RESEARCH ARTICLE

F.U. Vet. J. Health Sci.
2022; 36 (2): 116 - 121
http://www.fusabil.org

Protective Effects of Quercetin in 5-Fluorouracil-Induced Nephrotoxicity in Rats [*, **]

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This study aimed to determine the protective effects of Quercetin against 5-Fluorouracil (5-FU)-induced nephrotoxicity in rats. In this study, forty male adult rats weighing approximately 200-250 g, were used and the rats were randomly divided into five groups. According to the experimental protocol, Quercetin and 5-FU were administered to the rats, and at the end of the experimental study, intracardiac blood samples from the rats were taken under anesthesia and decapitated. Urea, creatinine, and blood urea nitrogen (BUN) values in serum samples were analyzed in an autoanalyzer. Malondialdehyde (MDA), superoxide dismutase (SOD), glutathione peroxidase (GPx) interleukin-33 (IL-33), aquaporin-1 (AQP-1), and Nephrin parameters in kidney tissues were analyzed by commercial ELISA kits. In addition, kidney tissues were subjected to histopathological evaluation by Mallory's triple staining modified by Crossman. Serum urea, creatinine, and BUN levels were significantly increased in the 5-FU group compared to the control, Quercetin100+5-FU, and the Quercetin100 groups. Quercetin had antioxidant activity against 5-FU-induced renal oxidative stress. Also, 5-FU stimulated inflammation by increasing renal IL-33 levels and Quercetin inhibited these increases. AQP-1 and Nephrin levels were not different among the experimental groups. Especially high dose of Quercetin prevented histopathological changes caused by 5-FU. As a result of this study, it was determined that Quercetin significantly prevented 5-FU-induced nephrotoxicity in rats.

Key Words: *5-fluorouracil, quercetin, oxidative stress, nephrotoxicity, rat*

Sıçanlarda 5-Florourasil ile İndüklenen Nefrotoksisitede Kuersetin'in Protektif Etkileri

Bu çalışmada, sıçanlarda 5-florourasil (5-FU) ile indüklenen nefrotoksisitede Kuersetin'in koruyucu etkilerinin belirlenmesi amaçlandı. Çalışmamızda yaklaşık 200-250 g ağırlığında 40 adet erişkin erkek sıçan kullanıldı ve sıçanlar rastgele beş gruba ayrıldı. Ratlara deney protokolüne göre Kuersetin ve 5-FU uygulandı ve deneysel çalışmanın sonunda sıçanlardan anestezi altında intrakardiyak kan örnekleri alındı ve dekapite edildi. Serum örneklerindeki üre, kreatinin ve kan üre nitrojen (BUN) değerleri otoanalizörde analiz edildi. Böbrek dokularındaki malondialdehit (MDA), süperoksit dismutaz (SOD), glutatyon peroksidaz (GPx), interlökin-33 (IL-33), aquaporin-1 (AQP-1) ve Nefrin parametreleri ticari ELISA kitleri ile analiz edildi. Ayrıca Crossman tarafından modifiye edilen Mallory'nin üçlü boyaması yapılarak böbrek dokuları histopatolojik değerlendirmeye alındı. Serum üre, kreatinin ve BUN seviyeleri kontrol, Kuersetin100+5-FU ve Kuersetin100 gruplarına kıyasla 5-FU grubunda önemli ölçüde arttı. 5-FU ile indüklenen renal oksidatif strese karşı Kuersetin antioksidan aktiviteye sahipti. Ayrıca 5-FU, renal IL-33 seviyesini artırarak inflamasyonu uyardı ve Kuersetin bu artışları inhibe etti. AQP-1 ve Nephrin seviyeleri deney grupları arasında farklı değildi. Özellikle yüksek doz Kuersetin 5-FU'nun neden olduğu histopatolojik değişiklikleri önledi. Bu çalışma sonucunda, Kuersetin'in sıçanlarda 5-FU kaynaklı nefrotoksisiteyi önemli ölçüde önlediği belirlendi.

