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Original Article
Özgün Araştırma

Taxifolin attenuates cisplatin-induced kidney damage in rats via suppressing p53 and iNOS

Gökhan Akçakavak[1*], Özhan Karataş[2], Zeynep Celik Kenar[3], Ayşenur Tural Çifci[4], Osman Dagar[5], Ahmed A.j. Jabbar[6], Bahadır Kılınç[7], Mehmet Tuzcu[8]

[1,4] Aksaray University, Faculty of Veterinary Medicine, Department of Pathology, Aksaray, Türkiye
[2] Sivas Cumhuriyet University, Faculty of Veterinary Medicine, Department of Pathology, Sivas, Türkiye
[3, 8] Selcuk University, Faculty of Veterinary Medicine, Department of Pathology, Konya, Türkiye
[5] Aksaray University, Vocational school, Aksaray, Türkiye
[6] Erbil Technical Health and Medical College, Erbil Polytechnic University, Department of Medical Laboratory Technology, Erbil, Iraq
[7] Etlik Central Veterinary Control and Research Institute, Pathology Department, Ankara, Türkiye

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Abstract:Cisplatin (CP) is a platinum-based anticancer drug used to treat many different solid tumors. Although CP has strong anticancer properties, its clinical use is limited due to side effects such as ototoxicity, neurotoxicity, myelosuppression and nephrotoxicity. Taxifolin (Tax) is reported to exhibit various possess effects such as anti-inflammatory, antioxidant, antimicrobial, antiviral and anticancer. In this study, we aimed to investigate the possible effects of Tax on CP-induced nephrotoxicity. This study consisted of Control (C), Taxifolin (Tax), Cisplatin (CP) and Cisplatin + Taxifolin (CP + Tax) groups, and there were 6 rats in each group. CP was administered to rats intraperitoneally (i.p.) in a single dose of 7 mg/kg, and Tax was administered orally at a dose of 50 mg/kg for 7 consecutive days. Histopathologically, significant changes such as tubular epithelial degeneration and necrosis, tubular dilatation, inflammatory cell infiltrates, hyaline cast, and glomerular atrophy were detected in the CP group. It was seen that the CP+Tax group significantly reduced histopathological changes ($p<0.001$). In addition, immunohistochemically, the expressions of inducible nitric oxide synthase (iNOS) and p53 were highly irregular in the CP group relative to the control groups ($p<0.001$). Taxifolin treatment (CP+Tax group) significantly decreased the expressions of iNOS and p53 ($p<0.001$). Current findings revealed nephroprotective and ameliorative effects of Tax against CP-induced kidney toxicity.

Keywords: Cisplatin, histopathology, iNOS, taxifolin, p53.

Taksifolin, p53 ve iNOS'u baskılayarak sıçanlarda sisplatin kaynaklı böbrek hasarını hafifletir

Özet: Sisplatin (SP), birçok farklı solid tümörün tedavisinde kullanılan platin bazlı bir antikanser ilaçtır. Sisplatin güçlü antikanser özelliklere sahip olmasına rağmen ototoksisite, nörotoksisite, miyelosüpresyon ve nefrotoksisite gibi yan etkileri nedeniyle klinik kullanımı sınırlıdır. Taksifolin (Tak)'in antiinflamatuar, antioksidan, antimikrobiyal, antiviral ve antikanser gibi çeşitli etkilere sahip olduğu bildirilmektedir. Bu çalışmada Tak'in SP kaynaklı nefrotoksisite üzerindeki olası etkilerinin araştırılması amaçlandı. Bu çalışma Kontrol (K), Taksifolin (Tak), Sisplatin (SP) ve Sisplatin+Taksifolin (SP+Tak) gruplarından oluştu ve her grupta 6 sıçan yer aldı. SP, sıçanlara intraperitoneal (i.p.) olarak tek doz 7 mg/kg uygulandı ve Tak, oral olarak 50 mg/kg dozunda ardışık 7 gün uygulandı. Histopatolojik olarak SP grubunda tübüler epitelyal dejenerasyon ve nekroz, tübüler dilatasyon, yangı hücre infiltrasyonu, hiyalin silindir ve glomerüler atrofi gibi önemli değişiklikler tespit edildi. SP+Tak grubunun histopatolojik değişiklikleri anlamlı düzeyde azalttığı görüldü ($p<0,001$). Ayrıca immünohistokimyasal olarak indüklenebilir nitrik oksit sentaz (iNOS) ve p53 ekspresyonlarının SP grubunda kontrol gruplarına göre oldukça düzensiz olduğu görüldü ($p<0,001$). Taksifolin tedavisi (SP+Tak grubu) iNOS ve p53 ekspresyonlarını anlamlı düzeyde azalttı ($p<0.001$). Mevcut bulgular, Tak'in SP kaynaklı böbrek toksisitesine karşı nefroprotektif ve iyileştirici etkileri ortaya koydu.

