

RESEARCH

Open Access



Cardioprotective effects of carvacrol in the isoproterenol-induced myocardial infarction model

Seda Koçak^{1*}, Kübra Tuğçe Kalkan², Ömürçan Sadettin Aydın³ and Kübra Öztürk⁴

Abstract

Objective Cardiovascular diseases are significant health problems that cause high mortality rates worldwide. Myocardial infarction (MI), in particular, is one of the leading conditions among these diseases. The aim of this study is to evaluate the potential therapeutic approach of carvacrol in the treatment of cardiovascular diseases by investigating its protective effects against myocardial infarction through oxidative stress and biomarker levels.

Materials and methods In this study, 28 male Wistar albino rats were used, and divided into 4 groups: Control, Carvacrol, Myocardial Infarction (MI), and MI + Carvacrol. Carvacrol was administered at a dose of 50 mg/kg for six weeks. The induction of MI was performed during the last 2 days of carvacrol administration by administering 100 mg/kg isoproterenol subcutaneously. At the end of the experiment, blood pressure, biomarkers such as troponin T, BNP, GDF-15, and IL-6 were measured, and cardiac tissue was histopathologically examined.

Results The results show that in the MI group, troponin T, BNP, IL-6 and GDF-15 levels were increased, while diastolic blood pressure and heart rate were decreased. In the carvacrol-treated group, troponin T, BNP, IL-6 and GDF-15 levels were decreased. Carvacrol did not significantly affect systolic, diastolic, mean arterial pressure, or heart rate in experimental groups. Moreover, carvacrol decreased necrosis, edema, and mononuclear cell infiltration in the heart tissue, which were increased due to MI.

Conclusion In conclusion, carvacrol demonstrated protective effects against myocardial infarction. Carvacrol alleviated histopathological damage by reducing inflammatory biomarkers. In addition to carvacrol improved troponin T and BNP markers. These findings suggest that carvacrol may be a promising agent in the treatment of cardiovascular diseases. However, more comprehensive and long-term studies are needed to confirm this effect and transfer it to clinical applications.

Keywords Myocardial infarction, carvacrol, GDF-15, IL-6, BNP, Troponin T

*Correspondence:

Seda Koçak
seda.kocak@ahievran.edu.tr

¹Department of Physiology, Kırşehir Ahi Evran University Faculty of Medicine, Kırşehir, Türkiye

²Department of Histology and Embryology, Kırşehir Ahi Evran University Faculty of Medicine, Kırşehir, Türkiye

³Kırşehir Ahi Evran University Faculty of Medicine, Kırşehir, Türkiye

⁴Faculty of Engineering and Architecture, Department of Genetics and Bioengineering, Kırşehir Ahi Evran University, Kırşehir, Türkiye



© The Author(s) 2025. **Open Access** This article is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License, which permits any non-commercial use, sharing, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if you modified the licensed material. You do not have permission under this licence to share adapted material derived from this article or parts of it. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by-nc-nd/4.0/>.

Introduction

Cardiovascular diseases generally refer to heart and blood vessel disorders, including coronary heart disease, cerebrovascular diseases, and other vascular disorders, encompassing a wide spectrum of clinical presentations ranging from common ischemic conditions to rare congenital syndromes such as Timothy syndrome [1]. Four out of every five deaths related to cardiovascular diseases are caused by heart attacks and strokes [2]. Ischemic heart disease was identified as the leading cause of death worldwide in a systematic analysis conducted in 2010 [3]. Molecules that neutralize free radicals formed in tissues are believed to be beneficial in the treatment of various pathologies, and this idea has paved the way for the development of drug candidates aimed at combating oxidative-mediated tissue damage [4]. A recent clinical study highlighted the significance of heart failure in terms of proteotoxicity and proteinopathy, as well as the pathogenic consequences of these conditions. The homeostatic balance between the synthesis and degradation of faulty proteins is critical for maintaining the health of dynamically active cardiomyocytes [5]. Therefore, the accumulation of reducing molecules can lead to reductive stress, which causes endoplasmic reticulum dysfunction and proteotoxicity [5, 6]. Similarly, reactive oxygen species (ROS), which induce oxidative stress, are involved not only in the pathological roles of heart diseases but also in physiological functions that regulate the survival and death of cardiomyocytes [7, 8].

Carvacrol (CAR), a monoterpenic phenol predominantly found in the essential oils of various species in the Labiatae family, such as *Origanum*, *Satureja*, *Thymbra*, *Thymus*, and *Corydorthymus*, has been used as a flavoring agent in food for centuries [9]. Previous studies have shown that CAR supports cyclooxygenase inhibition [10]. Additionally, carvacrol is responsible for a wide range of biological activities, including antimicrobial, antitumor, antimutagenic, antigenotoxic, analgesic, antispasmodic, anti-inflammatory, angiogenic, antiparasitic, antiplatelet, acetylcholinesterase inhibition, insecticidal, antihepatotoxic, and hepatoprotective effects [11]. The biological activities of carvacrol may potentially influence pathological processes in myocardial infarction, which are associated with important molecules such as IL-6 and GDF-15.

Growth differentiation factor 15 (GDF-15) is a member of the transforming growth factor- β superfamily and is widely present in most organs at low concentrations [12] and its regulatory pathways, particularly those involving TGF- β signaling, have been implicated in cardiac remodeling and fibroblast activation [13]. While physiological GDF-15 concentrations increase with age, its expression is elevated in pathological conditions such as inflammation, oxidative stress, and hypoxia [14]. In

cardiomyocytes, as in other cell types, GDF-15 is also found at very low levels [15].

IL-6 is produced by a variety of cell types and mediates numerous pathophysiological functions. In vascular biology, IL-6 is typically secreted by macrophages, monocytes, as well as fibroblasts and endothelial cells, following IL-1 stimulation, and is involved in atherothrombosis [16, 17]. It has long been recognized that inflammation plays a critical role in heart failure, similar to its role in systemic atherosclerosis [18].

The aim of this study is to investigate the cardioprotective effects of long-term carvacrol administration in an isoproterenol-induced myocardial infarction model in rats. In our study, we aimed to evaluate whether carvacrol has a protective potential against the development and progression of this pathological condition, both at the biochemical and histopathological levels.

Materials and methods

This study was conducted at the Animal Research Center of Kırşehir Ahi Evran University. Prior to the experimental procedures, approval was obtained from the Kırşehir Ahi Evran University Local Ethics Committee for Animal Experiments (Approval number:2024-08-06). The experiments were carried out in accordance with international guidelines for the use of laboratory animals. A total of 28 male Wistar albino rats were used in the study. Before and during the experiment, all animals were housed under a 12-hour light and 12-hour dark cycle in rooms with a constant temperature of 22–24 °C. The animals were fed with pellet chow and provided with tap water, and there were no restrictions on their food or water intake.

In our study, four groups were established, each consisting of 7 rats. The groups were as follows:

Control group (CONTROL, $n=7$) Rats in this group were provided with standard rat chow and tap water for 6 weeks. No other interventions were performed.

Carvacrol Group (CAR $n=7$) Rats in this group received standard rat chow and tap water for 6 weeks. Additionally, 50 mg/kg carvacrol (Lot:) was administered via oral gavage throughout the experiment.

Myocardial Infarction Group (MI $n=7$) Rats in this group were fed standard rat chow and tap water for 6 weeks. To induce myocardial infarction, rats were administered 100 mg/kg isoproterenol (Lot: 4122564, Merck, Germany) subcutaneously for the last 2 days of the study.

MI + Carvacrol Group (MI + CAR, $n=7$) Rats in this group received standard rat chow and tap water for 6 weeks. They were administered 50 mg/kg carvacrol via

oral gavage throughout the experiment. In the last 2 days, myocardial infarction was induced by subcutaneous injection of 100 mg/kg isoproterenol (Lot: 4122564, Merck, Germany).

