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Original Article

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The protective effect of naringenin on ciprofloxacin-induced cardiovascular toxicity in rats

Abstract

Aim: Ciprofloxacin (CIPRO) is an antibiotic in the quinolone group. It can exert cardiotoxic effects on the cardiovascular system through potential arrhythmic and oxidative stress. Naringenin (NRG) is a flavonoid compound found in various plant sources. It may protect the heart by lowering oxidative stress and inflammation. In this study, protective effects of NRG against CIPRO-induced cardiotoxicity was explored.

Material and Methods: Thirty-two adult male Sprague-Dawley rats were divided into four groups by simple randomization: Control, CIPRO (50 mg/kg CIPRO intraperitoneally (i.p.) twice a day for 7 days), NRG (25 mg/kg NRG oral gavage (p.o.), 28 days), and NRG+CIPRO (25 mg/kg NRG p.o. for 28 days, 50 mg/kg CIPRO i.p. twice a day from the 22nd day). Data on heart rate, blood pressure (BP), and electrocardiography (ECG) were recorded. The samples (heart and descending aorta) were prepared for histopathology and biochemical analysis. Malondialdehyde (MDA) and total glutathione (tGSH) levels, as well as superoxide dismutase (SOD) activity were evaluated in the heart tissue.

Results: The CIPRO group showed histopathological abnormalities such as infiltration and interstitial oedema. In the NRG+CIPRO group, infiltration was significantly reduced. In the NRG group, SOD activity greatly increased, while in the NRG+CIPRO group, tGSH level significantly increased. The control, CIPRO, and NRG+CIPRO groups showed significantly higher systolic and mean BP measurements than the NRG group. In comparison to the CIPRO and control groups, the QT interval was longer in the NRG group.

Conclusion: NRG can reduce CIPRO-induced cardiac damage in rats by increasing antioxidant enzymes and decreasing oxidative stress. With our histopathological evaluation, we have shown that CIPRO-induced cardiotoxicity may be ameliorated by pretreatment with NRG. NRG may also be effective in BP regulation. It should be kept in mind it is important to use NRG with caution and at appropriate doses, as it may prolong the QT interval.

Keywords: Cardiotoxicity, ciprofloxacin, naringenin, oxidative stress, rat

INTRODUCTION

Ciprofloxacin (CIPRO) is a fluoroquinolone group antibiotic with a wide range of antibacterial effects (1). Fluoroquinolones can cause a prolongation of QT interval and Torsades de Pointes (TdP). It is known that CIPRO, one of this group of antibiotics, may also prolong QT and cause TdP (2). CIPRO can cause cardiomyocyte damage by increasing oxidative stress and inflammation (3). In the previous experimental studies, it was found that oxidative stress and inflammation-related cardiotoxicity can be induced in rats by various drugs such as isoproterenol, doxorubicin, etc. (4,5).

Citrus fruits, tomato, strawberry, grapefruit, and chocolate are among the foods that contain the flavonoid component naringenin (NRG), also known as 4′,5,7-Trihydroxyflavanone. NRG has been demonstrated to have antitumor, antiinflammatory, anticarcinogenic, antiatherogenic, hepatoprotective,

nephroprotective, and antimutagenic properties (6). It has also been reported that NRG has antioxidant, antiulcer and antiproliferative properties (7).

The effect of NRG on different cardiotoxicity models has been investigated. In a study investigating the effects of various flavonoids on daunorubicin-induced cardiotoxicity, NRG was found to be the most effective compound after quercetin (8). It was also found to have protective effects on cardiac tissue in doxorubicin (DOX)-induced cardiotoxicity (9).

Oxidative stress is the disruption of the balance between oxidants and antioxidants in favour of the oxidant system. It is the formation of cellular damage in the organism as a result of lipid peroxidation and the release of free radical/reactive oxygen products. If the defence mechanisms of the organism against oxidative stress are insufficient, oxidative damage develops in cells, and cell functions are significantly disrupted. Oxidative stress, which is essential in the pathogenesis of many diseases, has a major effect on the etiology of cardiovascular (CV) disease (10,11).

Since NRG is known to exert antioxidant, antiinflammatory, and cardioprotective activities, the current study was planned to investigate the effectiveness of NRG in a rat model of CIPRO-induced cardiotoxicity.

