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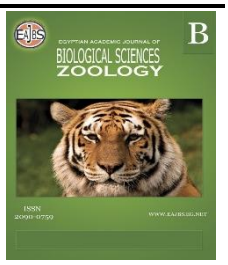

Effect of Gum Arabic on Chemically Induced Acute Renal Injury in Albino Rats.

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ABSTRACT

It has been concluded from several studies that Gum Arabic (GA) offers a protective effect as an anti-inflammatory and antioxidant agent against nephrotoxicity induced by some agents such as adenine and gentamicin. . In this study, the protective and/or treatment effect of GA against Cisplatin-induced acute nephrotoxicity in experimental rats were investigated through several biochemical, histological and immunohistochemical assessment of TGF- beta. Thirty male Wister albino rats were divided randomly into five groups, six rats in each. Group I (negative control), group II (GA) received 6% GA in drinking water, group III (Cisplatin) injected by CP (4.5 mg/kg b.w., i.p.) for two consecutive days, group IV (preventive) pretreated with GA 6% in drinking water daily for 4 weeks before Cisplatin injection and group V (treatment) co-treated by GA with Cisplatin injection (doses as mentioned before). Group III (Cisplatin) showed nephrotoxicity that was manifested by a significant increase in levels of serum Creatinine, urea, and potassium with elevation in kidney MDA level and a decrease in kidney GSH level. In addition, histopathological examination showed severe degeneration and necrosis in kidney tubules. These effects were significantly mitigated by GA administration in both groups IV and V, a result that proves the reno-protective effect of GA.

INTRODUCTION

The kidney is the master organ concerned with the conservation of body homeostasis by elimination of metabolic waste products through the production of urine, preservation of water and salts in the body, regulation of blood pressure, restoration of bicarbonate from filtrate which is important for acid-base balance, and involved into endocrine function through the production of some hormones (renin, erythropoietin), also activation of vitamin D to its active form (1,25 dihydroxycholecalciferol) (Jubb *et al.*, 2006, Stalker, 2007).

Renal failure is principally divided according to duration into acute and chronic renal failure. Acute renal failure (ARF) is characterized by an acute decline (hours to days) in glomerular filtration rate and other functions followed by anatomical alterations (Bonventre and Yang, 2011), resulting in an elevation in serum urea and creatinine levels also electrolyte imbalance with a decline in urine output (Bellomo *et al.*, 2012, Hoste *et al.*, 2018). Acute renal injury is one of the critical diseases that is linked with high morbidity

and mortality, As any non-treated acute alteration in kidney function can lead to more complications, such as chronic renal injury, end-stage kidney failure and death (Lameire *et al.*, 2013). The renal injury occurs as a result of several causes, one of them being nephrotoxic agents exposure and some chemotherapeutic agents. Cisplatin (cis-diamminedichloroplatinum II), (CP) is one of the widely used anticancer chemotherapeutic drugs, which is used effectively against various types of cancers, including ovary, cervix, breast, testis, prostate, bladder, head, neck, lung, esophagus, stomach, colon, as well as melanoma, lymphoma and mesothelioma (Tsang *et al.,* 2009) (Miller *et al.,* 2010) (Abdel-Daim *et al.,* 2017).

However, nephrotoxicity is the primarily dose-limiting adverse effect of Cisplatin-dependent chemotherapy in cancer patients, leading to acute kidney injury as well as tubular injury that causes an electrolyte imbalance. It is recommended to discover an agent that can ameliorate Cisplatin nephrotoxicity and at the same time doesn't alter the Cisplatin antitumor effect. In this study, GA was used to investigate its ameliorative effects against Cisplatin's adverse actions. GA is a polysaccharide water-soluble dietary fiber obtained from the branches and stems of Acacia trees as a dried exudate, it is rich in Magnesium, Calcium and potassium. It has been used as an effective therapeutic and ameliorating agent in the Middle East and North Africa in order to reduce the costs of drug therapy, dialysis and kidney transplantation in patients suffering from renal diseases especially those suffering from chronic kidney disease.

MATERIALS AND METHODS

This study was carried out in the Pathology Department, Faculty of Veterinary Medicine, Suez Canal University. the experiments were performed in accordance with the guidelines and protocols for the usage of laboratory animals as described by the local ethical committee (Research Ethics Committee of College of Veterinary medicine, Suez Canal University, Ismailia, Egypt). with a code number for an approved protocol (2018-68).

