Available online at www.medicinescience.org

ORIGINAL ARTICLE

Medicine Science International Medical Journal

Medicine Science 2023;12(2):579-86

Effects of mirtazapine on cisplatin cardiotoxicity in rats

Onural Ozhan[1], Zeynep Ulutas[2], Seray Serduman[1], Leyla Sahin Buyukkorkmaz[1], Azibe Yildiz[3], Ahmet Ulu[4], Nigar Vardi[3], Burhan Ates[4], Hakan Parlakpinar[1]

[1]*Inonu University, Faculty of Medicine, Department of Pharmacology, Malatya, Türkiye*
[2]*Inonu University, Faculty of Medicine, Department of Cardiology, Malatya, Türkiye*
[3]*Inonu University, Faculty of Medicine, Department of Histology and Embryology, Malatya, Türkiye*
[4]*Inonu University, Faculty of Science, Department of Chemistry, Malatya, Türkiye*

Received 06 March 2023; Accepted 26 May 2023
Available online .05.2023 with doi: 10.5455/medscience.2023.02.030

Abstract

Atypical antidepressant mirtazapine (MIR) is primarily used to treat major depressive disorder. It has not been clarified whether cardiovascular uncertainties and mechanisms of action emerge as problems during the use of mirtazapine. Cisplatin (CIS) is an effective anti-cancer medication used to treat a variety of human malignancies. There were four groups of 32 *Wistar albino* male rats in all. Rats were split into 4 groups at random. 1. Control Group, 2. CIS Group, 3. MIR Group, 4. MIR+CIS Group. On the 15th day of the study, ECG, heart rate, and blood pressure were determined. Histopathological and biochemical analyses were carried out on cardiac and vascular tissue samples. Comparing the CIS group to the other groups, blood pressure was considerably lower in the CIS group ($p<0.05$). In vascular tissue examination, catalase and superoxide dismutase levels were substantially higher in the control, MIR, and MIR+CIS groups, similar to those of the myocardium, compared to the CIS group ($p<0.05$). While the CIS group had the highest malondialdehyde level, it was much lower in all other groups in both myocardial and vascular tissue ($p<0.05$). It was observed that the congestion persisted, but the interstitial edema's intensity was much less severe in the MIR+CIS group than in the CIS group ($p=0.009$). We sought to clarify the function of the oxidative system, tissue-level histological alterations, the possibility that mirtazapine protects against CIS cardiotoxicity, and the role of MIR in cardio-oncology in this study. In this study, we demonstrated the possible protective effect of MIR in CIS-mediated cardiotoxicity and its antioxidant effect mechanism.

Keywords: Mirtazapine, cisplatin, cardiotoxicity, oxidative stress, rat

Introduction

Mirtazapine (MIR) is a sedative, anti-emetic, anxiolytic, and appetite-stimulating effect that is also used in diseases such as generalized anxiety disorder, insomnia, social anxiety disorder, panic disorder, post-traumatic stress disorder, obsessive-compulsive disorder, and migraine [1]. However, when using mirtazapine as an anti-depressant, its effects on cardiac and hemodynamic parameters are not known exactly.

Cisplatin (CIS) has a strong anti-tumor effect, but adverse reactions like nephrotoxicity, neurotoxicity, ototoxicity, and hepatotoxicity limit its clinical use. CIS, one of the platinum-containing chemotherapy agents, can cause vascular diseases such as vasospasm, myocardial infarction, arterial and venous thrombosis [2]. Less frequently, it may lead to myocardial dysfunction and heart failure (HF).

While oxidative stress is a major factor in all of these CIS side effects, apoptosis is also important. In addition, a direct cytotoxic effect on cardiac myocytes has been reported in CIS cardiotoxicity [3,4].

CITATION
Ozhan O, Ulutas Z, Serduman S, et al. Effects of mirtazapine on cisplatin cardiotoxicity in rats. Med Science. 2023;12(2):579-86.

Corresponding Author: Onural Ozhan, Inonu University, Faculty of Medicine, Department of Pharmacology, Malatya, Türkiye
Email: onural.ozhan@inonu.edu.tr

DOI: 10.5455/medscience.2023.02.030

There are experimental studies on the effect of MIR on CIS toxicity. It has been shown that MIR may have protective effects against oxidative stress and DNA damage in rats with CIS neurotoxicity [5]. In another study, the anticancer effect of MIR was investigated and compared with CIS. In adenocarcinoma-developed rats, MIR inhibited adenocarcinoma induction more than CIS [6].

The pathophysiological mechanisms underlying depression and cardiovascular diseases are highly intertwined. Depression is a prevalent condition in ischemic heart disease patients, and depressed patients seem to be more likely to have major cardiac events [7]. Considering the frequent comorbidity of these two diseases and the wide variety and serious cardiovascular side effects of anti-depressants, a better safety profile is warranted.

The goal of this study was to identify the cardioprotective effects of MIR on CIS-induced cardiotoxicity in rats and the role of the oxidative system.

Material and Methods

The approval of Inonu University Experimental Animals Ethics Committee was obtained (2016/A-46) before the initiation of this research. The number of rats to be included in each experimental group was determined by power analysis. When the effect size was estimated as 0.7434 in the comparison of four groups according to biochemical variables, the minimum number of samples that should be included in the study at the 90% power and 95% confidence level was calculated as 8 per group (n:8). In the experiment, 8 animals that were randomly selected with the same biological and physiological characteristics were grown in Inonu University Experimental Animals Research Unit and kept inside standard laboratory conditions (22±10C, 60% humidity, 12 hours light/12 hours dark cycle) and fed ad libitum.