MATERIAL AND METHODS

A total of thirty-two adult male Sprague-Dawley rats weighing between 350 and 450 g were obtained from the Experimental Animal Production and Research Center at Inonu University. To rule out any infection, the rats were observed for 15 days before to the experiments. The rats were kept in stainless steel-topped ventilated polypropylene cages with a standard air temperature of 25±0.5°C and a 12-hour light cycle. Every day, rats were given access to a regular food that was appropriately balanced. The Inonu University Experimental Animals Ethics Committee's advice and directives were followed throughout all procedures (Ethical Approval Number: 2017/A-20).

Thirty-two male Sprague-Dawley rats aged 10 months were divided into four groups in a simple randomised method.

1. Control Group; The group in which no medication was administered and only vehicle solution was administered (n=8),
2. CIPRO Group; 50 mg/kg CIPRO was administered intraperitoneally (i.p.) twice a day at 12-hour intervals for 7 days (n=8),
3. NRG Group; The group in which rats were sacrificed on the 29th day after oral administration of 25 mg/kg NRG for 28 days (n=8)
4. NRG+CIPRO Group; 25 mg/kg NRG was administered orally for 28 days, 50 mg/kg CIPRO was administered i.p. twice a day at 12-hour intervals for one week starting from the 22nd day and the rats were sacrificed on the 29th day (n=8).

Previous studies have been referenced in the selection of the dose, route of administration and dosage intervals of NRG (3,11). Before the experiment, under the 75 mg/kg ketamine (Ketasol %10; Richter Pharma Ag, Wels, Austria) and 5 mg/kg xylazine (XylazinBio %2, Bioveta PLC, Ivanovice na Hane, Czech Republic) anesthesia, blood pressure (BP) recordings of the systolic, diastolic, and mean were taken using a cannula placed into the carotid artery. In addition, heart rate (HR) and electrocardiography (ECG) (number and variety of arrhythmias) analysis were recorded. Antioxidant enzymes and oxidative stress markers were assayed by biochemical analyses from heart tissue obtained at the end of the study. Histopathological evaluations of heart and vascular (descending aorta) tissues were performed under light microscope.

Biochemical Analysis

Preparation of tissue homogenates

The heart tissues were weighed 100±10 mg and transferred to Eppendorf tubes. Afterward, 1 mL of ice-cold phosphate-buffered saline (PBS, 50 mM, pH 7.4) was added to the tubes. The weighed tissues were then homogenized under ice isolation with the help of an Ultra Turrax T25 basic homogenizer (IKA Labortechnik; IKA-Werke, Staufen, Germany). Following, the obtained homogenates were then sonicated 4 times for 15 sec with a sonicator (Bandelin Sonopuls HD 2070 ultrasonic homogenizer) under ice isolation, at 30-sec intervals. After that, the tissue homogenates were centrifuged at 14000 rpm for 15 min at +4ºC with the help of a refrigerated centrifuge (Hettich Universal 320R, Germany). Supernatants were transferred into Eppendorf tubes and stored at +4ºC for further biochemical analysis.

Malondialdehyde (MDA) Analysis

MDA measurement was determined using the method previously reported in the literature (12). The basis of the method is based on the measurement of the pink colored product formed as a result of the reaction of MDA, which is the breakdown product of peroxide lipids, with thiobarbituric acid (TBA) at 532 nm using a microplate reader (BioTek Instruments, USA). MDA concentrations were determined using this graph and expressed as nmol/mg protein using a standard graph created with 1,1,3,3 tetramethoxypropane,

Total Glutathione (tGSH) Analysis

tGSH was calculated using the Ellman method (13). The method is based on the spectrophotometric measurement of the increase in the formation of 5-thio-2-nitrobenzoate (TNB) resulting from the reaction of 5,5-dithio-bis-(2-nitrobenzoic acid) (DTNB), nicotinamide adenine dinucleotide phosphate (NADPH), and glutathione reductase. The absorption measurements were monitored at 412 nm using a microplate reader (BioTek Instruments, USA). Utilizing the glutathione standard graph for analysis, the findings were reported as nmol/mg protein.

Superoxide Dismutase (SOD) Analysis

The activity determination of the SOD enzyme was made according to the method previously mentioned in the literature (14). The SOD enzyme prevents superoxide radicals formed in the xanthine/xanthine oxidase system from reducing cytochrome C. The activity of the SOD enzyme is based on the measurement of this inhibition. The amount of SOD that inhibits this reaction by 50% was defined as 1 unit (U). SOD enzymatic activity was measured by kinetics at 550 nm using a microplate reader (BioTek Instruments, USA). U/mg protein was used to express the enzyme activity.

