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Research Article

Effect of Daidzein, Naringenin, and Icariin on Cisplatin-induced Nephrotoxicity in Experimental Mice

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ABSTRACT

Cisplatin is one of the most widely used and most potent chemotherapy drugs. However, side effects in normal tissues and organs, notably nephrotoxicity in the kidneys, limit the use of cisplatin and related platinum-based therapeutics. Renoprotective approaches are being discovered, but the protective effects are mostly partial, suggesting the need for combinatorial strategies. The cytoprotective efficacy of daidzein, naringenin, and icariin against cisplatin-induced nephrotoxicity in female swiss mice was examined in this work. All animals were divided into two sets i.e., pre-cisplatin (BA) and post-cisplatin (AA) administration and treated with daidzein, naringenin, and icariin. Nephrotoxicity was assessed by body weight and biochemical parameters i.e., serum creatinine, urea, uric acid. During this study body weight of the experimental animal changed by 5% maximum observed in both sets. Biochemical tests of kidney showed that pre-treated and post-treated with daidzein groups were most effective against nephrotoxicity. These findings are also confirmed by histopathology. The study has proven that pre-treatment with flavonoids was found more effective against cisplatin-induced cytotoxicity as compared to post-treatment.

Introduction

Cancer is a broad term, it describes the condition that occurs when cellular alterations promote uncontrolled cell growth and cellular division. Some cancer types promote fast cell growth, while certain cancer types cause cells to grow and divide more slowly than others. Certain forms of cancer result in obvious growths of tissue called tumors, while others, such as leukemia, do not cause apparent growths. To turn a normal cell into a cancer cell, the genes that control cell proliferation and differentiation must be altered.[1] In the US, cancer is the second most common cause of death. In 2021, there were 1.9 million new cancer cases diagnosed and 608,570 people died from cancer in the United States.[2] Up to 90% of cancer-related deaths are caused by drug resistance and the ensuing ineffectiveness of the treatment.[3] Despite decades of basic and clinical research and trials of promising new therapies, cancer remains a major cause of morbidity and mortality.

Cisplatin, cisplatinum, platamin, or cis-diamminedichloroplatinum (II) is an inorganic platinum-based chemotherapeutic drug. Cisplatin has been prescribed for the treatment of numerous human cancers since its FDA clearance in 1978.[4] it is frequently used in the treatment of a range of solid malignant tumors, including head and neck, lung, testis, ovarian, and bladder cancers.[5]

Mechanism of Cisplatin Toxicity

DNA has been shown to be cisplatin's primary target, and the formation of cisplatin adducts not only affects a number of DNA-dependent cellular functions, such as the

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inhibition of transcription and replication, cell cycle arrest, and DNA damage that leads to cell death and apoptosis, but it also has the potential to cause mutations.[6-9] Cisplatin attaches to DNA, leading to the formation of inter-and intrastral and cross-links. Cross-linking causes flawed DNA templates and halts the synthesis and replication of DNA. Cross-linking can further cause DNA damage in cells that divide quickly, such as those found in malignancies. Cross-linking can further cause DNA damage in cells that divide quickly, such as those found in malignancies. Mildly damaged DNA sometimes can be repaired, but severe DNA damage results in irreparable injury and cell death. Despite being a staple of cancer treatment, cisplatin's use is primarily constrained by two factors: developed resistance to it and severe adverse effects in normal tissues.[10]

The side effects of cisplatin on healthy tissues, such as neurotoxicity, ototoxicity, nausea and vomiting, and nephrotoxicity, are another important aspect that restricts its use. It is thought that cisplatin-induced toxicities may be caused by oxidative stress, DNA damage, mitochondrial malfunction, and the production of pro-inflammatory cytokines.[11,12] Many strategies have been tried over time to reduce these side effects to healthy tissues. One strategy is to synthesize novel cisplatin analogs and screen them for their decreased toxicity in healthy tissues. In this manner, a number of cisplatin analogues with milder side effects have been found, including carboplatin.[13] During cisplatin treatment, hydrating the patients has also been tried with some degree of benefit.[14,15] Despite these improvements, cisplatin's side effects, particularly nephrotoxicity, continue to play a significant role in limiting its use and effectiveness in cancer therapy. After a single dose of cisplatin injection (50-100 mg/m^2), about thirty percent of the patients develop nephrotoxi city.[16,17]