Experimental Animals:

Thirty apparent healthy male Wistar albino rats weighing 100–150 g were served for this acute study. All rats were obtained from the animal house of the Faculty of Veterinary Medicine, Suez Canal University, Ismailia, Egypt. Before the experiments, all rats were housed in standard plastic cages with a floor covered with sawdust under proper environmental conditions of temperature, light (25-27◦C and a 12 h light/dark cycle) with a relative humidity of approximately 50-60% in a well-ventilated room with free access to tap drinking water and standard granulated ration which formulated according to MRC. The animals were acclimatized to the laboratory conditions for 2 weeks prior to the experiment.

Chemicals:

Cisplatin (Cisplatin MYLAN® [1 mg/ml]) was obtained from Mylan Pharmaceuticals, France. Gum Arabic was purchased from Nature Gums company, in Sudan. Batch number (J1J3). commercially available kits for reduced glutathione (GSH) and Malondialdehyde (MDA) were purchased from BioVision Company, Cairo, Egypt. (GSSG/GSH Quantification Kit CAT. No. KT-768.

Experimental Design:

After the acclimatization period, rats were divided randomly into 5 groups (6 rats) for each. **Group I (control):** included non-treated rats. Group II (control GA): Rats received GA 6%$^{w/v}$ in drinking water, daily for 7 days, according to (Ali *et al.,* 2010) (Al-Majed *et al.,* 2003). Group III (control cisplatin): Rats were injected intraperitoneally (i.p.)

with 4.5 mg/kg cisplatin (0.9 % NaCl (w/v) for 2 consecutive days according to (Wu *et al.,* 2015). Group IV (preventive) was pretreated with GA 6%$^{w/v}$ in drinking water daily for four weeks (Ali *et al.,* 2010) before the induction of acute renal injury by CP injection (Wu *et al.,* 2015) and continued for another 7 days (Al-Majed *et al.,* 2003). Group V (treatment) was injected with cisplatin for 2 consecutive days and then received GA 6%$^{w/v}$ in drinking water daily till the 7th day of the experiment after the second dose of cisplatin.

Blood and Tissue Sampling:

Each rat was weighed prior to injection on day 0, and before being sacrificed on day 7. At the end of the experiment, rats were fasted overnight and were subjected to mild ether anesthesia, blood samples were collected from the retro-orbital venous plexus at the inner canthus of the eye. The blood samples were kept overnight in the fridge and then centrifuged at 3000 rpm for 15 minutes. The obtained clear sera were used for performing biochemical analysis. Rats were sacrificed, and their kidneys were removed immediately. the left kidney was stored at −20 °C for preparing tissue homogenates to assess malondialdehyde (MDA), and reduced glutathione (GSH) levels, while the right kidney was fixed in 10% neutral-buffered formalin and kept until performing a histopathological examination.

Serum Biochemical Analysis:

Serum Urea and Creatinine concentrations were assessed spectrophotometrically according to the manufacturer's instructions by the methods of (Bonsnss and Taussky, 1945, Hallett and Cook, 1971) and potassium (K+), analyzed by using commercially available kits according to the method of (Mohamed *et al.,* 2018).

Kidney Tissue Homogenate Biochemical Assay:

The kidney tissues were cut, weighed, homogenized in 4 mL physiological saline, and centrifuged at 5000 rpm for 20 min at 4 °C. The supernatant was used for the determination of oxidative stress parameters. GSH level was determined by measuring absorbance at 412 nm and is expressed as μmol GSH/g tissue (Sedlak and Lindsay, 1968). MDA level was determined by measuring the absorbance of a pink-colored thiobarbituric acid reactive substance at 532 nm and is expressed as nmol MDA/g tissue (Ohkawa *et al.,* 1979).

Kidney Histopathological Examination:

Kidney tissue was fixed in 10% buffered formalin saline for histopathological examination. Specimens were trimmed into 0.5 cm thickness sections and conventional paraffin-embedding techniques were used, tissues were processed to obtain 5-μm-thick paraffin sections and then stained with hematoxylin and eosin (H&E) (Bancroft and Gamble, 2008). Sections were carried out to assess morphological damage to the kidney after treatment with GA and cisplatin: Acute tubular necrosis was assessed in the outer strip of the medulla and cortex using a semiquantitative scale in which the percentage of tubules showing epithelial necrosis, brush-border loss, and cast formation was assigned a score: 0 = normal; 1 ≤ 10%; 2 = 11–25%; 3 = 26–45%; 4 = 46–75%; 5 ≥ 76%. Renal lesions in 10 randomly selected fields were examined and averaged (Fu *et al.,* 2019) (Ramesh *et al.,* 2007).

Statistical Analysis:

The results were expressed as mean ± SE of studied groups using the analysis of variance test (One-way ANOVA) followed by Duncan's multiple range test to determine the differences between the averages. All statistical analyses were performed by Statistical Package for the Social Sciences Software (Version 20, SPSS Inc., Chicago, IL, USA).