Protein Determination

Using bovine serum albumin as a reference, the protein content in tissue was assessed using the Bradford method (15).

Histopathological Analysis

The heart and vascular (descending aorta) tissues were obtained and preserved in 10% formaldehyde. Following the tissue processing and paraffin embedding tissue, sections 4-5 µm thick were cut from the paraffin blocks. Then the sections were stained with hematoxylin–eosin for histopathological evaluations.

Heart specimens were assessed for congestion, interstitial edema, and inflammatory cell infiltration. Ten randomly selected fields were inspected and the areas were scored agreeing to the degree of histological changes; 0: no change, 1: mild, 2: moderate, 3: severe change. Within the evaluation for the vessel, the entire region was inspected and degenerative changes in muscle cells (myofibril loss, pyknotic nucleus) were scored as 0: no change, 1: mild, 2: moderate, 3: severe changes. Analyzes were performed utilizing Leica DFC-280 investigative magnifying lens and Leica Q Win Picture Investigation Framework (Leica Micros Imaging Arrangements Ltd., Cambridge, UK).

Statistical Analysis

The Inonu University School of Medicine's Department of Biostatistics and Medical Informatics' statistical software package was used to conduct the statistical analysis. A normality test found that the measurable variables for all groups in the study were not normally distributed. Therefore, one of the nonparametric tests, Kruskal-Wallis, was used for the general comparison of groups on all variables. Using the Mann-Whitney U test, between-group comparisons were done. A statistically significant level of $p<0.05$ was used. According to the distribution, data were reported as the median (minimum-maximum) (16).

RESULTS

Rat Body and Heart Weights

All of the groups of rats had similar body and heart weights. There was no statistically significant difference between the groups ($p>0.05$) Table 1).

Table 1. Body and heart weights of rats at the end of the experiment

Groups	Rat weight (g)	Heart weight (g)
Control	430 (367-487)	1.49 (1.22-1.60)
CIPRO	450 (371-502)	1.60 (1.32-2.06)
NRG	466 (380-515)	1.66 (1.35-1.98)
NRG+CIPRO	448 (337-517)	1.58 (1.22-1.69)

There was no statistically significant difference between the groups ($p>0.05$)

Electrocardiogram and Hemodynamic Results

The control, CIPRO, and NRG+CIPRO groups had statistically significantly higher systolic and mean BP measurements than the NRG group ($p<0.05$). PR and QRS intervals were similar in all groups ($p>0.05$). In comparison to the NRG group, the QT distance was significantly different between the control and CIPRO groups. The QT interval was longer in the NRG group than in the CIPRO and control groups ($p<0.05$). Table 2 shows that there was no difference between the groups in HR, PR and QRS intervals were analyzed. ST depression was observed in two rats, T negativity in one rat,

Table 2. Heart rate, blood pressures and PR, QRS and QT intervals

Groups	HR (beats/min)	Systolic BP (mmHg)	Diastolic BP (mmHg)	Mean BP (mmHg)	PR (ms)	QRS (ms)	QT (ms)
Control	268 (182-320)	119 (93-142)[a]	67 (55-88)	89 (69-108)[a]	34 (30-40)	89 (78-122)	140 (124-154)[a]
CIPRO	270 (222-322)	121(93-140)[a]	70 (46-88)	89 (63-106)[a]	36 (34-44)	91 (80-112)	136 (124-150)[a]
NRG	223 (140-360)	87 (67-122)	47 (35-77)	65 (49-98)	40 (38-44)	102 (8-134)	158 (128-182)
NRG+CIPRO	235 (180-320)	121 (94-133)[a]	71 (55-74)	91 (70-96)[a]	38 (34-42)	95 (86-120)	141 (120-160)

a: there is a statistically significant difference compared to the NRG group ($p<0.05$)
HR: heart rate, BP: blood pressure

and branch block in one rat in the CIPRO group. Branch block was observed in three rats in the NRG group and ST depression was also present in two rats in the NRG+CIPRO group (Table 3).