MATERIALS AND METHOD

Drugs and Chemicals

Cisplatin was purchased from the local pharmacy as Cisplatin Injection Celplat-10 (Celon Labs Pvt. Ltd. India). Cisplatin was administered in a dose of 10 mg/kg/body wt, i.p injected for 14 consecutive days, this dose was selected according to the cisplatin mouse model study of Perse M and Sara J. Holditch, *et al.*[18,19]

Daidzein (purity ≥ 98%), naringenin (purity ≥ 95%), icariin (purity ≥ 94%) were purchased from Sigma Aldrich Chemical Pvt Ltd, Bangalore, India. Amifostine was purchased from the local market as amifostine injection cytofos 500 (Sun Pharmaceuticals Industries Ltd, India) and all other chemicals were of analytical grade. Daidzein, naringenin and icariin were suspended in the 0.5% CMC suspension and given orally to the respective groups.

Animals

Adult female wistar albino mice (20-22 g) were used for all experimental procedures. Animals were provided by the Department of Pharmacology, School of Studies in Pharmaceutical Science, Jiwaji University, Gwalior. The animals were housed in standard conditions of temperature (25 ± 20°C) and 12:12 h light-dark cycle. The mice were fed with a commercial diet and water ad *Libitum*. Mice were left for one week of acclimatization time before the beginning of the experiment. The experiment was approved by the institutional animal ethics committee of School of Studies in Pharmaceutical Science, Jiwaji University, Gwalior, M.P. India (Approval no. IAEC/JU/60 dated 03/06/2019).

Experimental Design

Mice, acclimatized with laboratory conditions, were divided into two sets of 36 each. In both sets of the experiment; the animals will divide into six treatment groups with six mice in each group. To the set-I dose of flavonoids and Amifostine were administered before 30 minutes of Cisplatin injection in which BA-I Without treatment (Normal Control), BA-II Cisplatin (Negative Control), BA-III cisplatin+ amifostine (Positive Control), BA-IV cisplatin + daidzein, BA-V cisplatin + naringenin and BA-VI cisplatin + icariin. To the set-II dose of amifostine and flavonoids were administered After 30 minutes of cisplatin injection in which BA-I without treatment (Normal Control), BA-II cisplatin (Negative Control), BA-III cisplatin+ amifostine (Positive Control), BA-IV cisplatin + daidzein, BA-V cisplatin + naringenin and BA-VI cisplatin + icariin.

Cisplatin(CP) (10 mg/kg)[19] and Amifostine (200mg/kg)[20] were injected intraperitoneally (i.p.) for 14 consecutive days. daidzein (40 mg/kg)[21], naringenin (50 mg/kg)[22] and icariin (30 mg/kg)[23] administrated orally by gavage every day, 30 minutes before and after cisplatin injection to respective set. These selected doses of flavonoids were previously reported and not to produce any significant toxicity. The animals were immediately kept in groups of three in metabolic cages after the final cisplatin dose in order to collect urine continuously throughout the day. Nephrotoxicity were assessed by determining various histopathology and biochemical parameters i.e., body weight, serum creatinine, urea, uric acid, serum electrolytes in mice before and after cisplatin administration.