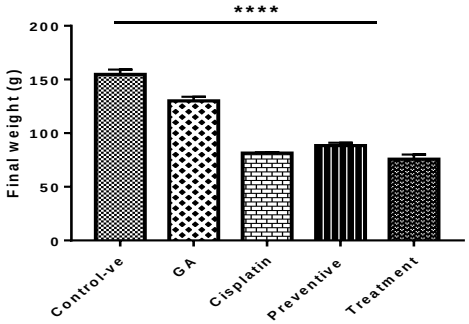
RESULTS

Clinical Signs:

The behavioral alterations observed among rats of the cisplatin group were a decrease in water, food consumption and growth rate, together with general weakness, cachexia and dullness. There were no clinical signs observed on rats of the control and GA groups throughout the experiment duration.

Final Body Weight (g):

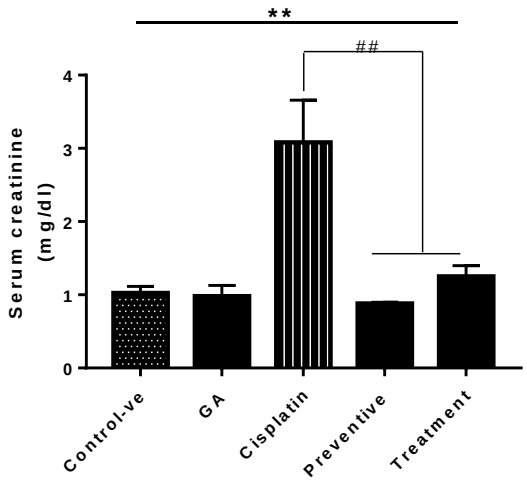
Control rats showed a gradual increase in body weight throughout the experimental period, while rats administered GA only showed a slight decrease in body weight ($p<0.0001$) and more decline was detected in rats injected with CP, compared with the control group ($p=0.0005$) (Graph 1.).



Graph (1): Final body weights in different groups (1st Experiment). Body weight was measured to assess the effect of both cisplatin and GA on it. ****, $p<0.0001$ between all different groups. N=3-5.

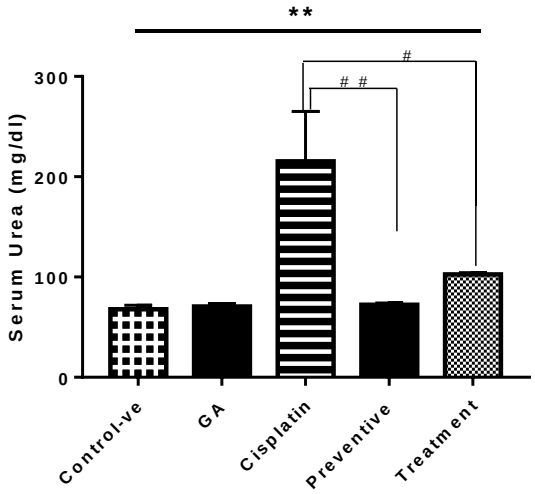
Serum Biochemical Analysis (kidney function test):

Serum Urea (Ur), Creatinine (Cr) and potassium (k+) levels are important indexes for evaluating renal function. As shown in Graphs (2,3 &4), there was an increase in the levels of Creatinine, Urea, and K+ (hyperkalemia) in the cisplatin group compared to the control ones and this increase in values was statistically significant ($P<0.05$), while GA administration in Group IV and group V showed significant suppression of those parameters near the control level with no significant difference between them.

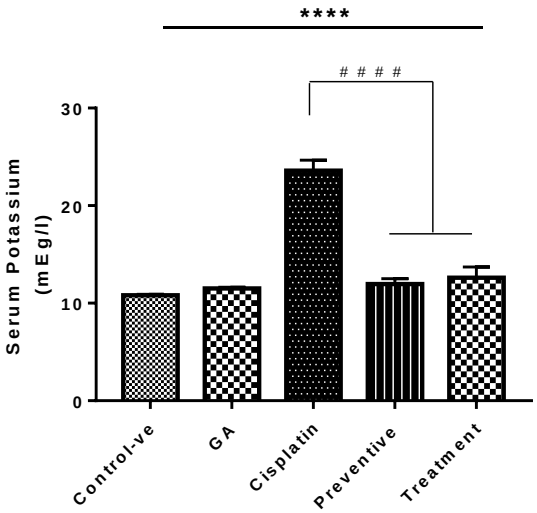


Graph (2): Serum creatinine levels in different groups. Serum creatinine was quantified as a function of the kidney as described in the methods. **, $p<0.001$ between all different

groups. ##, $p<0.05$ vs. cisplatin-treated. N=3-5.



