

Preventive and Protective Effects of Gum Arabic against Cisplatin-Induced Acute Kidney Injury in Rats: An Integrated Biochemical and Histological Study

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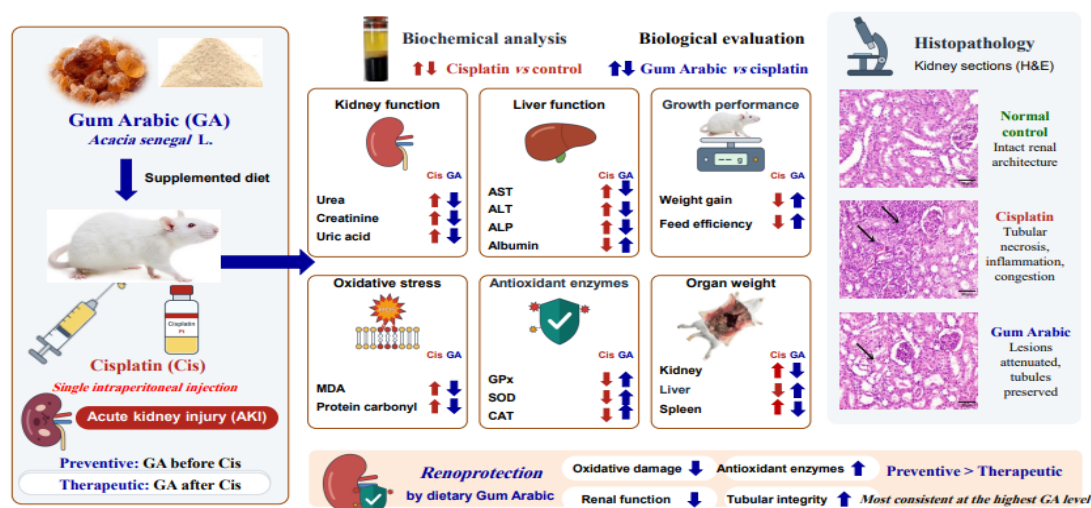
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Abstract: This study investigated the preventive and protective effects of Gum Arabic (GA) against cisplatin-induced acute kidney injury in 48 rats through biochemical and histopathological assessments. Rats were assigned to a normal control, cisplatin model, preventive GA groups receiving 2%, 3%, or 4%, and therapeutic groups for 28 days. Cisplatin reduced body weight gain and feed efficiency, increased kidney weight by 39.42%, increased serum AST, ALT, and ALP by 138.18%, 133.88%, and 106.49%, respectively, and decreased albumin by 46.46%. Renal dysfunction was pronounced, with urea, creatinine, and uric acid increasing by 406.24%, 380.77%, and 114.85%, respectively. Cisplatin suppressed renal GPx, SOD, and CAT activities by 65.28%, 42.99%, and 46.98%, while MDA and protein carbonyl increased by 98.05% and 200%. GA improved the parameters, with responses observed in preventive groups and at 4% concentration. Preventive 4% GA reduced urea, creatinine, and uric acid by 54.70%, 52.00%, and 42.88%, respectively, and increased GPx, SOD, and CAT activities by 68.12%, 59.17%, and 69.55%. It reduced MDA by 32.18% and protein carbonyl by 52.71%. Hematological abnormalities were attenuated, including improvements in RBCs, hemoglobin, hematocrit, and platelets, while leukocyte recovery was limited. Correlations showed associations between oxidative stress and renal dysfunction, including MDA with urea ($r=+0.8150$) and creatinine ($r=+0.7737$), and inverse relationships between MDA and GPx ($r=-0.8623$), SOD ($r=-0.8217$), and CAT ($r=-0.7946$). Histopathology confirmed tubular necrosis, inflammation, congestion, and vacuolar degeneration in cisplatin-treated rats, whereas GA reduced lesions and promoted tubular preservation and repair. Overall, GA, particularly 4% GA, demonstrated renoprotective effects against cisplatin-induced kidney injury.



Keywords: Dietary intervention, lipid peroxidation, protein oxidation, hepatic biomarkers, antioxidant defense, renal oxidative stress, renal histology

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1. Introduction

The kidneys are highly specialized paired organs that play a central role in maintaining whole-body homeostasis. Each kidney contains approximately one million nephrons, which constitute the fundamental functional units responsible for blood filtration and the subsequent regulation of water, electrolytes, and acid–base balance. Beyond their excretory function, the kidneys regulate extracellular fluid volume and osmolality, contribute to blood-pressure control through the renin–angiotensin system, and participate in endocrine regulation through the production of erythropoietin and the activation of vitamin D to its biologically active form, 1,25-dihydroxyvitamin D [1,2]. Through these integrated functions, the kidneys remove metabolic waste products and xenobiotics while maintaining the physiological composition of the internal environment. Consequently, impairment of renal structure or function can affect multiple organ systems and may lead to substantial metabolic, cardiovascular, hematological, and skeletal complications.

Renal injury can be defined as a range of renal pathological states from reversible, functional renal injury to acute kidney injury (AKI) and chronic kidney disease (CKD). In the case of AKI, the kidney function changes rapidly and in CKD, abnormalities in kidney structure or function last for more than three months and affect health [2]. Chronic or recurrent renal damage can lead to progressive loss of kidney function, reduction in filter function, accumulation of nitrogenous wastes, electrolyte and acid–base imbalances, anemia, mineral and bone abnormalities, hypertension, cardiovascular complications and renal failure, in which kidney replacement therapy is required. CKD is a significant global health problem; a previous systematic review suggested that the prevalence of all stages of CKD was about 13.4% of the world population, while more recent Global Burden of Disease studies estimated hundreds of millions of adults worldwide to be affected by CKD [3]. The burden is also high in Africa, though significantly higher depending on population characteristics, diagnostic criteria and data quality [4]. Alternatively, estimates of the prevalence of CKD in Egypt vary depending on the source and the methods used; a recent Egyptian study reported the prevalence of CKD to be about 7.32%, equating to an estimated 7.3 million people affected in 2021, according to data from the Global Burden of Disease [5]. There has also been a significant burden of advanced kidney disease in studies conducted in Egypt, with hypertension and diabetes being one of the recognized contributors to end-stage kidney disease (ESKD) [6]. Kidney disease may have more profound clinical implications in cancer patients, as kidney dysfunction may be a consequence of cancer or impact anticancer therapy. It is important for the pharmacokinetics and clearance of the anti-cancer drug to not be affected by renal impairment, which could lead to drug accumulation and toxicity; additionally, renal dysfunction may limit the use or dosage of potentially effective chemotherapy regimens [7,8].

One notable case is cisplatin, where nephrotoxicity is a key dose-limiting side effect, and exposure to cisplatin can

cause acute tubular injury through multiple pathways of oxidative stress, mitochondrial dysfunction, DNA damage, inflammatory signaling, endoplasmic-reticulum stress and cell death, with all these mechanisms interconnected [9]. While proper hydration, electrolyte supplementation, and renal monitoring can minimise the risk of cisplatin-induced kidney injury, clinically significant cisplatin-induced nephrotoxicity is a significant therapeutic concern [7,10]. Poor access to nephrology services, diagnostic facilities, advanced nephrology staff, dialysis and other kidney-supportive resources or tools, may exacerbate these challenges in low- and lower-middle-income countries, where renal disease and treatment-related complications may not be well prevented and managed [11,12]. Under such conditions, there is a greater argument for exploring safe, cost-effective, nutritionally adequate and readily available complementary strategies that could potentially aid in maintaining renal function. The interest lies in dietary interventions and those bioactive substances naturally present in diet that could potentially affect multiple pathways that contribute to renal injury, such as oxidative stress, inflammation, metabolic dysregulation, intestinal microbial metabolism, and the production of uremic toxins [13]. It is important to recognize that these approaches might be considered complementary rather than alternative to evidence-based medical care and efficacy and safety have yet to be tested through experiments and clinical trials.

