RESEARCH ARTICLE

Effects of Hesperidin on Cisplatin-Induced Haematological and Biochemical Alterations in Rats

Vishal L. Sorathiya[1], Priti D. Vihol[1], Jignesh M. Patel[1], Jatin H. Patel[2], Jaynudin H. Khorajiya[1], Kishan M. Patel[1]

Abstract

Cisplatin, known as "penicillin of cancer" is an inorganic compound that is considered one of the best and first metal-based chemotherapeutic drugs. Hesperidin is one of the major dietary flavanones that is found abundantly in many citrus fruits. The present study was aimed to evaluate the ameliorative effects of hesperidin (@100 & 200 mg/kg b. wt.) in cisplatin (@ 7.5 mg/kg b.wt.) induced haemato-biochemical alteration in rats (n=32) over a period of 14 days. There was a decrease in mean values of haemoglobin, packed cell volume, platelets, total erythrocyte count and total leukocyte count in Group II (cisplatin, 7.5 mg/kg) and III (cisplatin plus 100 mg/kg hesperidin) in comparison with Group I (control, 0.5 mL of carboxy methyl cellulose) and IV (cisplatin plus 200 mg/kg hesperidin) at 14th day of experiment. Similarly, a significant elevation in serum AST, ALT, cholesterol, urea, creatinine and triglyceride values as well as significant decrease in total protein and albumin values were noted in cisplatin treated rats (Group II) at 14th day of experiment.

Key words: Cisplatin, Haemato-biochemical alterations, Hesperidin, Rats.

Ind J Vet Sci and Biotech (2024): 10.48165/ijvsbt.20.4.21

Introduction

Cisplatin, known as the "penicillin of cancer" (Stephen, 2005), is an inorganic compound that is considered one of the best and first metal-based chemotherapeutic drugs (Hannon, 2007). Cisplatin has shown anticancer activity in variety of tumors in human (Hattori *et al*., 2013; Dasari and Tchounwou, 2014). Cisplatin can induce nephrotoxicity, hepatotoxicity, suppression of bone marrow, gastrointestinal toxicity, neurotoxicity, ototoxicity and hypersensitivity reactions (Stakisaitis *et al.,* 2010; Moneim, 2014).

Flavonoids, categorized as natural antioxidants, are widely distributed in plants. Flavonoids affect basic cell functions such as development, apoptosis and differentiation as a result of their profound scavenging activity and increasing cyclic-GMP-dependent relaxation (David *et al*., 2016) and it also exerts beneficial effects in coronary heart disease, hyper cholesterolemia, atherosclerosis and heart failure (Stoclet *et al.,* 2004). It is also reported that flavonoids are now considered as an indispensable component in a variety of nutraceutical, pharmaceutical, medicinal and cosmetic applications (Panche *et al.,* 2016). Hesperidin is one of the major dietary flavanones that are found abundantly in many citrus fruits. Hesperidin has beneficial effects on human health in its free state or as glycosides. Hesperidin has analgesic effects, antibacterial, antifungal, antiviral, anti-yeast, anti-fertility, anti-cancer, ultraviolet protection effects, anti-allergic, anti-ulcer and antipyretic effects (Garg *et al*., 2001). Recently there is a trend in toxicological research to explore health beneficial effects of various flanenoids. Hence, the present study was planned to explore ameliorative effects of hesperidin on cisplatin-induced haemato-biochemical alterations in rats.

[1]Department of Veterinary Pathology, College of Veterinary Science & Animal Husbandry, Kamdhenu University, Navsari-396450, Gujarat, India.

[2]Department of Veterinary Pharmacology and Toxicology, College of Veterinary Science & Animal Husbandry, Kamdhenu University, Navsari-396450, Gujarat, India.

Corresponding Author: Dr. Vishal L. Sorathiya, Department of Veterinary Pathology, College of Veterinary Science & Animal Husbandry, Kamdhenu University, Navsari-396450, Gujarat, India, e-mail: vishalsorathiya77@gmail.com

How to cite this article: Sorathiya, V. L., Vihol, P. D., Patel, J. M., Patel, J. H., Khorajiya, J. H., & Patel, K. M. (2024). Effects of Hesperidin on Cisplatin-Induced Haematological and Biochemical Alterations in Rats. Ind J Vet Sci and Biotech. 20(4), 100-104.

