https://doi.org/10.48047/AFJBS.6.13.2024.6337-6350

African Journal of Biological Sciences

Journal homepage: http://www.afjbs.com

Research Paper Open Access

EVALUATION OF THE ROLE OF FLAVONOIDSIN CISPLATIN-INDUCEDHEPATOTOXICITY IN MICE

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Volume 6, Issue 13, Aug 2024

Received: 15 June 2024

Accepted: 25 July 2024

Published: 15 Aug 2024

doi: 10.48047/AFJBS.6.13.2024.6337-6350

ABSTRACT

Introduction: Platinum-based drug cisplatin is frequently used as a first-line treatment for a variety of cancers. Despite its extensive anticancer efficacy, its use is constrained due to developed drug resistance and cytotoxicity to non-targeted normal tissues. Nephrotoxicity, ototoxicity, hepatotoxicity, and neurotoxicity are the major side effects of this drug. **Objective:** The cytoprotective efficacy of Daidzein, Naringenin, and Icariin against Cisplatin-induced hepatootoxicity in female Swiss mice was examined in this work. **Methods**: All animals were divided into two sets i.e. pre-cisplatin (BA) and post-cisplatin (AA) administration and treated with Daidzein, Naringenin, and Icariin., hepatotoxicity we assessed by body weight and biochemical parameters i.e., SGOT, SGPT, lipid peroxidation (MDA level). **Results:** During this study body weight of the experimental animal changed by 5% maximum observed in both sets. Biochemical tests of blood samples and liver tissue histopathology showed that pre-treated and post-treated with Naringenin were more effective against hepatotoxicity as compared to daidzein and icariin. These findings are also confirmed by histopathology. **Conclusion:** The study has proven that pre-treatment with flavonoids was found more effective against cisplatin-induced cytotoxicity as compared to post-treatment.

Keywords: Cytoprotective, Flavonoids, Cisplatin Cytotoxicity, hepatotoxicity.

INTRODUCTION

Fundamentally, cancer is a condition caused by an inability to control tissue growth. To turn a normal cell into a cancer cell, the genes that control cell proliferation and differentiation must be altered.[1] 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. 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 i

the United States.[2] Up to 90% of cancer-related deaths are caused by drug resistance and the ensuing ineffectiveness of the therapeutic treatment.[3]

Cisplatin, cisplatinum, platamin or cis-diamminedichloroplatinum(II) is a chemotherapeutic drug. Cisplatin has been prescribed for the treatment of numerous human cancers since its FDA clearance in 1978.[4,5] DNA is the proven primary target of cisplatin and cisplatin adduct formation not only affects several DNA-dependent cellular functions, including inhibition of replication and transcription, cell cycle arrest, and DNA damage resulting in cell death and apoptosis but also may result in mutations.[6–9]

Cisplatin also known as dichlorodiamino platinum, is an inorganic platinum-based chemotherapeutic drug. It is frequently used in the treatment of a range of solid malignant tumors, including head and neck, lung, testis, ovarian, and bladder cancers.[10] Cisplatin attaches to DNA, leading to the formation of inter-and intrastrand 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. 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.[11,12]

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. However, the neurotoxicity caused by cisplatin, which manifests as peripheral neuropathy, diminished recognition, tremor, and ataxia, is a well-defined dose-limiting side effect that restricts its therapeutic utility. It is thought that cisplatin-induced toxicities may be caused by oxidative stress, DNA damage, mitochondrial malfunction, and the production of pro-inflammatory cytokines.[13,14] Many strategies have been tried over time to reduce these side effects on 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 more mild side effects have been found, including carboplatin.[15]During cisplatin treatment, hydrating the patients has also been tried with some degree of benefit.[16,17] Despite these improvements, cisplatin's side effects, particularly nephrotoxicity, continue to play a significant role to restrict its use and effectiveness in cancer therapy. After a single dose of cisplatin injection (50-100mg/m2),

about thirty percent of the patients develop nephrotoxicity.[18,19]

METHODS

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.[20,21]

Daidzein (Purity ≥98%), Naringenin (Purity ≥95%), and 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% Carboxymethylcellulose (CMC) suspension and given orally to the respective groups.

