.04	63.39 ± 1.74	78.58 ± 1.78	74.4 ± 4.81

Evaluation of serum Creatinin kinase

The CK value of the MI group (718.8 ± 153.4) was significantly higher compared to the control group (481.0 ± 117.6) ($p = 0.023$). Similarly, a significant difference was detected between the MI group and the CRV group (497.3 ± 83,13) ($p = 0.037$). The mean CK of the MI + CRV group was 583.9 ± 226.6. There was also a difference between the MI group and the MI + CRV, but this difference was not statistically significant (Fig. 2).

Evaluation of serum LDH levels

When examining the LDH values, a significant difference was detected between the control group (506.5 ± 143.3) and the MI group (756.4 ± 237.3) ($p = 0.020$). A significant difference between the MI group and the MI + CRV group was found between LDH values (501.1 ± 64.49) ($p = 0.017$). A significant difference was also observed in the comparison between the MI group and the CRV (485.9 ± 145.1) group ($p = 0.011$) (Fig. 2).

Evaluation of serum Urea levels

No significant differences were found between the groups (Fig. 3).

Evaluation of serum creatinine levels

No significant differences were found between the groups (Fig. 3).

Evaluation of serum IL-6 levels

Significant differences were detected between the groups. A significant difference was found between the control group (59.70 ± 3.04) and the CRV group (74.4 ± 4.81) ($p = 0.012$) and between the control group and the MI + CRV (78.58 ± 1.78) ($p = 0.01$). There was also a significant difference between the MI group (63.39 ± 1.74) and the MI + CRV group (Fig. 4) ($p = 0.009$).

Evalution of serum GDF-15 levels

Significant differences were found between the groups. Significant differences were found between control group (109.1 ± 3.20) and MI + CRV group (137.9 ± 1.49) ($p < 0.001$) and between MI group (116.6 ± 3.73) and MI + CRV group ($p < 0.001$). There was also a significant difference between the MI + CRV group (137.9 ± 1.49) and the CRV group (113 ± 4.15) ($p < 0.001$) (Fig. 4).

Blood pressure measurements

The heart rate, systolic blood pressure, diastolic blood pressure and mean arterial pressure values of the control group, MI group, MI + CRV group and CRV group were compared. The Heart Rate and Blood Pressure Values are given in Table 4.

Evaluation of systolic blood pressure values

Systolic blood pressure of the MI group was found to be lower compared to the control group, and this difference was found to be statistically significant ($p = 0.04$). There was also a significant difference in systolic blood pressure values between the control group and the CRV group ($p = 0.002$). Similarly, a statistically significant difference in systolic blood pressure values was detected between