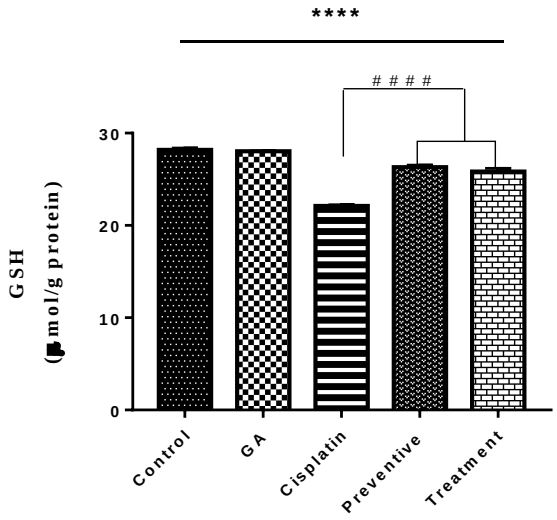
Graph (3): Serum urea levels in different groups. Serum urea was quantified as a function of the kidney as described in the methods. **, $p<0.005$ between all different groups. ##, $p=0.006$ cisplatin vs. Preventive. #, $p<0.05$ cisplatin vs. treatment. N=3-5.



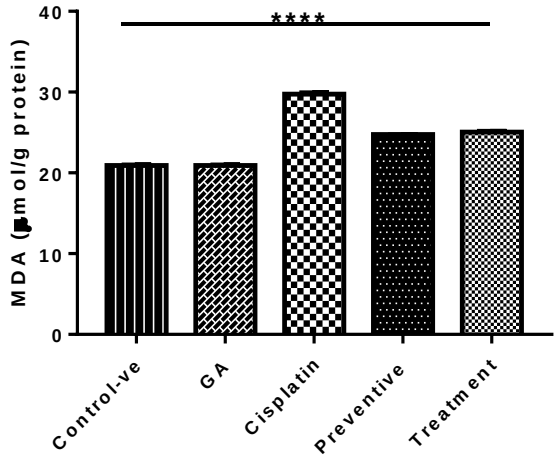
Graph (4): Serum potassium levels in different groups. Serum potassium was quantified as a function of the kidney as described in the methods. ****, $p<0.0001$ between all different groups. ####, $p<0.0001$ cisplatin vs. Preventive and treatment. N=3-5.

Biomarkers of Oxidative Stress:

production of reactive oxygen species (ROS) was a critical effector of CP-induced kidney injury. To investigate the antioxidant effects of GA, levels of GSH and MDA in kidney homogenates were measured. Graphs 5, and 6 show that cisplatin injection caused a markedly decrease in the activities of GSH and an increase in the level of MDA compared with the control group ($P < 0.0001$), while rats administered GA in group IV and group V showed significant amelioration in their levels near control levels ($p<0.0001$).



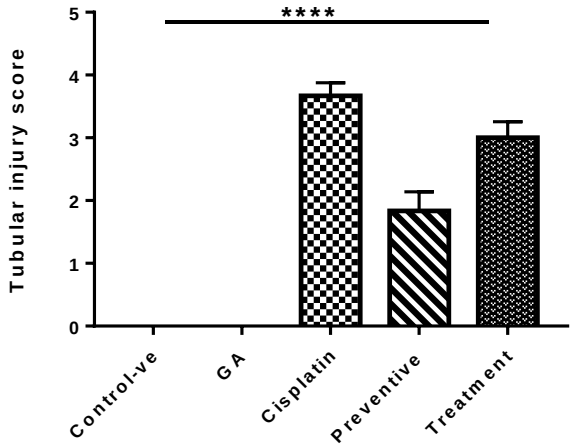
Graph (5): Kidney GSH levels (Mean ± SE) in different groups (1st Experiment). Kidney GSH level was quantified to evaluate the antioxidant properties of GA against Cisplatin-induced oxidative stress as described in methods. ****, $p<0.0001$ between all different groups. ####, $p<0.0001$ cisplatin vs. Preventive and treatment. N=3-5.



Graph (6): Kidney MDA levels (µmol/g protein) in different groups (1st Experiment). Kidney MDA level was quantified to evaluate the effect of GA against Cisplatin-induced oxidative stress as described in methods. ****, $p<0.0001$ between all different groups. N=3-5.