Gum Arabic (GA), or acacia gum, is a natural edible exudate that is harvested mainly from *Acacia senegal* and related *Acacia* species, mostly *Acacia seyal*. It has many historical uses in both food and traditional medicine and is used extensively in functional food ingredient due to its high solubility in water, emulsifying property, stabilizing power and compatibility with the food and pharmaceutical formulations [14,15,16,17,18,19]. The chemical nature of GA is a complex, highly branched, water-soluble polysaccharide-protein macromolecular system consisting primarily of arabinose, galactose, rhamnose, glucuronic acid residues, along with protein bound fractions and mineral components [14]. The major structural components of GA are the arabinogalactan, arabinogalactan–protein and glycoprotein components, whose molecular organization contribute to the peculiar physicochemical and biological properties of GA [20,21,22]. GA is not a typical phytochemical extract but rather a soluble fermentable dietary fibre, and its biological effects have been linked to the prebiotic properties, the modulation of intestinal microbial activities, and its reported antioxidant and anti-inflammatory effects [23,24]. As a result, GA has garnered growing interest as a functional dietary ingredient and complement to therapeutic regimens for several metabolic, inflammatory, gastrointestinal, oral, and renal diseases. Clinical studies give special importance to evidence. Highly fermentable GA fiber supplementation in chronic renal failure patients on a low-protein diet further enhanced fecal nitrogen excretion, and significantly lowered serum urea nitrogen, indicating a potential for GA in improving intestinal nitrogen disposal and decreasing systemic retention of nitrogenous metabolites in the low protein diet [25]. A randomized clinical trial conducted on patients with chronic renal failure who were receiving regular hemodialysis yielded

beneficial effects on serum urea, creatinine, uric acid and phosphorus levels, while serum calcium levels were elevated, but larger controlled studies are required to confirm these [22,23,26,27,28,29,30,31]. Recent studies have shown possible anti-inflammatory and antioxidant properties. In patients with CKD, Elamin et al., [32] found that GA supplementation lowered C-reactive protein, but did not significantly affect serum urea, creatinine, or indoxyl sulfate, suggesting that the renal benefits of GA might not be restricted to traditional renal markers of filtration. Additionally, a phase II clinical study in patients with hemodialysis showed that supplementation with GA led to a rise in total antioxidant capacity and a decrease in malondialdehyde and c-reactive protein in patients with advanced renal disease suggesting its antioxidant and anti-inflammatory activity in these patients [33]. A systematic review of clinical trials found that GA has shown promise in its impact on renal biochemical profiles, inflammatory markers, metabolic parameters, and other disease-related outcomes, highlighting the importance of further well-designed clinical studies to confirm its therapeutic effects and mechanisms [24]. Taken together, these results offer a rational basis to explore the possibility of using GA as a nutritional intervention in renal injury, especially when oxidative and inflammatory processes play a significant role in the pathogenesis of renal damage.

Although there is growing evidence for the biological activity of GA, the potential to prevent or attenuate cisplatin-induced acute kidney injury (CIKI) is poorly understood. In the context of multifunctional dietary interventions, cisplatin-induced renal injury is a possible model that can be used for evaluation due to its multifactorial mechanism of action, which includes the accumulation of the drug in the proximal tubules, excessive generation of reactive oxygen species, mitochondrial dysfunction, inflammatory responses, DNA damage, and apoptosis [9]. The antioxidant, anti-inflammatory, prebiotic and metabolic activities of GA indicate that it could exert its effects through several complementary mechanisms instead of by targeting a single molecular target. However, data from patients with chronic kidney disease (CKD) or end-stage renal disease (ESRD) may not be applicable to patients with acute toxic renal injury due to cisplatin. Therefore, an experimental investigation integrating functional biochemical indices with hematological and tissue-level assessments is warranted to determine whether GA can attenuate the systemic and renal consequences of cisplatin exposure. Such an integrated approach may provide a more comprehensive assessment of potential renoprotection than reliance on serum biochemical markers alone. Accordingly, the present study was designed to investigate the preventive and protective effects of Gum Arabic against cisplatin-induced acute kidney injury in rats through an integrated biochemical, and histological assessment, with the specific aim of determining whether GA supplementation can attenuate cisplatin-associated renal dysfunction, biochemical alterations, and structural kidney damage.

2. Materials and Methods

2.1. Materials

2.1.1. Gum Arabic Samples

Gum Arabic (*Acacia senegal* L.) was obtained in three batches from SAVANNA Companies Group (Processing Gums, Juices and Confectionery), Khartoum, Sudan. The Gum Arabic was characterized by an off-white colour, powder form, and a purity of $98.65 \pm 0.45\%$. Analytical-grade arginine, used for the induction of chronic kidney disease (CKD) in rats, was purchased from Sigma Chemical Co., St. Louis, MO, USA. Casein was obtained from Morgan Chemical Co., Cairo, Egypt. All other chemicals, reagents, and solvents used in the study were of analytical grade and were purchased from El-Gomhouria Co. for Trading Drugs, Chemicals, and Medical Instruments, Cairo, Egypt.

2.1.2. Chemicals, Kits and Equipment's

Cisplatin and thiobarbituric acid (TBA) were obtained from Sigma Chemical Co., St. Louis, MO, USA, while casein was purchased from Morgan Company for Chemicals, Cairo, Egypt. Unless otherwise specified, all chemicals, vitamins, mineral salts, reagents, and solvents were of analytical grade and were supplied by El-Gomhouria Company for Trading Drugs, Chemicals and Medical Instruments, Cairo, Egypt. The malondialdehyde (MDA) assay kit was obtained from Biodiagnostic, Dokki, Giza, Egypt. Renal protein carbonyl levels were determined using a Sigma-Aldrich assay kit (USA). Superoxide dismutase (SOD) activity was assessed using a kit supplied by Creative BioLab, NY, USA, whereas glutathione peroxidase (GPx) and catalase (CAT) activities were measured using kits from Abcam Limited, Cambridge, UK. Commercial assay kits for alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), albumin, creatinine, uric acid, and urea were obtained from El-Nasr Pharmaceutical Chemicals, Cairo, Egypt. All assay kits were used according to the manufacturers' instructions, with their analytical specificity and sensitivity established by the respective manufacturers. Biochemical parameters were measured using a UV-Visible spectrophotometer (UV-160A, Shimadzu Corporation, Tokyo, Japan) and a microplate reader (BioTek ELx808, USA).

2.1.3. Animals

Adult male albino rats, weighing approximately 150–160 g, were used as the experimental animals in this study. The rats were obtained from the Research Institute of Ophthalmology, Medical Analysis Department, Giza, Egypt. Before initiation of the experimental procedures, the animals were housed under appropriate laboratory conditions and allowed an adequate acclimatization period to minimize environmental stress and ensure their adaptation to the experimental setting.

2.1.4. Basal/Standard Diet

The basal diet (BD) was formulated according to the method described by Reeves et al., [34]. (1993). The diet consisted of 10% protein, 10% corn oil, 1% vitamin mixture, 4% mineral mixture, 0.2% choline chloride, 0.3% methionine, 5% cellulose, and 69.5% corn starch. The vitamin and mineral mixtures were prepared according to the formulation reported by Reeves et al., [34].

2.2. Methods

2.2.1. Ethical Considerations

All experimental procedures involving laboratory animals were conducted in accordance with the ethical guidelines of the Scientific Research Ethics Committee for Animal Care and Use, Faculty of Home Economics, Menoufia University, Egypt. The experimental protocol was reviewed and approved by the committee under approval number 09-SREC-07-2024. All procedures were performed in accordance with the approved ethical standards for the care and use of laboratory animals.

