ORIGINAL ARTICLE

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Effects of Quercetin on Cisplatin-Induced Renal Damage in Wistar Albino Rats

Wistar Albino Sıçanlarda Sisplatin ile Oluşan Böbrek Hasarında Kuersetinin Etkileri

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ABSTRACT

Aim: Cisplatin is one of the effective antineoplastic drugs widely used in the treatment of many types of cancer. Cisplatin has harmful effects such as nephrotoxicity, ototoxicity and cardiomyopathy. Quercetin is an antioxidant of the flavonoid group. In this study, it was aimed to investigate the therapeutic effects of quercetin against cisplatin-induced kidney damage in rats.

Materials and Methods: Twenty-eight male Wistar albino rats were randomly selected and divided into 4 groups: Group 1: Control (no application), Group 2: Quercetin (25 mg/kg/7 days/intraperitoneal), Group 3: Cisplatin (7 mg/kg/single dose/ intraperitoneal), Group 4: Cisplatin+quercetin (7 mg) /kg/single dose/ intraperitoneal cisplatin followed by 25 mg/kg/7 days/ intraperitoneal quercetin). After routine histological follow-up, hematoxylin eosin and periodic acid-schiff staining were performed. Histopathological damage score was calculated. Caspase-3 immunostaining was performed and scored.

Results: Control and quercetin groups had normal histological appearance. In the cisplatin group, dilatation of the tubules, epithelial shedding, vacuolization of the tubular epithelial cells, and loss of microvilli in the proximal tubules were detected. In addition, infiltration areas were also found in places. In addition, an increase in caspase-3 immunostaining intensity was detected in this group (p=0.000). Histopathological findings were significantly reduced in the cisplatin+quercetin group compared to the cisplatin group (p=0.001).

Conclusion: In this study, we think that quercetin is histopathologically beneficial in the treatment of cisplatin-induced kidney damage.

Keywords: Cisplatin, quercetin, caspase-3, kidney toxicity, apoptosis

ÖZ

Amaç: Sisplatin birçok kanser türünün tedavisinde yaygın olarak kullanılan etkili antineoplastik ilaçlardan biridir. Sisplatinin nefrotoksisite, ototoksisite ve kardiyomiyopati gibi zararlı etkileri vardır. Kuersetin flavonoid grubu bir antioksidandır. Bu çalışmada, sıçanlarda sisplatin ile oluşturulan böbrek hasarına karşı kuersetinin tedavi edici etkilerinin incelenmesi amaçlanmıştır.

Gereç ve Yöntem: Wistar albino cinsi 28 adet erkek sıçan rastgele seçilerek 4 gruba ayrıldı. Grup 1: Kontrol (uygulama yapılmadı), Grup 2: Kuersetin (25 mg/kg/7 gün/intraperitoneal), Grup 3: Sisplatin (7 mg/kg/tek doz/ intraperitoneal), Grup 4: Sisplatin+kuersetin (7 mg/kg/tek doz/ intraperitoneal sisplatin ardından 25 mg/kg/7 gün/ intraperitoneal kuersetin). Rutin histolojik takipten sonra hematoksilen-eozin ve periodic acid-schiff boyamaları yapıldı. Histopatolojik hasar skoru hesaplandı. Caspase-3 immün boyaması yapılarak skorlandı.

Bulgular: Kontrol ve kuersetin grupları normal histolojik görünümdeydi. Sisplatin grubunda tubuler dilatasyon, tubul epitelinde dökülme, tubul epitel hücrelerinde vakuolizasyon ve proksimal tubullerde mikrovillus kaybı tespit edildi. Ayrıca yer yer infiltrasyon alanlarına da rastlandı. Sisplatin grubunun caspase-3 immün boyanma yoğunluğunda kontrol grubuna göre anlamlı artış tespit edildi (p=0,000). Sisplatin+kuersetin grubunda histopatolojik bulgular sisplatin grubuna kıyasla anlamlı derecede azalmıştı (p=0,001).

Sonuç: Bu çalışmada, sisplatinin sebep olduğu böbrek hasarının tedavisinde kuersetinin histopatolojik açıdan yararlı olduğu düşüncesindeyiz.