Histopathological Examination of The Kidney:

Kidney sections of group I (control) similar to GA control group had normal architecture and histology, with the absence of any lesions (Figs. 1. and 2.). The kidney of the CP group showed extensive tubular degeneration, swelling, necrosis, sloughing of tubular epithelium, loss of brush borders, intratubular cast formation, and tubular dilatation **(Fig. 3.)**, an effect that was attenuated by GA administration in group IV **(**Fig. 4**.)** by a degree better than in group V **(**Fig. 5.). These results were further supported by quantification and scoring of kidney lesions, cisplatin caused a high level of tissue injury which is significantly reduced with GA administration **(**Graph 7.).



Graph (7): Kidney injury scoring in H&E-stained tissue sections of different groups. At the end of the experiment, kidney tissue was processed for staining and semi-quantitative scoring of tubular injury as described in the methods. Semi-quantitative scoring of tubular injury. ****, p<0.0001 between different groups.

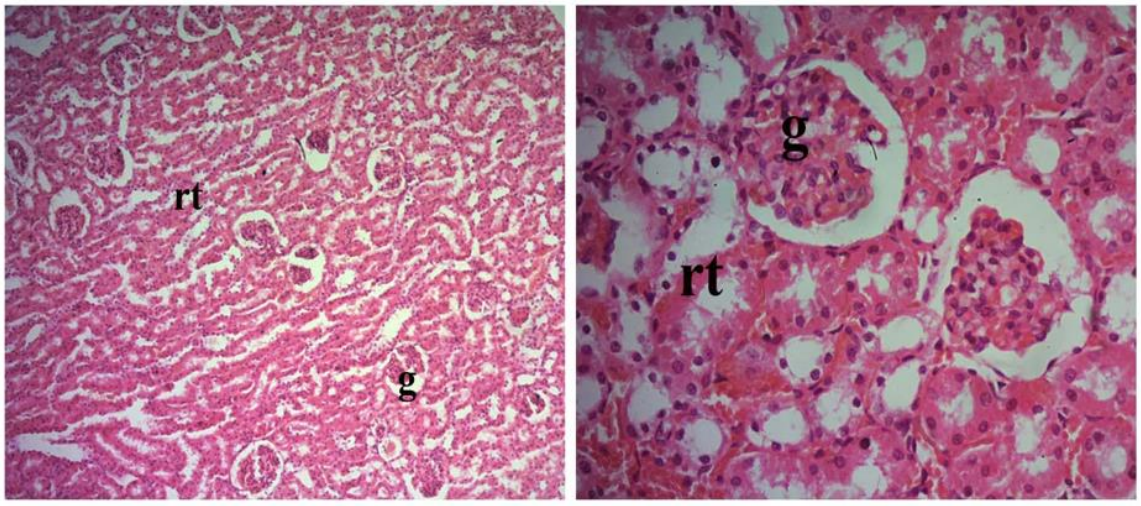


Fig. 1: Histopathological picture of the rat kidney, group I (control) showing a normal architecture of both (g) glomeruli and (rt) renal tubules of renal cortex. H&E, X 100 & 400.

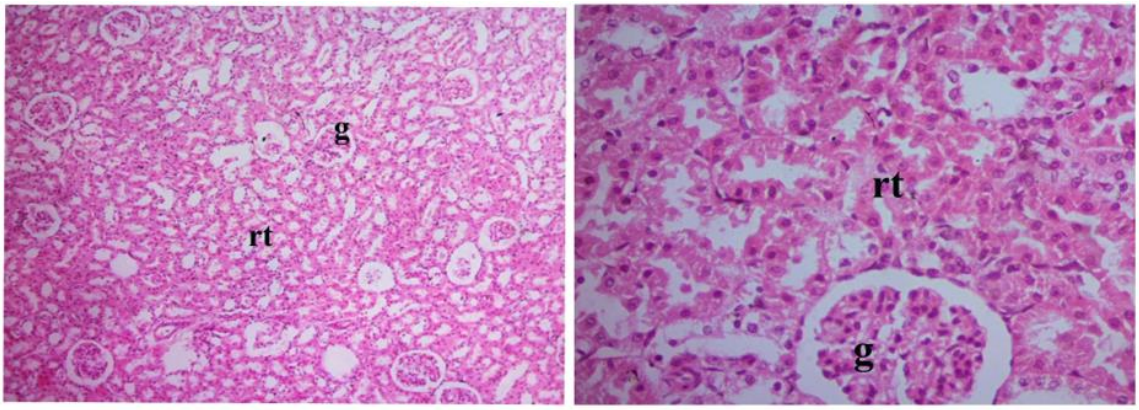


Fig. 2: Group II (GA) kidney H&E sections, X 100 & 400. group II (GA) shows a normal architecture of both (g) glomeruli and (rt) renal tubules of renal cortex.