Anahtar Kelimeler: *5-florourasil, kuersetin, oksidatif stres, nefrotoksisite, sıçan*

Introduction

Methods such as radiotherapy, ozone treatment, and surgical treatment are used for cancer treatment (1). Chemotherapy is one of the most common treatment method for cancer. 5-fluorouracil (5-FU) is a chemotherapeutic agent that has been used extensively in the treatment of many types of cancer such as ovarian, prostate, uterus, cervix, endometrium, bladder, pancreas, and liver cancer, especially colorectal cancer and breast cancer (2). 5-FU is converted into fluorodeoxyuridine monophosphate (FdUMP), fluorodeoxyuridine triphosphate, and fluorouridine triphosphate metabolites by the enzyme dihydropyrimidine dehydrogenase (3). 5-FU impairs both the functions of DNA and RNA and DNA synthesis and repair (4). Many studies reported that anticancer agents cause organ toxicities (5-10). The 5-FU, among one of these agents, induces multiple organ toxicities in the organism (5, 11) and nephrotoxicity is one of the most common side effects of the 5-FU. The 5-FU administration induces oxidative stress in

Received : 19.02.2022
Accepted : 28.04.2022

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[*] This study was supported by Atatürk University Scientific Research Projects Coordination Unit (Project ID: 2018-6470).
[**] This article has been produced from the master thesis titled “Protective Effects of Quercetin in 5-Fluorouracil-Induced Nephrotoxicity in Rats”.

kidney tissue as a result of the weakening of the antioxidant defense system and the release of lipid peroxidation products (12). The 5-FU causes severe nephrotoxicity, an increase in serum urea, creatinine, uric acid, and potassium (K^+) levels, and induced renal oxidative stress in rats. In addition, there is a significant reduction in serum protein, albumin, sodium (Na^+) and Magnesium (Mg) levels (13).

The effects of various flavonoids on kidney damage induced by anticancer agents have been investigated (5, 14). Quercetin is commonly distributed in certain plant species, and it is a flavonoid compound with anti-inflammatory, anticarcinogenic and antioxidant effects (2, 6, 15). Therapeutic or protective effects of Quercetin in organ toxicities induced by anticancer agents have been reported by many studies (6, 16). The protective effects of Quercetin on the renal toxicity induced by 5-FU in rats have not been determined yet. In line with the literature, this study was aimed to investigate possible protective effects of Quercetin in 5-FU-induced nephrotoxicity in rats.

Material and Methods

Research and Publication Ethics: This study was approved by Atatürk University Rectorate Animal Experimentation Local Ethics Committee (Protocol no: 2017/123).

Animals: In this study, 40 adults, Sprague Dawley rats, weighing 200-250 g, were used. The animals were housed in physiological conditions during the study period and were not exposed to any restrictions.

Experimental Protocol: In the study, five experimental groups were formed. There were eight rats in each group. Rats in the control group were given intra-gastric (i.g.) solvent (corn oil, 1 mL) for 14 days. 5-FU group was given i.g. corn oil, for 14 days and on the 11th day, a single dose of 5-FU [200-mg/kg, intraperitoneal (i.p.)] was injected. Quercetin50+5-FU and Quercetin100+5-FU groups were i.g. Quercetin was administered at doses of 50 and 100 mg/kg for 14 days, respectively, and on the 11th day, a single dose of 5-FU (200 mg/kg, i.p.) was injected. Quercetin100 group was administered 100 mg/kg dose of Quercetin for 14 days. On the 15th day of the experiment, the rats were anesthetized with thiopental sodium (20 mg/kg). They were decapitated after taking intra-cardiac blood samples from rats under general anesthesia. The left kidney of each rat was taken for biochemical analysis and kept at -20ºC until the analysed. The right kidneys were taken for histopathological evaluation and were fixed in 10% formol.

Analysis of Serum Urea, Creatinine and BUN Parameters: Blood samples was transferred to anticoagulant tubes and anticoagulant tubes were centrifuged at 5000 RPM at +4ºC for 10 minutes. The serum samples obtained were taken into Eppendorf tubes and kept at -20 ºC until analysed. Urea, creatinine and blood urea nitrogen (BUN) parameters in the serum were measured on the Modular PP auto-analyzer (Randox IV Monaco Auto-Chemistry Analyzer).

