



## RESEARCH ARTICLE

### Investigation of the efficacy of tyrosol on doxorubicin-induced acute cardiotoxicity in rats

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### Ratlarda doksorubisin ile oluşturulan akut kardiyotoksosite üzerine tyrosolün etkinliğinin araştırılması

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#### Öz

**Amaç:** Çalışmada, doksorubisin ile oluşturulan kardiyotoksosite üzerine tirozolün etkinliğinin araştırılması amaçlandı.

**Gereç ve Yöntem:** Ratlar 4 gruba ayrıldı ve her grupta 8 rat yer aldı. Grup 1 ve grup 2'ye 1 ml serum fizyolojik, grup 3 ve grup 4'e ise 20 mg/kg dozda tirozol uygulaması yapıldı. Serum fizyolojik ve tirozol uygulamalarında oral gavaj yöntemi kullanıldı. Ayrıca grup 2 ve grup 4'e denemenin 12. günü 15 mg/kg dozda ve tek doz intraperitoneal doksorubisin uygulaması yapıldı. Denemenin 14. gününde anestezi altındaki ratlardan serum ve doku örnekleri alındı ve daha sonra ötanazi edildi. Serum kreatin kinaz MB ve kreatin kinaz aktiviteleri analiz edildi. Kalp dokuları çıkarıldı ve bu dokularda histopatolojik ve oksidatif stres parametrelerine yönelik analizler yapıldı. Kalp dokusu malondialdehit ve redükte glutatyon düzeyleri ile katalaz ve glutatyon peroksidaz enzim aktiviteleri spektrofotometrik olarak belirlendi.

**Bulgular:** Tirozol ön tedavisinin doksorubisinin neden olduğu kalp dokusu malondialdehit düzeyindeki artışı ( $p<0.05$ ), redükte glutatyon düzeyi ve glutatyon peroksidaz enzim aktivitesindeki azalmaları engellediği ve doksorubisinin kalp dokusunda meydana getirdiği oksidatif stresi baskıladığı görüldü. Kalp dokusu katalaz enzim aktiviteleri açısından gruplar arasında farklılık gözlenmedi. Kalpteki oksidatif hasarın azalmasına bağlı olarak serum kreatin kinaz MB ve kreatin kinaz aktivitelerinin önemli oranda azaldığı ( $p<0.05$ ) tespit edildi. Ayrıca tirozol ön tedavisinin doksorubisinin kalp dokusunda meydana getirdiği histopatolojik lezyonları engellediği belirlendi.

**Öneri:** Tirozol uygulamasının doksorubisinin neden olduğu kardiyotoksositeyi azaltabileceği düşünülmektedir.

**Anahtar kelimeler:** Kardiyotoksosite, doksorubisin, tirozol

#### Abstract

**Aim:** In this study, it was aimed to investigate the efficacy of tyrosol on cardiotoxicity induced by doxorubicin.

**Materials and Methods:** Rats were divided into 4 groups and each group included 8 rats. Groups 1 and 2 were given 1 ml of physiological saline, while groups 3 and 4 were given 20 mg/kg of tyrosol. In saline and tyrosol administrations, the oral gavage method was used. In addition, a single dose of 15 mg/kg dose of doxorubicin was administered intraperitoneally to group 2 and group 4 on the 12th day of the trial. On the 14th day of the experiment, serum and tissue samples were taken from the anesthetized rats and then euthanized. Serum creatine kinase MB and creatine kinase activities were analyzed. Heart tissues were extracted, and histological and oxidative stress characteristics were measured in these tissues. Heart tissue malondialdehyde and reduced glutathione levels, catalase and glutathione peroxidase activities were assessed spectrophotometrically.

**Results:** Tyrosol pretreatment inhibited doxorubicin-induced increase in heart tissue malondialdehyde level ( $p<0.05$ ), the decrease in reduced glutathione level and glutathione peroxidase enzyme activity, and suppressed doxorubicin-induced oxidative stress in the heart tissue. In terms of cardiac tissue catalase enzyme activity, no differences were found between the groups. Because of the reduction in oxidative damage in the heart, the serum creatine kinase MB and creatine kinase activity decreased dramatically ( $p<0.05$ ). Furthermore, it was discovered that tyrosol pretreatment reduced the histopathological lesions caused by doxorubicin in cardiac tissue.