Table 3. ECG changes at the end of the experiment

Groups	n	Arrhythmia	ST depression	T negativity	Block
Control	8	0	0	1	1
CIPRO	8	0	2	1	1
NRG	8	0	1	0	3
NRG+CIPRO	8	0	2	0	1

Tissue Biochemical Findings

The levels of SOD, MDA, and tGSH in the heart tissue for the control, CIPRO, NRG, and NRG+CIPRO groups are presented in the Table 4. SOD, MDA, and tGSH levels in the cardiac tissues of rats exposed to CIPRO did not differ statistically from the control group ($p>0.05$). However, compared to the CIPRO group, NRG administration alone led to a statistically significant elevation in SOD and MDA levels in heart tissue compared to CIPRO and NRG+CIPRO groups ($p<0.05$). However, NRG administration had no statistically significant impact on tGSH levels ($p>0.05$). Comparing the NRG+CIPRO treatment to the control and CIPRO groups, SOD and MDA levels did not differ noticeably, ($p>0.05$) although tGSH levels did ($p<0.05$).

Table 4. Heart tissue SOD, MDA and tGSH results

Groups	Superoxide dismutase (U/mg protein)	Malondialdehyde (nmol/mg protein)	Total glutathione (nmol/mg protein)
Control	56.07 (51.22-62.56)	0.051 (0.05-0.06)	7.50 (6.78-8.25)[b]
CIPRO	56.22 (46.95-58.93)	0.05 (0.04-0.06)	7.53 (6.99-10.70)
NRG	65.38 (53.12-87.44)[a,b]	0.07 (0.05-0.11)[a,b]	7.03 (5.08-7.83)[b]
NRG+CIPRO	53.38 (49.75-61.64)	0.05 (0.04-0.06)	10.06 (6.40-12.01)

a: there is a statistically significant difference compared to the CIPRO group ($p<0.05$)
b: there is a statistically significant difference compared to the NRG+CIPRO group ($p<0.05$)

Histopathological Findings

Heart

Myocardium was evaluated for congestion, interstitial edema, and inflammatory cell infiltration. In the control and NRG groups, the myocardium had a normal histological appearance except for congestion (Figure 1A, 1B, 1C, 1D). On the other hand, interstitial edema and inflammatory cell infiltration were observed in the CIPRO group. (Figure 1E, 1F) The congestion observed in the CIPRO group was similar to the control group. However, edema and infiltration were statistically significantly increased in the CIPRO group compared to the control group (Figure 1E, 1F) ($p<0.05$). Congestion and interstitial edema persisted in the NRG+CIPRO group similarly to the CIPRO group ($p>0.05$). On the other hand, the NRG+CIPRO group's myocardium showed no signs of infiltration. The difference in infiltration between the CIPRO and the other groups was statistically significant (Figure 1G, 1H). Table 5 lists the findings of the histological assessment of the myocardium.

Descending Aorta

In all groups, the descending aorta showed a normal histological appearance except for mild myofibril loss in some muscle cells (Figure 2). The results of the histopathological evaluation of the descending aorta are given in Table 6.

Table 5. Histopathological evaluation results for myocardium

Groups	Congestion	Interstitial edema	Infiltration
Control	0.0 (0.0-2.0)	0.0 (0.0-1.0)	0.0 (0.0-0.0)[b]
CIPRO	1.0 (0.0-2.0)	0.0 (0.0-3.0)[a,c]	0.0 (0.0-3.0)
NRG	1.0 (0.0-2.0)	0.0 (0.0-1.0)	0.0 (0.0-0.0)[b]
NRG+CIPRO	0.0 (0.0-2.0)	0.0 (0.0-3.0)[a,c]	0.0 (0.0-0.0)[b]

a: significant increase compared to the control group ($p<0.05$)
b: significant decrease compared to the CIPRO group ($p<0.05$)
c: significant increase compared to the NRG group ($p<0.05$)

Table 6. Histopathological evaluation results for the descending aorta

Groups	Vascular muscle cell degeneration
Control	0.0 (0.0-1.0)
CIPRO	0.0 (0.0-1.0)
NRG	0.0 (0.0-1.0)
NRG+CIPRO	0.0 (0.0-1.0)