Carvacrol application

Different doses of carvacrol have been reported in various studies, including 5, 10, 15, 25, 50, and 100 mg/kg [19–21]. In our study, we administered carvacrol at a dose of 50 mg/kg orally (via gavage) for 6 weeks [19, 22].

Myocardial infarction induction

Isoproterenol at a dose of 100 mg/kg was administered subcutaneously to rats for 2 days to induce myocardial infarction [19, 23] after 6 weeks of carvacrol application. At the end of the experiment, rats were anesthetized intraperitoneally with sodium thiopental at a dose of 50 mg/kg. Under thiopental anesthesia, a thoracotomy was performed, followed by blood collection from the heart, and the animals were sacrificed. After this procedure, the heart tissue of the rats was quickly collected for histological analysis.

Blood pressure Measurement

To confirm myocardial infarction, blood pressures were measured before and after the experiment using tail cuff plethysmography (MAY NIBP250, Turkey). All animals were placed in a restrainer for 20 minutes, cuffs were applied to their tails, and blood pressures were recorded. For each animal, a total of five measurements were taken at 1 minute intervals. The highest and lowest measurements were excluded, and the average of the remaining three measurements was used to obtain systolic pressure, diastolic pressure, heart rate and mean arterial pressure data. Mean arterial pressure: $\text{Diastolic pressure} + (\text{Systolic pressure} - \text{Diastolic pressure}) / 3$. The formula used to calculate the mean arterial pressure.

Serum and heart tissue analysis

The blood collected in tubes was allowed to stand upright for 40 minutes and then centrifuged at 3000 rpm for 10 minutes. After centrifugation, serum was obtained and the Troponin T (Finetest Lot No: ER1396) and BNP (Finetest Lot No: ER0775) levels were measured using the ELISA method. The heart tissue was also analyzed for GDF-15 (Lot No: 202310, Sunred) and IL-6 (Lot No: 202310 Sunred) levels using the ELISA kit method.

Enzyme-Linked immunosorbent assay (ELISA) procedures for serum and cardiac tissue samples

In this study, ELISA analyses were performed to quantify specific inflammatory and stress-related biomarkers in rat cardiac tissue samples. Two commercial ELISA kits provided by SunRed Biotechnology were utilized

according to the manufacturers' instructions. The IL-6 (Interleukin-6) levels were measured using a rat-specific ELISA kit (SunRed, Catalog No: 201-11-0136), which has a sensitivity of 1.822 pg/ml and a dynamic range of 2–600 pg/ml. The GDF15 (Growth Differentiation Factor 15) concentrations were assessed using another rat-specific ELISA kit from the same supplier (Catalog No: 201-11-0551), with a sensitivity of 4.556 pg/ml and a range of 5–1000 pg/ml. Tissue samples were prepared at a 1:9 dilution ratio (i.e., 0.1 g of tissue was homogenized with 0.9 ml of 140 mmol/L potassium chloride (KCl) buffer). Following homogenization, the samples were centrifuged at 7000 rpm for 5 min at 4 °C. The resulting supernatant was collected and used for ELISA measurements. All absorbance readings were conducted using a BIO-TEK EL X 800 microplate reader, and washing steps were performed with a BIO-TEK EL X 50 automated strip washer [24]. Serum was obtained and the Troponin-T (Finetest Lot no: ER1396) and BNP (Finetest ER0775) levels were also measured using the ELISA method [25].

Histopathological evaluation

At the end of the experiment, tissue samples were collected and fixed in 10% formaldehyde. The heart tissue was then rinsed under tap water and placed through increasing grades of alcohol. Blocks were formed by embedding them in paraffin after clearing with xylol. Iron-Hematoxylin were used to stain 5- μ m sections, which were passed through an increasing alcohol series, xylol, and a coverslip before being evaluated under a light microscope (Nikon Eclipse Si, Tokyo, Japan). In this study, heart tissue was evaluated in terms of necrosis [26, 27], edema and mononuclear cell infiltration [28]. Heart tissue was measured semiquantitatively on a scale of 0 to 3 (0: None, 1: Mild, 2: moderate, 3: severe) scoring was given for each criterion.

Statistical analyses

The results obtained from biochemical and histological analyses were evaluated using the GraphPad Prism 9.0 statistical program. The Shapiro-Wilk test was performed to assess the normality of the data distribution. For comparisons involving multiple groups, one-way analysis of variance (ANOVA) and the Kruskal-Wallis test were utilized. Post hoc analyses were conducted using the Bonferroni test for ANOVA and the Dunn test for the Kruskal-Wallis test, both of which identified significant differences among the variables. A p-value below 0.05 was considered statistically significant for all analyses.

Results

Evaluation of weight changes in groups

The weights of the experimental animals showed a significant increase over time; however, no statistically

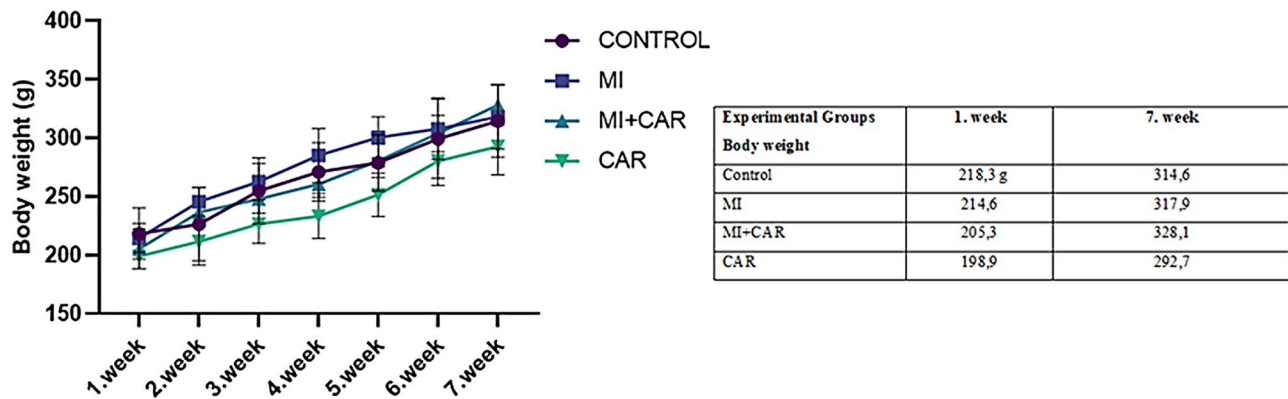


Fig. 1 Weight changes over the weeks in experimental groups

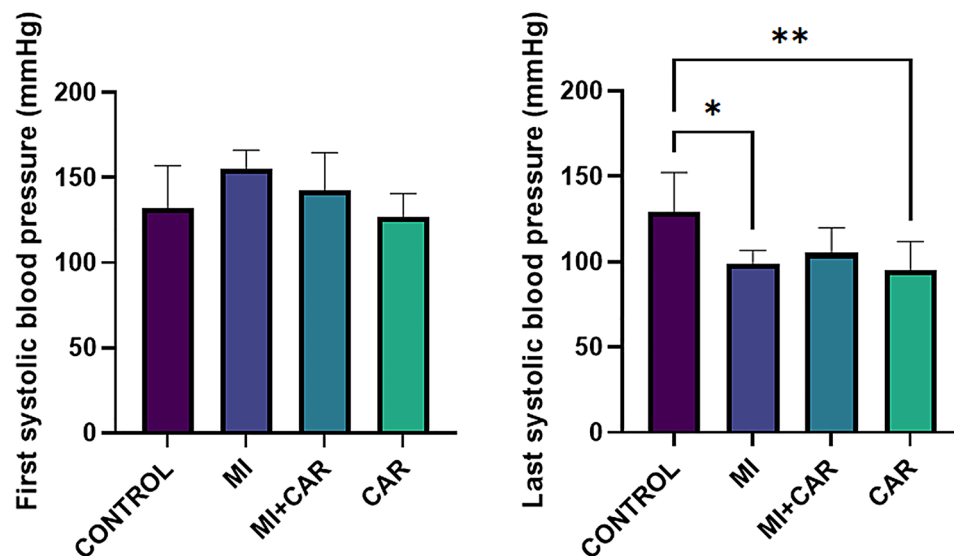


Fig. 2 Evaluation of systolic blood pressures before and after the treatment is shown in the graphs. Data are represented as mean $\pm$ standard deviation. * < 0.05 ** < 0.01

significant differences were found in the comparisons between groups. The control group gained 44% of their initial weight, the MI group gained 48%, the MI + CAR group gained 57%, and the CAR group gained 47% (Fig. 1).