Source of support: Nil

Conflict of interest: None

Submitted 11/03/2024 **Accepted** 28/04/2024 **Published** 10/07/2024

Materials and Methods

This study was carried out in rat model for a period of 14 days at the small animal house facilities of the College of Veterinary Science & Animal Husbandry, Kamdhenu University, Navsari (India) following approval of the Institutional Animal Ethics Committee vide No. 090-VCN-VPP-2020.

Design of the Experiment

A total of 32 adult Wistar rats of either sex weighing 200-350 gm, procured from Ribosome Research Center, Kim, Gujarat were used. Rats were maintained in an environment controlled room at a temperature of 22 °C and relative humidity of 40 to 70 %. The photoperiod was 12 h light and

12 h dark. Prior to the commencement of experiment, rats were acclimatized in an animal house for 7 days. Clean, dry and autoclaved rice husk was used as bedding material for experimental animals and it was changed every two days. Animals were fed a standard pellet (size 12 mm) diet. Rats were provided with *ad libitum* pellet feed which was procured from M/S VRK Nutrition Solution, Pune, Maharashtra. Rats were provided unlimited pure drinking water (RO water) in polypropylene bottles throughout the period of the experiment.

After acclimatization, rats were randomly divided into four groups each comprising of 4 males and 4 females. Animals were housed (4 rats of the same sex in each cage) in polypropylene cages with solid bottom. In Group I (Vehicle control Group), animals were administered 0.5 mL of carboxy methyl cellulose (CMC) daily for 14 days by oral gavage. In Group II, III and IV rats were given cisplatin at a dose rate of 7.5 mg/kg body weight intraperitoneally and hesperidin @ 00, 100 and 200 mg/kg body weight, respectively, by oral gavage daily for 14 days. Hesperidin was dissolved in 1% carboxy methyl cellulose (CMC).

Sample Collection and Haemato-Biochemical Analysis

Blood samples were collected from the rats of all the groups on the 0-day and 15th day of the experiment in sterile vials containing K_2EDTA at 1 mg/mL as well as plain vacutainers from the retro-orbital plexus for haematology and serum biochemical analysis, respectively.

At both intervals, blood samples were analyzed for detailed haematological indices using a haemato-analyser (Exigo EOS Vet, Sweden). The plain vacutainers containing blood samples were initially kept at room temperature for 30 min and later centrifuged at 112 g for 10 min to obtain serum, which was stored at -20 °C until further analyses. Serum samples were analyzed for the enzymatic activities of aspartate amino transferase (AST), alanine amino transferase (ALT), blood urea nitrogen (BUN), serum creatinine, total protein, albumin, cholesterol and triglycerides by using standard procedures and assay kits (Randox Laboratories Ltd) on biochemistry analyzer (Merck Instrument, Model: Microlab 300, India).

Statistical Analysis

The data were subjected to statistical analysis using SPSS 20.0 statistical software. A one-way analysis of variance followed by Duncan's multiple range test was performed to determine inter-group differences. The values were presented as mean ± standard error (SE). The criterion for statistical significance was $p<0.05$.

Results and Discussion

The mean ± SE values of the haematological and biochemical parameters observed in different treatment groups of rats on day 0 and day 15th of the experiment are presented in Tables 1 and 2, respectively.

Haematological Alterations

In present study, at the end of experiment, the Hb value was reduced significantly ($p<0.05$) in cisplatin-treated rats (Group II) as compared to Groups I, III and IV. Similarly cisplatin-treated rats had significantly ($p<0.05$) lower TEC and PCV values than Groups I, III and IV. Moreover, in Groups II and III mean values of TLC decreased significantly in comparison to Group I and IV. The mean platelets values in Groups II and III were significantly decreased than in Groups I and IV. Among haematological values, *viz.,* DLC (neutrophils, eosinophils, basophils, lymphocytes and monocytes), MCV, MCH and MCHC showed no significant difference.

In the current study, cisplatin caused a significant alteration in the mean values of TLC, TEC, PCV, Hb and platelets, which were in accordance with the findings of the earlier workers (Nasr, 2014; Karale and Kamath, 2017; Rajendrakumar *et al.,* 2020). Contrary to present findings, a significant increase in lymphocytes and TLC were noted by Karale and Kamath, (2017). It is reported that cytotoxic nature of cisplatin can easily cause DNA damage and myelotoxicity (bone marrow suppression) which ultimately leads to reduction in the RBCs number and decrease in platelets (Rajendrakumar *et al.,* 2020). The cisplatin administration also reduces erythropoietin and haemopoietic growth factors which results in an alteration of haematological parameters and increased osmotic fragility of RBCs (Rajendrakumar *et al.,* 2020). In the study cisplatin intoxication caused anaemia which might be due to result of either suppression of activity in haematopoietic tissues and impaired erythropoiesis or accelerated RBCs destruction because of the altered RBCs membrane permeability, increased RBCs mechanical fragility and defective iron metabolism (Nasr, 2014).