Anahtar kelimeler: histopatoloji, iNOS, taksifolin, p53, sisplatin

Introduction

Cisplatin (CP) is known as a platinum-derived anticancer agent used in the treatment of many tumors such as brain, kidney, lung, head and neck tumors, testicles, ovaries and bladder (Dasari and Tchounwou, 2014). CP is also used as a combination therapy in the treatment of squamous cell carcinoma and osteosarcoma (Wagner et al., 2016; Le and Hanna, 2018). CP is one of the most potent and effective chemotherapeutics with well-known antitumor ef-

Yazışma adresi / Correspondence: *Gökhan Akçakavak, Aksaray University Faculty of Veterinary Medicine, Merkez/Aksaray*
e-mail: gokhan.akcakavak@aksaray.edu.tr

ORCID IDs of the authors: *[1]0000-0001-5949-4752 • [2]0000-0002-2778-8059 • [3]0000-0002-9667-5728 • [4]0000-0003-1585-3359 • [5]0000-0003-2209-7512 • [6]0000-0001-9689-4018 • [7]0000-0003-3426-2116 • [8]0000-0003-3118-1054*

fects (Dasari and Tchounwou, 2014). In cases of cancer, CP cross-links with purine bases on DNA and is subsequently considered to induce cell cycle arrest and apoptosis in cancer cells (Dasari and Tchounwou, 2014).

Although CP has strong anticancer properties, its clinical use is limited due to side effects such as ototoxicity, neurotoxicity, myelosuppression and nephrotoxicity (Skinner et al., 1998; Ben Ayed et al., 2020). CP-induced nephrotoxicity includes important processes such as inflammation, vascular damage, oxidative stress, endoplasmic reticulum (ER) stress, cellular uptake and accumulation, necrosis, and apoptosis (Ben Ayed et al., 2020; McSweeney et al., 2021; Kazak et al., 2022; Akcakavak et al., 2023). It is stated that inflammation and oxidative stress, in particular, play a key role in CP-induced acute kidney injury (Ben Ayed et al., 2020; Alanezi et al., 2022).

Taxifolin (Tax), 3,5,7,3,4-pentahydroxyflavanone, is primarily known as a compound derived from Douglas fir and Larix gemelini (Jain and Vaidya, 2023; Yang et al., 2023). Tax is also found in various plants such as camphor pine, black pine, safflower and olive oil (Liu et al., 2014). Tax is reported to exhibit various possess effects such as anti-inflammatory, antioxidant, antimicrobial, antiviral and anticancer (Yang et al., 2021; Jain and Vaidya, 2023; Ölmeztürk Karakurt et al., 2023; Yang et al., 2023).

Although nephrotoxicity is common in patients treated with CP, treatments to reduce and/or prevent nephrotoxicity are of great importance today in order to eliminate its harmful effects and enable it to demonstrate clinically strong anticancer properties. In recent years, the therapeutic and/or protective effects of many different agents have been evaluated in different studies to reduce and/or minimize CP-induced nephrotoxicity. Tax is reported to have a nephroprotective effect against renal toxicity caused by various nephrotoxic agents (Topal et al., 2023). There are limited studies evaluating the effects of Tax on CP-induced nephrotoxicity (Kara et al., 2019; Alanezi et al., 2022). In present study, the effects of Tax on CP-induced nephrotoxicity were assessed histopathologically and immunohistochemically.

Material and Methods

Animals

Present study, 24 male Wistar Albino rats, 2 months old, weighing 250-300 g, were utilized. Rats were housed in rooms with a temperature of 20-22°C, in standard plastic cages, with 12 hours of light and 12 hours of darkness, and were fed *ad libitum*. Cisplatin (Cipintu 100 mg/100 ml, Istanbul, Türkiye) administration to rats was performed intraperitoneally (i.p.) at a dose of 7 mg/kg, according to a previously reported study (Aldemir et al., 2014). Taxifolin (Evalar, Russia) solution was prepared in physiological saline at 50 mg/kg and was administered by oral gavage (Erhan et al., 2021; Ersoy et al., 2021).