Evaluation of systolic blood pressure values

When examining the systolic blood pressure values before the treatments, no significant differences were observed between the groups. After the treatments, a statistically significant difference was observed between the control group (129.0 ± 23.32) and the MI group (99.10 ± 7.48) ($p = 0.013$). Additionally, a significant difference was found between the control group and the CAR group (94.93 ± 16.95) ($p = 0.004$) (Fig. 2).

Evaluation of diastolic blood pressure values

When examining diastolic blood pressures, a statistically significant difference was found between the control

group (86.46 ± 16.26) and the MI group (49.18 ± 14.21) ($p = 0.001$). No significant difference was observed between the other groups (MI + CAR: 72.07 ± 16.11 , CAR: 62.59 ± 18.43) (Fig. 3).

Evaluation of mean arterial pressure values

A statistically significant difference in mean arterial pressure values was observed between the control group (98.53 ± 11.08) and the MI group (74.64 ± 13.36) ($p = 0.012$). No significant difference was found between the other groups (MI + CAR: 83.58 ± 14.95 , CAR: 84.00 ± 12.93) (Fig. 4).

Evaluation of heart rate values

When examining heart rate values before the treatments, no significant differences were observed between the groups. However, when heart rates were analyzed, a statistically significant difference was found between the control group (358.8 ± 41.86) and the MI group

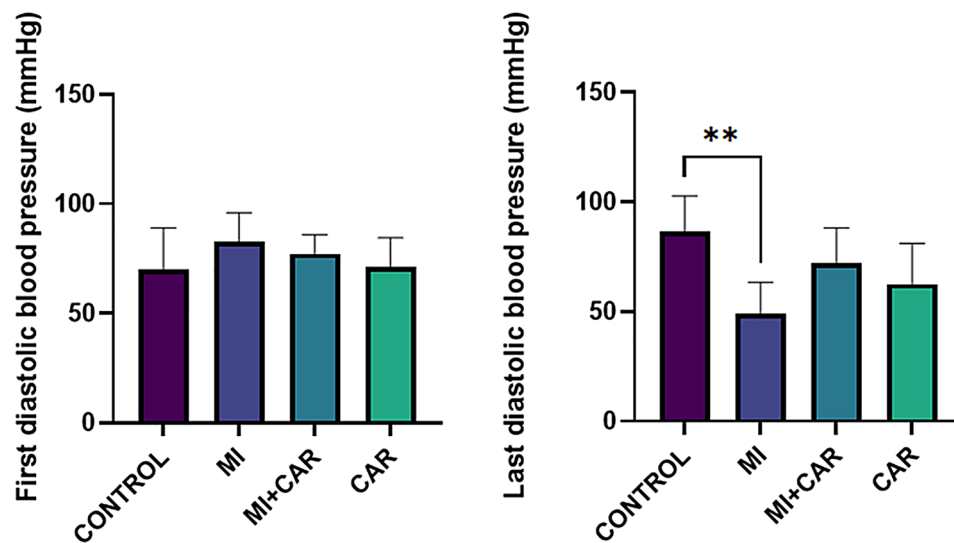


Fig. 3 Evaluation of diastolic blood pressures before and after the treatment is shown in the graphs. Data are represented as mean $\pm$ standard deviation. ** < 0.01

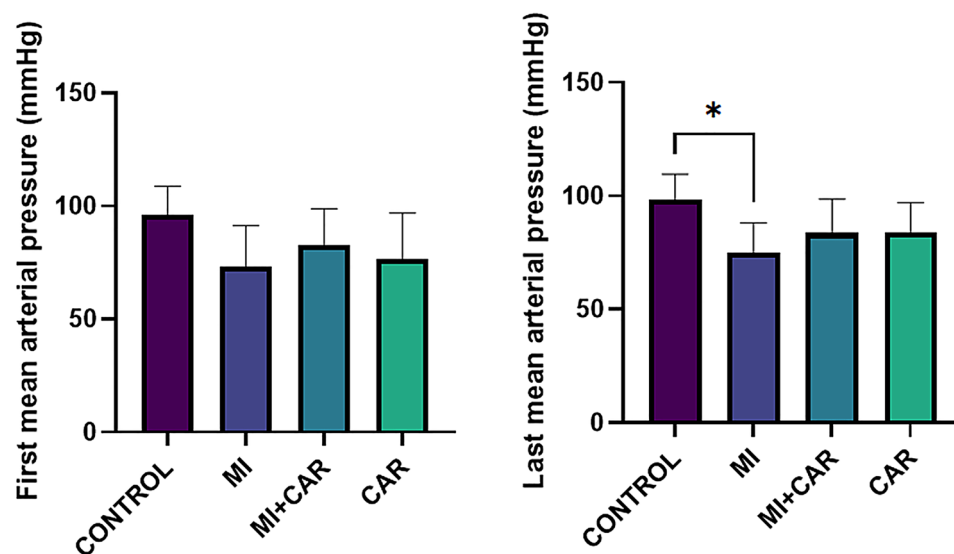


Fig. 4 Evaluation of mean arterial pressures before and after the treatment is shown in the graphs. Data are represented as mean $\pm$ standard deviation. * < 0.05

(244.5 ± 21.26) ($p=0.003$), as well as between the control group and the MI + CAR group (275.3 ± 76.48) ($p=0.036$) (Fig. 5).

Evaluation of troponin T in serums

A statistically significant difference in troponin T levels was observed between the control group and the MI group ($p=0.002$). Additionally, analyses between the control group and the CAR group revealed a significant difference in troponin T levels ($p<0.001$). Finally, a significant difference in troponin T levels was found in the comparisons between the MI group and the MI + CAR group ($p<0.001$) (Fig. 6).

Evaluation of serum BNP levels

A statistically significant difference in BNP values was found between the control group and the MI group ($p<0.001$). Additionally, analyses between the control group and the CAR group also revealed a significant difference in BNP values ($p<0.001$). Finally, a significant difference in BNP values was observed in the comparisons between the MI group and the MI + CAR group ($p<0.001$) (Fig. 7).