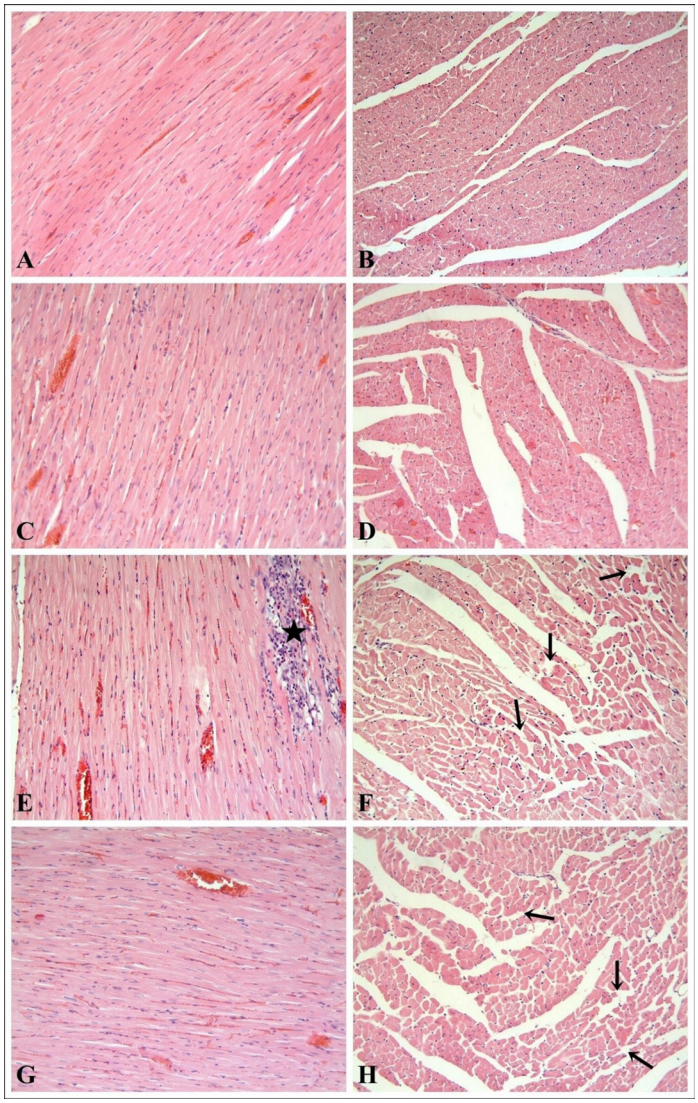

Figure 1. The appearance of myocardium in the control **(1A, 1B)** and NRG **(1C, 1D)** groups. In the CIPRO **(1E** and **1F)** group, infiltration (**1E**, star) and interstitial edema (**1F**, arrows) are observed between cardiomyocytes. It is noteworthy that in the NRG+CIPRO (**1G**) group no infiltration is observed. On the other hand edema (arrows) in the NRG+CIPRO group is observed as similar to the CIPRO group. H-E; x20

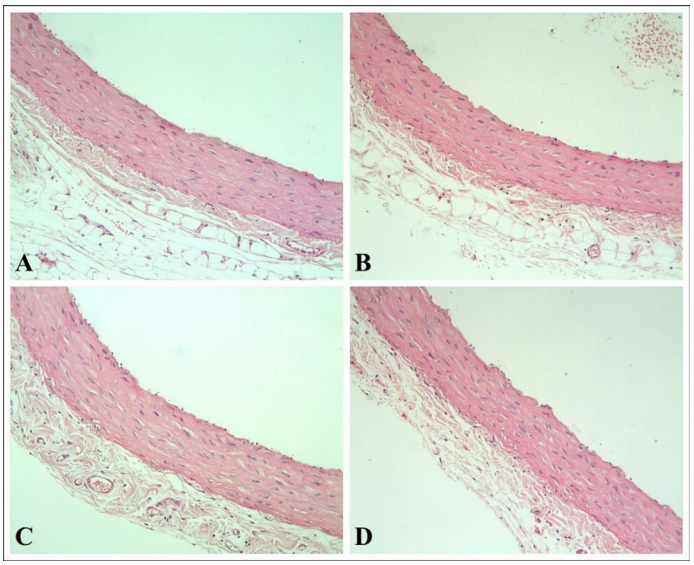

Figure 2. It was observed that the vessel wall has a similar histological appearance in the control (**2A**), NRG (**2B**), CIPRO (**2C**) and NRG+CIPRO (**2D**) groups

DISCUSSION

In the current study, we noticed that the NRG-treated groups had higher SOD and to tGSH activity. In terms of lipid peroxidation, we did not notice a similar beneficial effect. Only in the group receiving NRG treatment did systolic and mean BP considerably reduced. The fact that the QT interval was much longer in the NRG group than in the CIPRO and control groups is one of the study's most remarkable findings.