Collection and Storage of Blood and Urine Samples

Urine samples were taken while the animals were housed in metabolic cages. During the time of urine collection, animals had free access to drinking water. A drop of concentrated hydrochloric acid was mixed with the urine and then keep stored at 4˚C. Blood was drawn from

each animal at the end of the experiment by puncturing the retro-orbital plexus. For the serum analysis, blood samples were allowed to coagulate for 45 minutes at room temperature. Serum was separated by centrifuge the sample at 3000 rpm at 4˚C for 15 minutes and utilized for the evaluation of several biochemical parameters.

Biochemical Analysis in Blood and Urine Sample

Various biochemical parameters were estimated for nephroprotective activity e.g. serum creatinine, urea, uric acid. All parameters were estimated using commercially available kits and following the manufacturer's instructions.

Histological Examination

After the collection of urine and blood samples physical methods of euthanasia used for animal scarification. Animal packed in a chamber having chloroform dipped cotton when animal inhaled an excess number of vapors and it got anesthetized, followed by cervical dislocation. After sacrifice, the whole kidney tissues were collected carefully and dipped in 10% formalin solution and embedded in paraffin. The embedded tissues were then divided into sections that were 3 µm thick, placed on glass slides, and incubated at 75°C for 30 minutes. In order to rehydrate the materials, a graded ethanol series (95%, 85%, and 70% ethanol) was used, after being deparaffinized using xylene for 10 min. Following washing, the specimens were incubated with Haematoxylin for 2 minutes, rinsed in running tap water for 1 minute, and then incubated with acid alcohol for 1-second. Afterward, the specimen samples were incubated with ammonia water solution for 1-second and then rinsed in running tap water for 10 min. The specimens were dehydrated using 70%, 80%, 90%, and 100% ethanol after counterstaining with Eosin solution for 90 seconds. Finally, the specimens were mounted with a mounting medium, and examined under a microscope to determine the extent of the tissue damage.

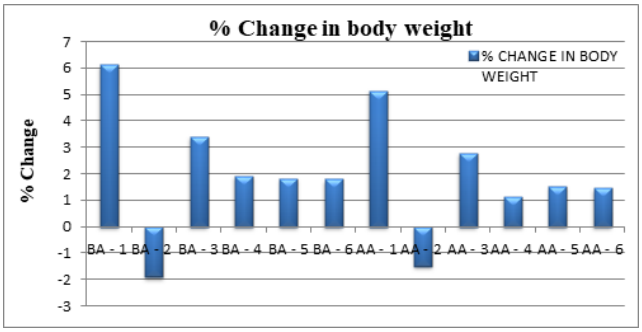

Fig 1: Percentage change in body weight

Table 1: Change in body weight (set-I)

Group	*Treatment*	*Body weight (gm)*		*% Change in body weight*
		Initial	Day 14	
BA - 1	Vehicle	20.6 ± 0.78	21.9 ± 0.44	6.13
BA - 2	Cisplatin	21.1 ± 0.41	20.7 ± 0.36	-1.90
BA - 3	Cisplatin+ Amifostine	20.5 ± 0.88	21.2 ± 0.23	3.41
BA - 4	Cisplatin + Daidzein	20.8 ± 0.55	21.2 ± 2.52	1.92
BA - 5	Cisplatin + Naringenin	21.5 ± 0.34	21.9 ± 0.36	1.83
BA - 6	Cisplatin + Icariin	22.2 ± 0.15	22.6 ± 0.25	1.80

Table 2: Change in body weight (set-II)

Group	*Treatment*	*Body weight (gm)*		*% Change in body weight*
		Initial	Day 14	
AA - 1	Vehicle	21.4 ± 0.78	22.5 ± 1.14	5.14
AA - 2	Cisplatin	20.2 ± 0.41	19.9 ± 1.06	-1.49
AA - 3	Cisplatin+ Amifostine	21.5 ± 1.88	22.1 ± 1.23	2.79
AA - 4	Cisplatin + Daidzein	19.9 ± 1.00	20.2 ± 1.12	1.12
AA - 5	Cisplatin + Naringenin	19.8 ± 0.45	20.1 ± 1.27	1.52
AA - 6	Cisplatin + Icariin	20.6 ± 1.26	20.9 ± 1.15	1.46

