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Research Article
Effect of Rutin on Cisplatin-Induced Oxidative Skeletal Muscle Damage in Rats

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Abstract

Background and Objective: Cisplatin is a drug used to treat cancer, but it causes oxidative damage to muscle tissue. Rutin has an antioxidant effect. The study aims to investigate the biochemical and histopathological effects of rutin on the oxidative damage of cisplatin in skeletal muscle tissue. **Materials and Methods:** Rats were divided into four groups: A control group (CG), an only cisplatin-administered group (CIS), a cisplatin and rutin 50 mg kg^{-1}-administered group (R-50) and a cisplatin and rutin 100 mg kg^{-1}-administered group (R-100). Analyses were performed from the hindlimb muscles of experimental animals. Analyses of malondialdehyde (MDA), Total Glutathione (tGSH), glutathione reductase (GSHRd), glutathione S-transferase (GST) and superoxide dismutase (SOD) were performed. Histopathologic examination was performed in all groups. The CG and the other groups were compared. **Results:** The CG and R-100 groups were similar in all biochemical examinations. A statistically significant difference was detected between the control group and the CIS and R-50 groups in all examinations. Histopathological examinations revealed oxidative damage of cisplatin in the CIS group and R-50 group. The findings in the R-100 group were similar to the control group. **Conclusion:** Cisplatin causes oxidative damage to skeletal muscle tissue. Rutin has the potential to prevent the formation of such oxidative damage.

Key words: Cisplatin, skeletal muscle, rutin, antioxidants, reactive oxygen species

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

The use of chemotherapeutic drugs in the treatment of cancer has begun to increase the quality of life of patients. Cisplatin is one of the important drugs used in the treatment of cancer[1]. However, there are many side effects, including nausea, anorexia, dysphagia, pain, fatigue and muscle toxicity. Cisplatin induces genes related to atrophy and causes inflammation in muscle cells[2]. Muscle toxicity causes muscle atrophy and a decrease in muscle mass. It affects the quality of life negatively and worsens the course of the disease. It has been reported that this toxic effect is formed by reducing protein synthesis in muscle cells and increasing protein destruction[3]. One of the toxic effects of cisplatin is oxidative stress[4]. The cause of oxidative stress in cells is the deterioration of the balance between the oxidant and antioxidant systems. As a result, reactive oxygen species (ROS) increase within cells. An ROS increase in muscle cells causes Mitochondrial DNA (mtDNA) damage. These changes in muscle cells cause muscle atrophy[5].

Oxidative stress is caused by insufficient detoxification of the ROS within cells. An ROS increase causes many harmful compounds in cells. Arachidonic acid, which can provide hydrogen to free radicals, is found in cell membranes. Malondialdehyde (MDA) is a reliable biomarker of oxidative stress. It is the major metabolite of arachidonic acid. Measuring MDA in blood, plasma and tissue homogenates is one of the key tests used to monitor oxidative stress[6]. To maintain tissue integrity and function at normal levels, the excess ROS are neutralized by endogenous Glutathione (GSH), glutathione reductase (GSHRd), glutathione S-transferase (GST), superoxide dismutase (SOD) and other antioxidant defense systems[7]. Glutathione reductase (GSHRd) provides reduced glutathione in cells. Reduced glutathione controls ROS in cells[8]. The GST is involved in the detoxification of ROS products using glutathione in cells. As a result of the decrease of total Glutathione (tGSH) levels within cells, oxidative products cause cell damage. The tGSH is one of the important antioxidant defense systems in cells[9]. The superoxide anion is formed in cells during aerobic respiration. This anion is metabolized by the SOD enzyme[10].