The study was designed to include 6 rats in each group. **Control (C) group;** Rats were administered 0.5 ml/rat saline i.p. once on the first day and distilled water was conducted orally once a day for 7 days. **Taxifolin (Tax) group:** Rats were administered 0.5 ml/rat physiological saline i.p. once on the first day, and 50 mg/kg Tax was conducted orally once a day for 7 days. **Cisplatin (CP) group**: Rats were administered 7 mg/kg CP i.p. once on the first day of the study, and distilled water was conducted orally once a day for 7 days. **Cisplatin+ Taxifolin (CP+Tax) group:** Rats were administered 7 mg/kg CP i.p. once on the first day of the study, and 50 mg/kg Tax was conducted orally once a day for 7 days. On day 8^{th} of the study, all rats were sacrificed under i.p. xylazine (10 mg/kg) and ketamine (100 mg/kg) anesthesia. Necropsies were performed and kidney tissues were removed. Afterwards, they were placed in neutral formaldehyde solution for histopathological and immunohistochemical examination.

Histopathological examination

The kidney tissues were fixed in 10% neutral formaldehyde solution for 24-48 hours. Afterwards, paraffin blocks were obtained through routine tissue follow-up. Sections were taken from paraffin blocks onto ground slides, stained with Hematoxylin-Eosin (H-E) and examined under light microscopy. Histopathological scoring was evaluated semi quantitatively in 10 different areas at x20 magnification (0; none, 1; mild, 2; moderate, 3; severe) (Akcakavak et al., 2023).

Immunohistochemical examination

Sections were cut from paraffin blocks onto adhesive slides. Immunohistochemical staining was done according to a previously mentioned study (Akcakavak et al., 2023). IHC staining was performed with the Ultra vision detection system anti-polyvalent, HRP (Thermo Scientific, TP-60-HL, USA) kit, in accordance with the manufacturer recommendations. Anti-iNOS (Abcam, ab283655, 1/200 dilution) and Anti-p53 (Proteintech, 60283-2-Ig, 1/500 dilution)

were utilized as primers. 3,3 diaminobenzidine (DAB) was used as chromogen and counterstaining was done with Mayers-Hematoxylin. Immunohistochemical scoring was evaluated semi-quantitatively in 20 different areas at x20 magnification the average was taken (0; none, 1; mild, 2; moderate, 3; severe)(Akcakavak et al., 2023).

Statistical analysis

Evaluation of data between groups was done with SPSS (Inc., Chicago, USA 25.0) statistical program. Histopathological and immunohistochemical scores were evaluated with Kruskal wallis. Mann-Whitney U test was utilized to determine the difference among groups. The accepted importance limit was $p < 0.05$.

Results

Histopathological results

Histopathological scores between the groups are shown in table 1. Control and Tax groups were found to exhibit normal histological appearance. In the CP group, significant histopathological changes such as degeneration and necrosis in the tubular epithelium, tubular dilation, hyaline cast, inflammatory cell infiltration and glomerular atrophy were determined. It was found that the CP+Tax group reduced the relevant changes at a statistically significant level ($p<0.001$). In addition, it was determined that there were occasional bleeding foci in the CP group. In the CP+Tax group, bleeding foci were less frequent.