Table 3: Urine collection and physical observation (set- I)

Group	*Treatment*	*Volume of urine (mL)*	*% Decrease*	*Physical observation*
BA - 1	Vehicle	2.82 ± 0.21	-	Clear
BA - 2	Cisplatin	2.12 ± 0.24	24.82	Pale yellow
BA - 3	Cisplatin+ Amifostine	2.48 ± 0.36	12.06	Light yellow
BA - 4	Cisplatin + Daidzein	2.46 ± 0.33	12.77	Light yellow
BA - 5	Cisplatin + Naringenin	2.43 ± 0.25	13.83	Light yellow
BA - 6	Cisplatin + Icariin	2.12 ± 0.44	24.82	Light yellow

Table 4: Urine collection and physical observation (set- II)

Group	*Treatment*	*Volume of urine (mL)*	*% Decrease*	*Physical observation*
AA - 1	Vehicle	2.52 ± 0.21	-	Clear
AA - 2	Cisplatin	2.16 ± 0.24	14.29	Pale yellow
AA - 3	Cisplatin+ Amifostine	2.04 ± 0.36	19.05	Light yellow
AA - 4	Cisplatin + Daidzein	2.16 ± 0.33	14.29	Light yellow
AA - 5	Cisplatin + Naringenin	2.21 ± 0.45	12.30	Light yellow
AA - 6	Cisplatin + Icariin	2.13 ± 0.34	15.47	Light yellow

Table 5: Urine analysis for kidney function test (set- I)

Group	*Treatment*	*Creatinine (mg/dL)*	*Uric acid (mg/dL)*	*Urea (mg/dL)*
BA - 1	Vehicle	0.20 ± 0.043	2.33 ± 0.19	34.10 ± 0.16
BA - 2	Cisplatin	0.90 ± 0.042a	5.00 ± 0.22a	92.30 ± 1.0 a
BA - 3	Cisplatin + Amifostine	0.27 ± 0.033b*	2.75 ± 0.34b*	42.33 ± 0.56b*
BA - 4	Cisplatin + Daidzein	0.34 ± 0.022b**	2.45 ± 0.09b*	51.25 ± 1.33b*
BA - 5	Cisplatin + Naringenin	0.42 ± 0.032a*	3.53 ± 0.23a*	62.14 ± 0.28a**
BA - 6	Cisplatin + Icariin	0.39 ± 0.053b*	2.78 ± 0.44b*	57.38 ± 0.52b*

All values are mean ± SEM, n= 6. *p < 0.05, **p < 0.01,
a. Significance difference as compared to BA-1 (Vehicle)
b. Significance difference as compared to BA-2 (Cisplatin)

Table 6: Urine analysis for kidney function test (set- II)

Group	*Treatment*	*Creatinine (mg/dL)*	*Urea acid (mg/dL)*	*Urea (mg/dL)*
AA - 1	Vehicle	0.21± 0.36	2.33 ± 0.19	33.21 ± 0.16
AA - 2	Cisplatin	0.92 ± 0.73a	5.10 ± 0.22a	93.21 ± 1.0 a
AA - 3	Cisplatin+ Amifostine	0.28± 0.27b*	2.25±0.34b**	44.33 ± 0.56b*
AA - 4	Cisplatin + Daidzein	0.37 ± 0.22b**	2.45 ± 0.09b*	56.51 ± 1.33b**
AA - 5	Cisplatin + Naringenin	0.46 ± 0.85a*	3.83 ± 0.76a*	62.73 ± 1.32a*
AA - 6	Cisplatin + Icariin	0.42 ±0.53b*	2.81 ± 0.53b**	59.62 ± 2.0b*