The information obtained from the literature suggests that oxidative stress is the major component in the pathogenesis of cisplatin-induced skeletal muscle damage and antioxidants may be useful in treatment. In the present study, the protective effect of rutin against oxidative skeletal muscle damage caused by cisplatin was investigated. Rutin is a flavonoid found in many fruits and vegetables that we consume daily[1]. It has anti-inflammatory, anticancer and antioxidant properties. Rutin reduces oxidative stress by decreasing lipid peroxidation and increasing antioxidant activity[11]. During rutin use, mitochondria biogenesis and function increase in skeletal muscle tissue[12]. Rutin prevents muscle atrophy via its protective effect on mitochondria and prevents their reduction[13]. In the literature, no studies have been done investigating the effects of rutin on cisplatin-induced skeletal muscle oxidative damage. Therefore, the aim of this study was to examine the effects of rutin on cisplatin-induced skeletal muscle damage by histopathologically and biochemically.

MATERIALS AND METHODS

Study area: The current study was carried out at Ataturk University Medical Experimental Application and Research Center in June to July, 2018.

Ethical consideration: The animal experiments were performed in accordance with the National Guidelines for the Use and Care of Laboratory Animals and were approved by the Local Animal Ethics Committee of Atatürk University, Erzurum, Turkey (Ethics Committee Number: 6/128, Dated: 22-05-2018).

Study animals: In all, 24 male albino Wistar rats weighing 250-265 g were used. The animals were obtained from the Medical Experimental Application and Research Centre at Atatürk University. Animals were housed and fed in groups at room temperature (22°C) for seven days before the test under appropriate conditions.

Chemical substances: The chemicals that were used in the experiments were as follows: Vials of cisplatin (50 mg/100 mL; cisplatin-Ebewe) were provided by Liba, Turkey; rutin (tablet form) was provided by Solgar America and thiopental sodium was provided by IE Ulagay.

Experimental groups: The animals were divided into a group that received cisplatin alone (CIS), a group that received cisplatin+50 mg kg^{-1} rutin (R-50), a group that received cisplatin+100 mg kg^{-1} rutin (R-100) and a control group that received no treatment (CG).

Experimental procedure: During the experiment, the R-50 group (n = 6) received 50 mg kg^{-1} rutin and the R-100 group (n = 6) received 100 mg kg^{-1} rutin by oral gavage. These doses of rutin have been shown to be effective in previous experimental studies by Nkpaa and Onyeso[14]. Only distilled water as solvent was injected intraperitoneally in the same volume (0.5 mL) for the CIS (n = 6) and CG (n = 6) groups. Cisplatin 5 mg kg^{-1} was administered intraperitoneally to all groups except CG 1 hr after the administration of rutin and distilled water. One hour before cisplatin, it is common practice to give experimental animals drugs that protect tissues from the toxic effects of cisplatin[15]. Rutin and distilled water were administered once daily for 8 days. For a total of 8 days, cisplatin was given every 2 days. At the end of this period, the muscles of the hind limbs were removed from the animals that had been euthanized with a high dose of sodium thiopental. The samples obtained were subjected to biochemical and histopathological examination. All the results obtained from the experiments have been compared with the CG.

Biochemical analysis

MDA analysis: A method based on that of Ohkawa *et al.*[16] was used to measure MDA. This method is based on the spectrophotometric measurement of the absorbance of the pink complex formed by MDA with thiobarbituric acid (TBA) at a high temperature (95°C) and a wavelength of 532 nm. The supernatants were used to determine the amount of MDA by centrifugation at 5000 g for 20 min. Subsequently, 250 µL homogenate, 100 µL 8% sodium dodecylsulphate (SDS), 750 µL 20% acetic acid, 750 µL 0.08% TBA and 150 µL purified water were vortexed into capping tubes. The mixture was incubated at 100°C for 60 min. About 2.5 mL of n-butanol was added and spectrophotometric measurements were made. The resulting amounts of red colour were read at 532 nm using 3 mL cuvettes. The amount of MDA in the samples was determined using the standard curve generated from the previously prepared MDA stock solution, taking into account the dilution coefficients.