Preparation of Renal Homogenates: The kidney tissues were homogenized to 5 µm in a TissueLyser II (Qiagen) with liquid nitrogen. Afterward, they were weighed and diluted to 1:20 with a phosphate buffer (pH 7.4) before homogenization. The homogenates were centrifuged for 20 min at 3000 rpm at 4 ºC, and the supernatant was used for enzyme-linked immunosorbent assay (ELISA) analysis.

Analysis of Lipid Peroxidation and Antioxidant Enzyme Activities: Lipid peroxidation and antioxidant enzyme markers were analyzed by using commercial ELISA kits. The levels of renal malondialdehyde (MDA) and the activities of renal superoxide dismutase (SOD) and glutathione peroxidase (GPx) were analyzed by using commercial ELISA kits (Sunred Biological Technology, Shangai, China) according to the manufacturer's protocol

Analysis of Interleukin-33 (IL-33), Aquaporin-1 (AQP-1), and Nephrin Levels: IL-33, AQP-1 and Nephrin levels were measured in renal supernatants with commercial ELISA kits (Sunred Biological Technology, Shangai, China) according to the manufacturer's protocol

Histopathological Evaluation: Kidney tissues taken from the rats sacrificed at the end of the study for histological examinations were detected in a 10% buffered formaldehyde solution for 48 hours. After, the tissues were passed through alcohol and xylol series by routine histological methods and embedded in paraffin blocks. Cross-sections taken from the paraffin blocks with Leica RM2125RT microtome (Leica Microsystems, Wetzlar, Germany) with a thickness of 5 µm were painted with Crossman-modified Mallory's triple staining and examined under light microscopy (Nikon Eclipse i50, Tokyo, Japan).

Statistical Analysis: The findings obtained as a result of our study were evaluated statistically. Since the sample size was 40, normality was checked with the Shapiro Wilk test. It was determined that the data showed normal distribution ($P>0.05$). The quantitative values obtained were evaluated in the SPSS 20.00 statistical data program using the Tukey test after one-way ANOVA. $P<0.05$ was considered statistically significant (2, 11).

Results

Serum urea, creatinine and BUN levels were significantly increased in the 5-FU group compared to the control ($P<0.05$). In particular, the high dose of Quercetin inhibited ($P<0.05$) the increases in these parameters. Serum urea, creatine, and BUN levels summarized in Table 1.

The MDA levels increased significantly in the 5-FU group compared to control, Quercetin100+5-FU and Quercetin100 groups (Figure 1A). SOD and GPx activities decreased in the 5-FU group compared to

control and Quercetin100 groups (Figure 1B and 1C, p<0.05). Especially, the high dose of Quercetin prevented to 5-FU induced renal oxidative stress (Figure 1A, 1B and 1C, P<0.05).

IL-33 levels increased significantly in the 5-FU group compared to other groups (Figure 2A, P<0.05). It was determined that AQP-1 and Nephrin levels did not differ between the experimental groups (Figure 2B and 2C, P>0.05).

The glomerular and tubular structures of the rats in the control and Quercetin100 groups had normal histological appearance (Figures 3A-3E). In the 5-FU group there were partly shrunken glomeruli and the bowman capsule of the renal corpuscles showed dilation. In tubular epithelium, cytoplasmic swelling, cytoplasmic vacuolization, hypertrophic changes and desquamation areas were observed. In addition, there was an intense connective tissue increase and dilatation in the vessels around Bowman capsules and in the intertubular areas (Figure 3B). In the renal tubule epithelium of the rats in the Quercetin50+5-FU group, moderate hypertrophic degeneration, cytoplasmic vacuolization, cytoplasmic swelling and desquamation were observed (Figure 3C). In the Quercetin100+5-FU group, decreased dilatation in Bowman's capsules, milder degeneration of tubular epithelium and increased connective tissue were observed (Figure 3D).

