ORIGINAL ARTICLE

Effects of cisplatin on renal biochemical and histological picture in male albino rats Role of propolis

MAHER IBRAHIM ISMAEL[1], IMAD ABDUL-JABBAR THANOON[2], MOHAMMAD K.SHINDALA[3]
B.Sc M.Sc (Pharmacology) M.B.Ch., B; M.Sc ;Ph.D (Pharmacology); Ph.D (Vet. Pharmacology & Toxicology)
[1]Ph.D student Dept. of Pharmacology-College of Medicine/University of Mosul
[2]Director of the Dept. of Pharmacology/College of Medicine/University of Mosul, Mosul-Iraq
[3]Professor Dr of Vet. Pharmacology & Toxicology, Dept of Physiology & Pharmacology-College of Vet. Medicine-Univ. of Mosul. Mosul-Iraq
Corresponding author: Email : imadpharma@yahoo.com

ABSTRACT

Aims: This study aimed to investigate the effects of cisplatin renal function tests with histological picture, and any possible role for propolis in ameliorating toxic changes, in comparison to controls.

Materials and Methods: This experimental work takes 6 weeks and involved 60 male albino rats ,weighed 230±40g , divided into 6 groups, each of 10 members.

Group A, received 3 doses of cisplatin at 4 mg/kg intraperitoneally (I.P) at weekly intervals starting by the end of the 2nd week, and killed by the end of the 6th week.

Group B, received propolis at 120 mg /day orally for 6 weeks.

Group C, received propolis 120 mg/day initially then by the end of the 2nd week started cisplatin 4mg I.P weekly for 3 doses.

Group D, received propolis 60 mg/day for 6 weeks.

Group E, received propolis 60 mg daily for 6 weeks, starting cisplatin I.P 4 mg 3 doses by the end of the 2nd week ,one week apart.

Group F, represent the control group, on normal saline orally for 6 weeks.

At the start the animals in all groups were weighed ,a blood sample was taken then, during the experiment , weighed , physical activity and food intake were recorded, by the end of the experimental duration weight were recorded, a blood sample were taken and the animals were killed , kidneys were taken for their weight and histological section with H& E staining.

The blood samples taken before and after the experiment were blood urea, serum creatinine, serum uric acid.

Results: By observation: By comparison of before and 6 weeks after the experiment , there was a significant weight reduction in the group A, with loss of 2 members of this group after the 3rd dose of cisplatin. While group B showed a significant weight gain. Clear and significant changes were recorded in parameters of renal function tests , in group A in comparison to control group, with a clear ameliorative effects of propolis especially noticed at 120 mg/d.

Also there was a clear changes in the histological picture of the kidney with obvious ameliorated effects of propolis especially noticed at 120 mg dose /day.

Conclusion: Propolis administration at a daily dose of 120 mg/day clearly ameliorated the toxic effects of cisplatin on the kidney at both functional and histological pictures.

INTRODUCTION

Cisplatin (CP) is a commonly used chemotherapeutic agent in the management of a number of solid tumors, of them, testicular, ovarian, lung, brain , head and neck tumors (1). Its use carry a serious adverse effects of these especially concerned , nephrotoxicity (2),and hepatotoxicity (3), which could be explained by the fact that more than 90% of the drug in the blood is covalently bound to plasma proteins and after administration high levels of the drug can be recovered in tissues of the kidney, liver, intestine and testis (4). After only few days from initiation of therapy ,about one-third of the cisplatin treated patients exhibited reduced glomerular filtration rates (5). Cisplatin is metabolized primarily by the kidneys. Although renal cells exhibit a low rate of division, they are sensitive to toxic injury owing to their high blood flow and their ability to concentrate toxins in the medullary interstitium and tubule epithelium (6). Little information is known about the underlying mechanism of hepatotoxicity induced by CP , although reportedly CP may interfere with tissue antioxidant defense system and generates highly reactive oxygen species (ROS). Therefore CP can cause oxidative damage to the liver (7). Recently attention has been given to the possible protective roles of dietary antioxidant against cisplatin nephrotoxicity and hepatotoxicity, of these propolis, daidzein, grape pomace extract have been evaluated (8,9,10). Propolis is a glue material, collected by honeybees from buds and exudates of plants (11). It contains more than 300 component, among them flavonoids and phenolic acid and their esters (12). Many in vivo and in vitro researches showed that propolis has several biological actions, such as scavenging of free radicals , antioxidant , antitumor , and immunomodulatory effects (13,14). This study aimed to assess the possible antioxidant ameliorated effects of propolis at 2 dose levels opposing the nephrotoxicity of cisplatin at both biochemical and histological levels.