CIPRO is an antibiotic in the quinolone group with broad antimicrobial activity. It may have side effects on the CV system such as arrhythmia, cardiotoxicity, and increased vascular permeability. The QT interval may be prolonged and the risk of TdP may increase with CIPRO (2).

NRG is a flavonoid that is a member of the isoflavonoid subclass and is typically found in citrus and grapes (17). Antiviral, antibacterial, antiinflammatory, and antioxidant activities are all present in NRG. For this reason, previous studies have been conducted to investigate its protective effect against CV diseases (18). Reactive oxygen species (ROS) and lipid peroxidation are decreased by NRG. By inhibiting apoptosis, it is crucial in lowering cardiac toxicity (19). The activities of endogenous antioxidants such as SOD, glutathione peroxidase (GPx), catalase (CAT), and GSH have been demonstrated to be increased by NRG (20).

In the present study, we did not observe any prolongation of the QT interval in rats treated with CIPRO. However, we observed a significant prolongation of the QT interval in the NRG group compared to the CIPRO and control groups. Antibiotics from the fluoroquinolone group block the delayed regulatory potassium current's fast component in a dose-dependent manner, which can lead to QT prolongation and TdP. Even though QT prolongation seems to be a class effect, there are variations

among class members (21,22). Prolongation of the QT interval by fluoroquinolones is possible, but contributing underlying factors must be considered. In an animal study, CIPRO and levofloxacin were administered to rats with and without isoproterenol-induced acute myocardial dysfunction and their effects on cardiac tissue were studied. The administering of the two antibiotics caused dose-dependent alterations in ECG parameters, according to the study's findings. These alterations were found to be more evident in rats with acute myocardial infarction (MI) (23).

There is also a contrary finding on the effect of CIPRO on QT interval. CIPRO has been reported to be one of the safest fluoroquinolones in terms of the risk of prolonging the QT interval and causing TdP (18). Again, in a study conducted in intensive care unit patients, no clinically significant QT prolongation or increased risk of TdP was observed with CIPRO (24). In fact, from 2004 to 2008, the FDA Adverse Event Reporting System declared CIPRO as the least likely antibacterial agent to induce TdP (25).

Studies regarding the effect of NRG on ECG records are limited. In a study investigating the effect of flavonoids on cardiac electrophysiology, it was reported that flavonoids prolonged corrected QT (QTc) in healthy volunteers as a result of the blockade of the human ether-a-go-go related gene (hERG) channels (26). In another study, it was reported that pink grapefruit juice prolonged cardiac repolarization and prolonged the QTc by inhibiting the fast component of the delayed rectifier K^+ current, possibly due to its high NRG content (27).

NRG may reduce BP and improve obesity-related hypertension by regulating lipid dysregulation and oxidative stress (28). The haemodynamic results of our study also showed that NRG may have a regulatory effect on BP. According to our results, in the NRG group, systolic and mean BP were lower than in all other groups.

In this study, SOD activity was increased in the NRG group and tGSH was increased in the NRG+CIPRO group. However, the MDA level indicating lipid peroxidation was higher in the NRG group. Thus, while NRG increased endogenous antioxidant levels, it also increased lipid peroxidation. In general, NRG is known to reduce oxidative stress. Additionally, NRG may increase the activity of enzymes that inhibit lipid peroxidation. However, the effects of NRG on lipid peroxidation may exert variability according to cell type, selected dose regimen, and study conditions (29).

The enzymatic activities (SOD and CAT etc.), and tGSH, form the basic defense system in cells and play important roles against diseases caused by oxidative damage (30). MDA, one of the end product of lipid peroxidation, is not a specific or quantitative index of fatty acid oxidation however it correlates well with the degree of lipid peroxidation. It has been evaluated in vivo and in vitro to measure the level of oxidative stress (31). Excessive MDA production has been associated with pathological conditions such as CV diseases as an indicator of oxidative stress (32).

In this study pretreatment with NRG led to a statistically significant elevation in SOD enzyme levels. The ability of NRG to chelate metals may be the cause of this increase. SOD enzyme cofactors include cupper and zinc. The SOD level may have increased because of the chelation of NRG with these metals. SOD levels in the NRG+CIPRO treatment group were similar in the control group. Both medications may produce myocardiotoxicity by causing oxidative stress, according to a study comparing the myocardiotoxic impact potential of CIPRO and ofloxacin in rats. Once more, it was noted that ofloxacin caused more toxicity then CIPRO. The MDA levels in the low-dose group and the control group did not significantly different (3). In the present study, MDA levels in the CIPRO and NRG+CIPRO groups did not differ significantly from the control group. Jijie et al. studied the effects of CIPRO on oxidative stress in zebrafish and found that the MDA level of the CIPRO group did not differ markedly from the control group, which is consistent with our findings (33). Even though the MDA level of the NRG group noticeably increased, the mechanism causing this increase is not entirely understood.