A total of 32 *Wistar albino* male rats consisting of four groups were used. Stripped away animal waste, provided water and food, and sanitized control of cages were done by the veterinarian and staff of the center. The current study was carried out as a multi-disciplinary study with the contributions of the experimental animals unit, department of cardiology, department of pharmacology, department of histology and embryology, and department of biochemistry within the body of Inonu University Faculty of Medicine.

Formation of Experimental Groups and Drug Administration

Wistar albino male rats were assigned to four distinct groups (n=8) randomly.

1.Control Group: The group in which vehicle solutions were administered for 14 days

2.CIS Group: On the 11th day of the experiment, 7 mg/kg of CIS was administered intraperitoneally (i.p.) single dose group

3.MIR Group: The group in which 30 mg/kg MIR was administered orally daily for a total of 14 days once

4.MIR+CIS Group: The group in which 30 mg/kg MIR was administered orally once a day for 14 days. On the 11th day of administration, 7 mg/kg of CIS was administered as a single dose i.p.

On the 15th day of the study, carotid artery cannulation was performed on rats under anesthesia. Electrocardiogram (ECG), heart rate, and blood pressure were determined by connecting chest ECG electrodes. After the recording procedures were completed, cardiac and vascular tissue samples were collected, and histopathological and biochemical evaluations were carried out.

The quickly removed heart tissue was sectioned on cold glass. Blood serum was obtained after centrifuging blood samples at 3000 rpm for 20 minutes at +4°C. The tissue and serum samples were kept at -80°C.

Biochemical Analysis Method

Malondialdehyde Analysis (MDA)

MDA, employed as an indicator of lipid peroxidation, was prepared using the Mihara and Uchiyama method [8]. The rat tissue sample was homogenized in 1.15% KCl solution for 1 minute on ice at 15000 rpm. The MDA analysis used this homogenate directly.

Test tubes were used to hold the prepared solutions, mixed thoroughly, and placed in boiling water (at least 95 ^{o}C) for 1 hour. The tubes were added with 2 mL of n-butanol and mixed thoroughly for 5 minutes. Then the samples were centrifuged at 3000xg for 10 minutes. The absorbances of the samples were measured in the spectrophotometer at 535 nm and 520 nm, MDA concentrations were calculated using a standard graph prepared with 1,1',3,3'tetramethoxypropane, and the results were reported as nmol/mg protein.

Glutathione Analysis (GSH)

Ellman's approach was employed for determining GSH [9]. The rat tissue sample was homogenized on ice to form 10% homogenate at 15000 rpm for 1–2 minutes. After that, the homogenate was centrifuged for 15 minutes at +4^{o}C at 3000 rpm. Trichloroacetic acid solution was added to the collected supernatant, mixed, and centrifuged one more to get the sample ready for GSH analysis. The prepared solutions were poured into the test tubes and properly mixed. After 5 minutes, the color concentration was measured at 410 nm using a spectrophotometer. The findings were calculated using the glutathione standard graph and permitted to be expressed as nmol/mg protein.

Copper-Zinc Superoxide Dismutase Analysis (Cu–Zn–SOD)

The method of Sun et al. was used to assess tissue SOD activity [10]. The rat tissue sample was homogenized on ice for 1 minute at 15000 rpm to create a 10% homogenate. This homogenate was centrifuged at 10000 rpm for 20 minutes. On this supernatant, the prepared chloroform/ethanol mixture (3 parts chloroform/5 parts ethanol) was added in a ratio of 3 to 5. After that, the samples were

DOI: 10.5455/medscience.2023.02.030

centrifuged at +4°C for 20 minutes at 5000 rpm. The CuZn-SOD analysis was performed using the clear, white chloroform that was carefully pipetted from the mixture's surface. The prepared test tubes were left in an incubator at a temperature of 25°C for 20 minutes. Each tube received 1 mL of CuC_{12} after the time interval, and the reaction was stopped when the concentration reached 0.8 mmol/L. The spectrophotometer was calibrated with distilled water after being set to a wavelength of 560 nm at the appropriate setting. The enzyme activity was calculated after recording the absorbance of the blanks and samples. Units of enzyme activity were calculated per mg of protein.

Protein Determination

Biuret protein analysis, with bovine serum albumin serving as the standard, was used to determine the amount of protein in the tissue [11].

Catalase Analysis (CAT)

According to Luck's method, CAT activity in tissue was analyzed and measured [12]. To produce a homogenate with a concentration of 10%, the sample of rat tissue was homogenized on ice for one minute at a speed of 15000 revolutions per minute. The supernatant from this homogenate was taken for CAT analysis after centrifuging it for 20 minutes at a speed of 10000 rpm. The absorbance was completely blindly set to zero and the spectrophotometer was set to 240 nm. As soon as possible after adding the supernatant to the sample tubes, the absorbance at 240 nm was determined. After that, a reading was taken every 15 seconds for the next 90 seconds to track how much the absorbance dropped. After the period, the absorbance value that was read was recorded. We considered the period during which there was a linear decrease in absorbance. The enzyme activity was expressed as U/mg protein.