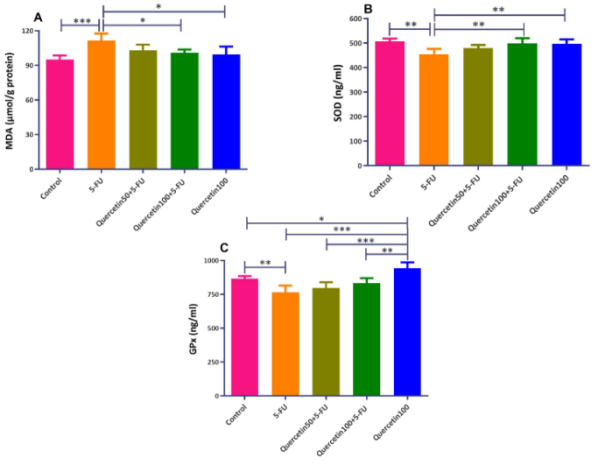

Figure 1. MDA (A) levels, SOD (B) and GPx (C) activities in experimental groups (*: P<0.01, **: P<0.001, P***: P<0.0001, n=8).

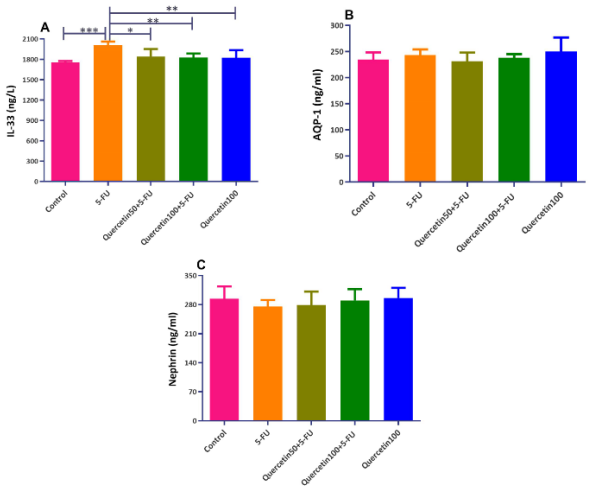

Figure 2. IL-33 (A), AQP-1 (B) and Nephrin (C) levels in experimental groups (*: P<0.01, **: P<0.001, ***:P<0.0001).

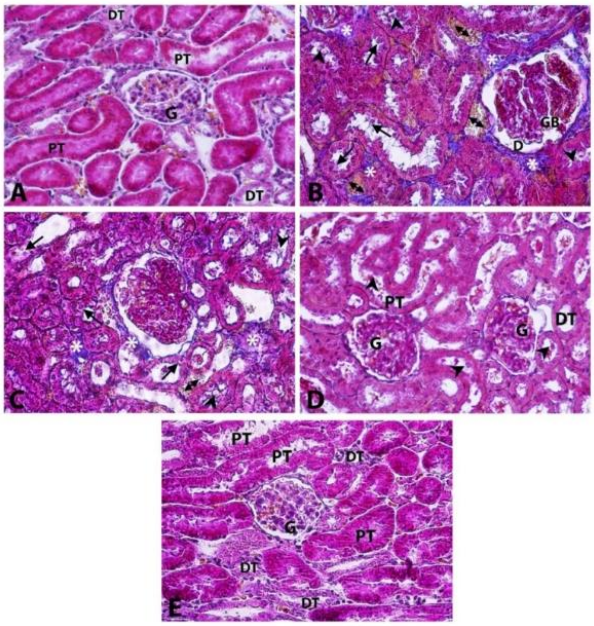

Figure 3. Light microscopic images of kidney tissue obtained from rats in the A: Control, B: 5-FU, C: Quercetin 50+5-FU, D:Quercetin 100+5-FU, E: Quercetin 100 groups. G:Glomerulus, PT: Proximal tubule, DT: Distal tubule, GB:Shrinkage in the glomerulus structure, D: Dilation in the Bowman capsule, *:Connective tissue increase, Arrow:Cytoplasmic swelling in tubular epithelium, Arrowhead:Hypertrophic changes and desquamation areas in tubular epithelium, Double-headed arrow: Dilation in the veins. Paint: Triple Paint of Crossman, Bar: 20 µm.