**Conclusion:** It is thought that the administration of tyrosol may reduce the cardiotoxicity caused by doxorubicin.

**Keywords:** Cardiotoxicity, doxorubicin, tyrosol





## Introduction

Doxorubicin, a member of the anthracycline drug group, is used to treat diseases such as leukemia, lymphoma, breast cancer, multiple myeloma, and lung cancer (Shaker et al 2018). Although it is an efficient anticancer drug, its usage is restricted because of its adverse effects on the heart, kidney, liver, ovary, and uterus (Granados Principal et al 2010, Jadhav et al 2013, Baris et al 2019). Doxorubicin administration may cause cardiotoxicity, especially (Granados Principal et al 2010). It may cause some cardiovascular disorders such as tachycardia, arrhythmia, hypotension, dilated cardiomyopathy and cardiac dysfunction in cancer patients (An et al 2009, Ibrahim et al 2017, McGowan et al 2017). Cardiotoxicity may also develop after single dose or cumulative dose administration (Uygur et al 2014). The pathogenesis of cardiotoxicity caused by doxorubicin has not been fully elucidated. Oxidative stress is important in the pathogenesis of doxorubicin cardiotoxicity, including the formation of iron-dependent free oxygen radicals and peroxidation of lipids in the myocardial mitochondrial membrane, which causes suppression of DNA, RNA and proteins (Thomas 2017). It has been reported that other factors such as inflammation, apoptotic cell death of cardiomyocytes, mitochondrial dysfunction, myofibril degeneration and calcium usage altered by the sarcoplasmic reticulum may be effective in the pathogenesis of cardiotoxicity (Wouters et al 2005, Gandhi et al 2013, Mantawy et al 2014, Pecoraro et al 2018). The increase in free radicals in the myocardium and the decrease in the activity of endogenous antioxidants have an important role in the pathogenesis of heart failure caused by doxorubicin (Lódi et al 2019).

Tyrosol (2-(4-hydroxyphenyl) ethanol), a phenolic compound, is found in olive oil and wine (Bu et al 2007, Thibault et al 2011). Many studies have proven that Tyrosol has antioxidant (Bu et al 2007, Thibault et al 2011, Guvenç et al 2019), anti-inflammatory (Kima et al 2017), antihyperlipidemic (Chandramohan and Pari 2021), neuroprotective, anti-apoptotic and anticancer effects (Plotnikov and Plotnikova 2021).

In this study, it was aimed to investigate the protective efficacy of tyrosol on cardiotoxicity induced by doxorubicin.

## Material and Methods

### *Animal material*

32 Wistar albino female rats weighing 180-250 g were used in the study. Experimental animals were housed in accordance with the care and use conditions of laboratory animals (12 hours light, 12 hours dark and 21±1°C). The

rats were given standard commercial feed (pellet feed) and water ad libitum.

### *Experimental groups*

The cardiotoxicity model with doxorubicin in rats was established based on the article by Ikewuchi et al (2021), and the dose of tyrosol in rats was calculated based on the article by Cellat et al (2021). The experimental groups of the study consisted of four groups: Group 1 (Control group), group 2 (Doxorubicin), group 3 (Tyrosol) and group 4 (Doxorubicin + Tyrosol). Each group consisted of 8 rats and a total of 32 female rats were used. For 14 days, rats in Groups 1 and 2 were given 1 ml of saline once a day. The rats in groups 3 and 4 were given tyrosol at a dose of 20 mg/kg in 1 ml of physiological saline once a day also for 14 days. Oral gavage method was used in saline and tyrosol applications. Also, on the 12th day of the experiment, the rats in groups 2 and 4 were intraperitoneally injected with doxorubicin at a concentration of 15 mg/kg (Ikewuchi et al 2021). On the 14th day of the experiment, blood samples were taken from the tail veins of the rats under ketamine (60 mg/kg IM) + xylazine (10 mg/kg IM) anesthesia to serum tubes, and then they were euthanized using the decapitation method. Then hearts of the euthanized rats were removed. The tissue samples were examined for histopathological and oxidative stress markers. The heart tissue samples removed for histopathological analysis were kept in 10% buffered formalin and stored until further analysis. The remaining tissue samples were kept in deep freezer (-80 °C) for oxidative parameter analysis.