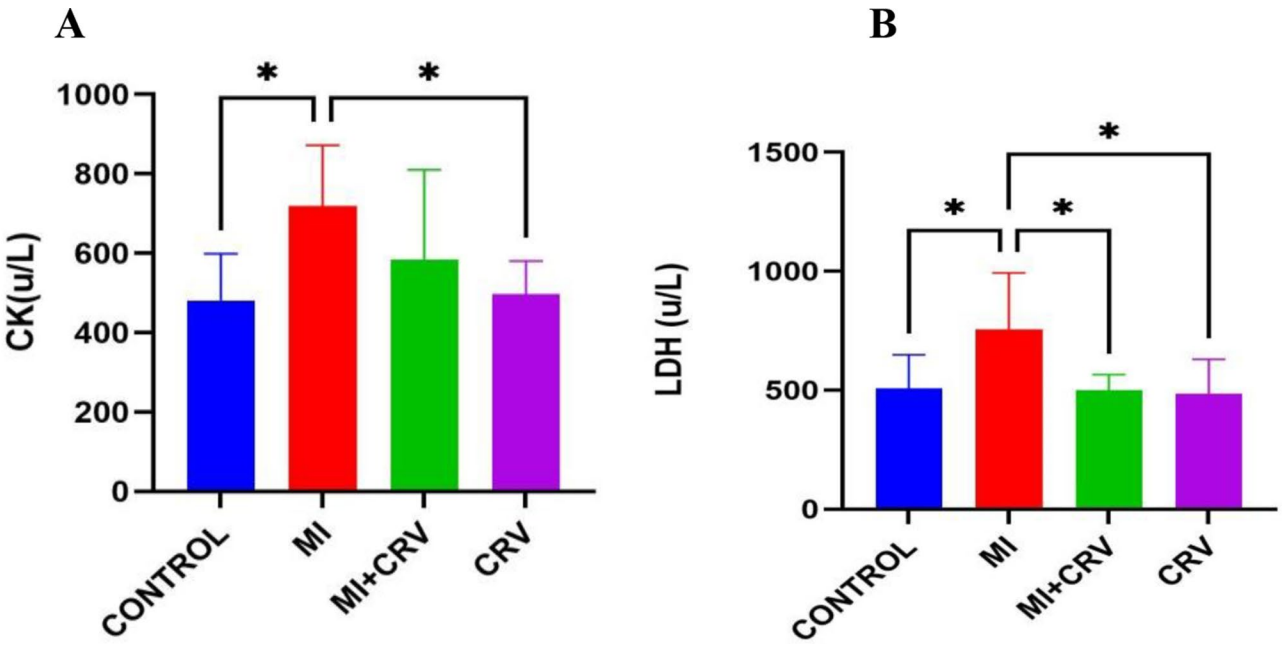

Fig. 2 Serum CK and LDH levels in Control, MI, MI + CRV and CRV. Data are presented as mean ± SEM ($n = 8$)

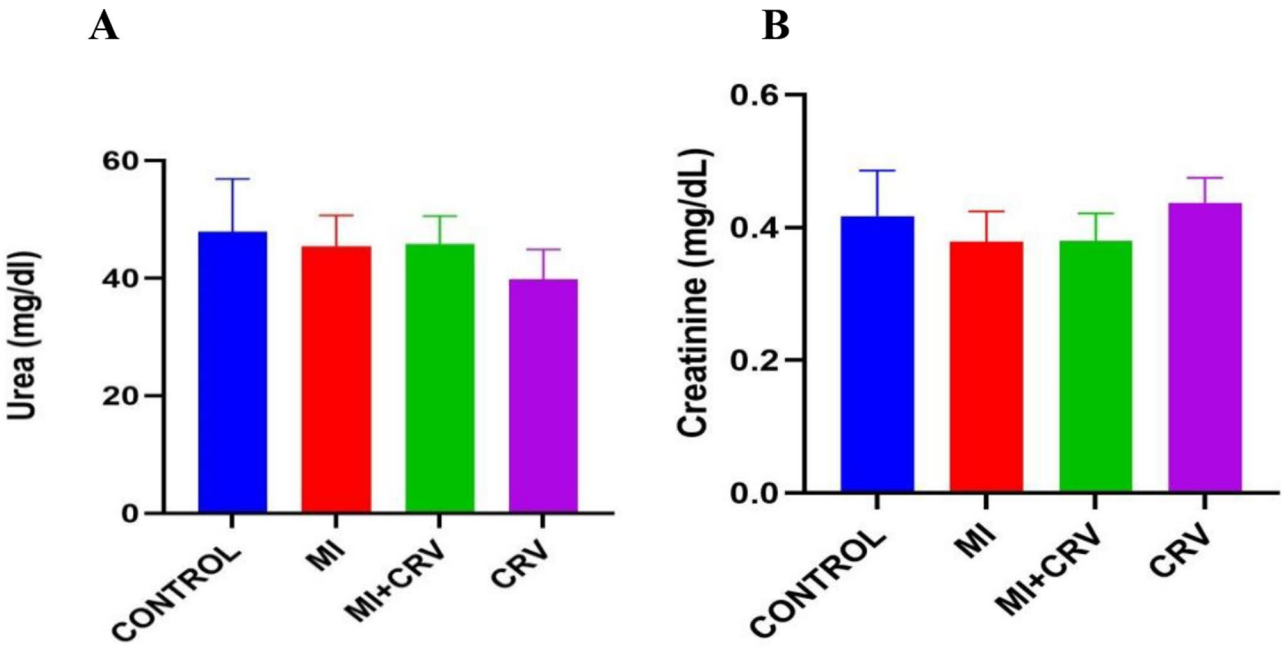

Fig. 3 Serum Urea and Creatinine levels in Control, MI, MI + CRV and CRV. Data are presented as mean ± SEM ($n = 8$)