2.2.2. Cisplatin-Induced Kidney Injury

Renal injury was induced by administering a single intraperitoneal injection of cisplatin at a dose of 6 mg/kg body weight. Cisplatin was freshly dissolved in sterile physiological saline immediately before administration. This dosing regimen and route of administration have been used in experimental rat models to induce cisplatin-associated renal injury. Following cisplatin administration, the animals were monitored daily for changes in general health status, body weight, food and water consumption, and other clinical manifestations of toxicity. Renal injury was assessed at the predetermined experimental endpoint following cisplatin administration. Previous experimental studies have demonstrated measurable renal and histopathological alterations several days following a single cisplatin injection, with day 5 being a commonly used assessment point in rat models.

2.2.3. Experimental Design

The biological experiments were conducted in the Biology Laboratory, Department of Nutrition and Food Science, Faculty of Home Economics, Menoufia University, Shebin El-Kom, Egypt. The experimental procedures were performed in accordance with the principles and recommendations of the Institute of Laboratory Animal Resources, Commission on Life Sciences, National Research Council (NRC, 1996). A total of 48 adult male albino rats were housed individually in wire-mesh cages under controlled laboratory conditions at a temperature of $25 \pm 2^\circ\text{C}$. Throughout the experimental period, the animals were maintained under standard environmental conditions with free access to food and water. Before treatment, all rats were fed the basal diet for one week to allow acclimatization to the laboratory environment. Following the acclimatization period, the animals were randomly allocated into eight experimental groups, with six rats assigned to each group. Group 1 (G1) served as the normal control and consisted of healthy rats fed the basal diet and receiving an equivalent administration of physiological saline. Group 2 (G2) served as the model control, in which cisplatin-induced renal injury was established while the animals continued to receive the basal diet without Gum Arabic treatment. Groups 3–5 (G3–G5) constituted the preventive-treatment groups. Animals in these groups received Gum Arabic (GA) incorporated into the basal diet at concentrations of 2, 3, and 4 g/100 g diet, respectively, prior to cisplatin administration. Groups 6–8 (G6–G8) constituted the therapeutic-treatment groups. Following induction of

cisplatin-associated renal injury, the animals received the basal diet supplemented with GA at the same concentrations of 2, 3, and 4 g/100 g diet, respectively. The selected GA levels were based on previously reported experimental studies [35,36]. The experimental treatments were continued for a total period of 28 days. Each group was maintained separately in designated cages throughout the study to ensure appropriate administration of the assigned dietary treatments and accurate monitoring of the animals.

2.2.4. Biological Evaluation

Body weight gain (BWG%), food intake (FI), and food efficiency ratio (FER) were determined throughout the 28-day experimental period. Body weight and food consumption were recorded weekly to monitor changes in growth and dietary intake. BWG and FER were calculated according to the method described by Chapman et al., [37], using the following equations:

$$\text{BWG (\%)} = [(\text{Final body weight} - \text{Initial body weight}) / \text{Initial body weight}] \times 100$$

$$\text{FER} = \text{Body weight gain (g)} / \text{Total food intake (g)}$$

2.2.5. Blood Sampling

At the end of the 28-day experimental period, the rats were fasted for 12 h before blood collection. The animals were anesthetized with diethyl ether, and blood samples were collected from the abdominal aorta into appropriate centrifuge tubes. The collected blood was allowed to clot at room temperature for approximately 35 min and was then centrifuged to separate the serum. The serum samples were carefully transferred into clean tubes and stored at -18°C until biochemical analyses were performed, following the procedure described by Schermer, [38].

2.2.6. Organ Sampling and Preparation of Kidney Homogenates

Following blood collection, the animals were euthanized, and the kidneys, liver, heart, spleen, and lungs were promptly excised, cleaned of adhering tissues, and weighed individually. Both kidneys were subsequently weighed. The left kidney from each animal was preserved for histopathological examination, whereas the right kidney was used for the preparation of tissue homogenates for biochemical analyses. Kidney tissue homogenates were prepared according to the procedure described by Wang et al., [39] with appropriate modifications where necessary. Briefly, the kidney tissue was rapidly excised, washed thoroughly with ice-cold physiological saline or phosphate-buffered saline (PBS) to remove residual blood, and maintained on ice throughout the preparation process. A known amount of tissue was weighed and transferred to a glass-Teflon homogenizer. Ice-cold homogenization buffer was then added at a ratio of approximately 1 g tissue to 10 mL buffer. The buffer contained 10 mM KCl, 1.5 mM MgCl_2 , 1 mM EDTA, 10 mM HEPES (pH 7.4–7.9), 0.1% Triton X-100, 0.5 mM dithiothreitol (DTT), and a protease inhibitor cocktail. The tissue was homogenized using approximately 8–15 strokes until a uniform suspension was obtained. The homogenate was maintained on ice for approximately 20 min and then centrifuged at approximately $3,000\text{--}10,000 \times g$ for 5–15

min at 4°C. The resulting supernatant was carefully collected and used as the kidney tissue homogenate for subsequent biochemical determinations. Samples not analyzed immediately were aliquoted and stored at -80°C until further analysis.

2.2.7. Biochemical and Hematological Analysis

2.2.7.1. Liver and Kidney Function Parameters

Serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) activities were determined using the modified kinetic method described by Tietz, [40]. Alkaline phosphatase (ALP) activity was assessed according to the procedure reported by Vassault et al., [41]. Serum albumin concentration was determined using the method of Doumas et al., [42], which is based on the interaction of albumin with bromocresol green. Serum total protein was measured according to the method of Gornall et al. [43]. Serum urea, creatinine, and uric acid concentrations were determined following the methods of Fawcett and Scott [44], Bartels et al., [45], and Barham and Trinder, [46], respectively.

2.2.7.2. Antioxidant Enzyme Activities

Renal glutathione peroxidase (GPx) and catalase (CAT) activities were determined according to the methods described by Splittgerber and Tappel [47], respectively. Renal superoxide dismutase (SOD) activity was assessed using a colorimetric method based on the procedure described by Engelbrecht et al., [48].

2.2.7.3. Oxidative Stress Markers

Renal lipid peroxidation was evaluated by determining the concentration of malondialdehyde (MDA), a major end product of lipid peroxidation. MDA levels were quantified using the colorimetric thiobarbituric acid (TBA) reaction according to the method of Buege and Aust, [49]. Renal protein oxidation was assessed by measuring protein carbonyl content following the procedure of. Briefly, protein carbonyl groups were derivatized with 2,4-dinitrophenylhydrazine (DNPH), resulting in the formation of stable dinitrophenyl (DNP) hydrazone derivatives. The absorbance of the resulting products was measured spectrophotometrically at 375 nm, with the absorbance being proportional to the carbonyl content of the protein samples.

2.2.8. Histopathological Examination

For histopathological assessment, the kidneys were rapidly removed and rinsed with ice-cold physiological saline (approximately 4°C) to eliminate residual blood. Representative tissue specimens were gently blotted with filter paper and immediately fixed in 10% neutral buffered formalin for at least one week. Following fixation, the tissue samples were processed through a graded series of ethanol concentrations, ranging from 75% to 100%, for dehydration. The dehydrated tissues were cleared in xylene and subsequently embedded in paraffin wax. Paraffin-embedded kidney tissues were sectioned at a thickness of approximately 1–2 µm, mounted on glass slides, and stained with hematoxylin and eosin (H&E). The stained sections were examined by light microscopy

to evaluate the general histological architecture and pathological alterations of the renal tissue at a magnification of approximately ×400, according to the method of Carleton, [50].