Animals: Adult female Wistar albino mice (20-22g) 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±20C) and 12:12 h light-dark cycle. The mice were fed 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) **(**10mg/kg)[21] and Amifostine (200mg/kg)[22] were injected intraperitoneally (i.p.) for 14 consecutive days. Daidzein (40mg/kg)[23], Naringenin (50mg/kg)[24] and Icariin (30mg/kg)[25] 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 to collect urine continuously throughout the day. Hepatotoxicity was assessed by determining various histopathology and biochemical parameters i.e. body weight, serum glutamic-oxaloacetic transaminase (SGOT), serum glutamate pyruvate transaminase (SGPT), Lipid peroxidation (MDA) 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, hepatoprotective and neuroprotective activity e.g. Serum Creatinine, Urea, uric acid, SGOT, SGPT, Lipid peroxidation. 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 were 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 liver 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 for 30 minutes at 75 °C. 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 hematoxylin 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.

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 the 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

Effect of Daidzein, Naringenin, Icariin and cisplatin on body weight

During this study body weight of the experimental animal changed by 5% maximum observed in both sets (table no 1, 2 and figure no 1).

Table 1: Percent 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	-1.90a*
BA - 3	Cisplatin+ Amifostine	20.5 ± 0.88	21.2 ± 0.23	3.41b*
BA - 4	Cisplatin + Daidzein	20.8 ± 0.55	21.2 ± 2.52	1.92b**
BA - 5	Cisplatin + Naringenin	21.5 ± 0.34	21.9 ± 0.36	1.83b**
BA - 6	Cisplatin + Icariin	22.2 ± 0.15	22.6 ± 0.25	1.80b**

Table 2: Percent 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	-1.49a*
AA - 3	Cisplatin+ Amifostine	21.5 ± 1.88	22.1 ± 1.23	2.79b*
AA - 4	Cisplatin + Daidzein	19.9 ± 1.00	20.2 ± 1.12	1.12b**
AA - 5	Cisplatin + Naringenin	19.8 ± 0.45	20.1 ± 1.27	1.52b**
AA - 6	Cisplatin + Icariin	20.6 ± 1.26	20.9 ± 1.15	1.46b**

All values are mean ± SEM, n = 6. *p<0.05, **p<0.01; a. Significance difference as compared to Vehicle; b. Significance difference as compared to Cisplatin