MATERIALS AND METHODS

A total of 60 adult male albino rats weighing 230±40 g ,obtained from the animal house in the College of Veterinary Medicine-University of Mosul, randomly divided into 6 groups each of 10 rats. The animals were housed in metallic cages and subjected to an adaptation period of two weeks ,photoperiod of (12 h:12h light/dark), 25º C± 2 º C

temperature and 45-50% humidity , receiving normal amount of water and food. Ethical approval reference number :UOM/COM/MREC/20-21(21).

Group A: received 4 mg cisplatin I.P by the end of the 2nd week for 3 doses one week apart.

Group B: received propolis 120 mg daily orally for 6 weeks.

Group C: Received propolis 120 mg daily orally for 6 weeks and by the end of the 2nd week starting cisplatin I.P 4 mg for 3 doses one week apart between a dose and the other.

Group D: received propolis 60 mg daily orally for 6 weeks.

Group E: received propolis 60 mg daily orally for 6 weeks and by the end of the 2nd week starting cisplatin 4 mg I.P for 3 doses one week apart between a dose and the other.

Group F: Control group receiving normal saline orally.

At the start of the experiment and by the end of the 6th week , a blood samples were taken from all the animals under study, for assessing renal function tests (blood urea and serum creatinine) with serum uric acid levels.

By the end of the end of the experiment duration animals were weighed , anesthetized and scarified, kidney weighed and preserved and later examined microscopically with H&E stain.

Statistical Analysis of the data: The results were expressed as mean± SD; Mann-Whitney test was used to compare of pre and post administration results within the group. Improvement (change) rate was calculated as

Improvement rate = result of pre-administration – result of after administration/ result of pre-administration x 100.

One-way ANOVA test with Tukey's Pair wise was used to compare results between different groups. The Statistical Minitab version 18 software program was used to perform statistical analysis of the data.

RESULTS

1. Biochemical results

Renal function tests and serum uric acid

a. Group A. By comparison of pre and post-administration results, there was a significant increase in blood urea and serum creatinine, with insignificant increase in serum uric acid levels. Table 1.
b. Group B. By comparison of pre and post-administration results , there was a significant reduction in blood urea with insignificant reduction in serum creatinine and serum uric acid levels. Table 2.
c. Group C. There was a significant increase in blood urea and serum creatinine, with a non-significant increase in serum uric acid levels ,by comparing pre to post-administration results. Table 3.
d. Group D. By comparison of the results of pre- and post-administration, there a significant decrease in blood urea and serum uric acid, with insignificant effects on serum creatinine. Table 4.
e. Group E. There was a significant increase in blood urea and serum creatinine, with a significant reduction in serum uric acid, on comparing results of pre- to post-administration. Table 5.
f. Group F. There was a non-significant effects of placebo on the results of pre- and post-administration of placebo. Table 6.

Table 7 shows a comparison between all 6 groups with regard renal function tests and serum uric acid, it revealed a significant differences in the levels of blood urea and serum creatinine between group A and the other groups.

2. Observational before dissection

a. Group A. Two of the members of this group died 3 days after the 3rd I.P dose of cisplatin both showed yellowish disclouration of the whole body , the other members showed clear weight loss ,with decrease in physical activity and food intake.
b. Group B. No death was reported in this group, members of this group looks fully active, with good food intake and obvious weight gain.
c. Group C. No death was reported in this group, with mild decrease in physical activity and food intake and mild weight loss.
d. Group D. No death was reported in this group, physically active with good food intake.
e. Group E. one death was recorded in this group ,with mild reduction in physical activity and food intake, with obvious weight loss.
f. Group F. No losses was reported in this group, all members active physically with good food intake.

Table 8 shows comparison between the 6 groups with regard weight changes before and after the 6 weeks intervention.