Evaluation of IL-6 levels in heart tissues

A statistically significant difference in IL-6 values was observed between the control group and the MI group

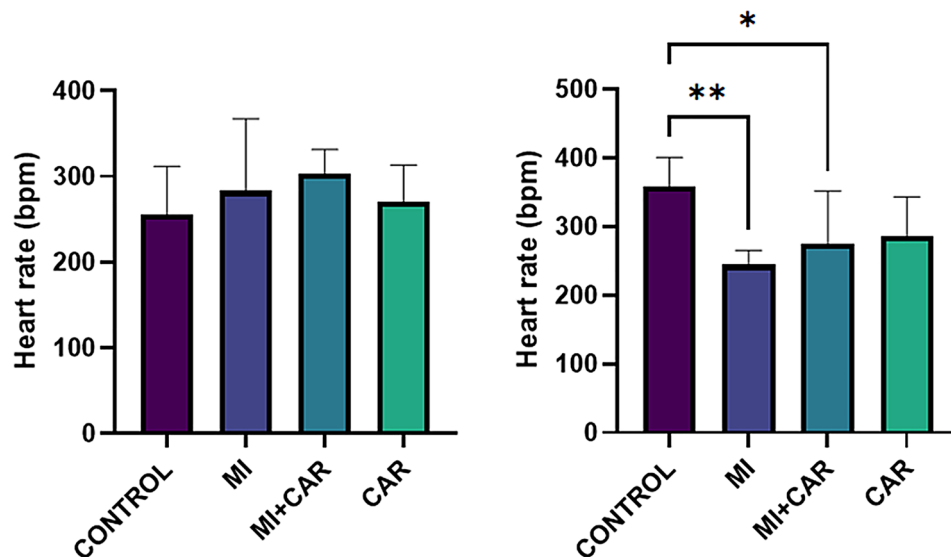


Fig. 5 Evaluation of heart rate values before and after the treatment is shown in the graphs. Data are represented as mean $\pm$ standard deviation. * < 0.05 ** < 0.01

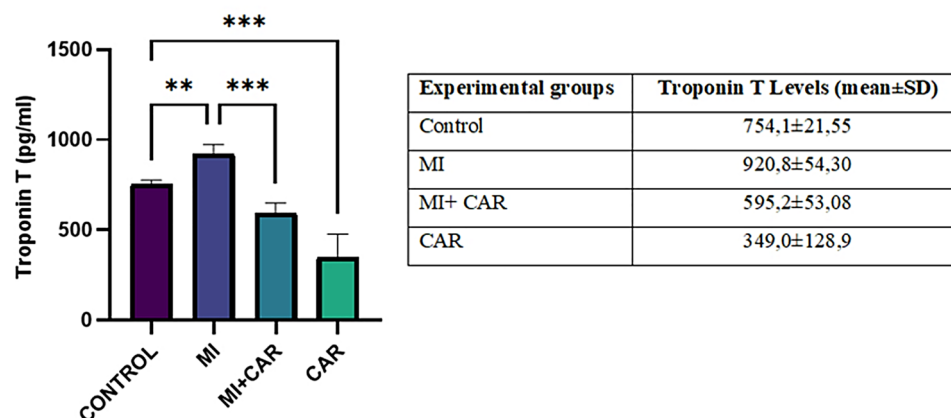


Fig. 6 Evaluation of serum troponin T between groups. Data are represented as mean $\pm$ standard deviation. * < 0.05 ** < 0.01 *** < 0.001

($p < 0.001$). Additionally, analyses between the control group and the CAR group revealed a significant difference in IL-6 values ($p = 0.016$). Furthermore, a significant difference in IL-6 values was found in the comparisons between the MI group and the MI+CAR group ($p = 0.001$) (Fig. 8).

Evaluation of GDF-15 levels in heart tissues

A statistically significant difference in GDF-15 values was observed between the control group and the MI group ($p = 0.014$). Analyses between the control group and the CAR group also revealed a significant difference in GDF-15 values ($p = 0.001$). Additionally, a significant difference in GDF-15 values was found in the comparisons between the MI group and the MI+CAR group ($p = 0.022$) (Fig. 9).

The heart tissue histopathology results

Figures 10 and 11 demonstrate the results of the Iron-Hematoxylin staining. Heart histology in the control (Figure a) and CAR groups (Figure f) showed a healthy architecture. Cardiac myocytes appeared normal with their long branched and regular structure. In the center of the cells were oval-shaped nuclei. In addition, the cytoplasm of the cells included striation. Discus intercalaris appeared to possess a healthy structure. The situation differed in the MI group. First and foremost, the striation structures of cardiac myocytes were reduced in appearance. The MI group had a significantly higher rate of mononuclear cell infiltration compared the control group ($p < 0.001$) (Figure b) (Table 1). In the MI group, myocardiocytes increased, resulting in necrosis ($p < 0.001$) (Figure c) and increased edema ($p < 0.001$) (Figure d), as in contrast to the control group (Table 1). The treatment of carvacrol decreased necrosis and edema in the MI+CAR

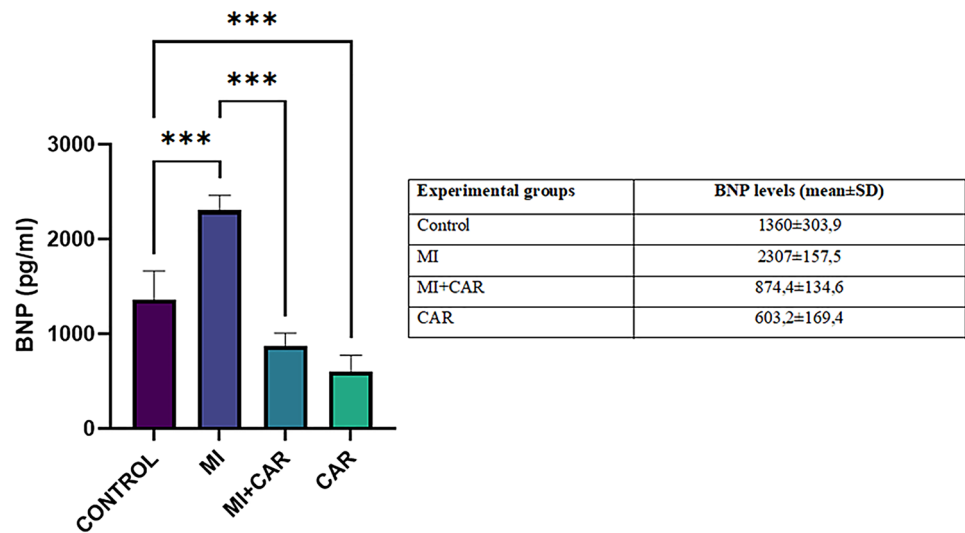


Fig. 7 Evaluation of serum BNP between groups. Data are represented as mean ± standard deviation. *** < 0.001

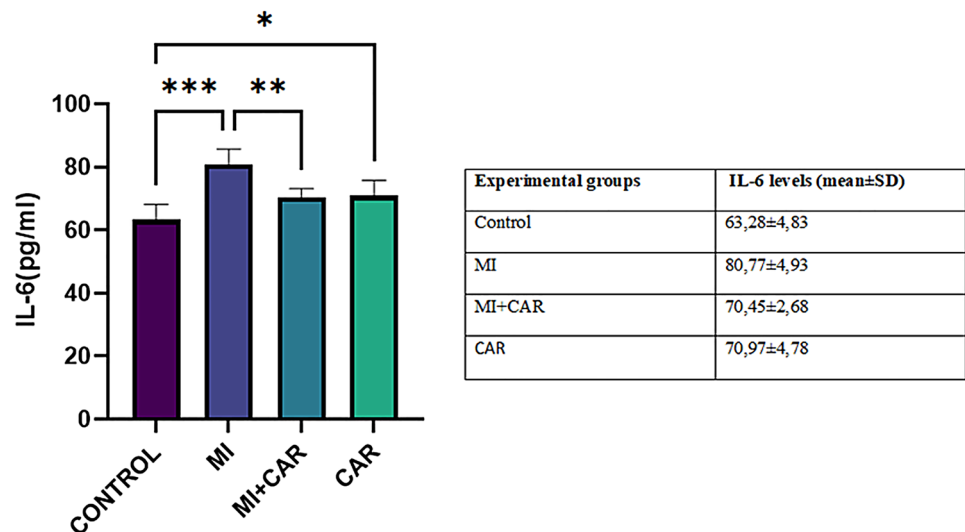


Fig. 8 Evaluation of heart IL-6 levels between groups. Data are represented as mean ± standard deviation. * < 0.05 ** < 0.01 *** < 0.001