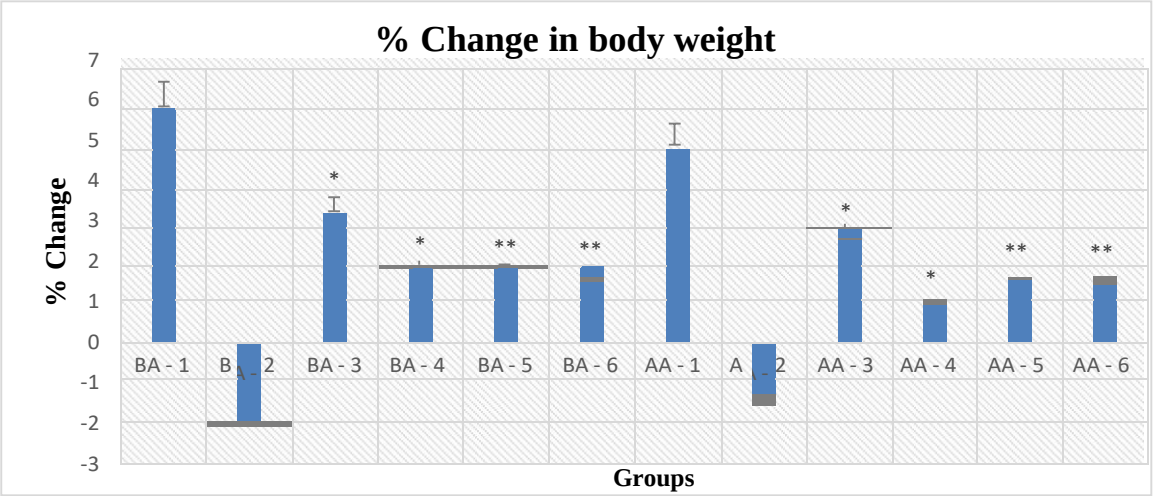

Figure 1: Percentage change in body weight. All values are mean ± SEM, n = 6. *p<0.05, **p<0.01; a. Significance difference as compared to Vehicle; b. Significance difference as compared to Cisplatin

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 no 3, 4 and figure no 2).

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

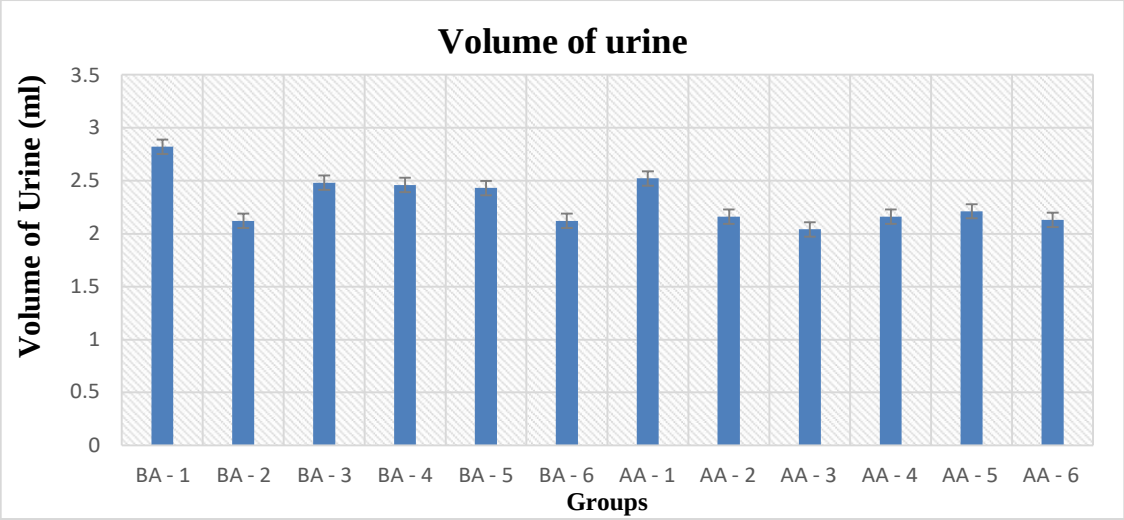

Figure 2: Volume of urine collected from both sets. All values are mean ± SEM, n = 6.

Effect of Daidzein, Naringenin, Icariin on Cisplatin-induced Hepatotoxicity

Effect of Daidzein, Naringenin, Icariin on Cisplatin-induced hepatotoxicity was determined by SGOT, SGPT and total Bilirubin in blood samples collected from both sets of mice (before and after treatment). Serum analysis for liver function tests significant recovery by Daidzein and Icariin treated groups in both sets. Biochemical observations were confirmed by liver histopathology showed less histopathological hepatic changes, showed a regression of the fatty changes in the liver cell cytoplasm. in both sets. A significant effect was shown in tables no.5, 5 and figures no 2 & 3.