### *Measurement of serum CK and CK-MB enzyme activities*

Blood samples were centrifuged at 3000 rpm for 15 minutes, their serum was removed and placed in eppendorf tubes. Creatine kinase (CK) and creatine kinase MB (CK-MB) activity levels were analyzed in fresh serum samples. Gesan brand automatic biochemistry analyzer device was used in the analysis process.

### *Analysis of oxidant and antioxidant parameters in heart tissue*

The concentration of thiobarbituric acid reagents and the level of lipid peroxidation were measured. The malondialdehyde (MDA) level, which was used as a lipid peroxidation index, was determined according to the method reported by Placer et al (1966) and was expressed as nanomoles per gram of protein. The reduced glutathione (GSH) level was measured according to the method reported by Sedlak and Lindsay (1968) and expressed as nanomoles per gram of protein. Glutathione peroxidase (GSH-Px, EC 1.11.1.9) enzyme activity analysis was performed according to the method reported by Lawrence and Burk

(1976). Activity findings were expressed in international units per gram of protein. The method reported by Aebi (1983) was used for the determination of catalase (CAT, EC 1.1.1.16) enzyme activity. Activity results were expressed as ku/protein. Protein analysis was performed based on the method of Lowry et al (1951).

### Histopathological analysis

At the end of the experiment, all rats were euthanized under anesthesia and their heart tissues were removed. Some of the heart tissue samples were separated for the analysis of oxidant and antioxidant parameters and stored in a deep freezer (-80 °C). Tissue samples separated for histopathological analysis were fixed in 10% buffered formaldehyde solution for 48 hours. They became transparent by passing through a series of xylene. Next, the samples were blocked in paraffin and sectioned at 5 µm thicknesses by rotary microtome (Leica, RM 2135). After that, the slides were stained with hematoxylin and eosin (H&E) for histopathological evaluation (Luna 1968). All slides were examined and microphotographed by using light microscope (Olympus BX50-F4, Tokyo, Japan) with imaging system (Olympus DP12-BSW, Tokyo, Japan) for detection of lesions in the brain.

### Statistical analysis

Using Shapiro-Wilk normality analysis in the data obtained in the study, it was evaluated whether the values of the groups had a normal distribution. As a result of the analysis,

it was seen that the values of all parameters had normal distribution. One-way analysis of variance (ANOVA) was used to compare group means. In addition, differences between groups were determined using the Tukey test. IBM SPSS Statistics 23 package program was used for statistical analysis and ( $p < 0.05$ ) was considered statistically significant.

### Results

Statistically significant increases were observed in serum CK and CK-MB enzyme activities of rats in the doxorubicin group ( $p < 0.05$ ). There was no significant difference between the control and tyrosol groups in terms of both parameters. When the serum CK and CK-MB activities of the rats in the group receiving doxorubicin plus tyrosol and in the group administered only doxorubicin were compared, it was determined that there were statistically significant decreases ( $p < 0.05$ ). These reductions were thought to be linked to tyrosol's antioxidant activity, which could mean less oxidative damage in heart tissue. Table 1 summarizes the findings for these parameters.