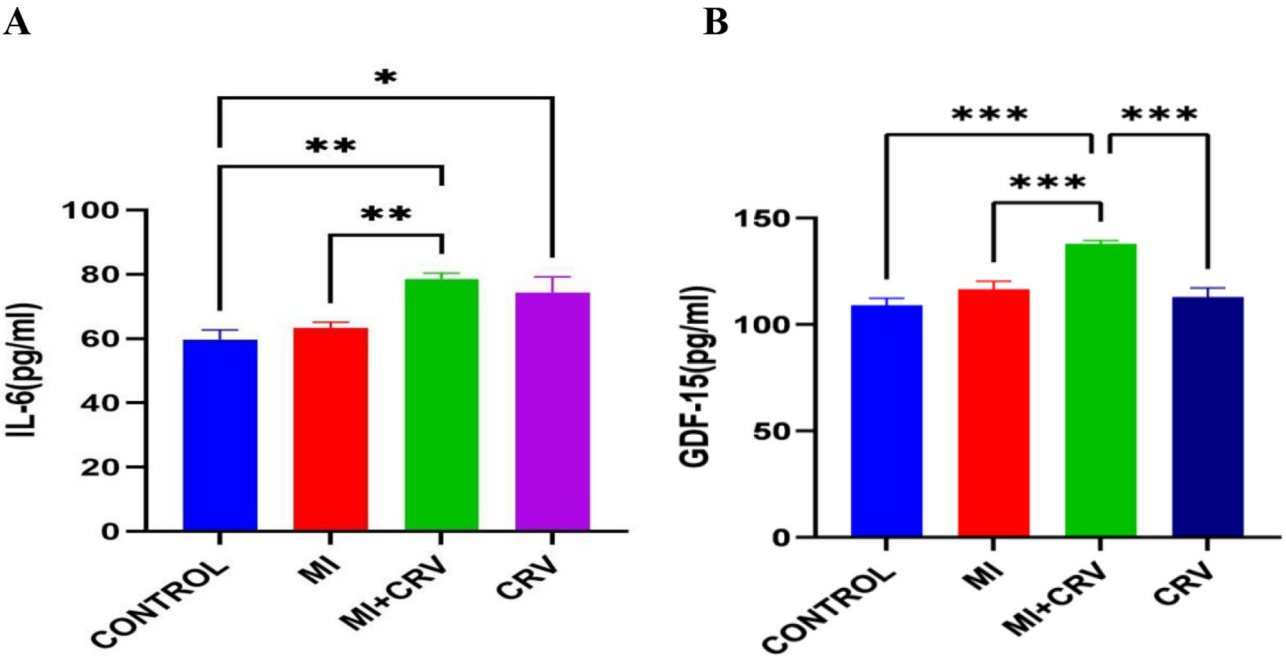

Fig. 4 Renal tissue levels of IL-6 and GDF-15 in Control, MI, MI + CRV and CRV. Data are presented as mean ± SEM ($n = 8$)

Table 4 Heart Rate and Blood Pressure Parameters in Experimental Groups (Mean ± SD)

	Heart Rate	Systolic Blood Pressure Values (mmHg)	Diastolic Blood Pressure Values (mmHg)	Mean Arterial Pressure Values mmHg)
Control Group	348.5 ± 48.39	129.1 ± 21.59	83.7 ± 16.95	98.85 ± 11.91
MI Group	247.4 ± 21.35	99.28 ± 6.94	55.41 ± 21.99	70.03 ± 15.83
MI + CRV Group	257.1 ± 87.56	106.6 ± 14.22	66.78 ± 21.12	80.04 ± 14.12
CRV Group	272.1 ± 100.9	97.55 ± 17.36	66.60 ± 20.49	76.92 ± 18.43