Table 5: Serum analysis for liver function tests (SET- I)

Group	Treatment	SGOT (IU/L)	SGPT (IU/L)	Total Bilirubin (mg/dl)
BA - 1	Vehicle	115.3 ± 11.3	23.3 ± 5.19	0.64 ± 0.06
BA - 2	Cisplatin	296.6 ± 26.3a	82.6 ± 4.62a	2.86 ± 0.04a
BA - 3	Cisplatin + Amifostine	146.8 ± 13.5b*	30.4 ± 7.34b**	0.92 ± 0.03b**
BA - 4	Cisplatin + Daidzein	178.3 ± 14.3b*	49.3 ± 6.43b*	1.27 ± 0.08b*
BA - 5	Cisplatin + Naringenin	164.6 ± 0.32a*	46.4 ± 3.96a*	1.19 ± 0.01a*
BA - 6	Cisplatin + Icariin	206.4 ± 0.53b*	64.7 ± 4.34a*	1.76± 0.02b*

All values are mean ± SEM, n = 6. *p<0.05, **p<0.01; a. Significance difference as compared to Vehicle; b. Significance difference as compared to Cisplatin**.**

Table 6: Serum analysis for liver function test (SET- II)

Group	Treatment	SGOT (IU/L)	SGPT (IU/L)	Total Bilirubin (mg/dl)
AA - 1	Vehicle	116.8 ± 13.6	27.7 ± 4.6	0.75 ± 0.11
AA - 2	Cisplatin	307.6 ± 17.3a	94.6 ± 5.3a	3.02 ± 0.9a
AA - 3	Cisplatin+ Amifostine	156.3 ± 14.6b*	36.2 ± 2.4b**	0.94 ± 0.2b**
AA - 4	Cisplatin + Daidzein	197.6 ± 22.7b*	54.7 ± 1.4b*	1.32 ± 0.8b*
AA - 5	Cisplatin + Naringenin	174.6 ± 18.5b*	43.5 ± 4.7a*	1.18 ± 0.4b*
AA - 6	Cisplatin + Icariin	237.5 ± 15.3b*	78.9 ± 5.3b*	1.82 ± 0.7b*

All values are mean ± SEM, n = 6. *p<0.05, **p<0.01; a. Significance difference as compared to Vehicle; b. Significance difference as compared to Cisplatin**.**

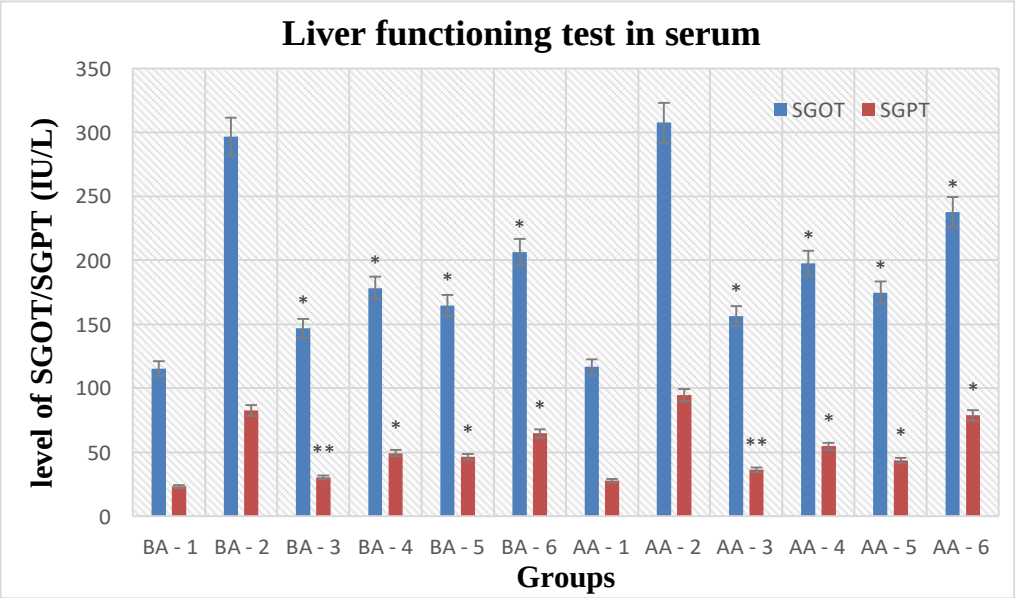

Figure 2: Level of SGPT and SGOT in serum of both sets of animals. All values are mean ± SEM, n = 6. *p<0.05, **p<0.01; a. Significance difference as compared to Vehicle; b. Significance difference as compared to Cisplatin**.**