tGSH analysis: The amount of GSH in total homogenate was measured by the Sedlak and Lindsay[17] method with some modifications. Sample was weighed and homogenised in 2 mL 50 mmol L^{-1} Tris-HCl buffer containing 20 mmol L^{-1} EDTA and 0.2 mmol L^{-1} sucrose, pH 7.5. The homogenate was immediately precipitated with 0.1 mL of 25% trichloroacetic acid and after centrifugation at 4200 rpm for 40 min at 4°C, the precipitate was removed and the supernatant was used for the determination of GSH levels. A total of 1500 µL of measurement buffer (200 mmol L^{-1} Tris-HCl buffer containing 0.2 mmol L^{-1} EDTA at pH 7.5), 500 µL of supernatant, 100 µL of DTNB (10 mmol L^{-1}) and 7900 µL of methanol were added to a tube. The mixture was vortexed and incubated at 37°C for 30 min. The 5,5-Dithiobis (2-Nitrobenzoic acid) (DTNB) was used as chromogen. It formed a yellow coloured complex with sulfhydryl groups. The absorbance was measured at 412 nm. A spectrophotometer (Beckman DU 500, USA) was used. The standard curve has been obtained with the use of reduced glutathione.

GSHRd analysis: The GSHRd activity was determined according to the method of Carlberg and Mannervik[18] by spectrophotometric measurement of the rate of NADPH oxidation at 340 nm. The supernatant was used for GSHRd measurement after tissue homogenisation. After adding NADPH and GSSG, a chronometer was switched on and the absorbance was measured spectrophotometrically at 340 nm for 5 min at 30 min intervals.

GST activity: The activity of the GST was carried out according to the method of Habig and Jakoby[19]. Briefly, in a 4 mL cuvette containing 0.1 M PBS (pH 6.5), 30 mM GSH, 30 mM 1-chloro-2,6-dinitrobenzene and tissue homogenate, enzyme activity was measured spectrophotometrically at 340 nm.

SOD analysis: The analysis of SOD was carried out according to the method proposed by Sun *et al.*[20]. The SOD is formed when xanthine is converted to uric acid by xanthine oxidase. The SOD reacts with NBT to form a purple formazan dye when nitro blue tetrazolium (NBT) is added to the reaction. The sample was weighed and homogenized in 2 mL of 20 mmol L^{-1} phosphate buffer containing 10 mmol L^{-1} EDTA at pH 7.8. The sample was centrifuged at a speed of 6000 rpm for 10 min. The brilliant supernatant was then used to assay. The measuring mixture containing 2450 µL of the measuring solution (0.3 mmol L^{-1} xanthine, 0.6 mmol L^{-1} EDTA, 150 µmol L^{-1} NBT, 0.4 mol L^{-1} Na_2CO_3 and 1 g L^{-1} bovine serum albumin), 500 µL supernatant and 50 µL xanthine oxidase (167 U L^{-1}) was vortexed. It was then left to incubate for 10 min. Formazan was formed at the end of the reaction. The absorbance of the purple formazan was measured at 560 nm.

Histopathological analysis: The hindlimb muscle tissues removed from the rats were fixed in a 10% formalin solution. After undertaking routine tissue follow-up procedures, the tissues were paraffin-embedded and sections of 4 μm thickness were cut and stained with Hematoxylin and Eosin (H&E). All the sections were coded and examined under a light microscope by a pathologist who was blinded to the treatment protocol (Olympus BX 52, Tokyo, Japan).

Statistical analysis: The results were presented for continuous variables as Mean±Standard Deviation, median and minimum-maximum. The normality of distribution for continuous variables was confirmed with the Kolmogorov-Smirnov test. For the comparison of independent continuous variables between three groups, ANOVA was used. Homogeneity of variances was confirmed using Levene's test. While comparing groups, Tukey's HSD was used as a *post hoc* test. The statistical level of significance for all tests was considered 0.05. Statistical analysis was performed using the IBM SPSS ver. 19 package program (IBM Corp. Released 2010. IBM SPSS Statistics for Windows, Version 19.0. Armonk, New York: IBM Corp).

RESULTS

The biochemical results of the study and the comparisons between the groups were shown in Table 1. Pairwise comparisons were made to detect differences between groups.

The MDA mean levels were compared between the study groups and there was a statistically significant difference between the groups (p<0.001). The CG was similar to the R-100 group (p>0.05) but statistically significantly different from the CIS and R-50 groups (respectively, p<0.001 and p<0.001). The CIS and R-50 groups were statistically significant different (p<0.001). The R-50 and R-100 groups were statistically significant different (p<0.001).