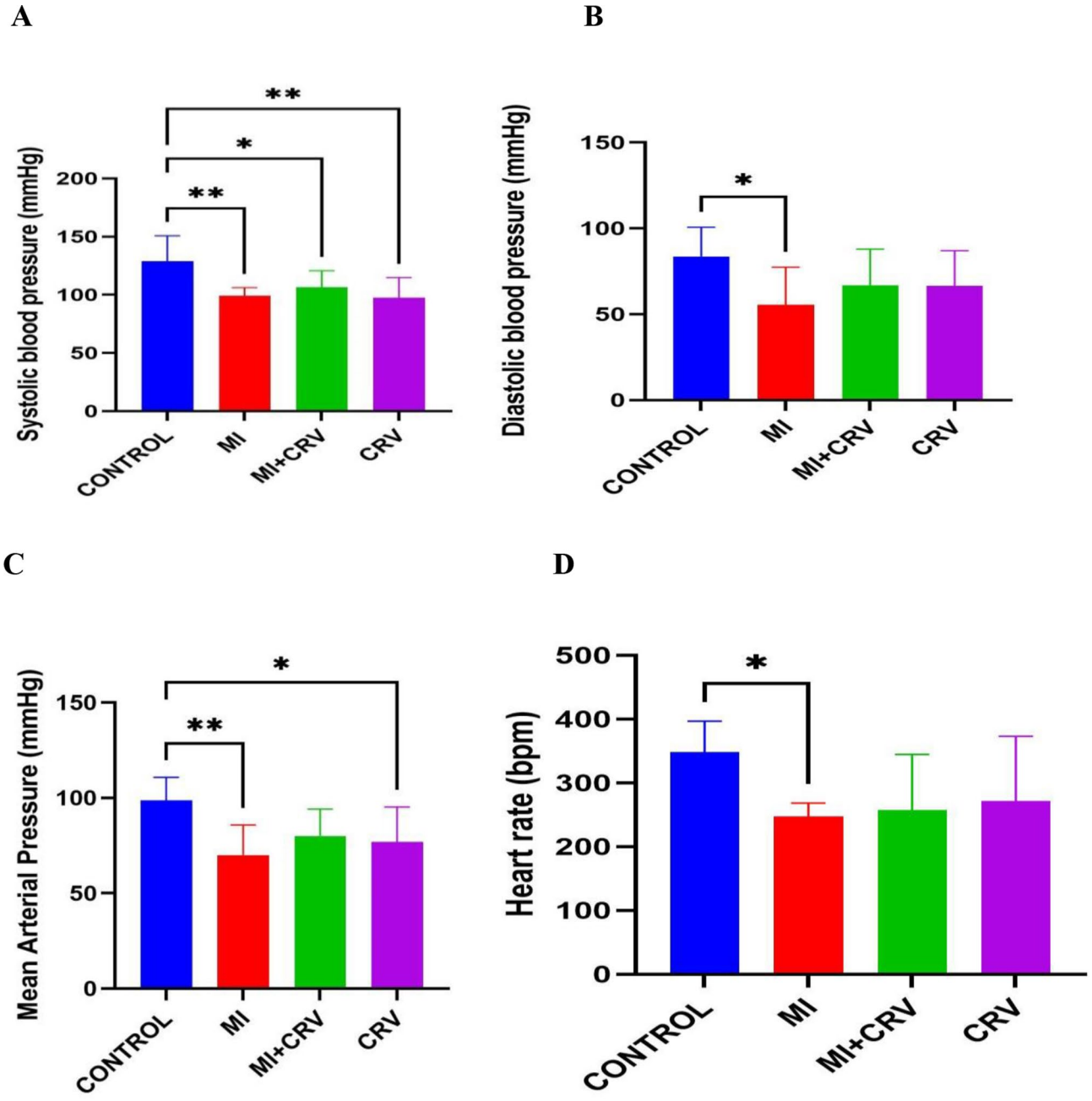

Fig. 5 Systolic blood pressure, diastolic blood pressure, mean arterial pressure, and heart rate values in Control, MI, MI + CRV and CRV. Data are presented as mean ± SEM ($n = 8$)

the control group and the MI + CRV group ($p = 0.04$) (Fig. 5).