2.3. Statistical Analysis

The experimental results were expressed as mean values ± standard deviation (SD). The data were initially organized using Microsoft Excel 2016. Statistical differences among the experimental groups were evaluated using one-way analysis of variance (ANOVA), followed by Tukey's multiple-comparison test for determining differences between individual group means. The statistical analysis was performed using Minitab statistical software, version 12 (Minitab Inc., State College, PA, USA). Differences were considered statistically significant at $P \leq 0.05$, in accordance with the statistical procedures described by Steel and Torrie, [51]. One-way ANOVA is appropriate for evaluating differences among means across multiple treatment groups, with post-hoc comparisons used to identify specific group differences.

3. Results and Discussion

3.1. Effects of Gum Arabic on Body Weight Gain, Food Intake, and Feed Efficiency Ratio in Cisplatin-induced Kidney Injury

The effects of gum arabic (GA), administered before or after cisplatin exposure, on body weight gain (BWG), food intake (FI), and feed efficiency ratio (FER) are presented in Table 1. Cisplatin markedly impaired growth and nutrient-use efficiency, with a much greater effect on BWG and FER than on FI. In G1, BWG, FI, and FER were $23.90 \pm 4.61\%$, 6.60 ± 0.43 , and 0.075 ± 0.002 , respectively, compared with $7.97 \pm 1.41\%$, 6.30 ± 0.53 , and 0.020 ± 0.003 in G2. Thus, BWG and FER decreased by 66.65% and 68.00%, respectively, whereas FI changed only slightly; G1 and G2 shared the "ab/b" designation for FI, with the supplied calculation indicating a 4.55% increase relative to the normal-control reference. This divergence indicates that cisplatin toxicity primarily impaired nutrient utilization and metabolic efficiency rather than markedly suppressing food consumption. Such growth impairment may reflect systemic consequences of renal dysfunction, including altered nutrient handling, inflammatory stress, dehydration, and increased metabolic demands. Cisplatin accumulation in the renal cortex and proximal tubular cells induces DNA and mitochondrial damage, excessive reactive oxygen species (ROS) generation, inflammatory signaling, and cell death, thereby disturbing whole-body homeostasis [52,53].

GA substantially improved the three parameters, particularly when administered preventively. In G3, G4, and G5, BWG increased to $19.20 \pm 5.30\%$, $19.55 \pm 4.77\%$, and $19.71 \pm 4.52\%$, representing increases of 140.90%, 145.30%, and 147.30%, respectively, relative to G2. All preventive groups carried the designation (b), indicating higher BWG than G2 but lower values than G1 (a). Their FI values were 6.32 ± 0.58 , 7.21 ± 0.23 , and 6.44 ± 0.36 ,

respectively, with G4 significantly higher than G2, whereas G3 and G5 were comparable with G2. Concurrently, FER increased to 0.060 ± 0.009 , 0.055 ± 0.006 , and 0.062 ± 0.005 , corresponding to increases of 150.00%, 129.17%, and 158.33%, respectively. G5 showed the highest numerical FER and was statistically comparable with G1, with both carrying the “ab” designation. Thus, the marked improvement in BWG and FER without a proportional increase in FI suggests improved nutrient utilization rather than simply increased food consumption. Increasing GA from 2 to 4 g/100 g diet did not produce a clear additional BWG benefit, suggesting a possible functional plateau. Moreover, preventive treatment restored approximately 80–83% of control BWG, compared with approximately 49–64% in the therapeutic groups, supporting a greater benefit when GA was present before the nephrotoxic insult. This may reflect preservation of physiological reserves before the rapid sequence of oxidative stress, inflammation, mitochondrial injury, and tubular-cell death initiated by cisplatin [52,54].

Therapeutic GA also improved BWG, FI, and FER, although restoration was less complete. BWG reached $13.13 \pm 2.28\%$, $11.70 \pm 4.91\%$, and $15.26 \pm 6.53\%$ in G6, G7, and G8, corresponding to increases of 64.74%, 46.80%, and 91.47%, respectively, relative to G2; G8 showed the greatest numerical improvement and G7 the smallest. G6 and G8 were significantly different from G2, while G7 was also classified separately from the model control but did not reach the response observed with G8. FI increased to 7.28 ± 0.22 , 6.80 ± 0.28 , and 6.96 ± 0.23 in G6, G7, and G8, respectively, and all therapeutic groups were statistically higher than G2. FER increased to 0.035 ± 0.005 , 0.033 ± 0.003 , and 0.043 ± 0.007 , representing increases of 45.83%, 37.50%, and 79.17%, respectively, with G8 again showing the strongest numerical recovery. Nevertheless, all therapeutic FER values remained below G1, indicating incomplete restoration. The non-monotonic response suggests that GA efficacy was not determined solely by concentration and may depend on treatment duration, intestinal fermentation, injury severity, and timing. The improvement in FI may also reflect reduced systemic effects of cisplatin toxicity, including inflammatory and gastrointestinal disturbances; however, because appetite-regulating cytokines and gastrointestinal function were not measured, a specific mechanism cannot be established from FI alone [55].

Therefore, direct renal antioxidant activity is likely not the sole mechanism for the beneficial response to GA. GA is not readily absorbed, is soluble in the diet and is likely to be metabolized by gut microorganisms and by gastrointestinal and systemic processes. Experimental renal studies suggest anti-inflammatory effects, anti-oxidative effects, [55,56] claimed that there was no significant effect on the renal glutathione, superoxide dismutase, ascorbic acid, lipid peroxidation index in healthy rats, therefore, indicating that the anti-oxidative effect is not simply direct in the kidney. In the same way, Al-Majed et al., [57] demonstrated that GA decreased the

lipid peroxidation induced by cisplatin and prevented histopathological renal injury, but not functional renal injury. This suggests that the many mechanisms of cisplatin toxicity cannot be partially overcome by oxidative modulation. A similar improvement in renal functional and histopathological parameters and decrease in inflammatory and oxidative changes was observed in adenine induced chronic renal failure by Ali et al., [55], which is mechanistically different from cisplatin induced acute tubular injury. Taken together, these observations suggest that the GA effect is not just an antioxidant effect dependent on concentration, but rather, a multifactorial effect involving oxidative and inflammatory modulation, gastrointestinal metabolic activity, and maintenance of renal function [56,57].

The results from the BWG, FI and FER showed that cisplatin-induced nephrotoxicity mainly affected growth and nutrient-use efficiency and relatively small effects on food intake. These changes were substantially mitigated by GA, and administration before the onset of these changes tended to result in more recovery from the changes than did administration after the onset of these changes. G5 had the most positive numerical preventive FER while G8 had the most positive numerical therapeutic recovery in BWG and FER. Such a greater preventive response is in line with intervention prior to the development of the cisplatin-induced pathogenic cascade [52,54]. The incomplete normalization is also in agreement with Al-Majed et al., [57] who showed that lipid peroxidation is reduced, but not prevented, and nephrotoxicity is still reduced. With the role of accumulation of platinum, damage to DNA, oxidative stress, inflammation, mitochondrial dysfunction and cell death, it is reasonable to believe that partial recovery is possible. The present results confirm the protective and partial restorative effect of GA against the metabolic consequences of cisplatin-induced renal injury, which is likely to be mediated by several interacting pathways [52,57].

3.2. Effects of Gum Arabic on Organ Weights in Cisplatin-induced Kidney Injury

The effects of 30-day gum arabic (GA) administration before or after cisplatin exposure on the absolute weights of the liver, kidney, heart, spleen, and lung are presented in Table 2. Because organ weight can be influenced by tissue injury, edema, inflammation, nutritional status, and overall body size, these values should be interpreted alongside the marked changes in BWG shown in Table 1. Thus, the present findings provide integrated evidence of systemic and organ-specific responses rather than independent proof of structural toxicity [58,59].