Anahtar Kelimeler: Sisplatin, kuersetin, caspase-3, böbrek toksisitesi, apoptoz

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INTRODUCTION

Cisplatin is one of the potential and widely used drugs in the treatment of various solid cancers such as testicular, ovarian, head and neck, bladder, lung, lymphoma, cervical cancer, and melanoma[1]. The anticarcinogenic effect of cisplatin occurs through the interaction with purine bases on DNA, causing deoxyribo nucleic acid (DNA) damage and activation of signal transduction pathways that lead to apoptosis (programmed cell death)[1]. It has been shown that cisplatin plays a role in the formation of reactive oxygen species, thus inducing apoptosis via intrinsic caspases and causing mitochondrial dysfunction[2]. Cisplatin fights tumors through the induction of apoptosis mediated by activation of various signal transduction pathways, including calcium signaling, death receptor signaling, and activation of mitochondrial pathways[2]. The most important limiting factor in the use of anticarcinogenic drugs is their side effects. Cisplatin is characterized by toxic effects such as nephrotoxicity, cardiotoxicity, hepatotoxicity, neurotoxicity and myelosuppression[3].

Quercetin (3,3',4',5,7-pentahydroxyflavone), a member of the flavonoid family, is one of the polyphenolic compounds found in various foods[4]. Quercetin is found in onions, apples, strawberries, cauliflower, cabbage and many other foods[5]. Studies have shown that quercetin has anticarcinogenic effects, but it reduces oxidative damage by inhibiting the activity of xanthine oxidase, a form of xanthine oxidoreductase, which is a type of enzyme that produces reactive oxygen species, and has anti-inflammatory activity by inhibiting the production of tumor necrosis factor alpha depending on the dose[6-8].

Caspase-3, a cysteine-aspartic acid protease, is not activated until it is cleaved by initiator caspases during the apoptotic flux[9]. After activation, it cuts non-caspase target proteins in cells from their specific regions[10,11]. Thus, it plays an important role in programmed cell death[12].

In this study, it was aimed to histopathologically examine the therapeutic effects of quercetin against cisplatin-induced kidney damage in rats.

MATERIALS AND METHODS

Groups

Approval for the study was obtained from the Animal Experiments Local Ethics Committee of İnönü University Medical Faculty (ethics committee no: 2012/A-103, date: 09.06.2012). Animal rights were protected in line with the principles of the 'Guide for the Care and Use of Laboratory Animals'. In line with these principles, 28 healthy male Wistar albino rats, 28-30 days old and weighing 300-350 grams, obtained from Inonu University Faculty of Medicine Experimental Research Laboratory, were used. The rats were left in a room with 12 hours of light and 12 hours of darkness, in a daylight rhythm, in a ventilated environment with a temperature of 21 °C and a humidity of 55-60% for 21 days. They were fed ad libitum with standard pellet feed and tap water in special cages. Randomly selected rats were divided into 4 equal groups, each with7 animals. Groups were organized as Group 1: Control (no application), Group 2: Quercetin (25 mg/kg/intraperitoneal for 7 days), Group 3: Cisplatin (single dose 7 mg/kg/intraperitoneal), Group 4: Cisplatin+quercetin (single dose 7 mg/kg/intraperitoneal cisplatin, then 25 mg/kg/intraperitoneal quercetin for 7 days). Quercetin (CAS Number: 117-39-5) and cisplatin (CAS number: 15663-27-1) were obtained from Sigma Chemical Co. (St. Louis, MO). Cisplatin and quercetin doses used in this study were determined according to previous studies in the literature[13,14].

Histopathological Analysis

At the end of the experiment, the rats were sacrificed under ketamine (90 mg/kg/intraperitoneal) anesthesia. Their kidneys were removed, rinsed with saline and fixed in 10% neutral buffered formalin solution for histological evaluation. After the tissues were fixed in formalin for 72 hours, they were dehydrated by passing through increasing alcohol series (70%, 80%, 96% and 100%). Finally, they were kept in xylene and embedded in paraffin. Tissue sections with 5 µm thickness were obtained using a fully automated microtome. Hematoxylin-eosin staining method was used to examine the general histological structure and periodic acid-schiff (PAS) staining method was used to observe glycogen accumulation.