Histological Analysis Method

After the study, the cardiac and vascular tissues were fixed in formaldehyde at a concentration of 10%. After the tissue follow-up procedures, paraffin blocks were prepared. These blocks were sliced into sections with a thickness of 4–5 micrometers. To investigate the overall morphological structure, sections were stained with a hematoxylin-eosin mixture before being examined.

In the evaluation for the heart, ten randomly selected areas were examined at x20 magnification and according to the severity of histological changes (congestion and interstitial edema) as 0: no change, 1: mild, 2: moderate, 3: severe change.

In the evaluation of the aorta, the whole area was examined on three separate sections for each sample. The histological changes observed in the vessel wall (myofibril loss in muscle cells, thinning and rupture of elastic lamellae) were scored as 0: no change, 1: mild, 2: moderate, and 3: severe change. In addition, tunica intima-media (TIM) thickness was measured by randomly selecting ten areas from each section.

Analyzes were performed using the Leica Q Win Image Analysis System (Leica Micros Imaging Solutions Ltd., Cambridge, UK) with a Leica DFC-280 research microscope.

Statistical Analysis

IBM SPSS (SPSS for Windows version 26, SPSS Inc., Chicago, IL) statistical software program was used for rat heart and body weights, hemodynamics, tissue and serum biochemical analysis, and histological analysis. Comparison between groups was performed via the ANOVA-Post Hoc Tukey test for normally distributed data and for data not normally distributed, the Kruskal-Wallis H test was used. Data were expressed as median (minimum-maximum) or arithmetic mean±standard deviation, depending on the distribution. A p-value of <0.05 was considered significant.

Results

Body and Heart Weights of Rats

There was no substantial difference in the heart weights of the rats after the experiment had been completed. The weights of the rats that were measured at the beginning of the experiment did not substantially differ from one another; however, the weight of the rats in the CIS group at the end of the experiment was substantially lower than the weight of the rats in the control group. Again it was determined that the weight of the MIR+CIS group was substantially lower than that of the MIR group (Table 1).

Table 1. Body and heart weights of rats

	Heart weight (g)	Rat weight before the experiment (g)	Rat weight after the experiment (g)
Control Group	1.27 ± 0.72	408.6 ± 24.2	422.8 ± 26.5[a]
CIS Group	1.2363±0.12	383.5±46.4	348.0±48.4[b]
MIR Group	1.2138±0.17	402.0±37.4	389.5±20.3[c]
MIR+CIS Group	1.1363±0.14	364.8±53.1	319.1±37.3

a: There is a statistically significant difference compared to the CIS group ($p<0.05$). b: There is a statistically significant difference compared to the MIR group ($p<0.05$). c: There is a statistically significant difference compared to the MIR+CIS group ($p<0.05$)

Hemodynamic Findings

In terms of heart rate, there was no statistically important difference between the two groups that participated in the experiment. The CIS group had substantially lower systolic blood pressure, diastolic blood pressure, and mean blood pressure when compared to all of the other groups. Each group had a PR interval that wasn't comparable to the others that is, this interval was similar for each group. The MIR+CIS group exhibited a QRS distance that was much greater than the CIS group as compared to the CIS group (Table 2).

In the control group, none of the abnormal heart rhythms of arrhythmia, ST depression, T negativity, or block were seen. One of the rats in the CIS group exhibited block behavior. One of the rats in the MIR group exhibited a T-negativity. Two of the rats in the MIR+CIS group exhibited ST depression, and two of the rats exhibited block (Table 3).

DOI: 10.5455/medscience.2023.02.030

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

	Heart Rate (beats/min)	Systolic Blood Pressure (mm-Hg)	Diastolic Blood Pressure (mm-Hg)	Median Blood Pressure (mm-Hg)	PR (ms)	QRS (ms)	QT (ms)
Control Group	251.3±22.5	101.0±16.4[a]	69.6±13.6[a]	79.9±8.1[a]	43.0±5.0	88.0±6.8	115.6±7.4[a]
CIS Group	277.4±48.7	72.9±12.6	45.3±5.3	53.3±4.5	44.0±8.6	82.8 ±12.8	138.3±8.4
MIR Group	258.1±60.6	93.0±12.5[a]	67.0±14.4[a]	76.0±7.9[a]	41.3±4.5	90.8±7.1	120.8±15.2[a]
MIR+CIS Group	291.8±55.5	91.5±7.1[a]	63.6±8.3[a]	80.8±7.4[a]	39.5±8.5	98.5±12.7[a]	112.3±8.8[a]

[a] There was a statistically significant difference compared to the CIS group ($p<0.05$)

Table 3. Changes in heart rhythm

	n	Arrhythmia	ST depression	T negativity	Block
Control Group	8	0	0	0	0
CIS Group	8	0	0	0	1
MIR Group	8	0	0	1	0
MIR+CIS Group	8	0	2	0	2

Tissue Biochemical Findings

When cardiac tissue biochemical parameters were analyzed, it was found that the control, MIR, and MIR+CIS groups had significantly greater catalase and SOD levels than the CIS group. Compared to MIR+CIS, total GSH was significantly greater in the MIR group. While the MDA level was highest in the CIS group, it was considerably decreased in all other groups (Table 4).