Observational after dissection

3. Histological picture

Kidney excessive +++; moderate++; mild +; no change - ve

a. Group A. There was an excessive atrophy of glomeruli, dilatation of bowman's space, vacuolar degeration and cellular swelling, hyaline casts with cellular necrosis and congestion, with moderate segmentation of glomeruli, pyknosis of nuclei, apoptosis with infiltration of inflammatory cells, mild degree of hemorrhage and cystic formation Figure 1.
b. Group B. There was a mild degree of segmentation of glomeruli, vacuolar degeneration and cell swelling, cellular necrosis, infiltration of inflammatory cells with congestion, there was no atrophy of glomeruli, no dilatation of bowman's space , no hyaline casts ,no pyknosis of nuclei, no apoptosis ,no hemorrhage or cystic formation nor fibrosis Figure 2.
c. Group C. There was a moderate degree of infiltration of inflammatory cells ,with mild degree of atrophy and segmentation of glomeruli, dilatation of bowman's space, vacuolar degeneration and cell swelling, pyknosis of nuclei, cellular necrosis, hemorrhage and congestion, with no hyaline casts, no apoptosis cystic formation nor fibrosis Figure 3.
d. Group D. There was a mild degree of atrophy and segmentation of glomeruli, vacuolar congestion and cell swelling, pyknosis of nuclei, necrosis of cells, infiltration of inflammatory cells with congestion. No dilatation of bowman's space, no hyaline casts,no apoptosis, no hemorrhage , no cystic formation nor fibrosis. Figure 4.
e. Group E. There was a moderate degree of atrophy of glomeruli, with vacuolar degeneration and cell swelling, cellular necrosis, infiltration of inflammatory cells, congestion with mild degree of segmentation of glomeruli, dilatation of bowman's space, hyaline

casts, pyknosis of nuclei with hemorrhage, but no apoptosis, no cystic formation nor fibrosis Figure 5.

f. Group F. Beside mild congestion, no other abnormality was detected. Figure 6.

Table 8 shows comparison between all 6 groups with regard diameter of glomeruli (µm), one can notice no differences between group F and Groups B,D, with a significant differences from groups A,C and E.

DISCUSSION

1. **Effects on body weight:** The reduction in body weight observed in this study in the cisplatin group , could be correlated with the reduced food intake noticed during the period of the experiment. Weight gain have been noticed in group C by adding propolis at 120 mg/d, but not at 60 mg/d, this is in agreement with the study conducted by El-Naggar et al., (8). They reported that propolis treatment after cyclophosphamide injection could protect partially the body from weight loss.

This is in agreement with study conducted by Denli *et al*, (15), whom reported that the addition of propolis in the diet significantly increase the growth parameter of quail chicks such as body weight gain and feed consumption and improvement feed efficacy compared with controls and they suggested that it could be due to antimicrobial activity of the propolis extract that resulted in improvement of intestinal hygiene that lead to improved digestion and absorption, beside that it has been suggested that bee propolis contain protein, amino acids, vitamins, and flavonoids, for this resinous it has been used by some people as a nutritional supplement (16).

2. **Effects on the kidney:** Our study concluded that cisplatin induces both functional and structural changes in the rat's kidney, characterized by significant increase in serum creatinine and blood urea and serum uric acid levels, in addition to reduction in serum albumin levels with obvious histopathological changes, and that propolis ameliorating the biochemical and histological picture induced by the cisplatin. This is in agreement with the study conducted by Yulug et al (17). They reported that the mean creatinine and blood urea values in cisplatin treated rats were significantly different from the controls. This is in agreement with results of the study conducted by Iseri et al.,(18). They reported that cisplatin causes a marked reduction in renal function characterized by significant increases in blood urea and serum creatinine. Nephrotoxicity was also revealed by the histopathological examination.

It could explained by the fact that renal cisplatin uptake stimulate oxidative stress(19,20), and that it is well known that the cisplatin concentration in the proximal convoluted tubule can be up to 5 times greater than in the blood and that the concentration in the kidney's is proportional to the blood concentration (21). This study reported that in groups C and E , although there was a significant increase in blood urea and serum creatinine but it does not reach the high levels associated with cisplatin alone, addressing to the ameliorating effects of propolis against cisplatin induced nephrotoxicity (22) The effects was dose dependent, which goes with the findings of the research conducted by Turedi et al (23). As they concluded that CP caused significant damage to kidney tissue and that propolis exhibited dose-dependent preventive tissue damage. Other study conducted by Aldahmash et al (24), concluded that the Co-administration of propolis with gentamicin showed significant decrease in blood urea levels, with the appearance of healthy glomeruli and normal cellularity, reduction of tubular injury, decrease of collagen and reticular fibres deposition, reduction of apoptosis, kidney injury and oxidative stress. Several reserchers demonstrated the renoprotective effects of natural antioxidants including green tea, grape seed, crocin against cisplatin-induced renal toxicity (25,26,27). Atasayar et al ., (28) reported that combined treatment of vitamin C and E with toxic dose of cisplatin able to normalize the histopathological alteration induced by cisplatin on the kidney as compared to cisplatin alone.El- Nagger et al.,(8) concluded that propolis significantly ameliorate the histological picture induced by cyclophosphamide on the kidney. Hyperuricemia associated with CP therapy is considered to be a consequence of CP-induced nephrotoxic reaction (29). In their study Yoshizumi et al, repoted that a continuous intake of propolis might be effective for the prevention and treatment of gout and hyperuricemia by a xanthine oxidase inhibitory activity (30).