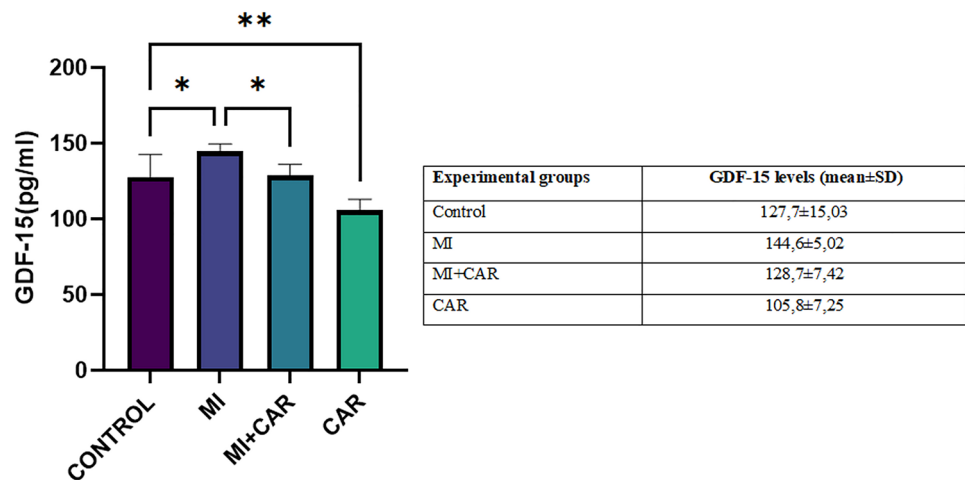


Fig. 9 Evaluation of heart GDF-15 levels between groups. Data are represented as mean ± standard deviation. * < 0.05 ** < 0.01 *** < 0.001

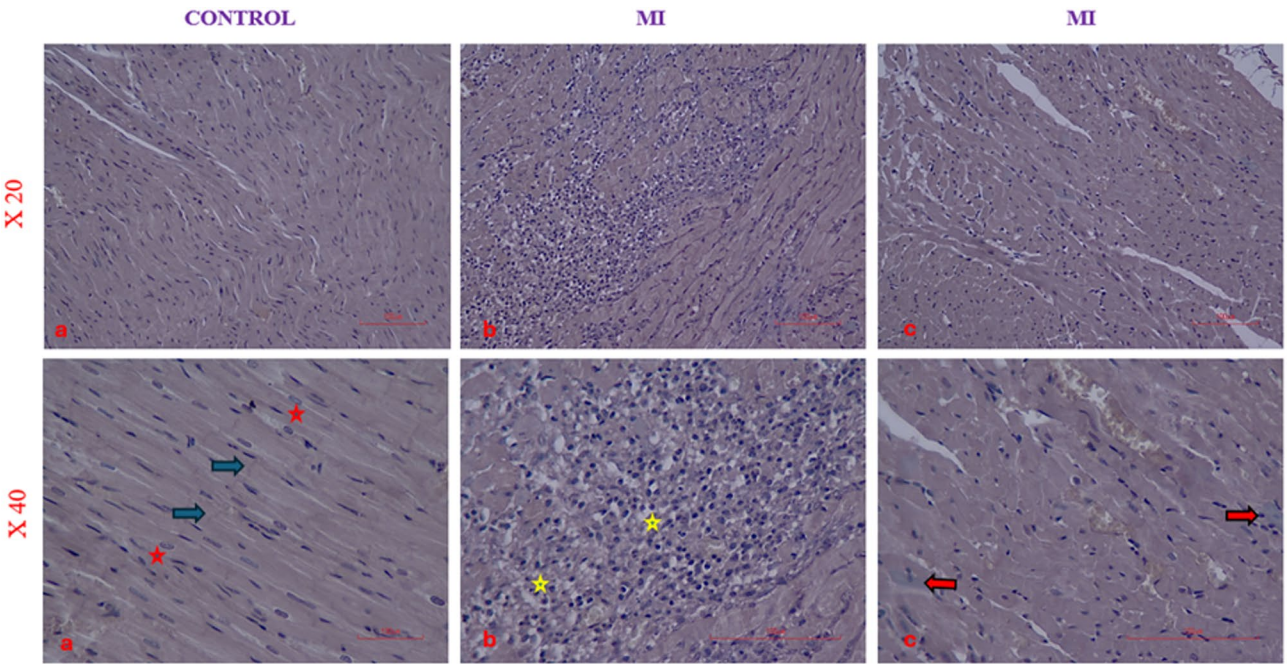


Fig. 10 Light microscopic findings in the rat heart tissue. **a**: Control group; Blue arrows: Healthy discus intercalaris, Red star: Centrally located and oval shaped cell nuclei. **b, c**: MI groups. Yellow star: Mononuclear cell infiltration. Red arrows: Necrotic myocardial cell. Iron- Hematoksilen (Nikon Eclipse Si, Tokyo, Japan, X20 and X40)

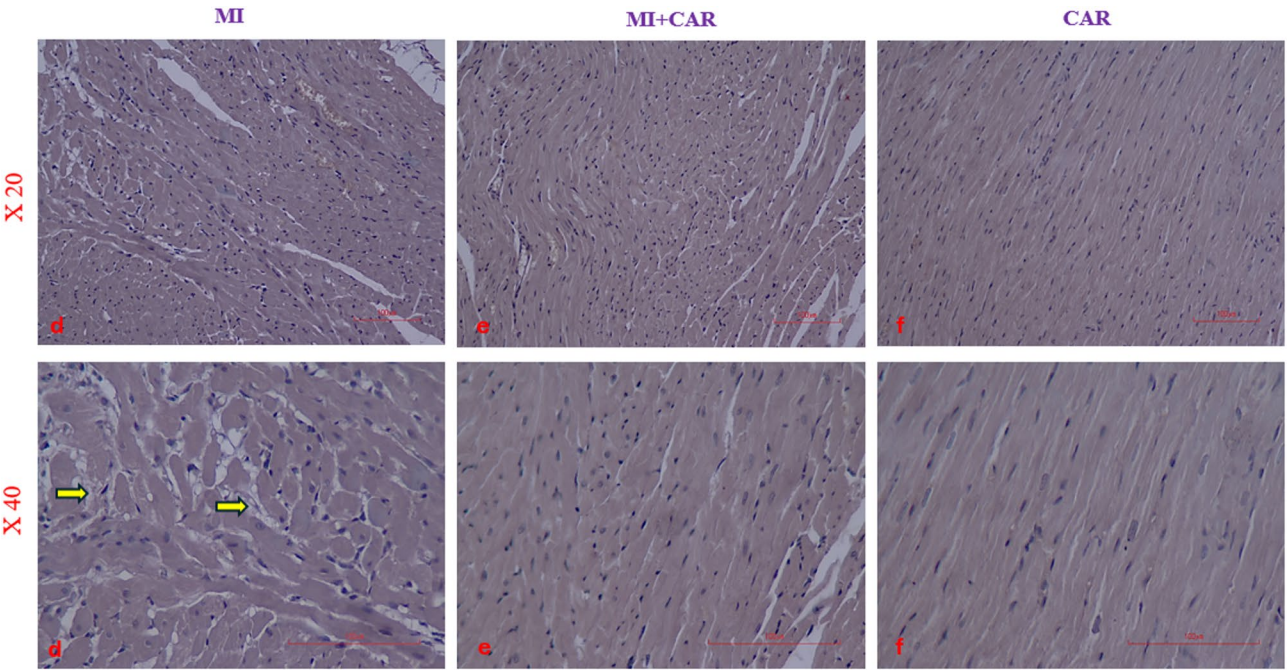


Fig. 11 Light microscopic findings in the rat heart tissue. **d**: MI group. Yellow arrows: Edema, **e**: MI+CAR group and **f**: CAR group. Iron Hemotoksilen (Nikon Eclipse Si, Tokyo, Japan, X20 and X40)