Table 4. Heart tissue CAT, SOD, Total GSH, and MDA results

Group	CAT (U/mg protein)	SOD (U/mg protein)	Total GSH (nmol/ mg protein)	MDA (nmol/mg protein)
Control Group	50.5±6.7[a]	145.7±25.3[a]	7.11±1.64	0.0861±0.13013[a]
CIS Group	22.7±5.0	85.5±15.7	6.63±1.44	0.7686±0.31312
MIR Group	43.8±3.5[a]	146.4±22.0[a]	8.09±2.08[b]	0.1305±0.19249[a]
MIR+CIS Group	46.3±6.6[a]	127.7±15.3[a]	5.61±0.73	0.0756±0.09493[a]

[a] There was a statistically significant difference compared to the CIS group ($p<0.05$)
[b] There was a statistically significant difference compared to the MIR+CIS group ($p<0.05$)

In vascular tissue examination, CAT and SOD levels were substantially higher in the control, MIR, and MIR+CIS groups, similar to those of the myocardium, compared to the CIS group. Total GSH was considerably lower in the CIS group than in the control group. While the MDA level was highest in the CIS group, it was considerably decreased in all other groups (Table 5).

Table 5. Vascular tissue CAT, SOD, Total GSH, and MDA results

	CAT (U/mg protein)	SOD (U/mg protein)	Total GSH (nmol/ mg protein)	MDA (nmol/mg protein)
Control Group	66.4±8.0[a]	36.2±8.7[a]	5.04±1.42[a]	0.4923±0.10811[a]
CIS Group	27.0±4.1	11.8±4.5	2.36±0.54	2.4004±1.86737
MIR Group	65.3±14.9[a]	30.3±7.5[a]	3.72±1.12	0.8729±0.51932[a]
MIR+CIS Group	55.3±7.1[a]	32.7±9.4[a]	3.99±1.82	0.7824±0.27039[a]

[a] There was a statistically significant difference compared to the CIS group ($p<0.05$)

Serum Biochemical Findings

The serum myoglobin levels of the different groups were comparable to one another. When particularly in comparison to the other groups, the LDH and CK levels seen in the CIS group were substantially higher than those seen in the other groups (Table 6).

Table 6. Serum Myoglobin, LDH, and CK results

	Myoglobin (ng/mL)	Lactate dehydrogenase (U/L)	Creatine kinase (U/L)
Control Group	164.1±69.1	556.8±326.6[a]	1061.1±324.7[a]
CIS Group	161.9±51.1	1772.6±818.8	3148.6±922.3
MIR Group	154.5±64.8	832.0±355.5[a]	1288.4±641.3[a]
MIR+CIS Group	154.3±99.9	622.9±169.6[a]	1154.3±448.4[a]

[a] There was a statistically significant difference compared to the CIS group ($p<0.05$)

Histological Findings

Cardiac tissue was observed in normal histological appearance in the control and MIR groups, except for mild changes (Figure 1. A and B). As compared to the control group, it was shown that the CIS group's congestion and interstitial edema severity increased, and this increase was statistically significant ($p<0.05$). In this group, degenerate cardiomyocytes, which are distinguished by their dense eosinophilic cytoplasm and pycnotic nuclei, were also found (Figure 1. C). Comparing the MIR+CIS group to the CIS group, however, revealed that although the congestion persisted, the interstitial edema's degree significantly lessened ($p<0.05$) (Figure 1.D).

Vascular tissue was observed in normal histological appearance in the control and MIR groups, except for the mild loss of myofibrils in muscle cells (Figure 2. A and B). TIM thickness was 113.39±17.63 µm in the control group; It was measured as 113.97±15.64 µm in the MIR group. It was determined that the appearance of the vessel wall in the CIS and MIR+CIS groups was similar to the control group (Figure 2. C and D). 115.83±19.55 µm in the CIS group; TIM thicknesses measured as 116.99±17.90 µm in the MIR+CIS group were also found to be similar in all groups. Histopathological score results were denoted in Table 7.