Histopathological Evaluation

Evaluation was done in a double-blind fashion by a histologist in the study. Renal damage was determined semi-quantitatively according to the degree and extent of histopathological changes. Tissues were examined for dilation of tubules, shedding of tubular epithelium, vacuolization of tubular epithelial cells, peritubular infiltration and loss of microvillus in proximal tubules. All sections were examined at 20X magnification in 10 different fields and scored as 0 (no change), 1 (mild), 2 (moderate), and 3 (severe) for each parameter[15]. The maximum mean histopathological damage score was 15. Tissue sections were examined with a Leica DFC 280 light microscope and Leica Q Win image analysis system (Leica Microscope Imaging Solution Ltd, Cambridge, UK) and evaluated, and their photographs were taken.

Immunohistochemical Analysis

Immunohistochemical (IHC) staining was performed using caspase-3 antibody (ab13847; Abcam, Kimera, Turkey). Tubular and glomerular caspase-3 immunoreactions were examined semi-quantitatively under a Leica DFC 280 light microscope.

To determine the staining intensity, 10 fields from each section were examined at X20 magnification and scored as (0) no staining, (1) weak staining, (2) moderate staining, and (3) severe staining. Tissue sections were examined with Leica DFC 280 light microscope and Leica Q Win image analysis system, scored and photographed.

Statistical Analysis

Statistical analyses were performed with SPSS (SPSS for Windows version 13.0) software. All results were expressed as arithmetic mean±standard error. In comparison of the groups, the Kruskal Wallis analysis of variance, which is one of the non-parametric tests, was used to compare all groups for all variables, while the Mann-Whitney U test was used for pairwise comparison of variables. A p value of <0.05 was considered statistically significant.

RESULTS

Histopathological Findings

The control group had normal histological appearance. The quercetin group had normal histological appearance like the control group. There was no statistically significant difference between the control group and the quercetin group in terms of histopathological findings (p>0.05). The mean histopathological damage score in the cisplatin group (Figure 1F) was statistically significantly increased compared to the control (Figure 1A) and quercetin (Figure 1B) groups (p=0.001). In the cisplatin group, dilatation of tubules, epithelial shedding into tubules (tubular caste), swelling and vacuolization of tubular epithelial cells and loss of microvillus in proximal tubules were detected (Figure 1C, 1E, 1H). In addition, increased PAS (+) staining intensity in the glomeruli, extensive hemorrhage, and occasionally peritubular infiltration areas were also observed in the cisplatin group (Figure 1D, 1F, 1G, 1H). All histopathological findings evaluated in the Cisplatin+Quercetin group were significantly reduced compared to the cisplatin group (p=0.001) (Table 1) (Figure 1C-K). The mean histopathological damage scores of all groups are given in Table 1.

Immunohistochemical Findings

Mild staining was detected in the control and quercetin groups with anti-Caspase-3 antibody (Figures 2A, 2B). In the cisplatin group, the intensity of the staining was noticeably increased,