Cisplatin produced contrasting changes among organs, with the most prominent responses occurring in the kidney and liver. Kidney weight increased significantly from 0.78 ± 0.11 g in G1 to 1.08 ± 0.14 g in G2, corresponding to a 39.42% increase. This renal enlargement is consistent with

Table 1. Effects of 30 days of gum arabic (GA) treatment and pretreatment on body weight gain (BWG), food intake (FI), and feed efficiency ratio (FER) in cisplatin-induced kidney injury

Value	G1 Normal control)	G2 Model control (Nephrotoxicity)	Prevention (GA concentration)			Treatment (GA concentration)		
			G3 (2%)	G4 (3%)	G5 (4%)	G6 (2%)	G7 (3%)	G8 (4%)
			Body weight gain (BWG, %)					
Mean	23.9 ^a	7.97 ^e	19.2 ^b	19.55 ^b	19.71 ^b	13.13 ^{cd}	11.7 ^d	15.26 ^c
SD	4.61	1.413	5.30	4.77	4.52	2.280	4.91	6.53
% of change	0.00	-66.65	+140.90	+145.30	+147.30	+64.74	+46.80	+91.47
			Feed intake (FI, g/28 day)					
Mean	6.60 ^{ab}	6.30 ^b	6.32 ^b	7.21 ^a	6.44 ^b	7.28 ^a	6.80 ^a	6.96 ^a
SD	0.43	0.53	0.58	0.23	0.36	0.22	0.28	0.23
% of change	0.00	+4.55	+0.23	+14.44	+2.22	+15.56	+7.94	+10.48
			Feed efficiency ratio (FER)					
Mean	0.075 ^a	0.02 ^e	0.060 ^b	0.055 ^b	0.062 ^{ab}	0.035 ^{cd}	0.033 ^d	0.043 ^c
SD	0.002	0.003	0.009	0.006	0.005	0.005	0.003	0.007
% of change	0.00	-68.00	+150.00	+129.17	+158.33	+45.83	+37.50	+79.17

Data are presented as the mean $\pm$ SD for six animals per group (n = 6). Values within the same row that are followed by different superscript letters differ significantly at $p \leq 0.05$. The experimental groups were designated as follows: G1, normal control (healthy untreated rats); G2, model control (cisplatin-induced kidney injury without treatment); GA, gum arabic. G3–G5 were the preventive groups, in which rats received gum arabic at dietary levels of 2, 3, and 4 g/100 g diet, respectively, before cisplatin administration. G6–G8 was the therapeutic groups, in which gum arabic was administered at the same dietary levels after cisplatin treatment. The percentage change (%) for the model control group was calculated relative to the normal control group, whereas the percentage change for the gum arabic-treated groups was calculated relative to the model control group.

cisplatin-induced tubular injury, in which preferential renal accumulation promotes oxidative stress, inflammatory signaling, mitochondrial dysfunction, vascular alterations, and tubular-cell death. These processes can cause cellular swelling, tubular dilation, inflammatory infiltration, and fluid accumulation, thereby increasing renal mass [52,54,58]. Consistently, Nematbakhsh et al. [58] reported significant associations between normalized kidney weight, serum creatinine, blood urea nitrogen, and histopathological damage in cisplatin-induced nephrotoxicity.

GA markedly attenuated this renal response. In the preventive groups, kidney weight decreased to 0.86 ± 0.02 , 0.77 ± 0.09 , and 0.83 ± 0.05 g in G3, G4, and G5, corresponding to decreases of 20.92%, 29.19%, and 23.68%, respectively, relative to G2. Particularly, G4 reached 0.77 g compared with 0.78 g in G1 and was significantly different from G2 (“c”), while G5 also approached the normal-control value. Therapeutic administration similarly reduced kidney weight to 0.81 ± 0.06 g in G6, 0.69 ± 0.09 g in G7, and 0.81 ± 0.09 g in G8, corresponding to reductions of 25.52%, 36.55%, and 25.52%, respectively, relative to G2. G6 was classified as “b,” whereas G7 and G8 were classified as “c.” These findings indicate that both GA regimens attenuated cisplatin-associated renal enlargement, with particularly strong normalization in preventive G4. However, the lower value in G7 than in G1 should not be interpreted as greater renoprotection because absolute kidney weight may also be affected by reduced body size, tissue loss, dehydration, or nutritional status. Relative kidney weight and histopathological findings would therefore be required for definitive interpretation.

In contrast, liver weight decreased from 4.57 ± 0.66 g in G1 to 2.60 ± 0.73 g in G2, representing a 48.11% reduction, with a significant difference between the groups. This reduction may reflect the combined effects of systemic toxicity, impaired growth, altered nutrient

utilization, and possible hepatic injury. Although the kidney is the primary target of cisplatin, hepatic oxidative injury has also been reported. Martins et al., [59] described increased hepatic and renal malondialdehyde, reduced antioxidant defenses, hepatic congestion, vascular dilation, and disruption of hepatic architecture after cisplatin exposure. Thus, the reduction in G2 may involve hepatic and systemic consequences rather than reduced body growth alone [59].

The hepatic response to GA was less uniform than the renal response. Preventive treatment produced liver weights of 2.08 ± 0.55 g, 3.14 ± 1.11 g, and 2.27 ± 0.46 g in G3, G4, and G5, respectively. G4 showed the greatest numerical recovery and was statistically comparable with G1 because both carried the “ab” designation, whereas G3 and G5 were designated “bc” and “b,” respectively. Therapeutic treatment resulted in 2.23 ± 0.90 g, 1.82 ± 0.20 g, and 2.10 ± 0.14 g in G6, G7, and G8, respectively, representing reductions of 14.23%, 30.00%, and 19.23% relative to G2. The lack of a consistent concentration-response relationship and the reduced BWG reported in Table 1 indicate that these changes should not be interpreted solely as direct hepatic effects. Nevertheless, the partial recovery observed with preventive GA, particularly G4, is compatible with the reported antioxidant and anti-inflammatory properties of GA [59]. Specific hepatoprotection would require confirmation using ALT, AST, hepatic oxidative-stress markers, and histopathology.

The remaining organs showed less pronounced or less specific responses. Heart weight ranged from 0.29 ± 0.09 g in G8 to 0.42 ± 0.04 g in G3, and all groups shared the “a” designation. Therefore, no difference was statistically significant at $p \leq 0.05$. This stability suggests that the gross organ-weight response to the present cisplatin exposure was predominantly renal rather than generalized. The preferential renal accumulation of cisplatin and the

susceptibility of proximal tubular cells to oxidative, mitochondrial, inflammatory, and DNA damage provide a plausible explanation [52,54]. Although G8 showed a numerically lower heart weight, its lack of statistical significance, together with the lower BWG reported in Table 1, argues against interpreting this finding as cardiac toxicity. Relative heart weight and histopathology would be needed for further assessment.

Spleen weight increased from 0.58 ± 0.09 g in G1 to 0.63 ± 0.11 g in G2, representing a 10.00% increase, with G1 classified as “b” and G2 as “a.” This change may reflect systemic inflammatory or immune responses to cisplatin because splenic mass can respond to altered inflammatory signaling and cellular activation [52,60]. Preventive GA resulted in 0.72 ± 0.05 g, 0.58 ± 0.12 g, and 0.57 ± 0.05 g in G3, G4, and G5, respectively, while therapeutic treatment produced 0.63 ± 0.11 g, 0.60 ± 0.22 g, and 0.46 ± 0.13 g in G6, G7, and G8, respectively. G3 and G5 were significantly different from G2 according to their superscript classifications, and G4 was also statistically separated from the model group. G8 showed the lowest splenic weight and was significantly different from G2. However, because spleen weight is sensitive to nutritional, hematological, and systemic inflammatory changes, these findings cannot by themselves establish a specific immunomodulatory effect of GA.