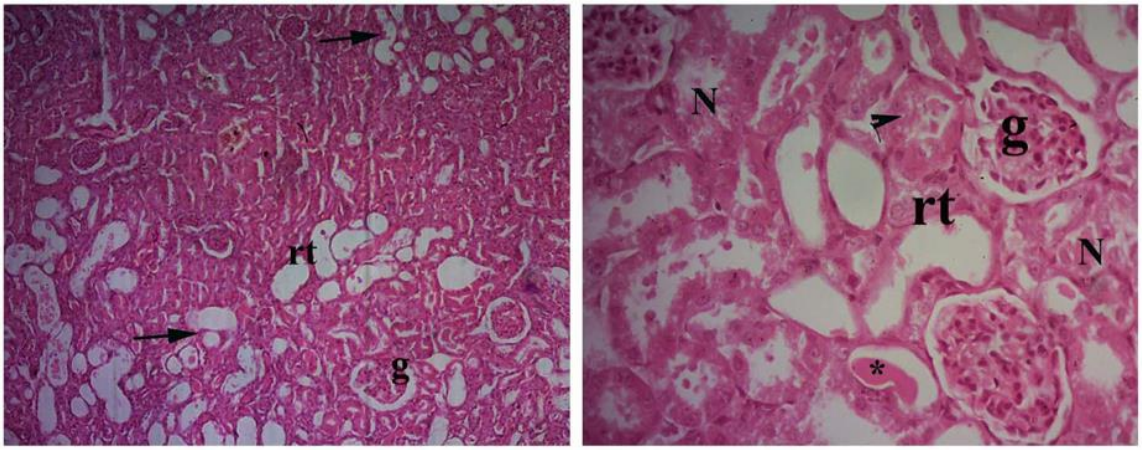


Fig. 3: group III (cisplatin) showing extensive tubular degeneration (arrowhead), tubular necrosis (N), cystic dilatation (arrow) and tubular casts (star). (g) glomeruli and (rt) renal tubules of renal cortex. H&E, X 100 & 400**.**

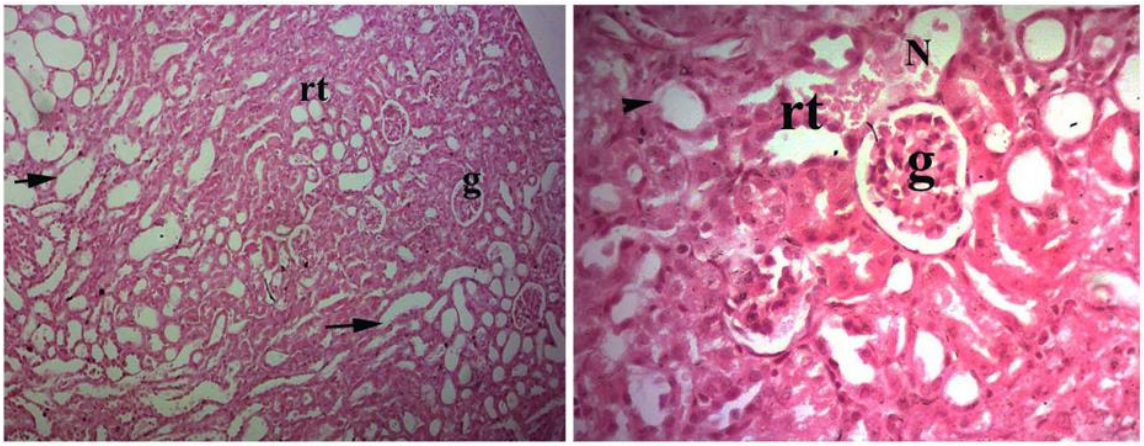


Fig. 4: Group IV (preventive) kidney H&E sections, X 100 & 400. Group IV (preventive) shows little areas of tubular degeneration (arrowhead), tubular necrosis (N), and cystic dilatation (arrow). (g), glomeruli and (rt), renal tubules of renal cortex.