Table 1. Serum urea, creatinine and BUN levels in experimental groups (n= 8)

Experimental Groups	Urea (mg/dL)	Creatinine (mg/dL)	BUN (mg/dL)
Control	29.00±4.00^{a}	0.45±0.05^{a}	17.21±1.41^{ac}
5-FU	45.33±2.58^{b}	0.65±0.06^{b}	26.43±3.79^{b}
Quercetin50+5-FU	41.00±5.03^{b}	0.51±0.14^{ab}	24.83±2.45^{b}
Quercetin100+5-FU	30.16±2.63^{a}	0.5±0.06^{a}	19.39±1.43^{a}
Quercetin100	29.66±4.88^{a}	0.43±0.05^{a}	14.71±1.44^{c}

Data are means ± SD

a,b; a,c: P<0.05; b,c: P<0.01, there is a statistical difference between the values expressed with different letters in the same column

Discussion

5-FU is a widely used chemotherapeutic in chemotherapy and causes multiple organ toxicities. The protective or therapeutic effects of flavonoids in organ toxicity models caused by anticancer agents have been reported in many studies. In our study, the protective effects of Quercetin in 5-FU-induced nephrotoxicity in rats were investigated.

Urea, creatinine and BUN levels are measured routinely in the evaluation of kidney functions in the clinic. As a result of many studies, increases in blood urea, creatinine and BUN levels are shown as evidence of renal dysfunction (17-18). In experimentally generated nephrotoxicity models, renal function tests are routinely evaluated. The therapeutic or protective effects of some agents on kidney functions impaired by toxic compounds or chemicals have been investigated in many studies (19, 20). Atessahin et al. (21) stated that rats treated with cisplatin experienced a decrease in glomerular filtration rate and an increase in serum urea and creatinine levels. Gelen et al. (5) determined that serum creatinine and BUN levels increased significantly in the nephrotoxicity model induced by 5-FU in rats and that the application of Naringin for protective purposes inhibited the increase in these parameters. In another study, it was determined that Quercetin administration prevented the increase in urea and creatine levels in cisplatin-induced acute nephrotoxicity model in rats (22). In our study, it was observed that urea, creatinine and BUN levels increased significantly in serum samples obtained 48 hours after 5-FU application compared to control in the 5-FU group and especially the high dose of Quercetin has a protective effect against 5-FU nephrotoxicity. It is thought that this effect of Quercetin prevents kidney damage caused by 5-FU and accordingly the increase in these parameters.

GSH, SOD and GPx are among the best-known antioxidants in tissues. GPx, enzyme-containing selenium in the GSH active region, reacts with hydrogen peroxide (H2O2) and organic peroxides, and removes H2O2 from the cell, and shows an antioxidant effect (23,24). Reactive oxygen species stimulate lipid peroxidation (LPO) by acting on fatty acids in the cell membrane. The best known of the aldehydes released by lipid peroxidation is MDA. Many studies have reported that anticancer agents stimulate oxidative stress in cells, decrease SOD and GPx activities and increase MDA levels (7, 16). Gelen et al. (5) determined that 5-FU administration causes hepatotoxicity and nephrotoxicity in rats, and 5-FU induces renal oxidative stress and causes a significant increase in MDA level and a decrease in SOD and GSH activities. Researchers reported that Quercetin prevents lipid peroxidation and oxidative stress in lung (6), liver (16,25), and renal (25) toxicity induced by anticancer agents in rats. In accordance with the literature, our study revealed that 5-FU induced renal oxidative stress in rats, increased kidney MDA levels, and significantly decreased SOD and GPx activities. It was determined that Quercetin prevents oxidative stress caused by 5-FU with its strong antioxidant activity.