Table 1 Heart tissue Histoscore statistics. the Shapiro-Wilk test was used to evaluate non-normal data distribution Med.(min-max); the quartile value range is shown inside the lines of brackets, whereas the median value is outside. Med: median, Min-max: Minimum-maximum

Heart Histoscore	Control	MI	MI + CAR	CAR	p-value
Necrosis	0,000 (0,000–1,000)	3,000 (2,000–3,000)	1,000 (0,000–2,000)	0,000 (0,000–1,000)	<,001
Edema	0,000 (0,000–1,000)	3,000 (1,000–3,000)	1,000 (0,000–2,000)	0,000 (0,000–1,000)	<,001
Mononuclear cell infiltration	0,000 (0,000–1,000)	3,000 (2,000–3,000)	0,500 (0,000–2,000)	0,000 (0,000–1,000)	<,001

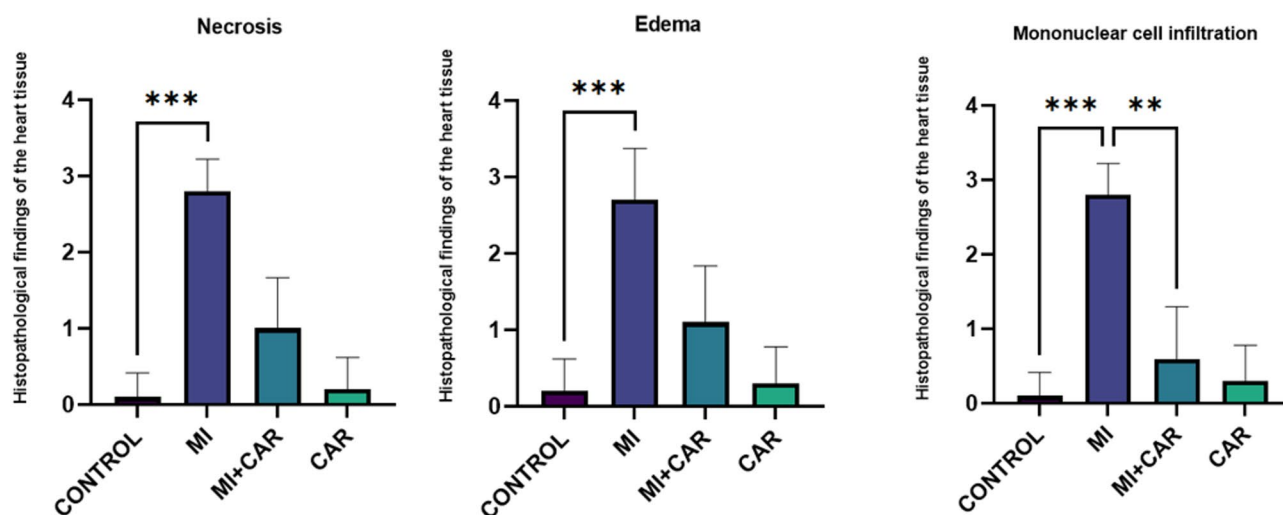


Fig. 12 Histopathological findings of rat heart tissue. Graph exhibiting necrosis, edema, and mononuclear cell infiltration in experimental groups. Data were presented as mean ± standard deviation and median (min-max); $p < 0.05$, *; $p < 0.01$, **; $p < 0.001$

group, although these decreases were not statistically significant ($p > 0.05$) (Table 1). After administering carvacrol, the MI + CAR group exhibited a statistically significant decrease in mononuclear cell infiltration, which had increased in the MI group ($p < 0.01$) (Table 1) (Figs. 10, 11 and 12).

Discussion

The presented study assess the protective effects of carvacrol against myocardial infarction in terms of cardiac biomarkers, hemodynamic parameters, and heart histology, thereby elucidating its potential role as a therapeutic agent in the treatment of cardiovascular diseases. The biochemical data obtained indicate that carvacrol provides protective effects against the pathophysiology of myocardial infarction by reducing levels of troponin T, BNP, IL-6, and GDF-15 in the MI model. Histopathological analysis further demonstrates that carvacrol reduces necrosis, edema, and mononuclear cell infiltration associated with myocardial infarction.

In the isoproterenol-induced myocardial infarction rat model, no statistically significant changes in body weight were observed when compared to the control group [29]. Similarly, in the heart failure model induced by coronary artery ligation, no significant differences in body weight were noted when compared to the control groups [30]. In the present study, no significant difference in weight

change was observed between the groups despite the administration of carvacrol. This result suggests that the effect of carvacrol on the overall body weight of rats may be minimal or negligible. Additionally, this may indicate that the impact of carvacrol on metabolic processes does not translate to changes in body weight, or that its effects may need to be assessed over a longer duration or using different parameters.

In acute myocardial infarction, low diastolic blood pressure and mean arterial pressure are among the key factors that exacerbate myocardial ischemia due to insufficient perfusion [31]. Additionally, changes in heart rate are considered a response of the autonomic nervous system. The disruption of sympathovagal balance after MI is directly related to heart rate changes, and a decrease in heart rate is observed due to the loss of vagal tone in response to increased sympathetic activity [32]. This imbalance in autonomic nervous system regulation may contribute to ventricular arrhythmias and increase the risk of sudden cardiac death [33]. In a study conducted on hypertensive rats, the group treated with carvacrol exhibited a reduction in blood pressure, a decrease in atherogenic indices, and improvements in the lipid parameters assessed [34]. It has been shown that carvacrol provides cardioprotective effects against myocardial ischemia/reperfusion injury by attenuating ST segment elevation on the electrocardiogram and, in a dose-dependent

manner, reducing infarct size [34]. Our findings are consistent with the literature, as changes in blood pressure parameters were observed as a result of the cardiotoxic effects of isoproterenol. In our study, the administration of carvacrol did not significantly alter the hemodynamic parameters associated with MI.

Troponin T is one of the most reliable biomarkers for the clinical diagnosis of myocardial infarction, serving as a specific protein marker released into circulation due to cardiomyocyte damage [35]. Brain Natriuretic Peptide (BNP), on the other hand, is a hormone secreted from ventricular myocytes during cardiac loading and stress, and is a key indicator, particularly for detecting left ventricular dysfunction following MI [36]. In MI studies conducted in rats, it has been observed that the levels of TnT and BNP increase compared to the control groups [37, 38]. A previous study demonstrated that the administration of different doses of carvacrol in an acute MI model resulted in a reduction of TnT levels [37]. In a cardiac hypertrophy rat model, carvacrol was shown to decrease BNP levels [22]. Consistent with these findings, our study also observed a reduction in elevated TnT and BNP levels following MI with carvacrol administration. Therefore, the attenuation of myocardial damage with carvacrol administration indicates a protective effect on cardiac cells.

GDF-15 is considered a critical regulator of stress responses and inflammation, and serves as a determinant biomarker in the prognosis of cardiovascular diseases. Recent studies have shown that circulating GDF-15 levels are significantly elevated in patients with acute MI, and this elevation is closely associated with inflammatory processes [39, 40]. It has been reported that cultured cardiomyocytes exhibit hypertrophic growth along with a reduction in apoptosis in response to GDF-15 [41]. GDF-15 is thought to exhibit both cardioprotective and pro-inflammatory effects; while low levels may support cellular repair, excessive production can trigger apoptotic processes, thereby exacerbating myocardial damage [42]. In this study, it was observed that GDF-15 levels were elevated in the group with MI induced by isoproterenol; however, treatment with carvacrol significantly reduced these levels. Furthermore, a decrease in GDF-15 levels was also observed in the group treated with carvacrol alone. This suggests that the anti-inflammatory and cardioprotective potential of carvacrol may be associated with the regulation of GDF-15 levels.