Lung weight increased significantly from 0.73 ± 0.08 g in G1 to 0.90 ± 0.16 g in G2, representing a 23.29% increase. This change may reflect systemic consequences of cisplatin toxicity, such as vascular congestion, fluid accumulation, or inflammatory alterations, although these

mechanisms were not directly assessed. Preventive GA resulted in 0.85 ± 0.10 g (G3), 0.65 ± 0.17 g (G4), and 0.85 ± 0.13 g (G5), with G4 statistically comparable with G1 and G3 remaining comparable with G2. Therapeutic treatment produced 0.77 ± 0.14 g, 0.76 ± 0.09 g, and 0.65 ± 0.046 g in G6, G7, and G8, respectively. G8 was statistically comparable with G1 and represented a 27.78% reduction relative to G2. Thus, GA attenuated the cisplatin-associated increase in lung weight, particularly with preventive 3% GA and therapeutic 4% GA. However, because lung-specific biochemical and histopathological endpoints were not measured, this finding is more appropriately interpreted as a possible reduction in systemic toxicity than as definitive pulmonary protection [59,53].

In summary, from the results in Table 2, the kidney is the most sensitive organ to the effect of cisplatin, recording a significant increase in weight by 39.42%, which was effectively reduced by GA. The increase in weight of the kidneys was accompanied by increases in BWG and FER, as shown in Table 1, indicating the protective action of GA against the overall effects of cisplatin-induced kidney damage. On the contrary, the liver showed a decrease in weight by 48.11%, while the heart showed no statistically significant change in weight. The spleen and lungs showed non-specific responses, perhaps as a result of the systemic effects of cisplatin, and the difference in body size. The stronger renal normalization observed with preventive treatment, particularly G4, further suggests that GA exposure before cisplatin may provide greater protection than treatment after injury has developed.

Table 2. Effects of 30 days of gum arabic (GA) treatment and pretreatment on organ weight in cisplatin-induced kidney injury

Value	G1 Normal control)	G2 Model control (Nephrotoxicity)	Prevention (GA concentration)			Treatment (GA concentration)		
			G3 (2%)	G4 (3%)	G5 (4%)	G6 (2%)	G7 (3%)	G8 (4%)
Liver (g)								
Mean	4.57 ^a	2.60 ^b	2.08 ^{bc}	3.14 ^{ab}	2.27 ^b	2.23 ^b	1.82 ^c	2.1 ^c
SD	0.66	0.73	0.55	1.11	0.46	0.9	0.20	0.14
% of change	0.00	-48.11	-20.00	+20.77	-12.69	-14.23	-30.00	-19.233
Kidney (g)								
Mean	0.78 ^{bc}	1.08 ^a	0.86 ^b	0.77 ^c	0.83 ^b	0.78 ^{bc}	0.81 ^b	0.69 ^c
SD	0.11	0.14	0.02	0.09	0.05	0.06	0.06	0.09
% of change	0.00	+39.42	-20.92	-29.19	-23.68	-28.28	-25.52	-36.55
Heart (g)								
Mean	0.38 ^a	0.40 ^a	0.42 ^a	0.39 ^a	0.39 ^a	0.38 ^a	0.40 ^a	0.29 ^a
SD	0.10	0.08	0.04	0.01	0.01	0.01	0.02	0.09
% of change	0.00	+5.92	+4.35	-3.11	-3.11	-5.59	-0.62	-27.95
Spleen (g)								
Mean	0.58 ^b	0.63 ^a	0.72 ^a	0.58 ^b	0.57 ^b	0.63 ^a	0.60 ^{ab}	0.46 ^c
SD	0.09	0.11	0.05	0.12	0.05	0.11	0.22	0.13
% of change	0.00	+10.00	+13.83	-8.69	-9.49	-0.39	-5.14	-27.27
Lung (g)								
Mean	0.73 ^b	0.90 ^a	0.85 ^a	0.65 ^b	0.85 ^a	0.77 ^{ab}	0.76 ^{ab}	0.65 ^b
SD	0.08	0.16	0.10	0.17	0.13	0.14	0.09	0.046
% of change	0.00	+23.29	-5.56	-27.78	-5.56	-14.44	-15.56	-27.78

Data are presented as the mean $\pm$ SD for six animals per group (n = 6). Values within the same row that are followed by different superscript letters differ significantly at $p \leq 0.05$. The experimental groups were designated as follows: G1, normal control (healthy untreated rats); G2, model control (cisplatin-induced kidney injury without treatment); GA, gum arabic. G3–G5 were the preventive groups, in which rats received gum arabic at dietary levels of 2, 3, and 4 g/100 g diet, respectively, before cisplatin administration. G6–G8 was the therapeutic groups, in which gum arabic was administered at the same dietary levels after cisplatin treatment. The percentage change (%) for the model control group was calculated relative to the normal control group, whereas the percentage change for the gum arabic-treated groups was calculated relative to the model control group.

The protective actions of GA cannot be attributed solely to the role of GA in antioxidative protection of the kidneys. Ali, [56] showed that GA does not significantly affect various renal antioxidative indices in healthy rats, whereas Ali et al. [55] confirmed the beneficial effect of GA in improving various changes in functional, histopathological, inflammatory and oxidative parameters associated with the development of chronic renal failure caused by adenine administration. Despite the different nature of the models used, there is a possibility of the general effect of GA on the system. In the case of cisplatin, evidence of GA's ability to protect against oxidative damage, but not against nephrotoxicity, was provided [57]. Therefore, the present organ-weight responses may reflect interacting effects on oxidative and inflammatory processes, systemic metabolic status, and renal functional integrity rather than a single mechanism [56,55].

One of the primary limitations associated with the interpretation is that the absolute values of organ weight have been used instead of relative organ weight values. As cisplatin had greatly inhibited the BWG and GA did not normalize the BWG, reduced weight of liver, heart, spleen, and lungs might have been due to the fact that the body weight was less. However, increased weight of kidney can be better explained by using relative weight values. Relative organ weights, along with serum creatinine, blood urea nitrogen, oxidative stress and inflammatory mediators, and antioxidant enzyme activity would help in interpreting the mechanism [58,52].

From Table 2, the overall findings indicate that GA is more renoprotective against cisplatin induced nephrotoxicity especially when GA is taken before the administration of cisplatin. This is based on the reduction in kidney size along with improved BWG and FER. Liver, spleen, and lungs findings indicate more generalized effects while there was no change in heart weight showing that there were no gross heart abnormalities in these conditions. Nevertheless, confirmation of organ-specific protection requires relative organ-weight analysis and complementary biochemical and histopathological endpoints.

3.3. Effects of Gum Arabic on Liver-function Biomarkers

As depicted in Table 3, there is a clear and consistent biochemical response to cisplatin, which consists of higher levels of AST, ALT, and ALP along with a reduction in albumin levels. Such findings suggest that, alongside kidney damage caused by cisplatin, there may also have been some systemic biochemical alterations involving the liver. Since organ weights, body weight gains, and nutritional status can affect circulating biochemical parameters, such findings should be evaluated along with the body weight gains and organ weights as shown in Tables 1 and 2. While the kidney is known to be the primary target for cisplatin-related injury, damage to the liver has also been shown in the past [53,60].