CONCLUSION

Giving propolis with cisplatin ameliorating the nephrotoxicity induced by cisplatin alone both at functional and histological picture levels.

Table (1): Effect of cisplatin 4 mg/kg [group A] on the RFT of sampled rats.

Parameters	Before Mean ± SD	After Mean ± SD	% Improvement rate	P-value*
Bl. urea (mg/dl)	47.13 ± 6.92	327.0 ± 172.0	- 593.8 %	0.001
S. creatinin (mg/dl)	0.500 ±0.076	2.063 ± 1.192	- 312.0 %	0.001
Uric acid (mg/dl)	1.18 ± 0.31	1.450 ± 0.34	- 22.9 %	0.060

* Mann-Whitney test was used. % Improvement rate = [(before – after) / Before] × 100.

Table (2): Effect of propolis 120 mg [group B] on the RFT of sampled rats.

Parameters	Before Mean ± SD	After Mean ± SD	% Improvement rate	P-value*
Bl. urea (mg/dl)	50.00 ± 7.84	40.38 ± 5.71	19.2 %	0.021
S. creatinin (mg/dl)	0.535 ± 0.093	0.443 ± 0.049	17.2 %	0.059
Uric acid (mg/dl)	1.35 ± 0.22	1.16 ± 0.24	14.1 %	0.169

* Mann-Whitney test was used. % Improvement rate = [(before – after) / Before] × 100.

Table (3): Effect of propolis 120 mg with cisplatin 4 mg/kg [group C] on the RFT of sampled rats.

Parameters	Before Mean ± SD	After Mean ± SD	% Improvement rate	P-value*
Bl. urea (mg/dl)	59.50 ± 10.50	129.5 ± 62.0	- 117.6 %	0.001
S. creatinin (mg/dl)	0.388 ± 0.113	0.912 ± 0.554	- 135.1 %	0.002
Uric acid (mg/dl)	0.93 ± 0.158	1.14 ± 0.256	23.0 %	0.077

* Mann-Whitney test was used. % Improvement rate = [(before – after) / Before] × 100.

Table (4): Effect of propolis 60 mg [group D] on the RFT of sampled rats.

Parameters	Before Mean ± SD	After Mean ± SD	% Improvement rate	P-value*
Bl. urea (mg/dl)	44.63 ± 4.31	38.50 ± 4.50	13.7 %	0.027
S. creatinin (mg/dl)	0.356 ± 0.050	0.363 ± 0.074	- 2.0 %	0.989
Uric acid (mg/dl)	1.14 ± 0.207	0.86 ± 0.119	24.6 %	0.005

* Mann-Whitney test was used.
% Improvement rate = [(before – after) / Before] × 100.

Table (5): Effect of propolis 60 mg with cisplatin 4 mg/kg [group E] on the RFT of sampled rats.

Parameters	Before Mean ± SD	After Mean ± SD	% Improvement rate	P-value*
Bl. urea (mg/dl)	35.63 ± 4.96	89.2 ± 52.2	- 150.4 %	0.014
S. creatinin (mg/dl)	0.27 ± 0.0886	0.663 ± 0.262	- 145.6 %	0.001
Uric acid (mg/dl)	1.13 ± 0.523	0.70 ± 0.0756	38.1 %	0.006

* Mann-Whitney test was used. % Improvement rate = [(before – after) / Before] × 100.

Table (6): Comparison of parameters of renal function tests and serum uric acid alter 6 weeks in control group.

Parameters	Beginning Mean ± SD	After 4 weeks Mean ± SD	% Improvement rate	P-value*
Bl. urea (mg/dl)	34.63 ± 6.67	34.25 ± 5.60	1.1 %	0.916
S. creatinin (mg/dl)	0.373 ± 0.041	0.373 ± 0.029	0.0 %	0.793
Uric acid (mg/dl)	1.09 ± 0.22	1.11 ± 0.29	- 1.8 %	0.745

* Mann-Whitney test was used. % Improvement rate = [(before – after) / Before] × 100.