Haematopoietic system is one of the most sensitive systems to evaluate the hazardous effects of poisons and drugs in humans and animals. Cisplatin is cytotoxic drug used to kill cancer cells, but as a side effect it also destroys the cells of immune system. Hesperidin affects the formation or secretion of erythropoietin, which stimulates stem cells in the bone marrow to produce red blood cells (Mahmoud, 2013; Ghaffar *et al.,* 2017). It also favours a haematopoietin-like effect or release of haematopoietin from haematopoetic organs such as the kidneys or liver (Ahmad *et al.,* 2012). Hesperidin at dose rate of 200 mg/kg body weight exerted good protective effect against cisplatin induced changes in blood in comparison to low dose of hesperidin.

Serum Biochemical Alterations

At the end of the present experiment, rats of Group II treated with cisplatin alone revealed a significant ($p<0.05$) rise in ALT, AST, BUN and creatinine values when compared with cisplatin plus hesperidin @ 100 mg/kg. b. wt. treatment Group III. However, values of cholesterol and triglycerides did not show any significant changes between these two

Table 1: Haematological values in different treatment groups of rats initially (day 0) and at 15th day of experiment (n=8)

Haematological parameters	Days	Experimental groups			
		Group I	Group II	Group III	Group IV
TEC (x 10^6/µL)	0 day	6.59^a ±0.08	6.53^a ±0.13	6.55^a ±0.10	6.50^a ±0.04
	15th day	7.37^a ±0.13	5.93^c ±0.03	6.92^b ±0.15	7.31^a ±0.15
Hb conc. (g/dL)	0 day	14.3^a ±0.13	14.4^a ±0.15	14.4^a ±0.14	14.5^a ±0.19
	15th day	14.6^a ±0.05	11.5^c ±0.26	12.9^b ±0.12	14.1^a ±0.17
Haematocrit (%)	0 day	36.6^a ±0.14	36.8^a ±0.25	36.7^a ±0.32	36.7^a ±0.21
	15th day	43.0^a ±0.05	34.9^c ±0.20	40.9^b ±0.49	42.3^a ±0.33
TLC (x 10^3/µL)	0 day	7.41^a ±0.14	7.46^a ±0.15	7.38^a ±0.10	7.36^a ±0.14
	15th day	7.28^a ±0.13	5.85^c ±0.25	6.56^b ±0.15	7.19^a ±0.12
Lymphocyte (%)	0 day	70.75^a ±0.36	71.12^a ±0.51	70.87^a ±0.44	71.14^a ±0.40
	15th day	71.75^a ±0.45	71.87^a ±0.58	72.00^a ±0.32	72.00^a ±0.56
Monocyte (%)	0 day	2.50^a ±0.37	2.62^a ±0.18	2.25^a ±0.31	2.57^a ±0.40
	15th day	2.87^a ±0.35	3.00^a ±0.18	3.12^a ±0.39	2.87^a ±0.22
Neutrophils (%)	0 day	24.37^a ±0.26	24.00^a ±0.26	24.37^a ±0.41	23.85^a ±0.50
	15th day	22.87^a ±0.54	22.75^a ±0.55	23.00^a ±0.46	22.50^a ±0.80
Eosinophils (%)	0 day	2.37^a ±0.18	2.25^a ±0.31	2.37^a ±0.18	2.57^a ±0.18
	15th day	2.50^a ±0.42	2.75^a ±0.31	2.37^a ±0.32	2.50^a ±0.32
Basophils (%)	0 day	0.00 ±0.00	0.00 ±0.00	0.00 ±0.00	0.00 ±0.00
	15th day	0.00 ±0.00	0.00 ±0.00	0.00 ±0.00	0.00 ±0.00
MCV (fL)	0 day	56.16^a ±0.63	56.43^a ±0.36	56.13^a ±0.97	56.49^a ±0.29
	15th day	59.71^a ±0.60	59.29^a ±0.36	59.38^a ±0.78	59.39^a ±0.93
MCH (pg)	0 day	19.88^a ±0.16	20.06^a ±0.53	20.16^a ±0.59	19.99^a ±0.50
	15th day	22.03^a ±0.44	22.10^a ±0.22	21.97^a ±0.18	22.07^a ±0.14
MCHC (g/dL)	0 day	33.07^a ±0.34	33.16^a ±0.13	32.93^a ±0.33	33.26^a ±0.19
	15th day	38.96^a ±0.69	39.04^a ±0.43	38.91^a ±0.43	39.30^a ±0.46
Platelets (x10^3/µL)	0 day	902.12^a ±3.91	903.62^a±3.37	904.12^a±4.75	904.00^a±2.69
	15th day	933.75^a ±3.87	641.37^c±4.45	883.12^b±4.47	926.12^a 4.04