In G2, serum AST increased from 34.26 ± 2.13 U/L in G1 to 81.60 ± 6.19 U/L, representing a 138.18% increase, with G1 and G2 assigned "d" and "a," respectively. ALT showed a comparable response, increasing from 29.16 ± 1.83 U/L in G1 to 68.20 ± 4.73 U/L in G2, corresponding

to a 133.88% increase and a significant difference between G1 ("d") and G2 ("a"). ALP also increased markedly, from 90.90 ± 5.93 U/L to 187.70 ± 11.80 U/L, representing a 106.49% increase. In contrast, albumin decreased from 5.51 ± 0.35 g/dL in G1 to 2.95 ± 0.18 g/dL in G2, corresponding to a 46.46% reduction, with G1 and G2 classified as "a" and "d," respectively. The concurrent elevation of three enzymes and reduction of albumin provides stronger evidence of systemic hepatic and metabolic disturbance than any single parameter alone.

The elevated levels of AST and ALT are consistent with damage to cells from the use of cisplatin. This is because AST is not specific to the liver but is found in skeletal and cardiac muscles as well as other organs. Therefore, the increase can be attributed to systemic cell damage in which the liver contributes significantly. ALT, being a better liver-related enzyme, adds strength to this observation. There have been reports of increased lipid peroxidation, mitochondrial dysfunction, reduced levels of glutathione, decreased NADPH activity, cell membrane damage, and cell death from previous studies on the use of cisplatin [59,60]. This would imply that oxidative stress resulting from the use of cisplatin can affect cell membranes and cause enzyme leakage. These mechanisms are also consistent with the broader systemic toxicity reported after cisplatin administration [53,54,57].

The ALP response further supports a biochemical disturbance associated with cisplatin exposure. Its increase from 90.90 ± 5.93 U/L in G1 to 187.70 ± 11.80 U/L in G2 may indicate altered hepatocellular or membrane-associated enzyme activity. However, ALP is not exclusively hepatic. Thus, without bilirubin, γ -glutamyl transferase, or histopathological findings, the present result should be considered evidence of hepatobiliary or systemic disturbance rather than definitive proof of cholestasis. The observed increase nevertheless agrees with previous reports of hepatic biochemical and structural abnormalities following cisplatin exposure [59].

GA substantially attenuated the enzyme elevations, with the preventive regimen generally producing the stronger response. AST decreased to 51.80 ± 3.23 , 46.80 ± 3.49 , and 44.56 ± 2.78 U/L in G3, G4, and G5, corresponding to reductions of 36.52%, 42.65%, and 45.39%, respectively, relative to G2. ALP similarly decreased to 132.10 ± 8.24 , 119.37 ± 8.90 , and 113.50 ± 7.08 U/L, representing reductions of 29.62%, 36.40%, and 39.53%, respectively. ALT declined to 44.92 ± 2.80 , 40.60 ± 3.03 , and 38.61 ± 2.40 U/L in G3, G4, and G5, corresponding to reductions of 34.13%, 40.47%, and 43.39%, respectively. Thus, G5 produced the greatest preventive reductions in AST, ALT, and ALP. Its ALT value was statistically classified as "c," indicating greater recovery toward the normal condition.

Therapeutic GA also improved all three enzyme markers, although the magnitude of recovery was generally lower than that observed with pretreatment. AST decreased to 59.43 ± 4.16 , 55.54 ± 3.60 , and 53.13 ± 3.31 U/L in G6, G7, and G8, corresponding to reductions of 27.17%, 31.94%, and 34.89%, respectively. ALP decreased to 145.90 ± 10.20 , 135.41 ± 8.80 , and 130.52 ± 8.14 U/L, representing reductions of 22.27%, 27.86%, and 30.46%, respectively. ALT decreased to 57.30 ± 4.02 , 53.75 ± 3.54 , and 51.22 ± 3.19 U/L, corresponding to

reductions of 15.98%, 21.19%, and 24.90%, respectively. The statistical classifications for ALT further support this pattern: G6 was “a,” similar to G2 (“a”), whereas G7 (“ab”) and G8 (“b”) showed greater improvement. Thus, therapeutic 4% GA produced the strongest post-cisplatin recovery among the therapeutic groups, although complete normalization was not achieved.

The albumin response complemented the enzyme findings but showed a different concentration pattern. Preventive GA increased albumin to 4.44 ± 0.27 g/dL in G3, 4.06 ± 0.28 g/dL in G4, and 3.79 ± 0.25 g/dL in G5. These values represented increases of 50.42%, 37.71%, and 28.31%, respectively, relative to G2. G3 produced the highest preventive albumin concentration and was classified as “ab,” indicating no significant difference from the normal-control group. Therapeutic treatment increased albumin to 3.83 ± 0.28 , 3.98 ± 0.34 , and 4.13 ± 0.37 g/dL in G6, G7, and G8, corresponding to increases of 29.75%, 34.75%, and 40.00%, respectively. G8 produced the highest therapeutic albumin concentration and shared the “a” designation with the normal control. These findings indicate that the concentration producing the greatest improvement may differ according to the biomarker assessed.

The decrease in albumin in G2 cannot be considered the result of only compromised synthesis of albumin in the liver. The factors affecting albumin include the nutrition, inflammation, hydration, vascular distribution, and proteinuria. The consideration is especially significant since cisplatin strongly inhibited BWG in Table 1 and resulted in renal damage in the current experiment. In other words, the 46.46% decline in albumin content is likely to be associated with a disturbance of protein homeostasis. On the other hand, the increase in the level of albumin after GA treatment can indicate a decrease in the extent of renal damage and inflammation. It is known from the literature that GA impacts inflammatory and oxidative dysfunction in experimental nephropathy [55]. However, proteinuria and inflammatory markers were not evaluated.

The general preventive benefit is also biologically reasonable. The mechanism for injury induced by cisplatin includes generation of ROS in mitochondria, decrease in GSH and NADPH levels, lipid peroxidation, altered energy metabolism, and activation of apoptosis [53,61]. Pre-exposure GA could thus be operating at an early stage of the injury cascade. Once the cell/mitochondrial damage has been initiated, treatment following injury may not be able to reverse the damage. This could be one reason why preventive GA caused greater reduction in AST, ALT, and ALP, while therapeutic 4% GA led to maximum recovery in albumin levels.

This is further supported by the current findings indicating that the activity of GA should not be viewed as being solely an activity of direct tissue antioxidant. For instance, Ali, [56] found that the activity of GA had no significant influence on various antioxidants in both the liver and the kidneys of healthy rats. The aforementioned findings do not support the hypothesis that the activity of GA is a simple and direct antioxidant function. The

compound GA is a complex polysaccharide that has effects both in the gastrointestinal tract and in the system as a whole. It may have activities such as modulation of inflammatory responses, gut metabolism, and redox balance [55,56]. Accordingly, the biochemical recovery observed here may result from combined effects on oxidative stress, inflammation, metabolic status, and tissue integrity rather than from a single mechanism.

3.4. Effects of Gum Arabic on Kidney Function Biomarkers

Table 4 demonstrates a pronounced impairment of renal function following cisplatin administration, with coordinated increases in serum urea, creatinine, and uric acid in G2 compared with G1. Serum urea increased from 28.03 ± 1.77 mg/dL to 141.90 ± 14.93 mg/dL, representing a 406.24% increase, while creatinine increased from 0.52 ± 0.03 to 2.50 ± 0.22 g/dL, corresponding to a 380.77% increase. Serum uric acid also increased from 3.30 ± 0.22 to 7.09 ± 0.66 mg/dL, representing a 114.85% increase. All three parameters were significantly higher in G2 than in G1, confirming substantial renal functional impairment. This pattern is consistent with cisplatin accumulation in proximal tubular cells, where oxidative stress, mitochondrial dysfunction, DNA and endoplasmic-reticulum stress, inflammatory signaling, and regulated cell death collectively compromise tubular integrity and renal clearance [9,62].