Table (7): Comparison in RFT among the six groups after 6weeks of intervention.

RFT	Groups						P-value*
	A Mean ± SD	B Mean ± SD	C Mean ± SD	D Mean ± SD	E Mean ± SD	Control Mean ± SD	
Bl. urea (mg/dl)	327.0 ± 172.0 ^{A}	40.38 ± 5.71 ^{B}	129.5 ± 62.0 ^{B}	38.50 ± 4.50 ^{B}	89.2 ± 52.2 ^{B}	34.25 ± 5.60 ^{B}	0.000
S. creatin (mg/dl)	2.063 ± 1.192 ^{A}	0.443 ± 0.049 ^{B}	0.912 ± 0.554 ^{B}	0.363 ± 0.074 ^{B}	0.663 ± 0.262 ^{B}	0.373 ± 0.029 ^{B}	0.000
Uric acid (mg/dl)	1.450 ± 0.34 ^{A}	1.16 ± 0.24 ^{AB}	1.14 ± 0.256 ^{AB}	0.86 ± 0.119 ^{BC}	0.70 ± 0.076 ^{C}	1.11 ± 0.29 ^{AB}	0.000

* One-way ANOVA-test with Tukey's Pair wise comparisons. Means that do not share a letter are significantly different.

Table (8a): Comparison in rat`s kidney weight among the six groups after 6 weeks of intervention.

Kidney	Groups						P-value*
	A Mean ± SD	B Mean ± SD	C Mean ± SD	D Mean ± SD	E Mean ± SD	Control Mean ± SD	
Weight (g)	1.33 ± 0.21 ^{B}	1.58 ± 0.06 ^{AB}	1.47 ± 0.13 ^{AB}	1.64 ± 0.17 ^{A}	1.61 ± 0.06 ^{A}	1.47 ± 0.32 ^{AB}	0.010
kidney\body weight ratiox1000	8.29 ± 1.14 ^{A}	6.42 ± 0.20 ^{B}	6.89 ± 0.80 ^{B}	6.56 ± 0.74 ^{B}	7.57 ± 1.23 ^{AB}	6.94 ± 1.15 ^{AB}	0.001
PCT (µm)	67.46 ±2.91 B	39.42±1.71 A	54.02±1.45 C	41.1± 1.13 A	47.4 ± 1.80 D	43.1 ±2.20 AD	0.000
DCT (µm)	49.82 ± 3.81 B	28.86 ± 1.13 ^{A}	42.02 ± 1.26 C	30.14 ± 1.07^{A}	39 ± 1.89 ^{D}	28.8 ± 1.28 ^{A}	0.000

Table (8 b): Comparison in rat`s kidney diameter of glomeruli and bowman's capsule space among the six groups after 6 weeks of intervention.

group parameter	Control Group F	Group A Cisplatin 4mg	Group B Propolis 120mg	Group C Propolis 120+ cisplatin 4mg	Group D Propolis 60mg	Group E Propolis 60mg+ cisplatin 4mg
Diameter of glomeruli/µm	112.25±2.6 a	87.91±1.3 b	108.75±1.9 a	95.275±0.7 c	109.76±1.2 a	92.81±2.1 b
Bowmans space//µm	6.3±0.31 a	15.7±1.1 b	6.8±0.85 a	12.2±0.8 b	5.1±0.11 a	11.6±1.2 b

The similar letters in rows means with no significant at ($p \leq 0.05$).
The different letters in rows means with significant difference at ($p \leq <0.05$).

GROUP (A) Cisplatin 4mg

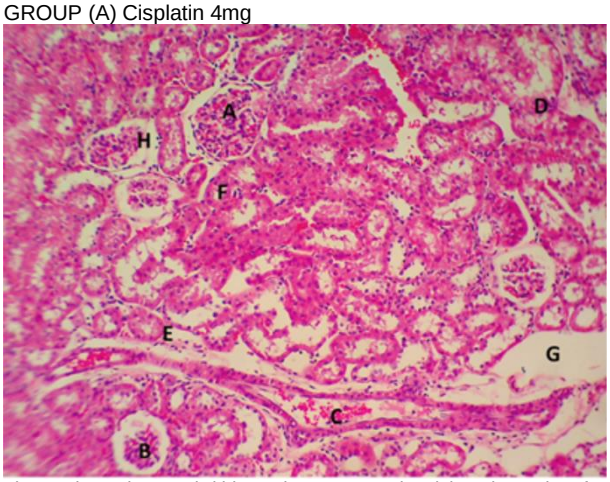

Fig. 1: photomicrograph kidney shows congestion (A) and atrophy of renal glomeruli (B), congested B.V. (C) , degeneration (cell swelling) of epithelium lining renal tubules (D), necrosis (E), apoptosis (F), cystic kidney formation (G) and dilation of Bowman's space (H). H&E stain. 100X. H&E stain. 100X.