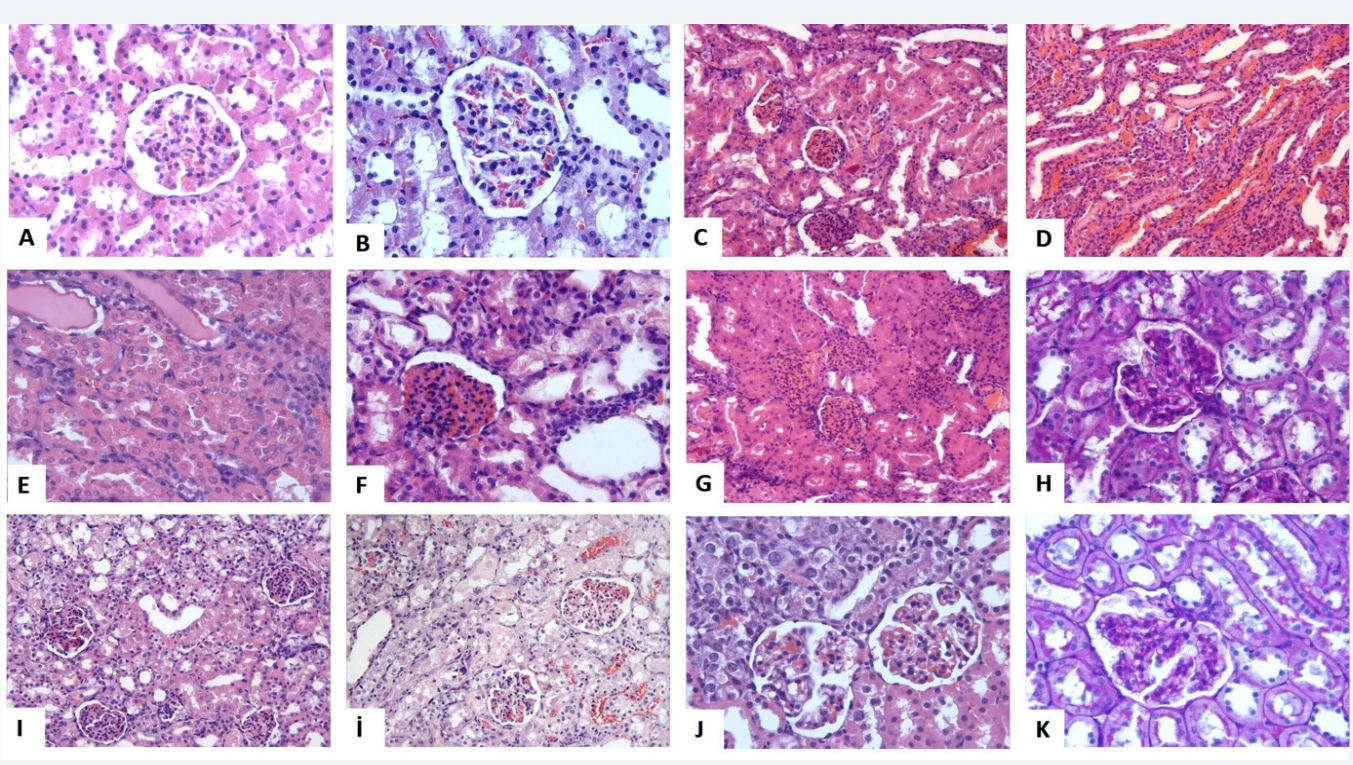

Figure 1. Kidney histopathology. Control group (A) and quercetin group (B) had normal histological appearance [hematoxylin-eosin (H-E) X20]. Many histopathological findings were found in the cisplatin group (C-H). In this group; dilatation in tubules (C), diffuse hemorrhage (D), epithelial shedding into tubules (E), swelling and vacuolization of tubular epithelial cells (E), peritubular infiltration (F, G), loss of microvillus in proximal tubules and increased PAS (+) staining in glomeruli (H) were detected. C. D. Cisplatin (H-E X10). E-F. Cisplatin (H-E X20). G. Cisplatin (H-E X10). H. Cisplatin (PAS X20). Histopathological findings were decreased in the cisplatin+quercetin group. I-J. Cisplatin+quercetin (H-E X20). K. Cisplatin+quercetin (PAS X20)

especially in the proximal tubules. When the Cisplatin and Cisplatin+Quercetin groups were compared, a statistically significant decrease in Caspase-3 IHC staining intensity was observed (p<0.005) (Figures 2C, 2D). The IHC scores of all groups are given in Table 2.

DISCUSSION

One of the most common side effects of cisplatin is dose-dependent renal toxicity[16]. Cisplatin nephrotoxicity may present with very different manifestations such as acute kidney injury, distal renal acidosis, hyperuricemia, hypomagnesemia, hypocalcemia or chronic kidney failure[17-22]. Cisplatin nephrotoxicity is the result of transport of cisplatin to renal epithelial cells, injury of nuclear and mitochondrial DNA, activation of cell death pathways, and initiation of a strong inflammatory response[23].

In a study, tubular degeneration and necrosis, hyaline eruptions in the tubules, intertubular hemorrhage, glomerular obstruction, and vacuolization were reported in the kidneys of male Sprague-Dawley rats weighing 200 grams that were administered a single intraperitoneal dose of 7 mg/kg

Table 1. Table of histopathological damage scores for all groups

Groups	Histopathological damage score
Group 1: Control	0.50±0.26
Group 2: Quercetin	0.87±0.35
Group 3: Cisplatin	11.37±0.56[a]
Group 4: Cisplatin+quercetin	7.62±0.37[b]

Data were expressed as arithmetic mean±standard error (n=7).
[a]Group 3 vs group 1 and group 2 p=0.001
[b]Group 4 vs group 3 p=0.001