Evaluation of diastolic blood pressure values

Diastolic blood pressure values of the MI group were significantly lower compared to the control group ($p = 0.043$). However, there was no significant difference in diastolic blood pressure values between the other groups (Fig. 5).

Evalution of mean arterial pressure values

In our study, the mean arterial pressure of the MI group (70.03 ± 15.83) in the mean arterial pressure analysis showed a significant reduction compared to the control group (98.85 ± 11.91) ($p = 0.004$). The mean arterial pressure of the CRV group was 76.92 ± 18.43. A significant difference between the mean artery pressure of the control group and the mean artery pressures of the CRV group was found ($p = 0.036$) (Fig. 5).

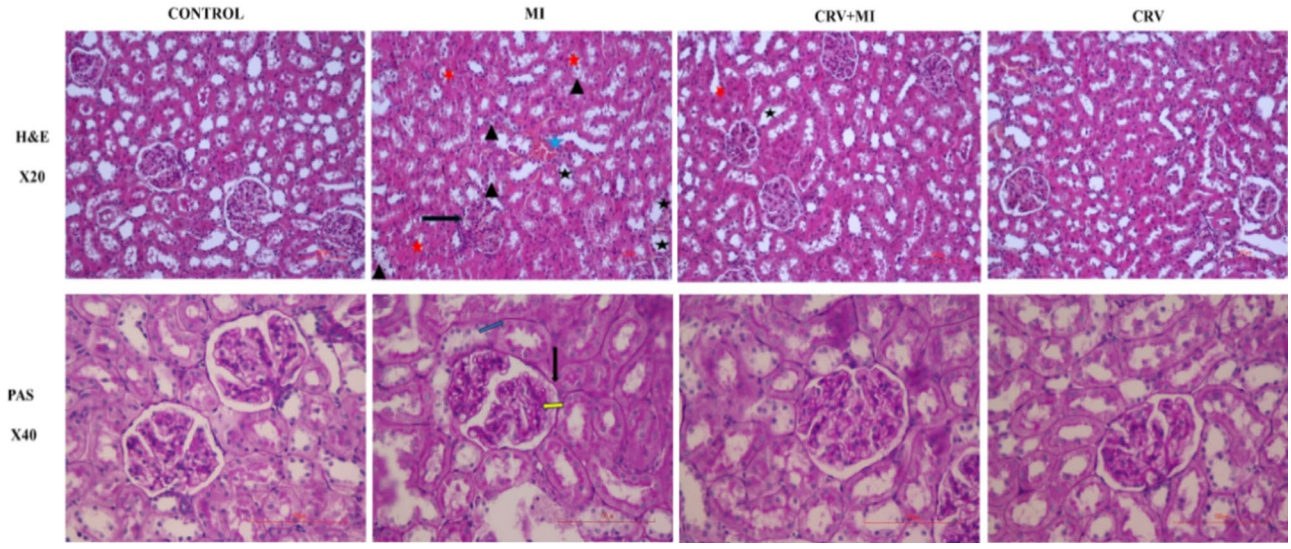

Fig. 6 Kidney sections H&E staining, magnification: X20, Bar: 100 µm. Control group, kidney tissue, normal histological appearance. MI group, renal tissue, tubule epithelium and diffuse hydropic degeneration (arrowhead) and coagulation necrosis (red star), dilation in tubules (black star), degeneration in glomeruli (black arrow), hyperemia in veins (blue arrow) Mild level of hydropic degeneration in CRV + MI group tubule epithelium, CRV group, kidney tissue, normal histological appearance. Kidney sections PAS staining, magnification: X40, Bar: 100 µm. In the MI group, tubular basement membrane thickening and glycogen accumulation (blue arrow), bowman capsule basement membrane (black arrow) and glomerular basement membrane thickening and mesangial matrix increase (yellow arrow)

Evaluation of heart rate values

When examining the heart rate values the heart rate of the MI group was significantly lower than that of the control group ($p = 0.041$). Among the other groups, there was no significant difference in heart rate (Fig. 5).