Means bearing different superscripts within a row differ significantly (p<0.05). Group I: Control – CMC vehicle @ 0.5 mL, *per os*; Group II: Cisplatin @ 7.5 mg/kg. body wt., I/P; Group III: HES @ 100 mg/kg body wt., *per os* and cisplatin @ 7.5 mg/kg. body wt., I/P; Group IV: HES @ 200 mg/kg body wt. *per os* and cisplatin @ 7.5 mg/kg. body wt., I/P.

groups, and their values were significantly higher than in Group I (Control) and IV (cisplatin plus hesperidin @ 200 mg/kg b.wt.). Among Groups II and III, the values of total protein and albumin were significantly (p<0.05) lower in Group II. There was no statistically significant difference in these values between Group IV and Group I. However in group I and IV, total protein and albumin concentration was found to be higher than group II and III. The ALT, AST, BUN and creatinine activity in cisplatin treated rats (Group II) was significantly (p<0.05) higher at the end of the experiment as compared to control Group I of rats, while in Group III and Group IV the ALT, AST, BUN and creatinine enzyme activity noted was significantly (p<0.05) lower in comparison to Group II.

In the present study, the increased values of ALT and AST observed in the cisplatin group were in agreement with those reported in cisplatin-induced toxicity by Ezz-Din *et al.* (2011), Karale and Kamath (2017), Abdel-Daim *et al*. (2019) and Ogbe *et al.* (2020). Total protein and albumin values were decreased following cisplatin treatment in current study and these findings were in line with the reports of earlier workers (Saad *et al.,* 2001; Tikoo *et al.,* 2007; Yadav, 2015). Hesperidin treatment improved concentration of total protein and albumin, which indicates its protective effect. Our findings supported the observations of earlier researchers (Elshazly and Mahmoud, 2014; Kamel *et al.,* 2014). Cisplatin treated group of rats showed increased cholesterol and triglycerides levels, which were in agreement with those observed in cisplatin-induced toxicity by Ogbe *et al*. (2020). Administration of hesperidin at a dose rate of 200 mg/kg. b. wt. improvised the toxic effects of cisplatin and this result supported the findings of Omar *et al.* (2016).

Table 2: Details of serum biochemical values recorded in different groups of rats