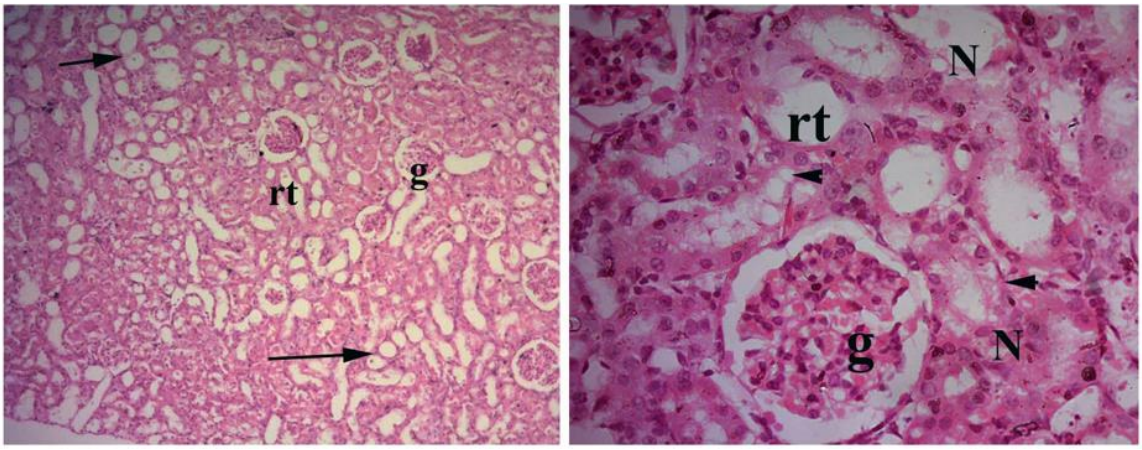


Fig. 5: Group V (treatment) kidney H&E sections, X 100 & 400. Group IV (preventive) showing multiple areas tubular degeneration (arrowhead), tubular necrosis (N), cystic dilatation (arrow). (g), glomeruli and (rt), renal tubules of renal cortex

DISCUSSION

The present study was conducted to determine whether GA can alleviate cisplatin nephrotoxicity and if it is effective, determine the underlying mechanisms. Our study showed that treatment with GA 6% in drinking water protects the kidney against cisplatin nephrotoxicity as indicated by serum Creatinine, urea, potassium level, kidney MDA and GSH level, as well as histopathology.

Final Body Weight:

In the present study, rats' body weights in groups injected with cisplatin were decreased during the whole experimental period compared to the control group. This decrease in body weight could be attributed to the alterations induced by cisplatin injection. As cisplatin disrupted energy generation and lipid metabolism as recorded by (Qu *et al.,* 2020) (Chang *et al.,* 2002). These results were in partial agreement with (Al-Majed *et al.,* 2003) who recorded that CP injection (7.5 mg/kg, i.p.) caused a progressive decrease in body weight along the period of the experiment compared to control one and cotreatment of rats with GA (7.5 g/kg) in drinking water failed to correct impairments that induced by CP. Also, agreed with (Nasir *et al.,* 2012) who indicated that GA administration for 2 weeks, did not significantly modify the body weight of the mice despite a significant decrease in food intake following GA treatment. On the other hand, (Ali *et al.,* 2010) and (Ali *et al.,* 2011) reported that concomitant treatment with GA at concentrations of 6%w/w, 12%w/w, and 10% (w/w) in water ameliorated the progressive decrease in body weight induced by adenine feeding.

Kidney Function Tests (Serum Creatinine & Urea):

Regarding the kidney function tests performed, cisplatin single high dose caused severe elevation in the levels of creatinine and blood urea nitrogen in the serum at different time intervals indicating renal failure. The main mechanism of cisplatin-induced renal injury evidenced by elevation in serum Cr and Urea is the combined outcome of the renal epithelial cells' uptake of cisplatin, destruction of nuclear and mitochondrial DNA, activation of several cell death, initiation of a vigorous inflammatory response and oxidative stress through lipid peroxidation, free radical generation in the tubular cells and extensive morphological damage and functional impairment ultimately lead to the failure of the kidneys to clear nitrogenous wastes from the blood as recorded by (Miller *et al.,* 2010, Volarevic *et al.,* 2019). These results came in accordance with (Sadeghi *et al.,* 2021) who stated that a single high dose of cisplatin (7 mg/kg i.p.) induced nephrotoxicity mainly for at least 3 days after the beginning of treatment, and its specific effects comprise a decrease in the glomerular filtration rate, an increase in serum creatinine and BUN levels, and a decrease in the ability of the kidneys for urine concentration.

GA 6% in drinking water coadministration at different time intervals in the two experiments could significantly mitigate this elevation in the concentration of serum Cr and BUN caused by cisplatin. The basis of this salutary effect of GA on renal function is probably a urea-lowering effect through utilizing the bowel as a ''substitute kidney'', increasing urea nitrogen excretion in stools, with a concomitant decrease in the total urea nitrogen excreted in urine (Ali *et al.,* 2010, Ali *et al.,* 2020). These results came in agreement with the studies done by (Ali et al., 2010, Mahmoud *et al.,* 2012, Al Suleimani *et al.,* 2015a, Said *et al.,* 2019) who reported that GA administration in drinking water at different doses for long period for significantly restored the level of serum creatinine and urea that was altered by adenine injection, while data obtained from acute study disagreed with (Al-Majed *et al.,* 2003) who concluded that there was no difference between CP and CP+AG groups in the level of serum creatinine and blood urea this may be due to the different dose and the short period of GA administration used in comparison with the

current study.