GROUP B/ Propolis 120mg

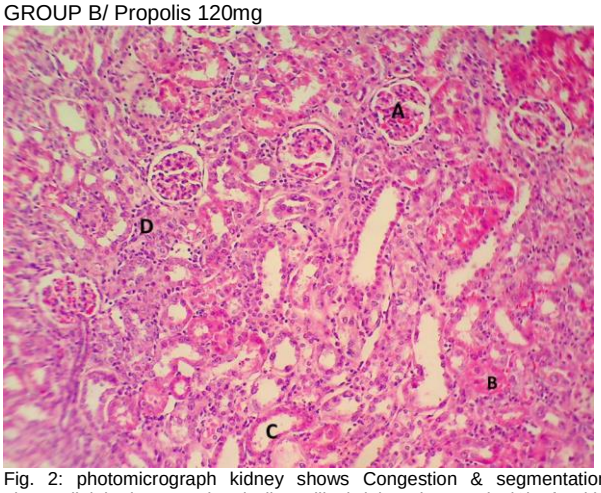

Fig. 2: photomicrograph kidney shows Congestion & segmentation of glomeruli (A), degeneration (cell swelling) (B) and necrosis (C) of epithelial cells lining renal tubules, and infiltration of inflammatory cells (D). H&E stain. 100X.

GROUP (C) Prplopolis 120 mg & cisplatin 4 mg

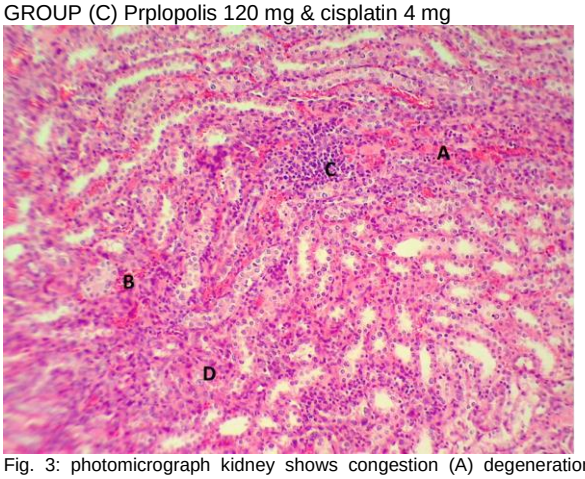

Fig. 3: photomicrograph kidney shows congestion (A) degeneration (cell swelling) of epithelium lining renal tubules (B), necrosis (C), and infiltration of inflammatory cells (D). H&E stain. 100X.

GROUP (D) propolis 60

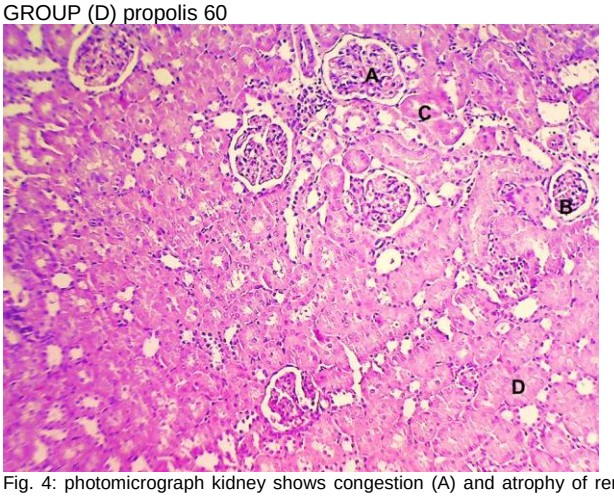

Fig. 4: photomicrograph kidney shows congestion (A) and atrophy of renal glomeruli (B), necrosis (C), degeneration (cell swelling) of epithelium lining renal tubules (D). H&E stain.