In this investigation, doxorubicin administration significantly increased MDA levels in cardiac tissue while lowering GSH levels and GSH-Px enzyme activity ( $p < 0.05$ ). The activity of the CAT enzyme did not differ significantly between the groups ( $p > 0.05$ ). In terms of MDA and GSH levels, as well as CAT and GSH-Px enzyme activity, there was no statistical difference between the control and tyrosol groups. While a significant decrease in heart tissue MDA level was determined in rats given doxorubicin plus tyrosol

Table 1. Serum CK and CK-MB enzyme activity levels

| Group/Parameter       | CK<br>(U/L)                | CK-MB<br>(U/L)             |
|-----------------------|----------------------------|----------------------------|
| Control               | 863.07±237.24 <sup>b</sup> | 895.03±95.01 <sup>c</sup>  |
| Doxorubicin           | 1482.08±93.46 <sup>a</sup> | 1581.58±62.55 <sup>a</sup> |
| Tyrosol               | 836.71±119.94 <sup>b</sup> | 876.97±65.43 <sup>c</sup>  |
| Doxorubicin + Tyrosol | 960.89±286.56 <sup>b</sup> | 1143.53±96.75 <sup>b</sup> |

<sup>a,b,c</sup> Varied characters in the same column are statistically different ( $p < 0.05$ ). CK, creatine kinase; CK-MB, creatine kinase MB

| Group/Parameter       | MDA<br>(nmol/g prot)    | GSH<br>(nmol/g prot)    | GSH-Px<br>(IU/gr prot)   | CAT<br>(KU/g prot) |
|-----------------------|-------------------------|-------------------------|--------------------------|--------------------|
| Control               | 7.83±1.16 <sup>bc</sup> | 1.11±0.17 <sup>a</sup>  | 47.87±9.90 <sup>a</sup>  | 31.63±3.81         |
| Doxorubicin           | 11.92±2.05 <sup>a</sup> | 0.87±0.14 <sup>b</sup>  | 38.94±4.96 <sup>b</sup>  | 28.43±8.37         |
| Tyrosol               | 7.18±0.84 <sup>c</sup>  | 1.16±0.18 <sup>a</sup>  | 48.85±4.06 <sup>a</sup>  | 32.27±2.37         |
| Doxorubicin + Tyrosol | 9.40±1.50 <sup>b</sup>  | 1.01±0.19 <sup>ab</sup> | 46.28±8.05 <sup>ab</sup> | 30.30±2.89         |

<sup>a,b,c</sup>: Varied characters in the same column are statistically different (p<0.05). MDA, malondialdehyde; GSH, reduced glutathione; CAT, catalase; GSH-Px, glutathione peroxidase

(p<0.05), the increase in GSH level and GSH-Px activity was not statistically significant. When these findings were examined, it was discovered that tyrosol has an antioxidant effect and it may alleviate the adverse effects of oxidative stress in cardiac tissue caused by doxorubicin. Table 2 shows the results of the oxidant and antioxidant parameters.

The examinations identified no macroscopic changes in any of the rat groups. The evaluation of heart tissue samples revealed that cardiac muscle cells in the control (Figure 1A) and tyrosol (Figure 1C) groups had normal histological features. Heart sections from the doxorubicin group rats showed mild to moderate degenerative and necrotic histopathological changes. Cardiomyocytes in this group showed hyaline degeneration, vacuolar degeneration (cytoplasmic vacuolization), and myocytolysis.

Cytoplasmic vacuoles were observed in the cytoplasm of cardiomyocytes as sharp-edged, non-staining spaces of varying sizes. The capillaries in several of the vessels were congested. In addition, some myocardial fibrils were disorganized as a result of degeneration. The transverse striations detected under a high magnification light microscope in these deteriorated heart muscle fibers disappeared with disorganization, according to the findings. Few inflammatory cells were seen between the muscle fibers once again. Some necrotic cells' nuclei were pycnotic and hyperchromatic, while others' nuclei had completely disappeared (Figure 1B). Only a slight congestion and a few hyaline degenerated myofibrils were identified in certain capillaries in the tyrosol with doxorubicin group. With the exception of minor histopathological changes, the rats in this group had near-normal cardiac muscle histology (Figure 1D). Figures 1A, B, C, and D show the histopathological findings of all groups.