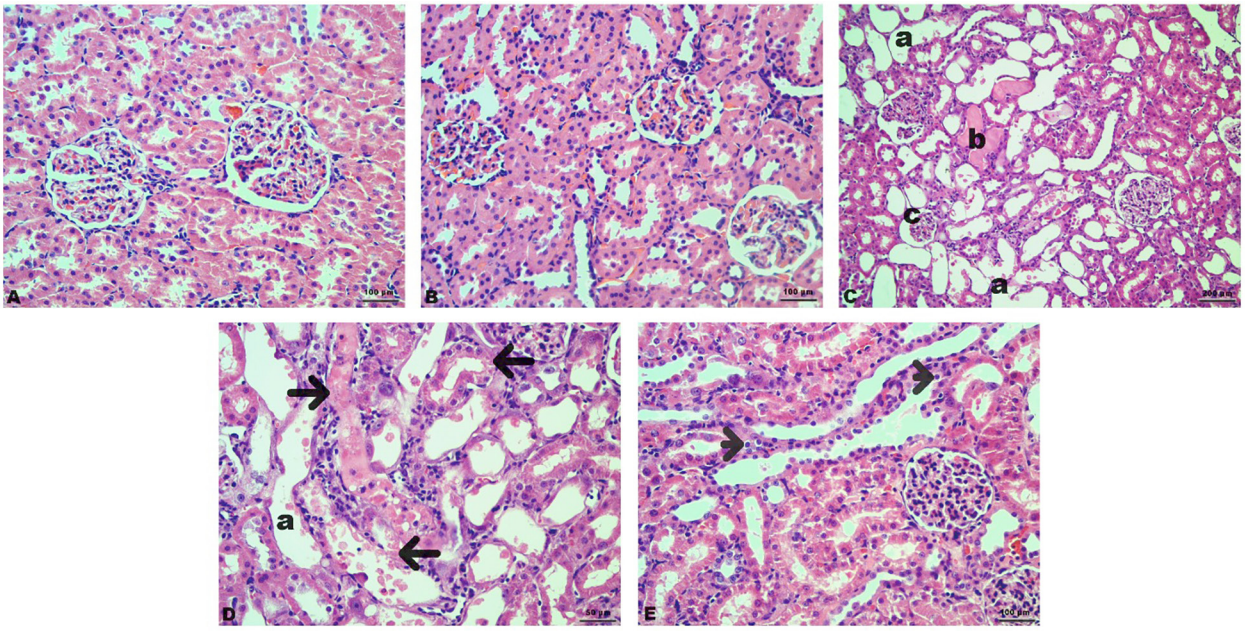

Figure 1. Histopathological evaluation of the effect of taxifolin on cisplatin-induced kidney damage, H-E, **A**; Control group, **B**; Tax group, **C-D**; CP group, **E**; CP+Tax group, necrosis of tubular epithelium (arrows), degeneration of tubular epithelium (arrowheads), tubular dilation (a), hyaline casts (b), glomerular atrophy (c).

Table 1. Histopathological scoring of the effects of taxifolin on cisplatin-induced renal injury.

Histopathological lesion	C	Tax	CP	CP+Tax
Degeneration of tubular epithelium	0.33±0.21^{c}	0.50±0.22^{c}	2.67±0.21^{a}	1.67±0.21^{b}
Necrosis of tubular epithelium	0.17±0.17^{c}	0.33±0.21^{c}	2.50±0.22^{a}	1.50±0.22^{b}
Inflammatory cell infiltration	0.50±0.22^{c}	0.67±0.21^{c}	2.17±0.17^{a}	1.33±0.21^{b}
Tubular dilation	0.50±0.22^{c}	0.67±0.21^{c}	2.17±0.30^{a}	1.33±0.21^{b}
Hyaline cast	0.33±0.21^{c}	0.33±0.21^{c}	2.50±0.22^{a}	1.50±0.22^{b}
Glomerular atrophy	0.50±0.22^{c}	0.67±0.21^{c}	2.17±0.17^{a}	1.33±0.21^{b}

$^{a-c}$ Letters in the same line indicate statistical significance ($p<0.001$). Group means were given as Mean ± SE (n;6). (C;Control, Tax;Taxifolin, CP;Cisplatin, CP+Tax; Cisplatin+Taxifolin)

Immunohistochemical results

The immunohistochemical scores between the groups are given in table 2. iNOS and p53 expressions were very mild or absent in the control groups. iNOS immunoreactive had luminar localized staining, and p53 had cytoplasmic and nuclear staining. Significant increases were determined in the relevant expressions (iNOS and p53) in the CP group ($p<0.001$). In the CP+Tax group, iNOS and p53 expression levels were found to be significantly reduced ($p<0.001$).