All values are mean ± SEM, n= 6. *p < 0.05, **p < 0.01
a. Significance difference as compared to AA-1 (Vehicle)
b. Significance difference as compared to AA-2 (Cisplatin)

Table 7: Serum analysis for kidney function test (set-I)

Group	*Treatment*	*Creatinine (mg/dL)*	*Uric acid (mg/dL)*	*Urea (mg/dL)*
BA - 1	Vehicle	0.13 ± 0.013	2.5 ± 0.34	9.5 ± 0.66
BA - 2	Cisplatin	0.38 ± 0.033a	4.33 ± 0.61 a	55.0 ± 0.44a
BA - 3	Cisplatin + Amifostine	0.19 ± 0.023b*	2.71 ± 0.15b*	15.2 ± 0.12b**
BA - 4	Cisplatin + Daidzein	0.18 ± 0.052b*	2.90 ± 0.49b*	20.5 ± 0.28 b**
BA - 5	Cisplatin + Naringenin	0.29 ± 0.042a*	3.93 ± 0.32a*	38.2 ± 0.42b**
BA - 6	Cisplatin + Icariin	0.25 ± 0.042b*	3.37 ± 0.42b*	27.8± 0.12b*

All values are mean ± SEM, n= 6. *p < 0.05, **p < 0.01
a. Significance difference as compared to BA-1 (Vehicle)
b. Significance difference as compared to BA-2 (Cisplatin)

Table 8: Serum analysis for kidney function test (set-II)

Group	*Treatment*	*Creatinine (mg/dL)*	*Uric acid (mg/dL)*	*Urea (mg/dL)*
AA - 1	Vehicle	0.13 ± 0.013	2.76 ± 0.52	9.15 ± 0.88
AA - 2	Cisplatin	0.39 ± 0.033a	5.42 ± 0.73a	55.6 ± 0.71a
AA - 3	Cisplatin + Amifostine	0.18 ± 0.023b*	3.26 ± 0.15b**	15.8 ± 0.17b**
AA - 4	Cisplatin + Daidzein	0.25 ± 0.052b*	3.39 ± 0.63b*	21.5 ± 0.28b**
AA - 5	Cisplatin + Naringenin	0.35 ± 0.52a**	4.15 ± 0.53 b*	42.74 ± 0.74a*
AA - 6	Cisplatin + Icariin	0.29 ± 0.63b*	3.73 ± 0.83 b*	28.21 ± 0.62a*

All values are mean ± SEM, n= 6. *p < 0.05, **p < 0.01
a. Significance difference as compared to AA-1 (Vehicle)
b. Significance difference as compared to AA-2 (Cisplatin)