IL-33, a proinflammatory cytokine, is released from necrotic cells and binds to STR2R receptors on immune cells (26). It increases the secretion of cytokines following its binding to related receptors, and inflammation is stimulated due to these events (27). IL-33 stimulates CD4 T cell infiltration in the kidneys, resulting in kidney damage. It was determined that the levels of IL-33 increased in the model of acute kidney injury induced by cisplatin and IL-33 was predominantly expressed in the glomeruli, blood vessels, and peritubular capillaries in the kidneys (28). Sengul et al. (17) reported that renal IL-33 levels significantly increased in acrylamide-induced nephrotoxicity in rats. Our findings were consistent with the literature, and it was determined that 5-FU administration significantly increased renal IL-33 levels, and Quercetin administration for protective purposes prevented the increase in IL-33 levels.

Kidneys are the most important organs where AQPs, known as specific water channels, are expressed in the organism. AQP-1 is the most expressed among the aquaporins defined in the kidney (AQP-1, AQP-2, AQP-3, AQP-4) and AQ1, especially in the proximal tubule where water resorption is most common, and in the thin descending arm of henella (29,30). Lajer et al. (31) reported that renal AQP-1 expression decreased statistically significantly in cisplatin-induced nephrotoxicity. Kucukler et al. (32) determined that AQP-1 levels were decreased in lead acetate-induced nephrotoxicity in rats and the administration of Chrysin, a flavonoid, prevented this decrease. In a another study, AQP-1 expression decreased significantly in the medulla and did not change in the cortex of cisplatin-administered rats (33). Contrary to the literature, according to the findings obtained from our study, it was determined that there was no difference between the experimental groups in the expression of renal AQP-1 in rats that we applied 5-FU and Quercetin.

The nephrin is a protein structure that is synthesized by podocytes in glomeruli, encoded by the Nephrotic Syndrome Type 1 gene, protecting the viability of podocytes, the structure of glomerulus, and functions in the kidneys of adults (34). Gu et al. (35) reported that nephrotoxicity induced by doxorubicin in rats significantly decreased expression of the nephrin compared to healthy rats. In the study conducted by Na et al. (36), in adriamycin-induced nephropathy in rats, the expression of the nephrin decreased significantly in the group treated with adriamycin compared to the control group. According to the findings obtained in our study, it was found that the levels of the nephrin decreased in the toxicity group compared to the control group in the 5-FU-induced nephrotoxicity model. However, it was not statistically significant as stated in the literature. It was determined that Quercetin administration did not cause a change in renal nephrin levels.

In the models of nephrotoxicity induced by anticancer agents, some pathologies occur in the histological structure of the kidney tissue. It has been reported that the administration of 5-FU, which is widely used in chemotherapy, causes kidney tissue damage,

degeneration and necrosis in tubular epithelial cells (37). Gelen et al. (5) reported to tubular dilatation, glomerular atrophy, Bowman's capsule dilatation, degeneration and necrosis in renal tubular epithelial cells in the histopathological evaluation of kidney tissues of rats administered 5-FU. Also, they have found that the application of Naringin, an antioxidant and anti-inflammatory flavonoid, prevented the formation of renal pathologies by providing a protective effect. In our study, it was determined that the histopathological findings of the kidney tissues of the rats in the experimental groups were compatible with the literature and there was shrinkage in the glomerulus, degeneration in the renal corpuscles and dilatation in the Bowman capsule in the 5-FU group. In addition, the presence of swelling, vacuolization, hypertrophic changes and desquamation areas in the tubular epithelium was determined. Intense connective tissue increase and dilatation of the vessels were among the findings obtained around Bowman capsules and in the intertubular areas. It was determined that the low dose of Quercetin prevented these pathologies at a moderate level, and the high dose prevented pathologies in the kidney tissue by providing a significant protective effect, reducing the dilatation in the Bowman capsules, reducing the degeneration in the tubular epithelium and there was no connective tissue increase.

In conclusion, in this study, we determined that 5-FU causes renal dysfunction by increasing oxidative stress in rat kidney tissue, deactivating the antioxidant defense system and causing inflammation and Quercetin administration protected against side effects of 5-FU in kidney tissue of rats.

Acknowledgment

We thank Assoc. Prof. Semin GEDİKLİ for histopathological results and support.