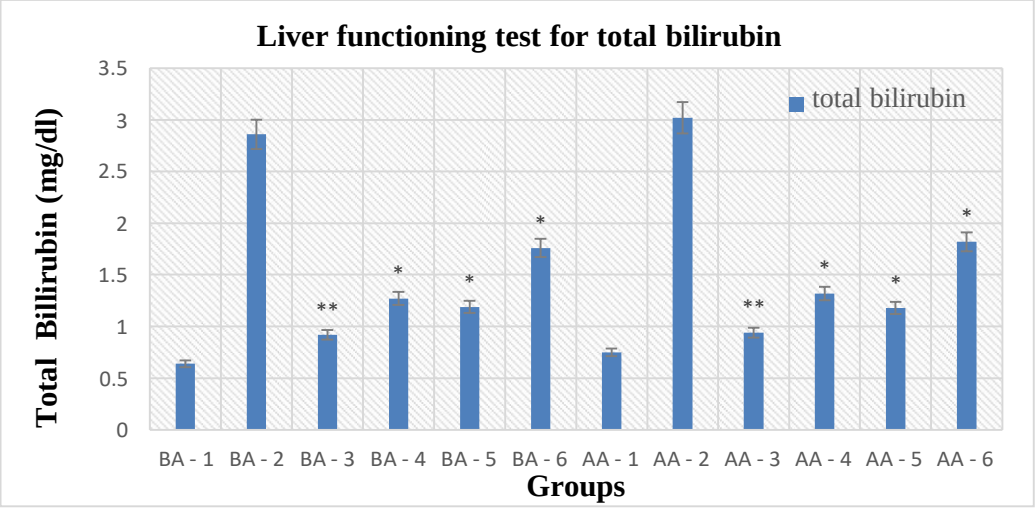

Figure 3: Level of total bilirubin in serum of both sets of animals. All values are mean ± SEM, n = 6. *p<0.05, **p<0.01; a. Significance difference as compared to Vehicle; b. Significance difference as compared to Cisplatin**.**

Liver Histopathology

The microscopic examination of the liver tissue sections from the control group showed large polygonal cells with a natural core arranged around the central vein and several hepatic sinuses (BA-1 and AA-1). On the other hand, the second group received only cisplatin, which revealed obvious histological abnormalities such as significant fatty change, congestion of the central venous sinus, and necrosis primarily around the central vein (BA-2 & AA-2). Histological analysis of the liver from mice group cisplatin-treated mice pretreated and post-treated with Amifostine (positive control) displayed minimal fatty changes in liver cell cytoplasm in regular morphology (BA-3 & AA-3), Histological analysis of the liver from cisplatin-treated mice pretreated and post-treated with Daidzein, Naringenin and Icariin (BA-4, BA-5 BA-6 & AA-4, AA-5, AA-6) showed less histopathological hepatic changes, showed a regression of the fatty changes in the liver cell cytoplasm. A greater improvement and the scattering of the apoptotic cells were seen in BA-4 & AA-4 and BA-6 & AA-6 groups. All observations are similar for both sets (I and II) as sown in figures 4 & 5.