Biochemical parameters	Days	Experimental groups			
		Group I	Group II	Group III	Group IV
AST (U/L)	0 day	108.36^{a} ±2.62	117.52^{a} ±4.13	114.25^{a} ±3.78	109.99^{a} ±3.46
	15th day	106.00^{a} ±1.23	193.47^{c} ±2.76	119.35^{b} ±4.00	108.11^{a} ±3.70
ALT (U/L)	0 day	27.51^{a} ±0.41	28.80^{a} ±0.20	27.43^{a} ±0.38	28.00^{a} ±0.34
	15th day	29.33^{a} ±0.49	47.15^{c} ±0.51	35.01^{b} ±0.64	30.59^{a} ±0.54
Albumin (mg/dL)	0 day	4.49^{a} ±0.03	4.48^{a} ±0.15	4.54^{a} ±0.14	4.56^{a} ±0.12
	15th day	4.28^{a} ±0.09	3.65^{c} ±0.06	3.96^{b} ±0.03	4.21^{a} ±0.02
Total protein (mg/dL)	0 day	6.08^{a} ±0.17	6.10^{a} ±0.34	6.12^{a} ±0.24	6.14^{a} ±0.13
	15th day	5.97^{a} ±0.02	4.14^{c} ±0.03	5.01^{b} ±0.02	5.90^{a} ±0.04
Cholesterol (mg/dL)	0 day	34.00^{a} ±0.57	35.12^{a} ±0.58	33.83^{a} ±0.38	34.38^{a} ±0.43
	15th day	33.79^{a}± 0.50	69.10^{b}± 0.69	67.72^{b}± 1.84	35.22^{a}± 0.76
Triglycerides (mg/dL)	0 day	92.48^{a} ±0.76	91.54^{a} ±1.08	89.28^{a} ±1.34	91.30^{a} ±0.77
	15th day	86.30^{a}± 0.88	144.05^{b}± 0.77	142.10^{b}± 0.71	88.83^{a}± 1.39
BUN (mg/dL)	0day	15.81^{a} ±0.43	15.16^{a} ±0.32	16.05^{a} ±0.35	16.37^{a} ±0.59
	15th day	17.42^{a} ±0.31	37.35^{c} ±0.37	24.03^{b} ±0.65	18.99^{a} ±0.81
Creatinine (mg/dL)	0 day	0.73^{a} ±0.01	0.71^{a} ±0.01	0.72^{a} ±0.02	0.75^{a} ±0.04
	15th day	0.82^{a} ±0.03	1.82^{c} ±0.10	0.95^{b} ±0.08	0.84^{a} ±0.01

Means bearing different superscripts within the rows differ significantly ($p<0.05$). Group I: Control – CMC vehicle @ 0.5 ml, *per os*; Group II: Cisplatin @ 7.5 mg/kg. body wt., I/P; Group III: HES @100 mg/kg body wt., *per og* and cisplatin @ 7.5 mg/kg. body wt., I/P; Group IV: HES @200 mg/kg body wt. *per og* and cisplatin @ 7.5 mg/kg. body wt., I/P.

Conclusion

The findings of the present study showed the most consistent haemato-biochemical alterations associated with cisplatin administration for 14 days, *i.e.,* reduced levels of haemoglobin, haemocrit and TEC, and increased levels of, ALT, AST, urea and creatinine due to an increased levels of generation of free-radicals that caused myelotoxicity, hepatotoxicity and nephrotoxicity. Hesperidin pre-treatment revealed good antioxidant activity with haemato-protective, hepato-protective, and nephro-protective effects against cisplatin induced organ toxicities in a dose dependant manner. Hesperidin pre-treatment at dose 200 mg/kg b. wt. was found to be protective against cisplatin induced dyslipidemia in rats. Moreover, hesperidin at 100 mg/kg b. wt was less effective as compared to 200 mg/kg b. wt.

Acknowledgement

We are highly thankful to Principal, College of Veterinary Science & Animal Husbandry, Kamdhenu University, Navsari, Gujarat for providing the necessary facility.

References

Abdel-Daim, M.M., Abushouk, A.I., Donia, T., Alarifi, S., Alkahtani, S., Aleya, L., & Bungau, S.G. (2019). The nephroprotective effects of allicin and ascorbic acid against cisplatin-induced toxicity in rats. *Environmental Science and Pollution Research*, *26*(13), 13502-13509.

Ahmad, S.T., Arjumand, W., Nafees, S., Seth, A., Ali, N., Rashid, S., & Sultana, S. (2012). Hesperidin alleviates acetaminophen induced toxicity in wistar rats by abrogation of oxidative stress, apoptosis and inflammation. *Toxicology Letters*, *208*(2), 149-161.

Dasari, S., & Tchounwou, P.B. (2014). Cisplatin in cancer therapy: molecular mechanisms of action. *European Journal of Pharmacology*, *740,* 364-378.

David, A.V.A., Satyanarayana, N., Parasuraman, S., Bharathi, S., & Arulmoli, R. (2016). Ameliorative effect of quercetin on methotrexate induced toxicity in sprague-dawley rats: A histopathological study. *International Journal of Pharmaceutical Education and Research*, *50*(3), 200-208.

Elshazly, S.M., & Mahmoud, A.A. (2014). Antifibrotic activity of hesperidin against dimethylnitrosamine-induced liver fibrosis in rats. *Naunyn-Schmiedeberg's Archives of Pharmacology*, *387*(6), 559-567.

Garg, A., Garg, S., Zaneveld, L.J.D., & Singla, A.K. (2001). Chemistry and pharmacology of the citrus bioflavonoid hesperidin. *Phytotherapy Research*, *15*(8), 655-669.