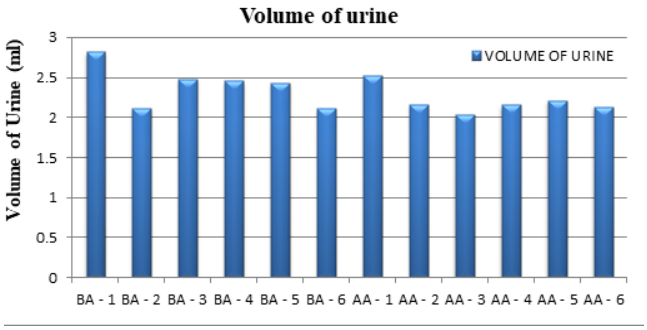

Fig. 2: Volume of urine collected from both set

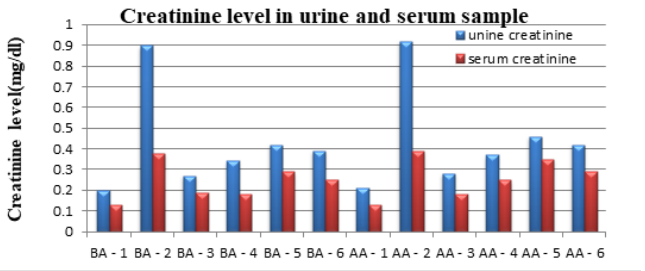

Fig. 4: Creatinine level in urine and serum samples

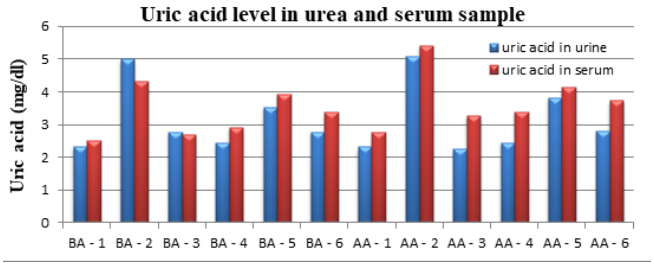

Fig. 5: Uric acid level in urine and serum samples

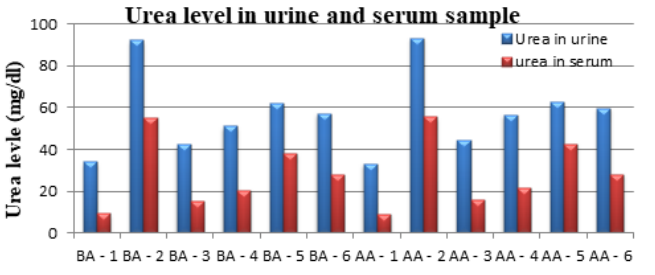

Fig. 6: Urea level in urine and serum samples

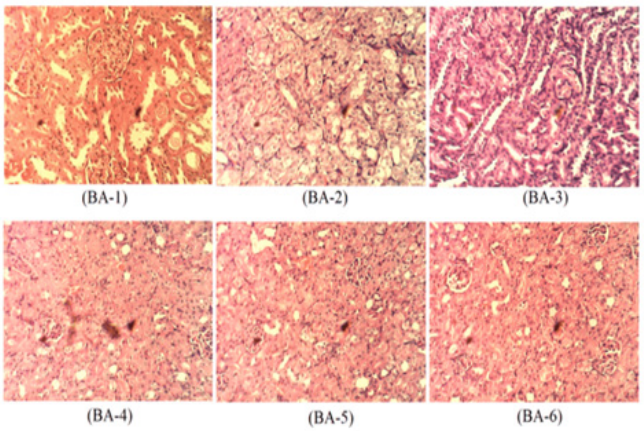

Fig. 3: Histopathology of kidneys obtained from set-I animals

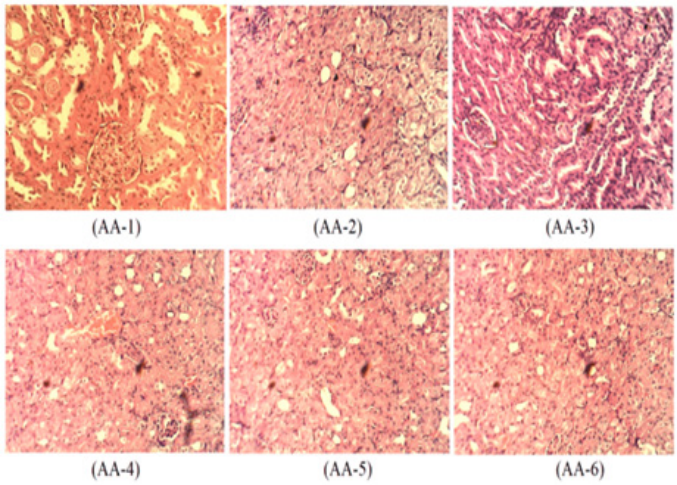

Fig. 4: Histopathology of kidneys obtained from set-II animals

Statistical Analysis

All data are expressed as means ± SEM (standard error of the mean). A statistical package for social sciences (SPSS) computer programme (version 22) was used to conduct the statistical study. To clarify significance between group means, a one-way analysis of variance (ANOVA) test was employed, followed by a Tukey-Kramer post hoc test for multiple comparisons. At $p < 0.05$, differences were considered significant.