GROUP (E) Propolis 60 mg + cisplatin 4 mg

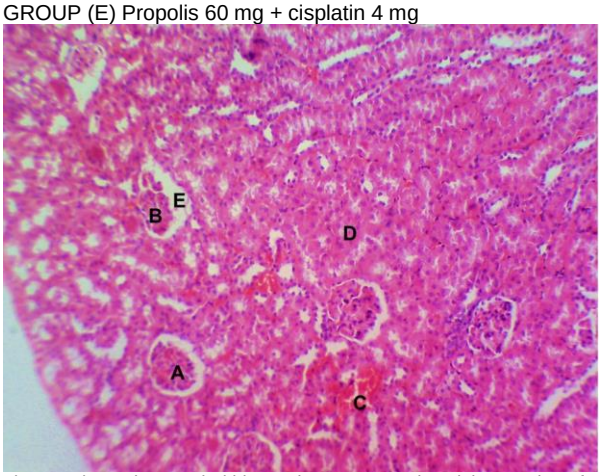

Fig. 5: photomicrograph kidney shows congestion (A), atrophy of renal glomeruli (B), congested B.V and hemorrhage (C) , degeneration (cell swelling) of epithelium lining renal tubules (D) and dilation of Bowman's space (E). H&E stain. 100X. H&E stain. 100X.

CONTROL - Group (F)

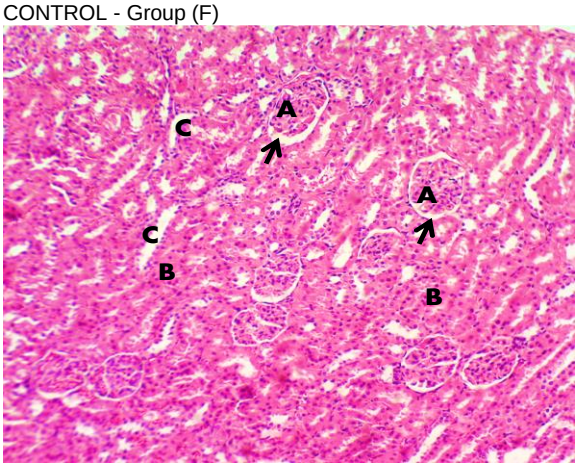

Fig. 6: Histological section of kidney (cortex) of control group showing of normal, glomeruli (A), proximal convoluted tubules (B), distal convoluted tubules (C), Bowman's space(↘). H&E stain 100X.