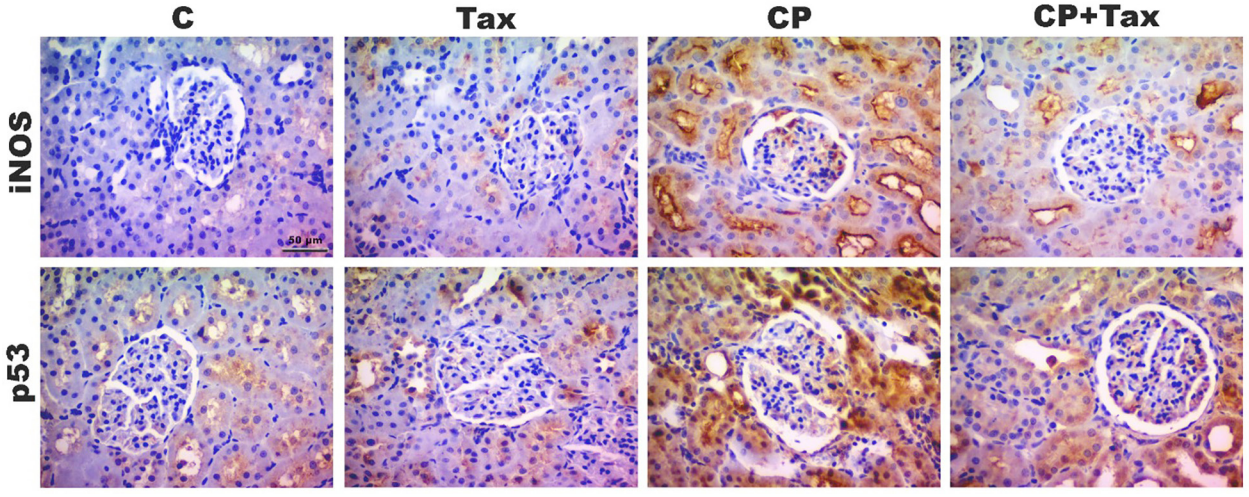

Figure 2. Immunohistochemical evaluation of the effect of taxifolin on iNOS and p53 expressions on cisplatin-induced kidney damage (C; Control, Tax; Taxifolin, CP; Cisplatin, CP+Tax; Cisplatin+Taxifolin groups, iNOS; inducible nitric oxide synthase).

Table 2. Immunohistochemical scoring of the effects of taxifolin on cisplatin-induced renal injury.

Primer Antibody	C	Tax	CP	CP+Tax
p53	0.33±0.21^{c}	0.50±0.22^{c}	2.67±0.21^{a}	1.67±0.21^{b}
iNOS	0.50±0.22^{c}	0.67±0.21^{c}	2.17±0.17^{a}	1.33±0.21^{b}

$^{a\text{-}c}$ Letters in the same line indicate statistical significance ($p<0.001$). Group means were given as Mean ± SE (n;6). (C;Control, Tax;Taxifolin, CP;Cisplatin, CP+Tax; Cisplatin+Taxifolin, iNOS; inducible nitric oxide synthase)

Discussion and Conclusion

Present study, we aimed to investigate the beneficial effects of Tax on CP-induced nephrotoxicity. Current findings showed that Tax had a nephroprotective/curative effect on kidney injury caused by CP treatment by reducing the expressions of iNOS and p53, improving histopathological changes.

Regarding the histopathological examination, the present study showed good evidence of nephrotoxicity after CP (7 mg/kg i.p.) injection. These changes were degeneration and necrosis of tubular epithelium, tubular dilation, hyaline casts, inflammatory cell infiltration, and glomerular atrophy. In addition, it was determined that there were occasional bleeding foci in the CP group. Researches on cisplatin-induced renal toxicity, it was reported that histopathologically, degeneration and necrosis of tubular epithelium, inflammatory cell infiltrations, hyaline cast, tubular dilatation and glomerular atrophy, edema and bleeding were detected (Kara et al., 2019; Alanezi et al., 2022; Kazak et al., 2022). Present study, histopathological findings were found to be compatible with the findings of previous studies.

In experimental toxicity studies induced by many different chemicals, taxifolin is reported to alleviate and/or improve histopathological changes and is attributed to its anitoxidative, anti-inflammatory and anti-apoptotic effects (Obeidat et al., 2022; Alanezi et al., 2022; Althunibat et al., 2023). The current study revealed that Tax significantly alleviated histopathological changes in CP-induced renal toxicity.

The mechanisms of cisplatin nephrotoxicity include many signals, such as oxidative damage and disruption of the inflammatory process in the kidney. In normal homeostasis, there is a balance between ROS production and the antioxidant defense system. CP may cause excessive ROS production and impairment of antioxidant defense systems,

leading to oxidative stress and mitochondrial dysfunction (Halliwell, 2006). In response to oxidative stress damage nuclear factor-kappa B (NF-kB) is activated, leading to ROS/RNS (reactive nitrogen species) stress imbalance and consequently increased cytokine release (Kurutas, 2015). It has also been reported to increase the synthesis of iNOS through the activation of NF-κB (Tuñón et al., 2003).