The renal tissue histopathology results

Histological examination of the renal tissues in the control group revealed that the parenchyma, cortex, and medulla had a normal structure. In the MI group, diffuse hydropic degeneration and coagulation necrosis of tubule epithelium, dilation of tubules, degeneration of glomeruli and hyperemia of vessels were observed when compared with renal tissue control group. When kidney tissues were examined in the MI + CRV group, mild dilation of the tubules and very few necrosis of coagulation were observed. Histomimaria in the CRV group was similar to the control group (Fig. 6). In the kidney sections stained with PAS, especially in the MI group, tubular epithelial cells and brushlike edges were painted more clearly. Thickness increase and mesangial matrix increase were observed in the basal membranes of glomeruli and tubules. Compared to the MI + CRV group, MI group and control groups, baseline membrane thicknesses were observed closer to the control group and glycogen staining in the cells was reduced (Fig. 6).

Discussion

The findings of this study demonstrate the systemic effects of MI and the potential modulatory role of CRV on these effects. Biochemical analyses demonstrated significant increases in CK and LDH levels, which are indicators of cardiac injury following MI. Moreover, the hemodynamic disturbances observed in the MI group, including reduced heart rate, diastolic blood pressure, systolic blood pressure, and mean arterial pressure, were partially improved with CRV treatment. Histopathological analyses supported these findings by showing that CRV reduced structural damage in kidney tissue and largely preserved tissue integrity. These results suggest that carvacrol may exert protective effects against MI-induced organ dysfunction, observable at both biochemical and histological levels.

The pathogenesis of MI is a complex process, with oxidative stress playing a central role, as demonstrated in various studies [40–42]. Oxidative stress is characterized by an increased production of reactive oxygen species (ROS), which disrupt the cellular redox balance. During MI, cardiomyocytes produce high levels of ROS in response to ischemia and hypoxia [43, 44]. This overproduction causes lipid peroxidation, protein oxidation, and DNA damage, which ultimately lead to cell death [45, 46]. In addition, due to the limited capacity of antioxidant defense mechanisms, cardiomyocytes are particularly susceptible to oxidative damage [41]. Therefore, suppression of oxidative stress is considered an effective strategy to prevent both cardiac and systemic organ injury.

In this regard, natural compounds with strong antioxidant properties have attracted significant attention. Carvacrol is a phenolic compound with well-documented antioxidative, anti-inflammatory, and antiapoptotic effects [40, 47]. The protective effects of antioxidant agents such as ascorbic acid and histidine against isoproterenol (ISO)-induced myocardial damage have previously been demonstrated, with their efficacy largely attributed to a reduction in free radical levels [48]. Similarly, betaine has been reported to alleviate ISO-induced cardiac injury by decreasing TNF-α levels [49]. Based on this literature, it is meaningful that carvacrol exhibits similar beneficial effects on both cardiac and renal tissues through related mechanisms.

Our study also found that inflammatory responses play an important role in kidney injury. Growth differentiation factor 15 (GDF-15), a member of the transforming growth factor-beta (TGF-β) superfamily, is a cytokine whose expression increases in response to stress. It is recognized as a significant biomarker in cardiovascular and renal diseases [50]. According to the literature, GDF-15 reduces acute kidney injury caused by toxic agents and supports renal function by preserving Klotho expression [51]. In our study, the increased levels of GDF-15 observed following CRV administration suggest that the protective effects of carvacrol are not limited to oxidative stress suppression, but may also involve modulation of stress-related signaling pathways. These findings imply that carvacrol may provide dual protection along the cardiorenal axis.

Another strength of our study is the consistency between the histopathological findings and the biochemical parameters. Histological damage such as hydropic degeneration, coagulative necrosis, and tubular dilation observed in the renal epithelium was significantly reduced with CRV treatment. In parallel with this histological improvement, previous studies have shown that carvacrol can protect kidney tissue by modulating oxidative stress markers (MDA, NO), inflammatory cytokines (TNF-α, IL-6), and apoptosis-related proteins (Bax, Bcl-2) [52–54]. Furthermore, a combination of Zataria multiflora and carvacrol has been shown to improve kidney tissue integrity against Adriamycin-induced nephrotoxicity [55], which is consistent with our findings.