Pretreatment with NRG promoted activation of the extracellular signal-regulated kinase 1/2 (ERK1/2)/nuclear factor erythroid 2–related factor 2 (NRF2)/NAD(P)H quinone dehydrogenase 1 (NQO1) pathway in rats with DOX-induced cardiotoxicity. As a result, it shielded the heart tissue from oxidative stress brought on by DOX (34). An antioxidant modulator NRF2 and NRG have been linked in a recent experimental study. NRG was found to have a protective effect against DOX-inducedcardiotoxicity (35). Another possibility is that NRG can bind with iron ions by blocking the iron-dependent Fenton process, which would lower the production of hydroxyl radicals. This property protects the cell from attacks by free radicals and prevents lipid peroxidation. Studies show that NRG increases the activities of SOD, CAT, and GPx, in rats exposed to cadmium and, through its antioxidant structure, preserves cells against ROS in the environment and cell death (36).

In the current study, it was observed that exposure to CIPRO alone did not cause a significant oxidative stress response in the heart tissue. As seen in the Table 4, no significant change in SOD level was observed. This is probably due to the inability of CIPRO to induce antioxidant enzymes and the different physiological characteristics of the tissues. Consistent with our results, Jijie et al. reported that the SOD level of the CIPRO group did not change significantly compared with the control group (33). In another study, CIPRO administered to male rats at 80 mg/kg/day did not significantly change the SOD level in liver and kidney tissue compared with control rats (37).

In this study, the myocardium had a normal histological appearance in the control and NRG groups. Interstitial edema

and inflammatory cell infiltration were increased in the myocardial tissue in the CIPRO group. The level of congestion in the CIPRO group was similar to the control group, but edema and infiltration were significantly increased compared with the control group. In the NRG+CIPRO group, congestion and interstitial edema persisted similarly to the CIPRO group. On the other hand, no signs of myocardial infiltration were observed in the NRG+CIPRO group. Infiltration was significantly reduced in the group pretreated with NRG. This result indicates that NRG may be a protective agent against CIPRO-induced cardiac damage. In previous studies, administration of NRG together with DOX improved biomarkers indicating cardiac damage. It has also been reported to decrease inflammation markers such as tumor necrosis factor alpha, interleukin-6, and interleukin-10. Thus, it has been shown histopathologically that pretreatment with NRG supplementation may be beneficial in reducing DOX toxicity (9). In another study, NRG was shown to inhibit apoptosis of cardiomyocyte cells in vitro on daunorubicin-induced cytotoxicity (8). In the DOX-induced cardiotoxicity model, morphological damage of the cells was attenuated in the NRG+DOX-treated groups compared to the DOX group. With these results, it was shown that NRG may protect cardiomyocytes from DOX-induced toxicity by stabilizing the cell membrane and reducing ROS generation (38). Finally, CIPRO further increased the hereditary defect in aortic elastic fibers and accelerated aortic root dilatation in Marfan mice. Although studies are emphasizing that this circumstance may increase the incidence of aortic dissection and rupture, (39) in this study, the descending aorta in all groups showed a normal histological appearance except for mild myofibril loss in some muscle cells. It was thought that further studies are needed to understand the effect on vascular structure.

CONCLUSION

NRG, which is known to have antioxidant, antiinflammatory, and antiapoptotic properties, has a cardioprotective effect in CIPRO-induced cardiac injury. We found that NRG decreased CIPRO-induced oxidative stress by increasing intracellular antioxidant enzymes rather than inhibiting lipid peroxidation. Histopathological evaluation showed that CIPRO-induced cardiotoxicity could be improved by pretreatment with NRG. We also observed that it was beneficial in BP regulation. Considering that the QT interval may be prolonged with NRG, it can be said that it is important to use it carefully and at appropriate doses.

Conflict of Interests: The authors declare that there are no conflict of interests.

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Ethics committee approval: Ethics committee approval was obtained Inonu University Experimental Animals Ethics Committee (Ethical Approval Number: 2017/A-20).

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