iNOS is a nitric oxide synthase (NOS) known to be the major producer of nitric oxide (NO). NO produced via iNOS is more important in inflammatory responses and diseases such as cancer (Vannini et al., 2015). It has been stated that iNOS expressions are upregulated in many cisplatin-induced renal toxicity studies (Chirino et al., 2008; Wang et al., 2018; Aladaileh et al., 2021). Pan et al. (2009) reported that in their cisplatin-induced renal toxicity study, canabidiol treatment resulted in the suppression of excessive iNOS expressions that occurred with cisplatin application and thus reduced renal tubular damage. Chirino et al. (2008) reported that selective iNOS inhibition attenuated cisplatin-induced nephrotoxicity. In a different study, it was reported that mesenchymal stem cells reduced cisplatin-induced nephrotoxicity via iNOS (Simovic Markovic et al., 2017). Increased levels of iNOS-mediated NO can cause apoptosis and DNA damage. Thus, stimulation of iNOS can result in tubular cytotoxicity and renal failure (Morsy et al., 2014; Akcakavak et al., 2024). It has been stated that inhibition of iNOS activity can decrease oxidative stress in renal tubular cells (Wu et al., 2007). Present study, iNOS expression was found to be significantly increased in the CP group relative to the control groups ($p<0.001$). Tax treatment reduced iNOS expressions and demonstrated nephroprotective effects against CP-induced renal toxicity. It was thought that this situation may be due to the antioxidant and anti-inflammatory effects of Tax (Jain and Vaidya, 2023; Ölmeztürk et al., 2023). A recent study reported that Taxifolin reduces oxidative stress and NF-kB cytokinin expressions in cisplatin-induced nephrotoxicity (Alanezi et al., 2022). Present study, NF-kB downregulation may have played a role in the decreased iNOS expressions.

p53 is a transcription factor that acts a central role in processes such as DNA repair, cell death, and cell cycle arrest, in response to various stress signals. The p53 gene is encoded by the TP53 gene locus, which is located on the short arm of human chromosome 17 (17p13.1) (Levine and Oren, 2009; Sabapathy and Lane, 2018). p53 tumor suppressor protein induces apoptosis in response to DNA damage and oncogene activation (Bassett et al., 2008). It has been reported that procedures aimed at p53 suppression reduce cisplatin-induced apoptosis and kidney damage (Molitoris et al., 2009; Zhang et al., 2020). Zhang et al. (2020) reported that Pioglitazone prevents cisplatin nephrotoxicity by suppressing the p53-mediated mitochondrial apoptotic pathway via SIRT1 activation. Wu et al. (2021) reported that Nicotinamide protects against cisplatin-induced tubular damage by suppressing the PARP1/p53 pathway. Research show that p53 can induce apoptosis due to oxidative stress, DNA damage and mitochondrial dysfunction in cisplatin-induced kidney toxicity. Indeed, DNA damage and the resulting DNA damage response are known to be the main trigger of p53 activation in the kidneys (Tang et al., 2019). It is also reported that it causes an increase in the expression of 8-hydroxy-2-deoxyguanosine (8-OHdG), which is the most important indicator of DNA damage in cisplatin-induced kidney toxicity studies (Geyikoglu et al., 2017; Mercantepe et al., 2018). Additionally, different studies have reported that taxifolin has reducing effects on 8-OhdG expressions (Unver et al., 2019; Okkay et al., 2022). In present study, an increase in p53 expression was detected in the CP group and was compatible with the findings of previous studies (Zhang et al., 2020; Wu et al., 2021). This situation was thought to cause p53 upregulation due to oxidative stress, DNA damage and mitochondrial dysfunction caused by cisplatin administration. Additionally, considering the findings of the study, it shows that the p53 gene plays an important role in the process of kidney damage caused by cisplatin. Taxifolin treatment (CP + Tax group) significantly reduced p53 expression and revealed that it had a tubular damage-reducing effect against CP-induced renal toxicity. It is possible to interpret that p53 downregulation may decrease apoptosis, especially in the CP + Tax group. Moreover, in a recent study, evidence that taxifolin reduced apoptosis in cisplatin-induced kidney toxicity further strengthened our opinion (Alanezi et al., 2022).

The current study shows that Tax given simultaneously with CP treatment acts a protective/curative role in alleviating CP-induced renal injury by suppressing histopathological changes and iNOS, p53 expressions. Thus, Tax may be a promising candidate for attenuating kidney damage in patients undergoing with CP chemotherapy.

Ethics committee for the use of experimental animals and other ethical committee decisions and permissions: Selcuk University Faculty of Veterinary Medicine Experimental Animal Production and Research Center Ethics Committee approved the ethical compliance of the study (Approval No: 2024/056).

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