DOI: 10.5455/medscience.2023.02.030

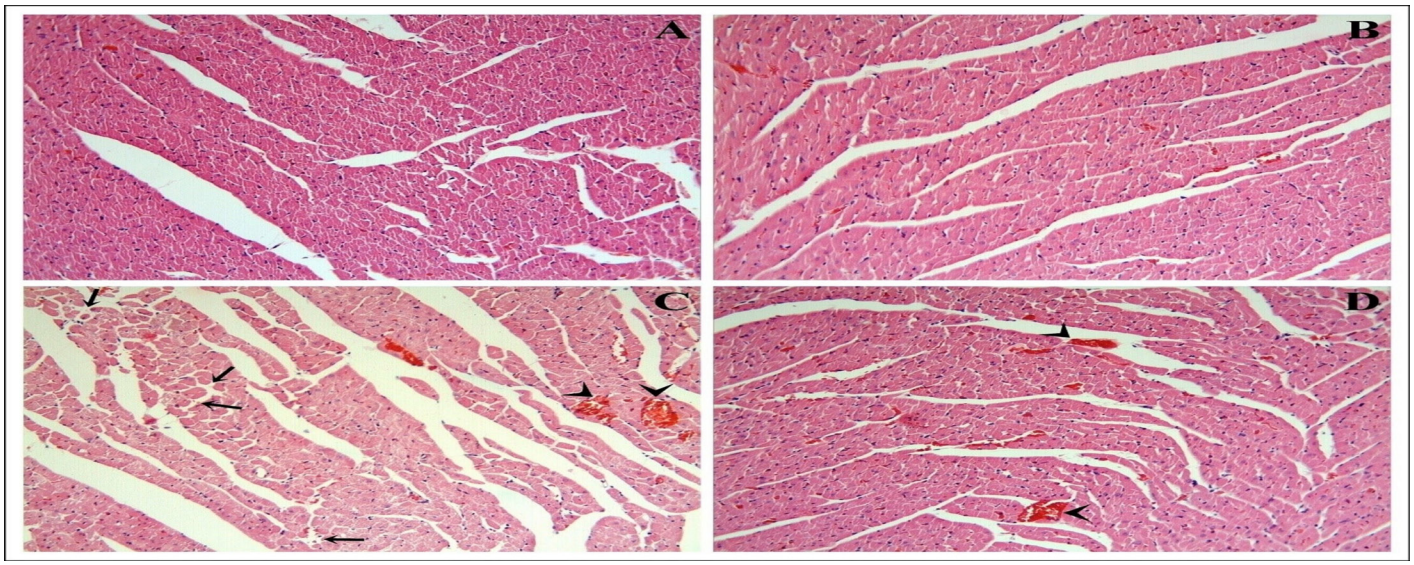

Figure 1. The appearance of cardiac tissue in control (A), MIR (B), CIS (C), and MIR+CIS (D) groups. Increased congestion (arrowheads) and interstitial edema (arrows) are observed in the CIS group. It is noteworthy that in the MIR+CIS group, the congestion continued similarly to the CIS group, while the edema decreased significantly. H-E; x20

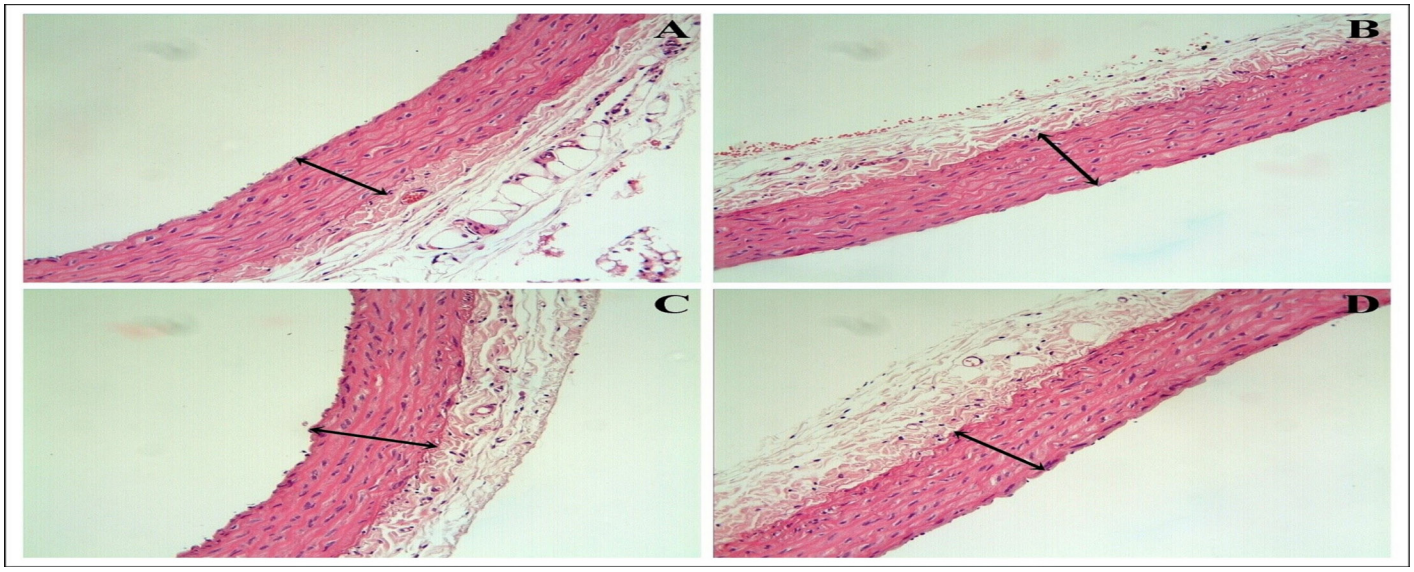

Figure 2. The appearance of vascular tissue in control (A), MIR (B), CIS (C), and MIR+CIS (D) groups. Double-headed arrows indicate TIM thickness. H-E; x20

Table 7. Serum Myoglobin, LDH, and CK results

Groups	Cardiac Injury Med (Min-Max)	Vascular Injury Med (Min-Max)	TIM thickness (µm) AM±SD
Control Group	0.0 (0.0-2.0)	0.0 (0.0-2.0)	113.39±17.63
CIS Group	1.0 (0.0-3.0)[a]	0.0 (0.0-2.0)	115.83±19.55
MIR Group	0.0 (0.0-2.0)	0.0 (0.0-2.0)	113.97±15.64
MIR+CIS Group	0.0 (0.0-2.0)[b]	0.0 (0.0-2.0)	116.99±17.90

[a] Significant increase compared to the control group ($p<0.0001$)
[b] Significant decrease compared to the CIS group ($p=0.009$)

Discussion

While depressive symptoms can be seen in cardiovascular diseases, major depressive disorders carry a risk in terms of cardiovascular diseases. The pathophysiological mechanisms underlying these two diseases are highly intertwined [13]. In the current study, we demonstrated that MIR may have a protective effect against CIS-mediated cardiotoxicity and the mechanism behind its antioxidant effect.