The mean levels of tGSH were compared between study groups and there was a statistically significant difference between the groups (p<0.001). The CG was similar to the R-100 (p>0.05) group but statistically significantly different from the CIS and R-50 groups (respectively, p<0.001 and p<0.001). The CIS and R-50 groups were statistically significant different (p<0.001). The R-50 and R-100 groups were statistically significantly different (p<0.001).

The mean levels of GSHRd were compared between study groups and there was a statistically significant difference between the groups (p<0.001). The CG was similar to the R-100 group (p>0.05) but statistically significantly different from the CIS and R-50 groups (respectively, p<0.001, p<0.001). The CIS and R-50 groups were statistically significant different (p<0.001). The R-50 and R-100 groups were statistically significantly different (p<0.001).

The mean levels of GST were compared between study groups and there was a statistically significant difference between the groups (p<0.001). The CG was similar to the R-100 group (p>0.05) but was statistically significantly different from the CIS and R-50 groups (respectively, p<0.001, p<0.001). The CIS and R-50 groups were statistically significantly different (p<0.05). The R-50 and R-100 groups were statistically significantly different (p<0.05).

The mean levels of SOD were compared between study groups and there was a statistically significant difference between the groups (p<0.001). The CG was similar to the R-100 group (p>0.05) but was statistically significant different from the CIS and R-50 groups (respectively, p<0.001 and

Table 1: Antioxidants levels according to study groups

	Groups				
Variables	CG	CIS	R-50	R-100	p-value
MDA (μmol g^{-1})	4.2±0.2^{bc}	14.5±1.9^{acd}	8.1±0.6^{abd}	5.1±0.4^{bc}	<0.001
	4.1 (3.9-4.6)	14.5 (12.0-17.0)	8.1 (7.1-8.8)	5.1 (4.6-5.9)	
tGSH (nmol g^{-1})	9.3±0.5^{bc}	4.2±0.4^{acd}	5.8±0.4^{abd}	8.8±0.2^{bc}	<0.001
	9.3 (8.3-9.9)	4.1 (3.8-4.7)	5.8 (5.1-6.3)	8.8 (8.4-9.1)	
GSHRd (μ/gr)	10.3±1.1^{bc}	4.0±0.7^{acd}	7.0±0.7^{abd}	9.7±0.7^{bc}	<0.001
	9.9 (9.1-12.0)	4.0 (3.1-5.0)	6.9 (6.1-7.9)	9.7 (8.7-11.0)	
GST (μ/gr)	14.5±1.9^{bc}	7.1±0.6^{acd}	10.3±0.9^{abd}	13.0±1.4^{bc}	<0.001
	14.5 (12.0-17.0)	7.0 (6.4-8.1)	9.9 (9.6-12.0)	13.0 (11.0-15.0)	
SOD (μ/gr)	9.6±0.2^{bc}	2.5±0.5^{acd}	4.8±0.5^{abd}	8.8±0.6^{bc}	<0.001
	9.6 (9.3-9.8)	2.3 (2.0-3.0)	4.7 (4.1-5.5)	8.7 (8.1-9.8)	

Variables were shown as Mean±Standard Deviation, median (minimum-maximum) value, Statistically significant (p<0.05) when compared with a: CG group, b: CIS group, c: R-50 group and d: R-100 group