RESULTS

Changes in Body Weight

During this study body weight of the experimental animal changed 5% maximum observed in both sets (Table 1, 2 and Fig. 1).

Urine Collection and Physical Observation

Collected urine volume ranges from 2.0 to 2.82 ml and % decrease 12 to 24.82 %, physically clear to light yellow color observed (Table 3, 4 and Fig. 2).

Renal Histopathology

Tissues obtained from the kidney of control group mice displayed regular morphology of normal glomerulus and tubules (BA-1 and AA-1), Histological examination of the kidneys of mice treated with cisplatin revealed severe and widespread necrosis with proximal tubule enlargement, which resulted in tubular cell desquamation, loss of tubular architecture, vacuolization, and the formation of intraluminal casts. (BA-2 and AA-2), Histological examination of the kidneys from mice group cisplatin-treated mice pre-treated and post-treated with amifostine (positive control) displayed minimal glomerulus and tubules in regular morphology (BA-3 and AA-3), Histological analysis of the kidneys of cisplatin-treated mice pre-treated and post-treated with Daidzein, Naringenin and Icariin (BA-4, BA-5 BA-6 and AA-4, AA-5, AA-6) showed less histopathological renal changes. Greater improvements were seen in BA-4 & AA-4 and BA-6 and AA-6. All observations are similar for both set (I and II) as shown in fig. 3 and 4.

Discussion

Cytoprotective potential of daidzein, naringenin, icariin flavonoids were evaluated against cisplatin-induced nephrotoxicity in mice. Total 36 wistar albino mice divided into two sets were taken and acclimatized with laboratory conditions through standard procedure. The nephrotoxicity, hepatotoxicity and neurotoxicity of cisplatin are the major side effects of this drug. Nephrotoxicity, was assessed by determining various biochemical parameters i.e. body weight, Serum Creatinine, urea, uric acid in mice before and after cisplatin administration. Histopathology findings in different tissues of the mice revealed cell degeneration and necrosis on the 14th day after the execution of a single dose of cisplatin per day.

Effect of daidzein, naringenin, icariinon cisplatin-induced nephrotoxicity was determined by estimation of creatinine, urea and uric acid in blood and urine samples collected from mice in both sets of mice (before and after treatment)(Fig. 4-6). Kidney function tests revealed daidzein and Icariin treated groups found significant differences in creatinine, urea and uric acid level in urine and serum in comparison to respective cisplatin-treated groups in both sets. Histopathology of the kidney confirmed all biochemical observations.[17](Fig. 3-4)

Histological studies were carried out in the brain, kidney, and liver tissues to examine the impact of cisplatin on these tissues. The previous reports have also demonstrated the toxic effect of cisplatin in oxidative stress and injury to kidney tissue.[6] In the current investigation, it was found that cisplatin's cytotoxic properties caused kidney tissue to lose tubular architecture, vacuolize, desquamate, and form intraluminal casts. The daidzein treatment greatly lessen the tissue damage to the kidney caused by the administration of cisplatin.

Finally, based on our research, we can conclude that pre-treatment with flavonoids was found more effective against cisplatin-induced cytotoxicity as compared to post-treatment. Furthermore, daidzein groups were most effective against nephrotoxicity likely due to their antioxidant and anti-inflammatory actions. However, the results of our study are restricted to relationships in female mice only, necessitating molecular research to expand on the mechanisms and validate our findings.

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Nil

Conflicts of Interests

There are no conflicts of interest.

Abbreviations

FDA: Food and Drug Administration; ANOVA: One-way analysis of variance; BA: Before Administration; AA: After Administration; SEM: Scanning Electron Microscope; MDA: Malondialdehyde; GSH: Glutathione.

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