REFERENCES

1. Cavaletti G, Fabbrica D, Minoia C, Frattola L, Tredici G. Carboplatin toxic effects on the peripheral nervous system of the rat. Annals of Oncology.1998;9(4): 443-8.
2. Pabla N, Dong Z. Cisplatin nephrotoxicity: mechanisms and renoprotective strategies. Kidney Int.2008;73:994-007.
3. Zicca A, Cafaggi S, Mariggio MA, Vannozzi MO, Ottone M, Bocchini V et al. Reduction of cisplatin hepatotoxicity by procainamide hydrochloride in rats. Eur J Pharmacol.2002;10; 442(3):262-72.
4. Bau M, Hettich D, Huguet N. Nephrotoxicity mechanism of cisplatin (11) diamiue dichloride in mice. Toxicol Lett. 1994; 71(2): 161-8.
5. Palipoch S, Punsawad C. Biochemical and histological study of rat liver and kidney injury induced by cisplatin. J Toxicol Pathol. 2013;26:293-99.
6. Boogaard PJ, Nagelkerke JF, Mulder GJ. Renal proximal tubular cells in suspension or in primary culture as in vitro models to study nephrotoxicity. Chem Biol Interact. 1990;76:281–291.
7. Ezz-Din D, Gabry MS, Farrag AR, Abdel Moneim AE. Phsiological and histological impact of Azadirachta idica (neem) leaves plants extract in a rat model of cisplatin-induced hepto and nephrotoxicity. J Med Res.2011;5: 499-06.
8. El-Naggar SAA, Elm-Eldeen A, Germoush M, El-Boray K, El-gebaly HA. Ameliorative effect of propolis against cyclophosphamide-induced toxicity in mice. Pharmaceutical Biol.2015;53(2):235-41.
9. Meng H, Fu G, Shen j, Shen K, Xu Z, Wang Y et al. Ameliorative effect of daidzein on cisplatin-induced nephrotoxicity in mice via modulation of inflammation, oxidative stress and cell death. Oxidative Medicine Cellular Longevity.2017;2017:3140680.
10. Neg MA, Mitre CI, Mitre AO, Morhan V, Catinean A, Botan EC et al. Paradoxical effect of grape pomace extract on cisplatin-induced acute kidney injury in rats.Pharmaceutics.2019;11:656.
11. Kaya E, Yilmaz S, Ceribasi S. Protective role of propolis on low and high furan-induced hepatotoxicity and oxidative stress in rats. J Vet Res.2019;63:423-31.
12. Lotfy M. Biological activity of bee propolis in health and disease. Asian Pac J Cancer Prev.2006;7:22-31.
13. Pascual C, Gonzalez R, Torricella RG. Scavenging action of propolis extract against oxygen radicals. J Ethnopharmacol.1994;41:9-13.
14. Yilmaz S, Tatli Seven P, Kaya E. Effects of propolis ,royal jelly, bee pollen and ronozyme supplementation in diets of Japanese quails (coturnix coturnix japonica) on yolk lipid perioxidation. Int J Vet Health Sci Res.2017;5:183-89.
15. Denli M, Cankaya S, Silici1 S, Okan F, Uluocak A N. Effect of Dietary Addition of Turkish Propolis on the Growth Performance, Carcass Characteristics and Serum Variables of Quail (Coturnix coturnix japonica). Ascian–Australasian Journal of Animal Sciences. 2005;18,(6) : 848-854.
16. Lee SW, Kim HJ, Hwangbo S. Studies on the chemical characteristic of Korean propolis. Korean Journal Society for Food Science of Animal Resources 2001 ;21 :383-388.
17. Yulug E, Turedi S, Yildirim O, Yenilmez E, Aliyazicioglu Y, Demir S et al. Biochemicalandmorphological evaluation of the effects of propolis on cisplatin induced kidney damage in rats. Biotech Histochem.2019;94(3) :204-13.
18. Iseri S, Ercan F, Gedik N, Yuksel M, Alican I. Simvastatin attenuates cisplatin-induced kidney and liver damage in rats. Toxicology.2007;230 :256-64.
19. Pabla N, Murphy RF, Liu K, Dong Z. The copper transporter Ctr1 contributes to cisplatin uptake by renal tubular cells during cisplatin nephrotoxicity. Am J Physiol Ren Physiol.2009;296:F505-F511.
20. Devipriya S, Shamala D. Protective effects of quercetin in cisplatin-induced cell injury in the rat kidney.Ind J Pharmacol.1999;3:422-26.
21. Yao X, Panichpisal K, Kurtzman N, Nugent K. Cisplatin nephrotoxicity. A review. Am J Med Sci. 2007;334:115-124.
22. Abdel-Daim MM, Abdellatief SA. Attenuating effects of caffeic acid phenethyl ester and betaine on abamectin-induced hepatotoxicity and nephrotoxicity. Environ Sci Pollut Res Int.2018;25:15909-17.
23. Turedi EYS, Yenilmez ÖYE, Aliyazicioglu Y, Demir S, Özer-Yaman S, Menteşe A. Biochemical and morphological evaluation of the effects of propolis on cisplatin-induced kidney damage in rats.Biotech & Histochemistry.2019;94 (3):204-213.
24. Aldahmash BA, EL-Nagar DM, Ibrahim KE. Reno-protective effects of propolis on gentamicin-induced acute renal toxicity in swiss albino mice. Nefrologia.2016;36(6) :643-52.
25. Khan SA, Priyamvada S, Khan W, Khan S, Farooq N, Yusufi ANK. Studies on the protective effect of green tea against cisplatin induced nephrotoxicity. Pharmacol Res 2009;60:382-91.
26. Yousef MI, Saad AA, El-Shennawy LK. Protective effect of grape seed proanthocyanidin extract against oxidative stress induced by cisplatin in rats. Food Chem Toxicol.2009;47:1176-83.
27. Naghizadeh B, Boroushaki MT, Vahdati MN, Mansouri MT. Protective effects of crocin against cisplatin-induced acute renal failure and oxidative stress in rats. Iran Biomed J.2008;12:93-100.
28. Atasayar S, Gurer-Orhan H, Gurel B, Girgin G, Ozgunes H. Preventive effect of aminoguanidine compared to vitamin E and C on cisplatin-induced nephrotoxicity in rats. Exp Toxicol Pathol 2009.61:23-32.
29. Nanji AA, Mikhael NZ, Stewart DJ. Increase in serum uric acid level associated with cisplatin therapy.Correlation with liver but not kidney platinum concentrations. Arch Intern Med.1985; 145(11): 2013-2014.
30. Yoshizumi K, Nishioka N, Tsuji T. Xanthine oxidase inhibitory activity and hypouricemia effect of propolis in rats. Yakugaku Zasshi.2005;125(3):315-21.