However, no significant changes were observed in kidney function tests in our study. This may be due to the short duration between the induction of MI and tissue sampling. The 24 h interval might have been insufficient for the full biological response to manifest at the biochemical level. Future studies with longer observation periods may help to better evaluate the effects of carvacrol on renal function.

Additionally, CRV has been shown to inhibit toxicity induced by mercuric chloride (HgCl2) in rat testicular tissue. It achieved this effect by suppressing HgCl2-induced increases in oxidative stress, inflammation, apoptosis, autophagy, and disruption of tissue integrity, indicating that CRV may represent an effective therapeutic option [56].

Sodium arsenite induces toxic damage in rat liver tissues by activating oxidative stress, inflammation, apoptosis, and autophagic damage pathways and impairing tissue integrity. CRV has demonstrated protective properties against this toxicity by reducing the activation of these harmful pathways and preserving tissue structure [57].

Moreover, CRV has shown promising cardioprotective effects against cisplatin-induced cardiotoxicity by improving cardiac injury markers. Its therapeutic action was associated with a reduction in oxidative stress, inflammation, apoptosis, and autophagy. In addition, the Notch signaling pathway, which was impaired by cisplatin, was reversed with CRV treatment. This finding suggests a possible role for the Notch pathway in the pathogenesis of cisplatin-induced cardiotoxicity [58].

Finally, chrysin has been shown to have therapeutic effects against bortezomib-induced nephrotoxicity. These effects are attributed to its antioxidant, anti-inflammatory, and antiapoptotic properties, as well as its ability to preserve the structural integrity of renal tissue [59].

However, no significant changes in kidney function tests were observed in our study. This condition is thought to occur due to insufficient time for biological responses to occur. Sampling only 24 h after the myocardial infarction may result in the effects at the biochemical level not being fully reflected. By opting for longer follow-up times in future studies, the effects of CRV on kidney function can be assessed more clearly.

While this study reveals the renal damage-reducing effects of CRV after ISO-induced MI, further analyses are needed to further explain its mechanistic aspects. In particular, studies in which the gene and protein expression levels of molecular targets such as GDF-15, Klotho, Bcl-2/Bax will be examined in detail will reveal the effects of CRV in more depth. In addition, studies at different doses will contribute to determining the spectrum of action of CRV.

Conclusion

This study shows that CRV can provide indirect renal protection by reducing both its effects directly on kidney tissue and the systemic repercussions of damage to heart tissue. CRV has pharmacological potential as a cardiorenal protective agent thanks to these multifaceted effects. In this context, the evaluation of natural compounds as supporting agents in the prevention and treatment of diseases can be an important step in the transition from traditional medicine to modern therapeutic approaches.

Limitations

This study has several limitations that should be considered when interpreting the results. Firstly, the sample size was limited to 32 rats, which may affect the generalizability of the findings. Secondly, although the biochemical and histopathological parameters were evaluated, molecular mechanisms underlying the observed effects were not fully investigated. Thirdly, the study focused only on short-term effects; long-term outcomes of CRV administration were not assessed. Additionally, the study used only male rats, which may limit the applicability of the findings to both sexes. Finally, the MI model induced by ISO may not fully mimic the complexity of human myocardial infarction.

Abbreviations

CRS	Cardiorenal syndrome
CRV	CRV
CK	Creatinine Kinase
GDF-15	Growth Differentiotion Factor
LDH	Lactate Dehydrogenase
IL-16	Interleukin 16
ISO	Isoproterenol
MI	Myocardial İnfarction

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Author contributions

G.U. conceived and designed the study. G.U., H.T.Y., and O.M.Y. conducted the experiments. All authors reviewed and revised the manuscript. All authors read and approved the final version of the manuscript.

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Data availability

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The experiments were conducted in accordance with the revised Animals (Scientific Procedures) Act 1986 in the UK and Directive 2010/63/EU in Europe. Ethical approval was obtained from Kirsehir Ahi Evran University Local Ethics Committee for Animal Experiments (Aprroval number: 2024-08-7).

Consest for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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