The cardio-oncology population may often require additional supportive or palliative treatments. One of the most important of these is antidepressants. Many of these agents can inhibit or induce CYP3A4, CYP2D6, and other CYP enzymes. For this reason, the reaction of the antidepressant treatment with the

DOI: 10.5455/medscience.2023.02.030

chemotherapeutic agent is important. Mirtazapine is a minimally effective agent on CYP2D6, and for this reason, it is an agent that can be preferred especially in cardio-oncology patients who will be given tamoxifen [14].

MIR is an antidepressant that acts on both noradrenergic and serotonergic receptors specifically. It is used as an anti-depressant and anxiolytic agent in the treatment of major depression and severe depressive psychiatric conditions. MIR acts as an antagonist on alpha 2–adrenergic auto-receptors as well as heteroreceptors in norepinephrine and serotonin (5-HT) pre-synaptic axons. In addition to this, it is a highly effective antagonist of postsynaptic $5HT_2$ and $5HT_3$ receptors. Thus, noradrenergic activity increases with serotonergic activity [15]. While maintaining its antidepressant efficacy, its mechanism of action reduces the occurrence of many of the negative effects associated with selective serotonin reuptake inhibitors (SSRIs) and other tricyclic antidepressants.

It can be thought that MIR may affect the cardiovascular system through noradrenaline, which mediates transmission at the neuro-effector junction in the autonomic nervous system and may cause some changes in hemodynamic parameters.

Antidepressants are known to have a wide range of adverse effects on the cardiovascular system, some of which can be life-threatening, including bradycardia, tachycardia, hypotension, and hypertension [16]. Serious cardiovascular side effects may complicate the clinical use of anti-depressant drugs. Sedation, increased appetite, headache, and postural hypotension are known side effects of MIR [17]. It seems to offer advantages over other antidepressants, as it does not cause cardiotoxicity.

CIS is an effective chemotherapeutic that can be used in ovarian, cervix, testis, bladder, and lung cancers. CIS causes cell damage through the generation of reactive oxygen species, inflammation, activation of the caspase system, and apoptosis [18]. In the case of CIS toxicity, oxidative stress is caused when there is a disruption in the oxidant-antioxidant balance in the cell. It can alter the redox balance in cells by the disruption of mitochondrial respiration caused by excess reactive oxygen species (ROS). In the presence of an excess of ROS, lipid peroxidation is a reflection of oxidative stress. Oxidative stress is the primary mechanism that is responsible for the cardiac toxicity that is caused by CIS [19]. CIS is an effective inhibitor of fatty acid oxidation, which is the primary route by which cells obtain their supply of energy. As a result, the accumulation of CIS leads to mitochondrial dysfunction, which in turn reduces the amount of energy present within the cell, which ultimately results in the death of the cell. In cardiac toxicity caused by CIS, pro-inflammatory factors trigger inflammation and cellular damage [20]. CIS administered to cancer patients can cause electrocardiographic changes, arrhythmias, HF, and sudden cardiac death with its cardiotoxic effects [21].

In this study, there was no considerable difference between the experimental groups in terms of heart rate. Although one study reported that MIR caused a decrease in heart rate variability in infarct patients in a placebo-controlled randomized controlled trial, MIR did not cause substantial changes in heart rate, blood pressure or PR, QRS, and QTc intervals [22]. Additionally, systolic, diastolic, and median blood pressure were substantially lower in the CIS group compared to all other groups. No significant blood pressure changes were found in the MIR groups. MIR has a negligible impact on blood pressure but has the potential to very infrequently cause orthostatic hypotension. Theoretically, increased noradrenergic transmission by MIR may increase blood pressure, but MIR blocks alpha 1–adrenoceptors, resulting in a hypotensive effect [23]. In a separate study, MIR did not affect the hypotensive activity of enalapril or propranolol when given to rats that exhibited spontaneously elevated blood pressure. Based on these findings, it appears that MIR may be an effective drug in the treatment of patients who suffer from depression in addition to hypertension [24]. Although rare, adverse effects of MIR such as blood pressure elevation and peripheral edema have been reported, but the contributing mechanisms are not fully understood [25]. In the Myocardial Infarction and Depression Intervention trial (MIND-IT) study, when MIR was used with an agent that will affect the alpha–2 pathway, such as clonidine, hypertension was reported. However, due to the small number of patients and the fact that most of them were out of follow-up during the study, it was also emphasized that the results should be carefully evaluated [22].

In our study, the PR interval was similar between the groups. However, the QRS was substantially longer in the MIR+CIS group compared to the CIS group. Arrhythmia, ST depression, T negativity, and block were not seen in the control group. Block was observed in 1 rat in the CIS group. T negativity was present in 1 rat in the MIR group. In the MIR+CIS group, 2 rats had ST depression and 2 rats had block. With the prolongation of interventricular conduction, a block was observed in 2 rats in the MIR+CIS group. Although rare, ventricular extra arrhythmias and QT prolongation have been reported due to MIR. The results of our study may also support this. As a result, extreme caution ought to be exercised before beginning MIR treatment in patients who have a preexisting risk of arrhythmias. ST depression was observed in the MIR+CIS group. According to this result, it may be said that if MIR is to be used together with a cardiotoxic agent such as CIS, attention should be paid to ischemic events as well as arrhythmia [26].