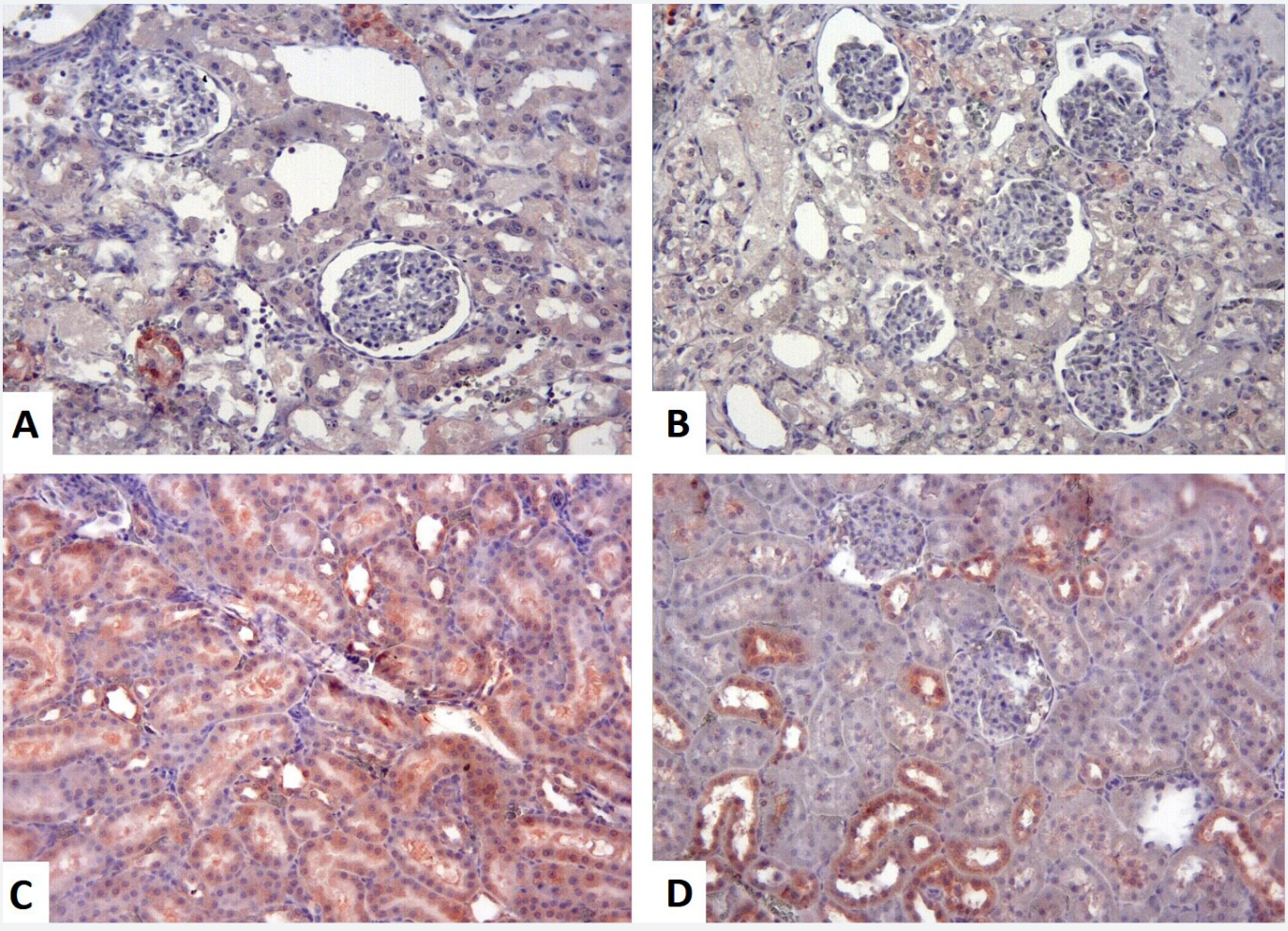

Figure 2. Immunohistochemical (IHC) staining with anti-caspase-3 antibody. Mild staining was detected in the control group (A) and quercetin group (B) (anti-caspase-3 X20). C. In the cisplatin group, the intensity of staining with anti-caspase-3 was increased especially in the proximal tubules (anti-caspase-3 X20). D. A decrease in IHC staining intensity was observed in the cisplatin+quercetin group (anti-caspase-3 X20)

Table 2. Caspase-3 immune score table for all groups

Groups	Caspase-3 staining intensity
Group 1: Control	0.37±0.18
Group 2: Quercetin	0.62±0.18
Group 3: Cisplatin	2.37±0.18[a]
Group 4: Cisplatin+quercetin	1.37±0.18[b]

Data were expressed as arithmetic mean±standard error (n=7).