Ghaffar, F.R.A., Hassouna, I.A., Ibrahim, H.M., & Elelaimy, I.A. (2017). The protective effect of hesperidin or garlic oil against the hemotoxicity of diazinon in male albino rats. *Journal of Bioscience and Applied Research*, *3*(1), 23-36.

Hannon, M.J. (2007). Metal-based anticancer drugs: from a past anchored in platinum chemistry to a post-genomic future of diverse chemistry and biology. *Pure and Applied Chemistry*, *79*(12), 2243-2261.

Hattori, T., Yakabi, K., & Takeda, H. (2013). Cisplatin-induced anorexia and ghrelin. *Vitamins & Hormones*, *92,* 301-317.

Kamel, K.M., Abd El-Raouf, O.M., Metwally, S.A., Abd El-Latif, H.A., & El-sayed, M.E. (2014). Hesperidin and rutin, antioxidant citrus flavonoids, attenuate cisplatin-induced nephrotoxicity

in rats. *Journal of Biochemical and Molecular Toxicology*, *28*(7), 312-319.

Karale, S., & Kamath, J. V. (2017). Effect of daidzein on cisplatin-induced hematotoxicity and hepatotoxicity in experimental rats. *Indian Journal of Pharmacology*, *49*(1), 49.

Mahmoud, A.M. (2013). Hematological alterations in diabetic rats-role of adipocytokines and effect of citrus flavonoids. *Excli Journal*, *12,* 647-653.

Moneim, A.E.A. (2014). *Azadirachta indica* attenuates cisplatin-induced neurotoxicity in rats. *Indian Journal of Pharmacology*, *46*(3), 316.

Nasr, A.Y. (2014). Protective effect of aged garlic extract against the oxidative stress induced by cisplatin on blood cells parameters and hepatic antioxidant enzymes in rats. *Toxicology Reports*, 1, 682-691.

Ogbe, R., Agbese, S.P., & Abu, A.H. (2020). Protective effect of aqueous extract of lophira lanceolata leaf against cisplatin-induced hepatorenal injuries and dyslipidemia in wistar rats. *Clinical Phytoscience*, *6*(1), 1-11.

Omar, H.A., Mohamed, W.R., Arafa, E.S.A., Shehata, B.A., El Sherbiny, G.A., Arab, H.H., & Elgendy, A.N.A. (2016). Hesperidin alleviates cisplatin induced hepatotoxicity in rats without inhibiting its antitumor activity. *Pharmacological Reports*, *68*(2), 349-356.

Rajendrakumar, T., Suguna, R.M.L., Satyanarayana, H.D., Narayanaswamy, S.M., Gowda, S.M., & Shridhar, N.B. (2020). Haematological alterations in cisplatin induced toxicity in rats and its amelioration by *andrographispaniculata*. *International Journal of Current Microbiology and Applied Sciences*, *9*(4), 525-532.

Saad, S.Y., Najjar, T.A., Noreddin, A.M., & Al-Rikabi, A.C. (2001). Effects of gemcitabine on cisplatin-induced nephrotoxicity in rats: schedule-dependent study. *Pharmacological Research*, *43*(2), 193-198.

Stakisaitis, D., Dudeniene, G., Jankunas, R.J., Grazeliene, G., Didziapetriene, J., & Pundziene, B. (2010). Cisplatin increases urinary sodium excretion in rats: gender-related differences. *Medicina*, *46*(1), 45.

Stephen, T. (2005). Cisplatin. *Chemical and Engineering News*, *83,* 52.

Stoclet, J.C., Chataigneau, T., Ndiaye, M., Oak, M.H., El Bedoui, J., Chataigneau, M., & Schini-Kerth, V.B. (2004). Vascular protection by dietary polyphenols. *European Journal of Pharmacology*, *500*(1-3), 299-313.

Tikoo, K., Bhatt, D.K., Gaikwad, A. B., Sharma, V., & Kabra, D.G. (2007). Differential effects of tannic acid on cisplatin-induced nephrotoxicity in rats. *Federation of European Biochemical Societies*, *581*(10), 2027-2035.

Yadav, Y.C. (2015). Hepatoprotective effect of ficus religiosa latex on cisplatin induced liver injury in wistar rats. *Revista Brasileira de Farmacognosia*, *25*(3), 278 283.