Depression is more common in patients who have HF, and it is associated with an increased risk of mortality that can be as high as eight times higher. Patients who suffer from depression may also be at a higher risk for arrhythmias [27, 28]. Therefore, careful evaluation is important when starting antidepressants in patients with a history of heart failure or arrhythmia. Although Acharya et al. found a considerably significant positive relationship between MIR and HF in their study, they stated that additional trials are needed for the use of MIR in patients with HF and depression [29].

DOI: 10.5455/medscience.2023.02.030

In this study, we evaluated MDA measurement in heart tissue and myoglobin, LDH, CK parameters, and histopathology in serum to demonstrate cardiotoxicity. When myocardial tissue biochemical parameters were examined, CAT and SOD levels were substantially higher in the control, MIR, and MIR+CIS groups compared to the CIS group. Total GSH was considerably higher in the MIR group compared to MIR+CIS group. While the MDA level was highest in the CIS group, it was decreased in all other groups.

In vascular tissue examination, CAT and SOD levels were substantially higher in the control, MIR, and MIR+CIS groups, similar to those of the myocardium, compared to the CIS group. Total GSH was considerably lower in the CIS group than in the control group. While the MDA level was highest in the CIS group, it was considerably decreased in all other groups.

While oxidation products such as MDA increased in the heart and vascular tissue in the CIS group, anti-oxidant enzymes such as CAT, GSH, and SOD decreased. In plasma, LDH and CK, which were indicators of tissue damage, were found to be increased in the CIS group. MIR treatment decreased the oxidative stress in the tissue by increasing the antioxidant capacity. In line with these data, it could be stated that MIR may have a protective effect against CIS-induced cardiac damage.

In an experimental study on ovarian toxicity due to CIS, it was reported that MIR could reduce oxidative stress in a dose-dependent manner. Thus, it was emphasized that ovarian toxicity may be reversed by MIR [30]. In another study, it was shown that MIR could reduce MDA and myeloperoxidase activity levels in rats with CIS-induced nephrotoxicity compared to the CIS group. On the other hand, it increased the total glutathione level. The study reported that histopathological findings were mild in the MIR groups compared to the CIS group [31]. As a result, the antioxidant properties of MIR were emphasized in all of these studies. Similarly, in this study, it was thought that CIS might cause cardiotoxic effect by increasing oxidative stress and it was investigated whether MIR could be a cardioprotective agent.

In our study, when the heart tissue was histologically examined, morphological deterioration, congestion, and interstitial edema developed in the CIS group, and degenerated cardiomyocytes, which were distinguished by their dense eosinophilic cytoplasm and pycnotic nuclei, were found in the CIS group. In the MIR+CIS group compared with the CIS group, the severity of interstitial edema was markedly reduced even though the congestion persisted. A significant improvement in the MIR+CIS group was consistent with tissue and serum biochemical results. In the experimental toxicity model we created with CIS, we assumed that MIR may enhance its possible protective role in heart tissue with antioxidant and free radical scavenging effects.

Depressed patients are at increased risk of cardiovascular disease. If cardiovascular disease is accompanied by depression, the risk of death is higher. For this reason, the safety of antidepressants in patients with cardiovascular disease is important. Ischemic heart disease patients frequently suffer from depression and compared to the general population, depressed patients have a higher risk of developing atherosclerosis and experiencing major cardiac events. Although it is believed that MIR may indirectly affect the cardiovascular system by causing weight gain and hyperlipidemia, it does not appear to have any obvious adverse effects on the cardiovascular system [15].

In this study, the evaluation of biochemical parameters such as CK-MB, cardiac troponin T (cTnT), and β-natriuretic peptide (BNP) could have shown cardiotoxicity more clearly. Tumor necrosis factor alpha (TNF-α) and myeloperoxidase (MPO) activity, caspase-3 gene expression, which is associated with apoptosis, and nuclear DNA fragmentation could be studied to demonstrate inflammation. In addition, cardiac functions could be visualized by transthoracic echocardiography. These were among the limitations of our research.

Conclusion

As a result, when the possible protective and anti-oxidant role of MIR in the experimental toxicity model induced by CIS was investigated in cardiac tissues, it has been supported biochemically and histologically that MIR has a curative effect with antioxidant and free radical mechanisms. MIR reduces CIS-induced free radical damage, lipid peroxidation, and MPO activity in heart tissue; It has been shown by increasing antioxidants such as GSH, CAT, and SOD.

Based on the results of this study, considering the frequency of depression in oncology patients under chemotherapy, MIR may be an appropriate antidepressant option in patients with cardiovascular disease or CIS chemotherapy.

Conflict of interests
The authors declare that there is no conflict of interest in the study.

Financial Disclosure
This work was supported by The Scientific and Technological Research Council of Turkey (Application number: 1919B011703124).

Ethical approval
Ethics approval was obtained from the Experimental Animal Ethics Board at Inonu University (2016/A-46).

References

1. Jilani TN, Gibbons JR, Faizy RM, Saadabadi A. Mirtazapine. StatPearls. Treasure Island (FL): StatPearls Publishing Copyright, StatPearls Publishing LLC.; 2022.

2. Lyon AR, López-Fernández T, Couch LS, et al. 2022 ESC guidelines on cardio-oncology developed in collaboration with the european hematology association (EHA), the european society for therapeutic radiology and oncology (ESTRO) and the international cardio-oncology society (IC-OS). Eur Heart J. 2022;43:4229-361.