References

1. Adams RN, Mosher CE, Blair CK, et al. Cancer survivors' uptake and adherence in diet and exercise intervention trials: An integrative data analysis. Cancer 2015; 121: 77-83.
2. Sengul E, Gelen V, Gedikli S. Cardioprotective activities of quercetin and rutin in sprague dawley rats treated with 5-fluorouracil. J Anim Plant Sci 2021; 31: 423-431.
3. Miura K, Kinouchi M, Ishida K, et al. 5-FU metabolism in cancer and orally-administrable 5-fu drugs. Cancers 2010; 2: 1717-1730.
4. Longley DB, Harkin DP, Johnston PG. 5-fluorouracil: Mechanisms of action and clinical strategies. Nat Rev 2003; 3: 330-338.
5. Gelen V, Şengül E, Yıldırım S, etal. The protective effects of naringin against 5-fluorouracil-induced hepatotoxicity and nephrotoxicity in rats. Iran J Basic Med Sci 2018; 21: 404-410.
6. Şengül E, Gelen V, Gedikli S, et al. The protective effect of quercetin on cyclophosphamide-induced lung toxicity in rats. Biomed Pharmacother 2017; 92: 303-307.
7. Gelen V, Şengül E, Yıldırım S, et al. Effects of Rutin on bladder contractility and histopathology in cyclophosphamide-induced hemorrhagic cystitis in rats. Atatürk University J Vet Sci 2017; 13: 337-346.
8. Sengul E, Gelen SU, Yıldırım S, et al. Probiotic bacteria attenuates cisplatin-induced nephrotoxicity through modulation of oxidative stress, inflammation and apoptosis in rats. Asian Pac J Trop Biomed 2019; 9: 116-122.
9. Gedikli S, Şengül E. Ratlarda siklofosfamid ile indüklenen hepatotoksisite üzerine kuersetinin etkileri. Dicle Tip Derg 2019; 46: 41-50.
10. Gelen V, Şengül E. Antioxidant, anti-inflammatory and antiapoptotic effects of Naringin on cardiac damage induced by cisplatin. Indian J Tradit Knowl 2020; 19: 459-465.
11. Elghareeb MM, Elshopakey GE, Hendam BM, et al. Synergistic effects of Ficus Carica extract and extra virgin olive oil against oxidative injury, cytokine liberation, and inflammation mediated by 5-Fluorouracil in cardiac and renal tissues of male albino rats. Environ Sci Pollut Res 2021; 28: 4558-4572.
12. Rashid S, Ali N, Nafees S, et al. Mitigation of 5-Fluorouracil induced renal toxicity by chrysin via targeting oxidative stress and apoptosis in wistar rats. Food Chem Toxicol 2014; 66: 185-193.
13. Akindele AJ, Oludadepo GO, Amagon KI, et al. Protective effect of carvedilol alone and coadministered with diltiazem and prednisolone on doxorubicin and 5-fluorouracil-induced hepatotoxicity and nephrotoxicity in rats. Pharmacol Res Perspect 2018; 6: e00381.
14. Çayır K, Karadeniz A, Şimşek N, et al. Pomegranate seed extract attenuates chemotherapy-induced acute nephrotoxicity and hepatotoxicity in rats. J Med Food 2011; 14: 1254-1262.
15. Gelen V, Şengül E, Gedikli S, et al. Therapeutic effect of quercetin on renal function and tissue damage in the obesity induced rats. Biomed Pharmacother 2017; 89: 524-528.
16. Gelen V, Şengül E, Gedikli S, et al. The protective effect of rutin and quercetin on 5-FU-induced hepatotoxicity in rats. Asian Pac J Trop Biomed 2017; 7: 647-653.
17. Sengul E, Gelen V, Yildirim S, et al. The effects of selenium in acrylamide-induced nephrotoxicity in rats: roles of oxidative stress, inflammation, apoptosis, and DNA damage. Biol Trace Elem Res 2021; 199: 173-184.
18. Dağ Y, Şengül E, Selçuk M, et al. Ratlarda Cyclophosphamide ile İndüklenen Nefrotoksisitede Bazı Hematolojik Parametreler ve Böbreğin Histopatolojisi Üzerine Naringinin Protektif Etkileri. Atatürk Üniv Vet Bil Derg 2018; 13: 219-228.
19. El-Sayed EM, Abd-Allah AR, Mansour AM, et al. Thymol and carvacrol prevent cisplatin-induced nephrotoxicity by abrogation of oxidative stress, inflammation, and apoptosis in rats. J Biochem Mol 2015; 29: 165-172.