IL-6 is one of the most important mediators of the acute phase response and plays a critical role in triggering inflammation during the MI process. Studies have shown that IL-6, along with TNF- α and IL-1 β , exacerbates myocardial inflammation and leads to cardiomyocyte damage during MI [43]. Additionally, elevated IL-6 levels have been reported to contribute to fibrosis and remodeling

following MI [44]. In our study, we observed a significant increase in IL-6 levels in rats with MI induced by isoproterenol; however, treatment with carvacrol significantly reduced these levels. This finding suggests that carvacrol may exert a protective effect in the MI process by suppressing IL-6-mediated inflammatory responses. Other studies investigating the anti-inflammatory effects of carvacrol support these findings. It has been reported that carvacrol reduces inflammation-induced cardiac damage by inhibiting the production of pro-inflammatory cytokines such as IL-6 and TNF- α [45]. In another study, elevations in serum levels of LDH, creatinine, TNF- α , IL-1 β , and IL-6 induced by cecal ligation and puncture were completely prevented by carvacrol treatment [46]. In light of these findings, it can be suggested that GDF-15 and IL-6 play critical roles in the inflammatory pathogenesis of myocardial infarction and that carvacrol may offer a potential cardioprotective strategy capable of slowing MI progression and reversing histopathological changes.

In a study using the isoproterenol-induced myocardial infarction (MI) model, deterioration in myofibril organization, necrotic areas, and high neutrophil infiltration were observed in heart histology [47]. In another study conducted by Rababa'h et al., serious damage to cardiomyocytes, loss of nuclei, and lymphocytic inflammation were noted in isoproterenol-induced MI. However, *Origanum majorana* L. extract corrected these findings and exhibited its protective effect [48]. In our study, carvacrol also corrected these histopathological changes and demonstrated its potential effect.

However, this study has some limitations. In our study, only specific biomarkers (Troponin T, BNP, GDF-15, IL-6) were investigated, and other molecular and cellular mechanisms that may play a role in the pathogenesis of myocardial infarction were not thoroughly examined. In addition to oxidative stress, the examination of other biological processes such as inflammation, apoptosis, and autophagy could have helped us better understand the protective effects of carvacrol. Third, the effects of carvacrol in our study were evaluated only at a specific dose and within a limited time frame. Further research is needed to determine the dose-dependent effects of carvacrol, the outcomes of long-term use, and its optimal dosage.

The findings obtained in this study highlight reveal the therapeutic potential of carvacrol on biochemical and histopathological indicators of cardiac damage after MI. Increased cardiac stress and inflammation markers such as troponin T, BNP, IL-6 and GDF-15, as well as decreased diastolic blood pressure and heart rate observed in the MI group indicate cardiovascular dysfunction. Carvacrol treatment attenuated the inflammatory response by significantly reducing the levels of these biomarkers and promoted tissue healing by reducing

necrosis, oedema and mononuclear cell infiltration in cardiac tissue. However, carvacrol had no significant effect on systemic haemodynamic parameters. These results suggest that carvacrol may have protective effects on cardiac tissue after MI and may be a supportive treatment option targeting inflammation.

Acknowledgements

The authors would like to thank Davut Yolcu and Firat Akat for his technical support. In addition to, Tubitak-2209 A partially supported this project.

Author contributions

S K, K T K, Ö S A and K Ö analyzed the data. S K, K T K and K Ö edited the manuscript. All authors reviewed the manuscript.

Funding

Tubitak 2209 partially funded this project.

Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethical approval

This study was conducted at the Animal Research Center of Kırşehir Ahi Evran University. Prior to the experimental procedures, approval was obtained from the Kırşehir Ahi Evran University Local Ethics Committee for Animal Experiments (Aproval number:2024-08-06).

Consent to participate

N/A.

Consent for publication

N/A.

Competing interests

The authors declare no competing interests.