[a]Group 3 vs group 1 and group 2 p=0.000

[b]Group 3 vs group 4 p<0.005

cisplatin[24]. We also applied the same dose of cisplatin in our study and observed the findings of dilatation and epithelial shedding (tubular caste) in the renal tubules. In another recent study, perivascular inflammatory cell infiltration, as well as tubular vacuolar degeneration and hyaline desquamation in the lumen of the tubules, was detected in the kidneys of rats administered the same dose of cisplatin as ours[25]. These findings also support our study.

In a study conducted to observe the antioxidant effects against cisplatin renal toxicity, microvillus deformation in the tubules and focal loss were observed in electron microscopic imaging of kidney tissue[26]. In our study, we observed loss of microvillus in the proximal tubules in sections with PAS staining.

Due to the serious side effects of cisplatin, various agents with antioxidant activity are being tested with this chemotherapeutic drug[27]. Quercetin is one of the most common dietary polyphenolic compounds, which is abundant in many foods. It is an effective antioxidant against radical oxygen species that prevents oxidation of low-density lipoproteins by scavenging free radicals and chelating transition metal ions[6,28]. It has anti-inflammatory, anticarcinogenic and antiviral properties[29-31].

In a study conducted to reverse the effects of nephrotoxicity, it was observed that histopathological findings such as renal tubular degeneration caused by lead element, necrosis, vacuolization and mononuclear cell infiltration regressed with 10 mg/kg quercetin and returned to normal histological appearance[32]. In our study, we found that dilatation in the renal tubules and vacuolization in tubular epithelial cells improved in the Cisplatin+quercetin group compared to the cisplatin group.

In renal damage induced by cyclosporine, quercetin has been found to reduce the findings of interstitial fibrosis, arteriopathy, glomerular basement membrane thickening, vacuolization of tubular epithelial cells and desquamation into the tubular lumen[33]. In our study, we observed that epithelial shedding (tubular caste) and vacuolization findings decreased with the application of quercetin.

In a study investigating the effects of quercetin in a diabetic nephropathy model, it was reported that histopathological findings such as epithelial desquamation, intracytoplasmic vacuolization, loss of brush border in the proximal tubules, and peritubular infiltration were reduced by the administration of quercetin[15]. In our study, we found that tubular dilatation, epithelial shedding in the tubule lumen (tubular caste), vacuolization in tubular epithelial cells, and loss of microvilli in the proximal tubules improved with the application of quercetin.

Caspase-3 is a key zymogen in cell apoptosis[9]. In a study, rats with experimental mammary adenocarcinoma were administered 4 mg/kg cisplatin and then 50 mg/kg quercetin. It has been observed that cisplatin causes shedding of renal tubular epithelial cells, loss of brush border, hyaline deposition in the tubule lumen, and enlargement of tubules. It has been reported that as a result of caspase-3 immunostaining, the staining intensity increased with cisplatin, but the staining intensity decreased in the cisplatin+quercetin group[34]. In our study, 7 mg/kg cisplatin and 25 mg/kg quercetin were administered and it was determined that the staining intensity increased with caspase-3 antibody.

Study Limitations

Although the current study has given the expected results, it has some limitations. The most important limitation is that there had to be biochemical data because quercetin is an antioxidant substance. In addition, validation of data obtained from examinations with electron microscopy can make the results even more reliable.

CONCLUSION

As a result, it is seen that quercetin is histopathologically beneficial in the treatment of kidney toxicity caused by cisplatin and has a positive effect on apoptotic pathways. We think that further studies on this subject with different doses and durations will contribute to the literature.

Ethics

Ethics Committee Approval: The study was approved by the İnönü University Medical Faculty Animal Experiments Local Ethics Committee (ethics committee no: 2012/A-103, date: 09.06.2012).

Informed Consent: It is an animal experiment.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: H.E., E.T., N.B., A.T., Concept: H.E., E.T., N.B., A.T., Design: H.E., E.T., N.B., A.T., Data Collection or Processing: H.E., E.T., N.B., A.T., Analysis or Interpretation: H.E., E.T., N.B., A.T., D.Ç., Literature Search: D.Ç., H.E., Writing: D.Ç. H.E.

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