20. Somchit MN, Sanat F, Hui GE, et al. Mefenamic acid induced nephrotoxicity: An animal model. Adv Pharm Bull 2014; 4: 401-404.

21. Atessahin A, Yilmaz S, Karahan I, et al. Effects of lycopene against cisplatin-induced nephrotoxicity and oxidative stress in rats. Toxicology 2005; 212: 116-123.

22. Kadhim S, Al-Rekabi M, Mohammed N, et al. Potential protective effect of quercetin against cisplatin-induced acute nephrotoxicity in male rats. Syst Rev Pharm 2021; 12: 248-252.

23. Kara A, Gedikli S, Sengul E, et al. Oxidative stress and autophagy. Free Radicals and Diseases 2016; 69-86.

24. Akbari M, Ostadmohammadi V, Lankarani KB, et al. The effects of vitamin D supplementation on biomarkers of inflammation and oxidative stress among women with polycystic ovary syndrome: A systematic review and meta-analysis of randomized controlled trials. Horm Metab Res 2018; 50: 271-279.

25. Kocahan S, Dogan Z, Erdemli E, et al. Protective effect of quercetin against oxidative stress-induced toxicity associated with doxorubicin and cyclophosphamide in rat kidney and liver tissue. Iran J Kidney Dis 2017; 11: 124-131.

26. Moussion C, Ortega N, Girard J-P. The IL-1-like cytokine IL-33 is constitutively expressed in the nucleus of endothelial cells and epithelial cells in vivo: A novel 'alarmin'? PloS one 2008; 3: e3331.

27. Lamkanfi M, Dixit VM. IL-33 raises alarm. Immunity 2009; 31: 5-7.

28. Akcay A, Nguyen Q, He Z, et al. IL-33 exacerbates acute kidney injury. Am Soc Nephrol 2011; 22: 2057-2067.

29. Preston GM, Jung JS, Guggino W, et al. The mercury-sensitive residue at cysteine 189 in the CHIP28 water channel. J Biol Chem 1993; 268: 17-20.

30. Tradtrantip L, Tajima M, Li L, et al. Aquaporin water channels in transepithelial fluid transport. J Med Investig 2009; 56: 179-184.

31. Lajer H, Kristensen M, Hansen H, et al. Magnesium depletion enhances cisplatin-induced nephrotoxicity. Cancer Chemother Pharmacol 2005; 56: 535-542.

32. Kucukler S, Benzer F, Yildirim S, et al. Protective effects of chrysin against oxidative stress and inflammation induced by lead acetate in rat kidneys: A biochemical and histopathological approach. Biol Trace Elem Res 2021; 199: 1501-1514.

33. Kishore BK, Krane CM, Di Iulio D, et al. Expression of renal aquaporins 1, 2, and 3 in a rat model of cisplatin-induced polyuria. Kidney Int 2000; 58: 701-711.

34. Li X, Chuang PY, D'Agati VD, et al. Nephrin preserves podocyte viability and glomerular structure and function in adult kidneys. J Am Soc Nephrol 2015; 26: 2361-2377.

35. Gu Y, Ju A, Jiang B, et al. Yiqi Fumai lyophilized injection attenuates doxorubicin-induced cardiotoxicity, hepatotoxicity and nephrotoxicity in rats by inhibition of oxidative stress, inflammation and apoptosis. RSC Adv 2018; 8: 40894-40911.

36. Na W, Ri-Bao W, Qing-Ping L, et al. Protective effects of astragaloside in rats with adriamycin nephropathy and underlying mechanism. Chin J Nat Med 2016; 14: 270-277.

37. Hak HNGE, Moawad TIS, Hafez GA-A. Histological study of the effect of chemotherapy with 5-Fluorouracil on normal liver and kidney of mice. Int J Nov Res Life Sci 2015; 2: 8-13.