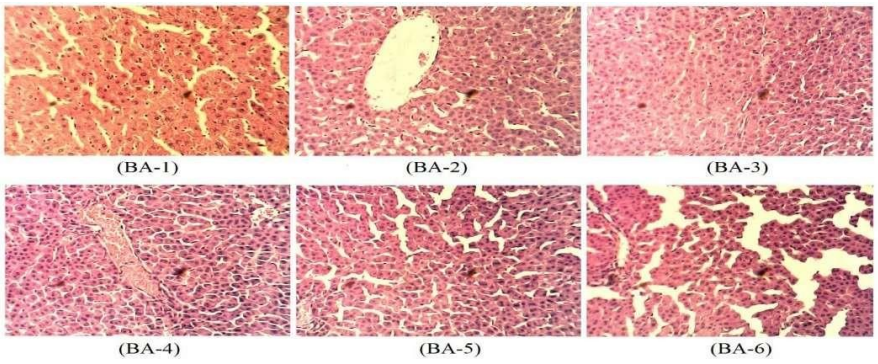

Figure 4: Histopathology of Liver obtained from set-I animals. H&E x 100

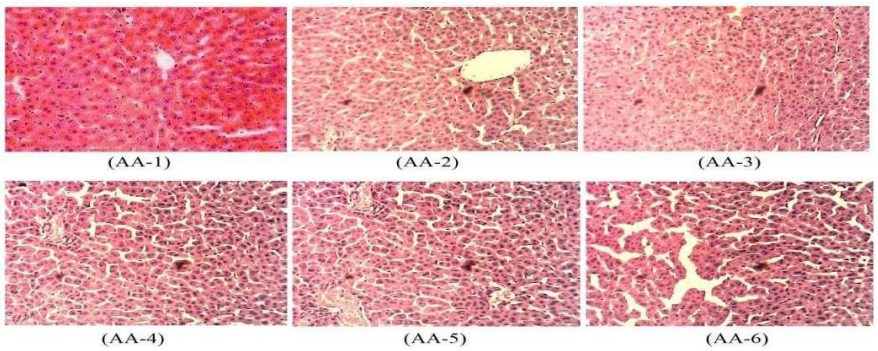

Figure 5: Histopathology of Liver obtained from set-II animals. H&E x 100

DISCUSSION

Evaluation of hepatoprotective Potential of Daidzein, Naringenin, Icariin Flavonoids Against Cisplatin Induced toxicity in Mice. A total of 36 Wistar albino mice divided into two sets were taken and acclimatized to laboratory conditions through standard procedure. The Nephrotoxicity and hepatotoxicity of cisplatin are the major side effects of this drug. In present research work hepatotoxicity was assessed by determining various physiological and biochemical parameters *i.e.* body weight, SGOT, SGPT, Lipid peroxidation (MDA) in mice before and after cisplatin administration. Histopathology findings in different tissues of the mice revealed cell degeneration and necrosis on the 14^{th} day after the execution of a single dose of cisplatin per day.

Effect of Daidzein, Naringenin, Icariin on Cisplatin-induced hepatotoxicity was determined by SGOT, SGPT and total Bilirubin in blood samples collected from both sets of mice (before and after treatment). Serum analysis for liver function tests significant recovery by Daidzein and Icariin treated groups in both sets. Biochemical observations were confirmed by liver histopathology showed less histopathological hepatic changes, showed a regression of the fatty changes in the liver cell cytoplasm. in both sets.

Histological studies were carried out in the 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 liver tissue.[6] In the current investigation, it was found that cisplatin's cytotoxic properties caused congestion of the central venous sinus, necrosis primarily around the central vein in the liver. The Daidzein, Naringenin, and Icariin on treatment also greatly lessens the tissue damage to these organs caused by the administration of cisplatin.

CONCLUSION

Finally, based on our research, we can conclude that pretreatment with flavonoids was found more effective against cisplatin-induced cytotoxicity as compared to posttreatment. Furthermore,

Naringenin effective against hepatotoxicity 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.

ACKNOWLEDGMENTS

Authors thanks to Dr Sandeep Balvant Patil, Founder and Chairman, Biocyte Institute of Research and Development (BIRD), Sangli, Maharashtra for providing facility for preparing histopathology slides and examining cytotoxicity in different organs.

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.

Ethics approval

The authors declare that this work involved animal study and 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).

Consent to participate

Not Applicable

Consent for publication

All authors of this paper have read and approved the final version submitted and give our consent for publication.

Funding

The authors declare that no funds, grants, or other support were received during the preparation of this manuscript.

Competing interests

The authors declare that they have no competing interests regarding the publication of this manuscript.

Availability of data and material

All data provided in the manuscript are available upon request.

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