3. Dugbartey GJ, Peppone LJ, de Graaf IA. An integrative view of cisplatin-induced renal and cardiac toxicities: molecular mechanisms, current treatment challenges and potential protective measures. Toxicol. 2016;371:58-66.

4. Başak Türkmen N, Aşkın Özek D, Taşlıdere A, et al. Protective role of

diospyros lotus L. in cisplatin-induced cardiotoxicity: cardiac damage and oxidative stress in rats. Turk J Pharm Sci. 2022;19:132-7.

5. Gulec M, Oral E, Dursun OB, et al. Mirtazapine protects against cisplatin-induced oxidative stress and DNA damage in the rat brain. Psychiatry Clin Neurosci. 2013;67:50-8.

6. Bilici M, Cayir K, Tekin SB, et al. Effect of mirtazapine on MNNG-induced gastric adenocarcinoma in rats. Asian Pac J Cancer Prev. 2012;13:4897-900.

7. Pivato CA, Chandiramani R, Petrovic M, et al. Depression and ischemic heart disease. Int J Cardiol. 2022;364:9-15.

8. Mihara M, Uchiyama M. Determination of malonaldehyde precursor in tissues by thiobarbituric acid test. Anal Biochem. 1978;86:271-8.

9. Ellman GL. Tissue sulfhydryl groups. Arch Biochem Biophys. 1959;82:70-7.

10. Sun Y, Oberley LW, Li Y. A simple method for clinical assay of superoxide dismutase. Clin Chem. 1988;34:497-500.

11. Hiller A, Greif RL, Beckman WW. Determination of protein in urine by the biuret method. J Biol Chem. 1948;176:1421-9.

12. Lück H. Catalase. Methods of enzymatic analysis: Elsevier; 1965;885-94.

13. Teply RM, Packard KA, White ND, et al. Treatment of depression in patients with concomitant cardiac disease. Prog Cardiovasc Dis. 2016;58:514-28.

14. Beavers CJ, Rodgers JE, Bagnola AJ, et al. American heart association clinical pharmacology committee and cardio-oncology committee of the council on clinical cardiology and council on genomic and precision medicine; and the council on peripheral vascular disease. cardio-oncology drug interactions: a scientific statement from the american heart association. Circulation. 2022;145:811-38.

15. Mago R, Tripathi N, Andrade C. Cardiovascular adverse effects of newer antidepressants. Expert Rev Neurother. 2014;14:539-51.

16. Sarlon J, Habich O, Schneider B. Elevated rest heart rate in psychiatric patients and different effects of psychotropic medication. Pharmacopsychiatry. 2016;49:18-22.

17. Stimmel GL, Dopheide JA, Stahl SM. Mirtazapine: an antidepressant with noradrenergic and specific serotonergic effects. Pharmacotherapy. 1997;17:10-21.

18. Dasari S, Tchounwou PB. Cisplatin in cancer therapy: molecular mechanisms of action. Eur J Pharmacol. 2014;740:364-78.

19. Petrović M, Todorović DJ. Series: medicine, biology. biochemical and molecular mechanisms of action of cisplatin in cancer cells. 2016:12-8.

20. Fuertes MA, Castilla J, Alonso C, et al. Cisplatin biochemical mechanism of action: from cytotoxicity to induction of cell death through interconnections between apoptotic and necrotic pathways. Curr Med Chem. 2003;10:257-66.

21. Bahadır A, Ceyhan A, Öz Gergin Ö, et al. Protective effects of curcumin and beta-carotene on cisplatin-induced cardiotoxicity: an experimental rat model. Anatol J Cardiol. 2018;19:213-21.

22. Honig A, Kuyper AM, Schene AH, et al. Treatment of post-myocardial infarction depressive disorder: a randomized, placebo-controlled trial with mirtazapine. Psychosom Med. 2007;69:606-13.

23. Calvi A, Fischetti I, Verzicco I, et al. Antidepressant drugs effects on blood pressure. Front Cardiovasc Med. 2021;8:704281.

24. Andrzejczak D, Kocon K, Zieba R. Influence of mirtazapine on the hypotensive activity of enalapril and propranolol in spontaneously hypertensive rats. Basic Clin Pharmacol Toxicol. 2008;103:450-4.

25. Montgomery SA. Safety of mirtazapine: a review. Int Clin Psychopharmacol. 1995;10:37-45.

26. Hirsch M, Birnbaum RJ. Atypical antidepressants: Pharmacology, administration, and side effects. UpToDate. Waltham (MA): WoltersKluwer. 2020.

27. Jiang W, Kuchibhatla M, Clary GL, et al. Relationship between depressive symptoms and long-term mortality in patients with heart failure. Am Heart J. 2007;154:102-8.

28. Alvarez W Jr, Pickworth KK. Safety of antidepressant drugs in the patient with cardiac disease: a review of the literature. Pharmacotherapy. 2003;23:754-71.

29. Acharya T, Acharya S, Tringali S, Huang J. Association of antidepressant and atypical antipsychotic use with cardiovascular events and mortality in a veteran population. Pharmacotherapy. 2013;33:1053-61.

30. Altuner D, Gulaboglu M, Yapca OE, et al. The effect of mirtazapine on cisplatin-induced oxidative damage and infertility in rat ovaries. Scientific World Journal. 2013;2013:327240.

31. Sener MT, Sener E, Tok A, et al. Biochemical and histologic study of lethal cisplatin nephrotoxicity prevention by mirtazapine. Pharmacol Rep. 2012;64:594-602.