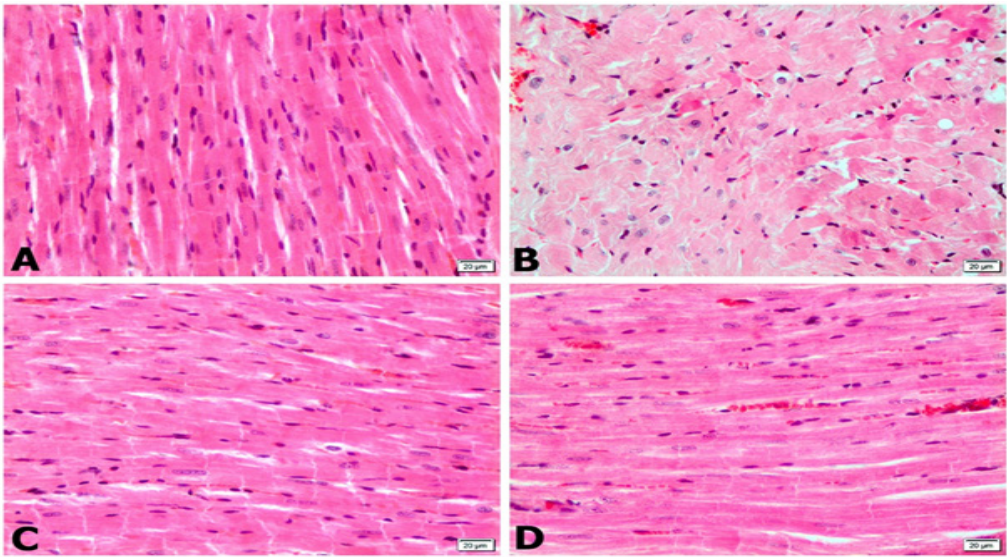


Figure 1. Histopathological view of heart tissue with H&E staining. Normal histological structure in the Control groups (A). Mild to moderate degenerative and necrotic changes in heart muscle in the Doxorubicin group (B). Normal histological appearance in the Tyrosol group (C). Mild degenerative changes in heart muscle Doxorubicin + Tyrosol group (D)



## Discussion

Doxorubicin is an anthracycline group antibiotic used to treat a variety of cancers, including hematologic cancer, solid tumors, and soft tissue sarcomas, and can commonly cause heart failure and heart damage as a side effect (Pehlivan et al 2020). Doxorubicin causes serious morphological and functional cardiac changes and ultimately irreversible cardiomyopathy and heart failure (Gandhi et al 2013, Kim et al 2017, Guo et al 2018). According to Rašković et al (2011), doxorubicin causes cardiotoxicity by disrupting the balance between reactive oxygen species (ROS) and antioxidant enzyme levels. Oxidative stress and lipid peroxidation are the most important causes of doxorubicin-induced cardiotoxicity according to in vivo and in vitro investigations (Gandhi et al 2013). Due to the presence of cardiolipin in cardiac mitochondria, cardiomyocytes are significantly more vulnerable to oxidative stress (Tahover et al 2015, Giampieri et al 2016). Anionic cardiolipin found in the mitochondrial inner membrane has a high affinity for binding with the cationic drug doxorubicin. Therefore, mitochondria play an important role in doxorubicin-induced cardiotoxicity (Octavia et al 2012, Nebigil and Desaubry 2018). The nicotinamide adenine dinucleotide hydrogen dehydrogenase (NADH) enzyme in the mitochondria reacts with molecular oxygen to reduce doxorubicin to the semiquinone radical. Semiquinone plays a role in the formation of hydrogen peroxide, hydroxyl and superoxide radicals (Volkova and Russell 2012). Excessive ROS production causes cell damage and, consequently, increased lipid peroxidation and increased MDA production (Subbarao et al 2018). MDA is a stable lipid peroxidation end product that can be used to predict lipid peroxidation and tissue damage induced by free radicals (Xiao 2015). In many scientific studies, it has been reported that doxorubicin administration increases the level of heart tissue MDA in experimental animals (Haybara et al 2019, Zare et al 2019, Mohammeda et al 2020, Sandamali et al 2020, Sheibani et al 2020, Ahmed et al 2021, Ikewuchi et al 2021). The heart tissue MDA level of the rats in the doxorubicin-only group increased considerably as compared to the control group in this study. In an experimental asthma model established using ovalbumin tyrosol caused a decrease in lung tissue MDA level, an increase in GSH level and GSH-Px enzyme activity, had a strong antioxidant effect, and prevented lung damage. According to the same study, tyrosol had no effect on catalase enzyme activity in lung tissue (Cellat et al 2021). In a dextran sulfate sodium (DSS)-induced ulcerative colitis model in rats, tyrosol lowered the MDA value of the colon tissue, increased the GSH level, CAT, and GSH-Px enzyme activities to levels similar to the control group, and protected the colon tissue from ulcerative colitis (Guvenc et al 2019). The cardiac tissue MDA levels of the rats in the group given tyrosol and doxorubicin showed statistically significant reduction in this investigation. The