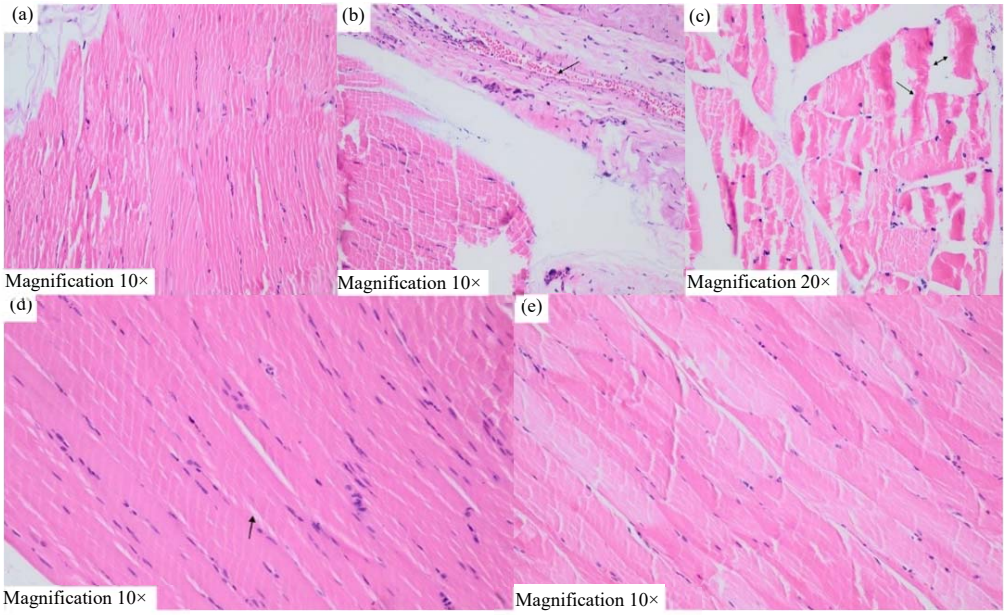

Fig. 1(a-e): Findings of histopathological examination, (a) CG, H&E-×200, (b) CIS, dilated congested blood vessel (straight arrow), H&E-×200, (c) CIS, muscle destruction (straight arrow), edema (duble sided arrow), H&E-×400, (d) R-50, mild edema (straight arrow), H&E-×200 and (e) R-100 has similar appearance to the CG, H&E-×200

p<0.001). The CIS and R-50 groups were statistically significantly different (p<0.001). The R-50 and R-100 groups were statistically significantly different (p<0.001).

Histopathological results: In the study, histopathological examination was performed in all groups and the results of the examination were shown in Fig. 1. The CG examinations were shown in Fig. 1a. In the CIS group, dilated congested blood vessels (Fig. 1b), muscle destruction and edema (Fig. 1c) were detected. In the R-50 group, mild edema (Fig. 1d) was detected. The R-100 group (Fig. 1e) was similar to the CG.

DISCUSSION

Cisplatin is known to cause muscle atrophy in experimental animals. As mentioned above, it was stated that cisplatin had a toxic effect on mitochondria by increasing ROS production in muscle cells and significantly reducing the number of mitochondria[3]. Cisplatin causes the activation of ATP and ubiquitin-dependent pathways that cause protein degradation in muscle cells. Cisplatin activates the NF-κB pathway in muscle cells. The activation of this pathway causes toxic effects on muscle cells. It is one of the causes of atrophy. The toxic effects of cisplatin on muscle tissue are closely related to poor prognosis, poor response to treatment and negative impact on survival[21]. The Ser/Thr Akt kinase enzyme in skeletal muscle is responsible for the main balance between protein production and degradation. Cisplatin disrupts the Akt signaling pathway in skeletal muscles. As a result, it activates protein degradation and autophagy systems, resulting in atrophy. One cause of cisplatin-induced skeletal muscle atrophy is oxidative stress[22]. Oxidative stress is caused by the imbalance between ROS and detoxifying systems. Oxidative stress increases the amount of free calcium and iron in cells. Increased free calcium causes DNA damage[6]. Oxidative stress causes increased lipid peroxidation in cells. Lipid peroxidation is a series of chain reactions that result in cell damage. The MDA is the end product of this lipid peroxidation[1]. Intracellular MDA determination indicates MDA-DNA damage. It is an important determinant in the monitoring of DNA damage in oxidative stress[6]. The MDA levels were increased in experimental animals treated with cisplatin[23]. The MDA levels were increased in experimental animals given cisplatin alone. There was no significant increase in MDA levels in the group treated with rutin before cisplatin administration[24]. In the present study, MDA levels increased significantly in the CIS group compared to the CG. The R-100 group and the CG were similar. Current study results were compatible with previous studies. The tGSH is one of the most important non-enzymatic antioxidants that protects cells against oxidative stress or ROS damage. In the present study, there was a significant decrease in tGSH values in the CIS group. The R-100 group had similar