Received: 14 February 2025 / Accepted: 9 July 2025

Published online: 14 July 2025

References

1. Zhang Z, Wu K, Wu Z, Xiao Y, Wang Y, Lin Q, et al. A case of pioneering subcutaneous implantable cardioverter defibrillator intervention in timothy syndrome. *BMC Pediatr*. 2024;24(1):729.
2. Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, et al. Heart disease and stroke statistics—2015 update: a report from the American heart association. *Circulation*. 2015;131(4):e29–322.
3. Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the global burden of disease study 2010. *Lancet*. 2012;380(9859):2095–128.
4. Liu M, Chen R, Zheng Z, Xu S, Hou C, Ding Y, et al. Mechanisms of inflammatory microenvironment formation in cardiometabolic diseases: molecular and cellular perspectives. *Front Cardiovasc Med*. 2025;11:1529903.
5. Willis MS, Patterson C. Proteotoxicity and cardiac dysfunction—Alzheimer's disease of the heart? *N Engl J Med*. 2013;368(5):455–64.
6. Christians ES, Benjamin IJ. Proteostasis and REDOX state in the heart. *Am J Physiol Heart Circ Physiol*. 2012;302(1):H24–37.
7. Santos CX, Anilkumar N, Zhang M, Brewer AC, Shah AM. Redox signaling in cardiac myocytes. *Free Radic Biol Med*. 2011;50(7):777–93.
8. Deng J, Liu Q, Ye L, Wang S, Song Z, Zhu M, et al. The Janus face of mitophagy in myocardial ischemia/reperfusion injury and recovery. *Biomed Pharmacother*. 2024;173:116337.
9. De Vincenzi M, Stammati A, De Vincenzi A, Silano M. Constituents of aromatic plants: carvacrol. *Fitoterapia*. 2004;75(7–8):801–4.
10. Wagner H, Wierer M, Bauer R. [In vitro Inhibition of prostaglandin biosynthesis by essential oils and phenolic compounds]. *Planta Med*. 1986(3):184–7.
11. Baser KH. Biological and Pharmacological activities of carvacrol and carvacrol bearing essential oils. *Curr Pharm Des*. 2008;14(29):3106–19.
12. Unsicker K, Spittau B, Kriegelstein K. The multiple facets of the TGF- β family cytokine growth/differentiation factor-15/macrophage inhibitory cytokine-1. *Cytokine Growth Factor Rev*. 2013;24(4):373–84.
13. Jiang C, Xie N, Sun T, Ma W, Zhang B, Li W. Xanthohumol inhibits TGF- β 1-induced cardiac fibroblasts activation via mediating PTEN/Akt/mTOR signaling pathway. *Drug Des Devel Ther*. 2020:5431–9.
14. Eggers KM, Kempf T, Wallentin L, Wollert KC, Lind L. Change in growth differentiation factor 15 concentrations over time independently predicts mortality in community-dwelling elderly individuals. *Clin Chem*. 2013;59(7):1091–8.
15. Kristono GA, Holley AS, Hally KE, Brunton-O'Sullivan MM, Shi B, Harding SA, et al. An IL-6-IL-8 score derived from principal component analysis is predictive of adverse outcome in acute myocardial infarction. *Cytokine X*. 2020;2(4):100037.
16. Loppnow H, Libby P. Adult human vascular endothelial cells express the IL6 gene differentially in response to LPS or IL1. *Cell Immunol*. 1989;122(2):493–503.
17. Loppnow H, Libby P. Proliferating or Interleukin 1-activated human vascular smooth muscle cells secrete copious Interleukin 6. *J Clin Invest*. 1990;85(3):731–8.
18. Shirazi LF, Bissett J, Romeo F, Mehta JL. Role of inflammation in heart failure. *Curr Atheroscler Rep*. 2017;19(6):27.
19. Chen Y, Ba L, Huang W, Liu Y, Pan H, Mingyao E, et al. Role of carvacrol in cardioprotection against myocardial ischemia/reperfusion injury in rats through activation of MAPK/ERK and akt/enos signaling pathways. *Eur J Pharmacol*. 2017;796:90–100.
20. Nafees S, Ahmad ST, Arjumand W, Rashid S, Ali N, Sultana S. Carvacrol ameliorates thioacetamide-induced hepatotoxicity by abrogation of oxidative stress, inflammation, and apoptosis in liver of Wistar rats. *Hum Exp Toxicol*. 2013;32(12):1292–304.
21. Gunes S, Ayhanci A, Sahinturk V, Altay DU, Uyar R. Carvacrol attenuates cyclophosphamide-induced oxidative stress in rat kidney. *Can J Physiol Pharmacol*. 2017;95(7):844–9.
22. Jamhiri M, Safi Dahaj F, Astani A, Hejazian SH, Hafizbarjin Z, Ghobadi M, et al. Carvacrol ameliorates pathological cardiac hypertrophy in both in-vivo and in-vitro models. *Iran J Pharm Res*. 2019;18(3):1380–94.
23. Pan Y, Gao J, Gu R, Song W, Li H, Wang J, et al. Effect of injection of different doses of isoproterenol on the hearts of mice. *BMC Cardiovasc Disord*. 2022;22(1):409.
24. Tancin Lambert A, Kong XY, Ratajczak-Tretel B, Atar D, Russell D, Skjelland M, et al. Biomarkers associated with atrial fibrillation in patients with ischemic stroke: a pilot study from the NOR-FIB study. *Cerebrovasc Dis Extra*. 2020;10(1):11–20.
25. Fathil M, Arshad MM, Gopinath SC, Hashim U, Adzhri R, Ayub R, et al. Diagnostics on acute myocardial infarction: cardiac troponin biomarkers. *Biosens Bioelectron*. 2015;70:209–20.
26. Kalkan KT, Yalçın B, Mat ÖC, Yay AH. Histopathological and immunohistochemical evaluation of Methotrexate-Induced gonadal damage in rats: role of SCF, mTOR, and SIRT-1. *Medeniyet Med J*. 2024;39(4):283.
27. Demir F, Narin F, Akgün H, Üzümlü K, Saraymen R, Baykan A, et al. Doksozobisin ile Oluşturulmuş Deneysel kardiyotoksiste Üzerine melatoninin etkisi. *Çocuk Sağlığı ve Hastalıkları Dergisi*. 2004;47(4):260–8.
28. Tüfekçioğlu NK, Büyük B. Sıçanlarda İzoproterenol ile Oluşturulan Miyokardiyal Enfarktüs Modelinde Melatoninin Akuaaporin Kanalları Üzerindeki Etkileri. 2023.
29. Patel V, Upaganlawar A, Zalawadia R, Balaraman R. Cardioprotective effect of melatonin against isoproterenol induced myocardial infarction in rats: A biochemical, electrocardiographic and histoarchitectural evaluation. *Eur J Pharmacol*. 2010;644(1–3):160–8.
30. Francis J, Weiss R, Wei S, Johnson A, Felder R. Progression of heart failure after myocardial infarction in the rat. *Am J Physiology-Regulatory Integr Comp Physiol*. 2001;281(5):R1734–45.
31. Wu Q, He C, Huang W, Song C, Hao X, Zeng Q, et al. Gastroesophageal reflux disease influences blood pressure components, lipid profile and cardiovascular diseases: evidence from a Mendelian randomization study. *J Translational Intern Med*. 2024;12(5):510–25.
32. Yin X, Cai D, Song Z, Song C. Nourishment of nerves and innervation: A novel approach for the treatment of myocardial infarction. *Cardiology*. 2025;1–37.

33. Basalay MV, Korsak A, He Z, Gourine AV, Davidson SM, Yellon DM. SGLT2 Inhibition induces cardioprotection by increasing parasympathetic activity. *Circul Res*. 2025;136(2):229–31.
34. Costa HA, Dias CJM, Martins VA, de Araujo SA, da Silva DP, Mendes VS, et al. Effect of treatment with carvedilol and aerobic training on cardiovascular function in spontaneously hypertensive rats. *Exp Physiol*. 2021;106(4):891–901.
35. Aldous SJ. Cardiac biomarkers in acute myocardial infarction. *Int J Cardiol*. 2013;164(3):282–94.
36. Sarzani R, Allevi M, Di Pentima C, Schiavi P, Spannella F, Giuliotti F. Role of cardiac natriuretic peptides in heart structure and function. *Int J Mol Sci*. 2022;23(22):14415.
37. Yu W, Liu Q, Zhu S. Carvedilol protects against acute myocardial infarction of rats via anti-oxidative and anti-apoptotic pathways. *Biol Pharm Bull*. 2013;36(4):579–84.
38. Hasić S, Hadžović-Džuvo A, Jadrić R, Kiseljaković E. B-type natriuretic peptide and adiponectin releases in rat model of myocardial damage induced by isoproterenol administration. *Bosnian J Basic Med Sci*. 2013;13(4):225.
39. Schwarz A, Kinscherf R, Bonaterra GA. Role of the stress-and inflammation-induced cytokine GDF-15 in cardiovascular diseases: from basic research to clinical relevance. *Rev Cardiovasc Med*. 2023;24(3):81.
40. Wollert KC. Growth-differentiation factor-15 in cardiovascular disease. *Basic Res Cardiol*. 2007;102(5).
41. Heger J, Schiegnitz E, Von Waldhausen D, Anwar M, Piper H, Euler G. Growth differentiation factor 15 acts anti-apoptotic and pro-hypertrophic in adult cardiomyocytes. *J Cell Physiol*. 2010;224(1):120–6.
42. di Candia AM, de Avila DX, Moreira GR, Villacorta H, Maisel AS. Growth differentiation factor-15, a novel systemic biomarker of oxidative stress, inflammation, and cellular aging: potential role in cardiovascular diseases. *Am Heart J Plus: Cardiol Res Pract*. 2021;9:100046.
43. Mitsis A, Kadooglou NP, Lambadiari V, Alexiou S, Theodoropoulos KC, Avraamides P, et al. Prognostic role of inflammatory cytokines and novel adipokines in acute myocardial infarction: an updated and comprehensive review. *Cytokine*. 2022;153:155848.
44. Zhang Z, Yang Y. Advances in cytokine-mediated mechanisms for cardiac regeneration and repair post-myocardial infarction: a comprehensive review. *Pharmacol Discov*. 2024;4(3):16.
45. Ölmeztürk Karakurt TC, Emir İ, Bedir Z, Ozkaloglu Erdem KT, Süleyman H, Sarigül C, et al. Effects of carvedilol on ketamine-induced cardiac injury in rats: an experimental study. *Drug Chem Toxicol*. 2024;47(2):166–71.
46. Ozer EK, Goktas MT, Toker A, Bariskaner H, Ugurluoglu C, Iskit AB. Effects of carvedilol on survival, mesenteric blood flow, aortic function and multiple organ injury in a murine model of polymicrobial sepsis. *Inflammation*. 2017;40:1654–63.
47. Rong N, Yang R, Ibrahim IAA, Zhang W. Cardioprotective role of scopoletin on isoproterenol-induced myocardial infarction in rats. *Appl Biochem Biotechnol*. 2023;195(2):919–32.
48. Rababa'h AM, Alzoubi MA. *Origanum majorana* L. extract protects against isoproterenol-induced cardiotoxicity in rats. *Cardiovasc Toxicol*. 2021;21(7):543–52.

Publisher's note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.