difference between the control and tyrosol groups was not significant. GSH, an intracellular hydrophilic antioxidant, protects cells from free radical damage (Pandey and Rizvi 2010). It has been reported that the amount of GSH in the heart tissue decreased significantly in rats given doxorubicin (Haybara et al 2019, Zare et al 2019, Alanazi et al 2020, Mohammeda et al 2020, Sandamali et al 2020, Sheibani et al 2020, Ahmed et al 2021, Ikewuchi et al 2021). The GSH level in heart tissue was shown to be lower in the doxorubicin group in this investigation. The results related to GSH are consistent with what has been published in the literature. There is additional information that doxorubicin treatment raises GSH levels in cardiac tissue (Zare et al 2019). The inconsistency with the GSH finding of this study could be due to variances in the dose and duration of doxorubicin administration. The tissue GSH levels of rats in the control and tyrosol groups did not differ significantly. The cardiac tissue GSH level in rats given doxorubicin and tyrosol was found to be similar to that of the control group.

Antioxidant enzymes such as GSH-Px and CAT protect the body against tissue damage caused by oxidative stress (Afsar et al 2017). Doxorubicin causes decreases in the activities of antioxidant enzymes such as CAT and superoxide dismutase (SOD). Because cardiac tissues have less antioxidant reserve than other organs in the body, they are more vulnerable to doxorubicin damage (Halestrap 2006). The hydrogen peroxide formed in the heart tissue as a result of doxorubicin's effect is converted into water and molecular oxygen by the enzyme catalase. Therefore, increased ROS generation during doxorubicin treatment lowers the level of catalase, reducing cardiomyocytes' ability to detoxify ROS (Afsar et al 2017, Bhatt and Joshi 2017). Doxorubicin decreases cardiac tissue catalase enzyme activity according to a substantial body of literature (Zhang et al 2017, Haybara et al 2019, Wu et al 2019, Birari et al 2020, Li et al 2020, Sandamali et al 2020, Ikewuchi et al 2021). Some researchers, however, suggested that doxorubicin treatment had no effect on heart tissue catalase activity (Al Taei et al 2019). When comparing the doxorubicin group to the control group, it was discovered that the CAT enzyme activity of the doxorubicin group caused a decrease in CAT activity, however this decline was not statistically significant. In terms of CAT enzyme activity, there was no statistically significant difference between the groups. Our findings on CAT enzyme activity are in agreement with those of Al-Taei et al (2019). It was thought that the inconsistency with other literature might be due to the application time and dose of doxorubicin. GSH-Px acts as a catalyst in the reaction of hydroperoxidase with GSH (Sumitra et al 2001). Doxorubicin treatment has been shown to cause statistically significant decreases in GSH-Px enzyme activity in cardiac tissue (Zhang et al 2017, Zhao et al 2018, Haybara et al 2019, Öner et al 2019, Wu et al 2019, Li et al 2020, Sandamali et al 2020, Ikewuchi et al 2021). There is additional evidence in the literature that the





same application has no effect on the activity of the GSH-Px enzyme in cardiac tissue (Kumrala et al 2015). The amount of GSH-Px enzyme activity in cardiac tissue was shown to be considerably decreased after doxorubicin administration in this investigation. There was no statistically significant difference between the control and tyrosol groups. There were increases in cardiac tissue GSH-Px enzyme activity in the group receiving tyrosol and doxorubicin, but these increases were not statistically significant. When the oxidant and antioxidant parameters of heart tissue were analyzed in the study, it was found that tyrosol had an antioxidant effect and as a result it could alleviate oxidative stress in the heart tissue caused by doxorubicin.