values to the CG. Rutin significantly increased the level of tGSH. There was a significant decrease in the levels of tGSH in the experimental animals given cisplatin compared to the CG[25]. Rutin administration prevented a reduction in tGSH levels caused by cisplatin[11]. Rutin increased the decreasing tGSH values, which may be due to the antioxidant effects of rutin[26]. Current study results were consistent with previous studies. The GST suppresses activity by adding glutathione to reactive molecules and protects cells from oxidative damage[27]. The GST forms a cisplatin-GSH complex by adding glutathione to cisplatin. This conjugate is removed from the cells[28]. Cisplatin-GSH drug conjugates reduce GST activity. Decreased GST activity causes an increase in cell toxicity[29]. In the present study, cisplatin significantly decreased GST levels compared to the CG. The R-100 values were similar to the CG. There was a significant increase in GST values after rutin administration. In one study, there was a 100% increase in GST values after rutin administration[30]. In another study, GST values increased significantly after rutin administration[31]. Current study results were consistent with previous studies. The GSHRd converts the oxide glutathione into reduced glutathione[32]. In experimental animals given cisplatin, GSHRd inhibition occurs. Therefore, reduced glutathione does not occur and oxidized glutathione increases. The increased oxidized glutathione causes oxidative stress in the tissue[33]. Increased glutathione reductase enzyme activity in skeletal muscle tissue prevents damage[34]. Rutin administration to experimental animals after cisplatin resulted in increased glutathione reductase enzyme activity and increased glutathione[1]. In the present study, there was a significant decrease in GSHRd enzyme activity in the CIS group compared to the CG. The R-100 group and the CG were similar. There was no decrease in GSHRd activity in the R-100 group. Current study results were consistent with previous studies. In one study, glutathione reductase enzyme activity did not change significantly after cisplatin. However, this result was explained by the low dose of cisplatin used in the experiment[35]. The SOD catalyzes the superoxide radical[26]. In one study, cisplatin inhibited SOD activity in muscle tissue[36]. In another study, decreased SOD activity was normalized after rutin administration[37]. In the present study, SOD activity decreased significantly in experimental animals after cisplatin administration compared to the CG. The SOD activity in the R-100 group was similar to the CG. Current study results were consistent with previous studies.

In the histopathological examination, in the CIS group, muscle tissue deformation, dilatation of the vessels and congestion and edema were detected. Only edema was detected in the R-50 group. The R-100 group was similar to the CG. In one study, after the administration of cisplatin, interstitial congestion and focal mononuclear cell infiltration were detected in the tissue[24]. In another study, oxidative damage in the muscle tissue was prevented histopathologically following rutin administration[38].

In the present study, it has been observed that the oxidant effect mechanism is important on muscle toxicity and the antioxidant effect is important in preventing this side effect. A small number of animals were included in the study. Larger studies could provide more detailed information.

CONCLUSION

As a result, after cisplatin administration, oxidative stress was detected in skeletal muscle tissue. The MDA levels significantly increased and tGSH, GSHRd, GST and SOD levels were significantly decreased. There was no oxidative damage caused by cisplatin in the R-100 group. Histopathological examinations revealed that cisplatin causes oxidative damage in skeletal muscle tissue. In the R-100 group, the protective effect of rutin from oxidative damage increased compared to the R-50 group. As mentioned above, cisplatin causes damage to skeletal muscle tissue via many mechanisms. Oxidative stress is one of these mechanisms. Results suggested that rutin can be useful in preventing this oxidative stress.

SIGNIFICANCE STATEMENT

Cisplatin is a drug used in cancer treatment and one of its side effects is muscle toxicity. This toxic effect causes muscle atrophy and loss of muscle mass. One of the reasons for this side effect is oxidative stress. Rutin is a flavonoid with antioxidant effects. It was seen in current study that rutin prevented the oxidative effects of cisplatin on muscle tissue. Preventing the toxic effects of cisplatin on muscle improves the quality of life of patients.

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