Serum Potassium Level:

At this point of the study, results revealed that cisplatin high dose injection caused a significant elevation in serum potassium concentration (hyperkalemia) and coadministration of GA 6% in drinking water in group IV (preventive) and group V (treatment) could significantly restore serum potassium level near to control level. The mechanism by which cisplatin-induced hyperkalemia could be attributed to Complications of cisplatin-induced AKI resulted in impaired excretory, endocrine, and metabolic kidney functions. Decreased GFR and tubular function lead to retained water and solutes, manifested by volume overload and hyperkalemia as mentioned by (Levey and James, 2017).

These results came in agreement with (Choudhury and Ahmed, 2006, Saleh *et al.*, 2014) who reported that cisplatin nephrotoxicity causes tubular damage and tubular dysfunction with sodium, potassium, and magnesium wasting, which may be resulted from the decrease in glomerular filtration rate. The curative effect of GA against renal injury is illustrated by the restoration of serum potassium levels as reported by (Ibrahim, 2014, Mohamed *et al.*, 2018).

Renal Tissue Oxidative Stress Biomarkers:

Results obtained from the present study revealed a significant reduction in the activities of renal GSH enzyme induced by high doses for two consecutive days. The mechanism by which cisplatin reduced renal GSH levels could be related to the generation of reactive oxygen species (ROS) (Ozkok and Edelstein, 2014). Moreover, cisplatin is bio-transformed by the microsomal cytochrome-P450 system into a highly reactive thiol form, depleting glutathione during this reaction. Further, it causes mitochondrial dysfunction, leading to the exhaustion of the mitochondrial antioxidants and oxidative stress-mediated cytotoxicity (Volarevic *et al.*, 2019). Moreover, data showed that cisplatin-induced significant elevation in kidney MDA level. This elevation of lipid peroxidation products in kidneys and suppressed antioxidant systems are thought to be major mechanisms of cisplatin-induced kidney injury. Within the cell, cisplatin is converted into a highly reactive form rapidly reacting with thiol-containing antioxidant molecules such as glutathione. Consequently, depletion of glutathione leads to increased oxidative stress within the cells. elevated oxidative stress in cisplatin nephrotoxicity is may be as a result of disrupted respiratory chain and decline in antioxidant activity as mitochondria is the major source and target organ for ROS damage (Galley, 2011) (Ozkok and Edelstein, 2014, Manohar and Leung, 2018). GA 6% in drinking water significantly restored levels of both MDA and GSH toward their normal values. A result that supports the studies of (Al-Majed *et al.*, 2002, Gamal el-din *et al.*, 2003, Ali *et al.*, 2010, Ali *et al.*, 2013, Al Suleimani *et al.*, 2015b, Hammad *et al.*, 2019) who suggested antioxidant properties of GA as a potent superoxide scavenger giving protective effect against nephrotoxicity.

Histopathological Examination:

Regarding the histopathological results. The data revealed that cisplatin-induced severe tubular degenerative changes, swelling, necrosis, desquamation of tubular epithelium, loss of brush borders, intratubular cast formation, and tubular cystic dilatation as reported by (L.Z *et al.*, 2013, Perše and Večerić-Haler, 2018). The mechanism behind these destructive effects of cisplatin on kidney tissue especially renal tubules is returned to that cisplatin is a neutral low molecular weight compound filtered freely in the glomerulus and almost entirely retrieved in urine. In this process, the drug penetrates the tubular cells and reaches high concentrations in the proximal tubular cells of the inner renal cortex and outer medulla (S3 segment), the sites most dramatically affected by cisplatin. In the present study GA, 6% in drinking water showed pronounced improvement

in a histopathological picture of the kidney by routine H&E staining where lesions were mild cystic dilatation and degeneration compared to the cisplatin group with preservation of brush borders. These results came in accordance with (Shafeek *et al.,* 2019, Kandeal *et al.*, 2021) who described that administration of GA before or concomitant with alternative injections of cisplatin, showed some histopathological signs of improvement indicated by intact glomeruli and convoluted tubules architecture.

Conclusions:

Gum Arabic oral administration suppressed cisplatin-induced nephrotoxicity. Taken together all the results suggest that regular use of gum arabic may be attractive and useful therapeutic candidates to protect the kidney against the harmful effects of toxic agents and can be used as protective-cisplatin dependent chemotherapy. The anti-inflammatory and antioxidant properties of gum arabic should provide useful information in the possible application in kidney injury prevention and therapy. This may be promising in delaying kidney failure, minimizing the damage to kidney cells, or reducing complications.

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