CK is one of the specific and sensitive markers of cardiac muscle damage (Asiri 2010). CK-MB is normally present in the cellular compartment, but with myocardial damage, it leaks into the circulation due to the breakdown of contractile components and the sarcoplasmic reticulum (Akila and Vennila 2016). It has been stated that doxorubicin produces a rise in the release of enzymes like CK, which is caused by the activation of lipid peroxidation in cardiac membranes (Saad et al 2001). The significant increase in serum CK and CK-MB levels after doxorubicin treatment is due to increased lipid peroxidation and oxidative stress in heart tissue (Ammar et al 2013). In many scientific studies, it is emphasized that doxorubicin administration causes significant increases in serum CK (Haybara et al 2019, Li et al 2020, Liao et al 2020, Yuan et al 2020, Ahmed et al 2021, Ikewuchi et al 2021, Wan et al 2021) and CK-MB (Al Taei et al 2019, Zare et al 2019, Alanazi et al 2020, Li et al 2020, Liao et al 2020, Sheibani et al 2020, Tiana et al 2020, Yuan et al 2020, Zhang et al 2020, Ikewuchi et al 2021, Wan et al 2021) levels in experimental animals. In this study, it was discovered that rats receiving only doxorubicin had statistically significant increases in serum CK and CK-MB levels. There was no difference between the control and tyrosol groups. Serum CK and CK-MB levels were found to be significantly lower in the group that received tyrosol in addition to doxorubicin. These decreases were thought to be due to tyrosol's antioxidant effect on heart tissue, which inhibits lipid peroxidation.

Doxorubicin administration causes various histopathological changes, such as cardiomyocyte vacuolization in heart tissue, increased extracellular fibrosis, muscle fiber disorder, myofibril loss, enlarged and abnormally shaped mitochondria, inflammatory cell infiltration, increased cell death, cardiomyocyte apoptosis, edema of myocardial cells, myocardial tissue hemorrhage, blood vessel occlusion, pycnotic nuclei and necrosis (Kumrala et al 2015, Haybara et al 2019, Ma et al 2019, Öner et al 2019, Liao et al 2020, Sandamali et al 2020, Tiana et al 2020, Yuan et al 2020, Ahmed et al 2021, Wan et al 2021). When the heart tissue samples from the control and tyrosol groups were examined, the cardiac muscle cells were found to have

normal histological features. Degenerative and necrotic histopathological changes ranging from mild to moderate, such as hyaline degeneration of cardiomyocytes in some areas, vacuolar degeneration (cytoplasmic vacuolization), myocytolysis, congestion in capillaries, loss of transverse striations in degenerated heart muscle fibrils, sporadic infiltration of inflammatory cells between muscle fibers, pycnotic and hyperchromatic appearance of the nuclei of some necrotic cells, and complete disappearance of the nuclei of some cells were detected in the heart tissue of the rats in the doxorubicin group. The histology of heart tissue in the group given tyrosol and doxorubicin was mostly close to normal, with the exception of histopathological changes, such as very minor congestion in certain capillaries and a few myofibrils with hyaline degeneration. The biochemical and histological findings revealed that tyrosol pretreatment protected against doxorubicin-induced cardiotoxicity.

## Conclusion

Pre-treatment with tyrosol reduced cardiotoxicity, which is the most serious side effect of doxorubicin. In order to better elucidate the effect of tyrosol on the cardiotoxicity of doxorubicin, new studies at the molecular level are needed on different doses and durations of use of tyrosol.

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## Conflict of Interest

The authors did not report any conflict of interest or financial support.

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During this study, any pharmaceutical company which has a direct connection with the research subject, a company that provides and / or manufactures medical instruments, equipment and materials or any commercial company may have a negative impact on the decision to be made during the evaluation process of the study or no moral support.

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## Ethical Approval

The presented study was carried out with the approval and permission of Hatay Mustafa Kemal University Animal Experiments Local Ethics Committee with the decision numbered 2021/07-01 dated 31.12.2021.

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