GA substantially attenuated these abnormalities. Preventive administration reduced urea to 74.79 ± 4.66 , 67.50 ± 5.03 , and 64.28 ± 4.01 mg/dL in G3, G4, and G5, corresponding to reductions of 47.29%, 52.43%, and 54.70%, respectively, relative to G2. The corresponding creatinine concentrations were 1.39 ± 0.08 , 1.26 ± 0.09 , and 1.20 ± 0.07 , representing reductions of 44.40%, 49.60%, and 52.00%. Uric acid similarly decreased to 4.70 ± 0.29 , 4.26 ± 0.30 , and 4.05 ± 0.25 mg/dL, corresponding to reductions of 33.71%, 39.92%, and 42.88%. Thus, G5 produced the lowest concentrations of all three biomarkers among the preventive groups, indicating the strongest overall biochemical improvement within this regimen. The statistical classifications further support significant improvement relative to G2, particularly for creatinine and uric acid.

Therapeutic GA also improved renal function, although the response differed somewhat among the biomarkers. Urea decreased to 67.31 ± 4.72 , 63.07 ± 4.13 , and 60.18 ± 3.75 mg/dL in G6, G7, and G8, corresponding to reductions of 52.57%, 55.55%, and 57.59%, respectively. Creatinine decreased to 1.72 ± 0.12 , 1.59 ± 0.10 , and 1.54 ± 0.09 , representing reductions of 31.20%, 36.40%, and 38.40%, while uric acid decreased to 5.30 ± 0.37 , 5.00 ± 0.34 , and 4.73 ± 0.29 mg/dL, corresponding to reductions of 25.25%, 29.48%, and 33.29%. G8 therefore produced the lowest value for each renal biomarker among the therapeutic groups. Nevertheless, the therapeutic values remained above G1, particularly for creatinine and uric acid, indicating incomplete recovery of renal function.

Table 3. Effects of 30 days of gum arabic (GA) treatment and pretreatment on liver functions in cisplatin-induced kidney injury

Value	G1 Normal control	G2 Model control (Nephrotoxicity)	Prevention (GA concentration)			Treatment (GA concentration)		
			G3 (2%)	G4 (3%)	G5 (4%)	G6 (2%)	G7 (3%)	G8 (4%)
			Serum aspartate aminotransferase (AST, U/L)					
Mean	34.26 ^d	81.6 ^a	51.8 ^{bc}	46.8 ^c	44.56 ^c	59.43 ^b	55.54 ^b	53.13 ^b
SD	2.13	6.19	3.23	3.49	2.78	4.16	3.60	3.31
% of change	0.00	+138.18	-36.52	-42.65	-45.39	-27.17	-31.94	-34.89
Alkaline Phosphatase (ALP, U/L)								
Mean	90.9 ^d	187.7 ^a	132.1 ^b	119.37 ^c	113.5 ^c	145.9 ^b	135.41 ^b	130.52 ^b
SD	5.93	11.8	8.24	8.90	7.08	10.2	8.8	8.14
% of change	0.00	+106.49	-29.62	-36.40	-39.53	-22.27	-27.86	-30.46
Serum alanine aminotransferase (ALT, U/L)								
Mean	29.16 ^d	68.20 ^a	44.92 ^{bc}	40.60 ^c	38.61 ^c	57.30 ^a	53.75 ^{ab}	51.22 ^b
SD	1.83	4.73	2.80	3.029	2.40	4.016	3.54	3.19
% of change	0.00	+133.88	-34.13	-40.47	-43.39	-15.98	-21.19	-24.90
Albumin(ALB)(g/dL)								
Mean	5.51 ^a	2.95 ^d	4.44 ^{ab}	4.06 ^b	3.79 ^c	3.83 ^{bc}	3.98 ^b	4.13 ^a
SD	0.35	0.18	0.27	0.28	0.25	0.28	0.34	0.37
% of change	0.00	-46.46	+50.42	+37.71	+28.31	+29.75	+34.75	+40.00

Data are presented as the mean $\pm$ SD for six animals per group (n = 6). Values within the same row that are followed by different superscript letters differ significantly at $p \leq 0.05$. The experimental groups were designated as follows: G1, normal control (healthy untreated rats); G2, model control (cisplatin-induced kidney injury without treatment); GA, gum arabic. G3–G5 were the preventive groups, in which rats received gum arabic at dietary levels of 2, 3, and 4 g/100 g diet, respectively, before cisplatin administration. G6–G8 was the therapeutic groups, in which gum arabic was administered at the same dietary levels after cisplatin treatment. The percentage change (%) for the model control group was calculated relative to the normal control group, whereas the percentage change for the gum arabic-treated groups was calculated relative to the model control group.

The concordant improvement in urea, creatinine, and uric acid strengthens the interpretation that GA exerted a genuine renoprotective and/or renal-recovery effect rather than selectively modifying a single biochemical pathway. Urea and creatinine primarily reflect impaired renal clearance, whereas uric acid is additionally influenced by production, tubular reabsorption, secretion, and excretion. Their simultaneous reduction therefore provides complementary evidence of improved renal excretory function. These findings agree with Al-Majed et al. [57], who reported nephroprotective effects of GA in cisplatin-treated rats, and with Ali et al. [55], who demonstrated reductions in plasma urea and creatinine together with improvement in oxidative and inflammatory abnormalities in experimental renal failure.

The superiority of the 4% concentration was found to be true for both the ways of administration. The group G5 has the least concentrations of urea, creatinine, and uric acid compared to other preventative groups, while G8 has the least concentration compared to other therapeutic groups. It may be concluded that 4% GA has the best

effect among the concentrations. But it is to be noted that this is the optimum concentration only within the current range of experiments since only three concentrations have been used here.

However, the larger reduction in the levels of creatinine and uric acid in the preventive group compared to the curative group further indicates that the time of GA treatment might have affected the drug's effectiveness. The pretreatment could give enough time for GA to be administered before severe cisplatin-mediated tubular injury occurs in order to restrict the oxidative, mitochondrial, inflammatory, and DNA damage processes at an early stage. Once there is significant cell death, the post-exposure treatment might help in recovery rather than prevention of damage. This explanation is in line with the multiple pathophysiological processes involved in the development of cisplatin nephrotoxicity including oxidative stress, mitochondrial dysfunction, DNA damage, endoplasmic-reticulum stress, inflammation, apoptosis, necroptosis, autophagy, and cellular senescence [9,63].

Table 4. Effects of 30 days of gum arabic (GA) treatment and pretreatment on kidney function in cisplatin-induced kidney injury

Value	G1 Normal control)	G2 Model control (Nephrotoxicity)	Prevention (GA concentration)			Treatment (GA concentration)		
			G3 (2%)	G4 (3%)	G5 (4%)	G6 (2%)	G7 (3%)	G8 (4%)
Serum urea concentration(mg/dl)								
Mean	28.03 ^d	141.9 ^a	74.79 ^b	67.5 ^b	64.28 ^{bc}	67.31 ^b	63.07 ^c	60.18 ^c
SD	1.77	14.93	4.66	5.03	4.01	4.72	4.134524	3.753624
% of change	0.00	+406.24	-47.29	-52.43	-54.70	-52.57	-55.55	-57.59
Serum creatinine concentration(g/dl)								
Mean	0.52 ^d	2.50 ^a	1.39 ^{bc}	1.26 ^c	1.20 ^c	1.72 ^b	1.59 ^b	1.54 ^b
SD	0.03	0.22	0.08	0.09	0.07	0.12	0.1	0.09
% of change	0.00	+380.77	-44.40	-49.60	-52.00	-31.20	-36.40	-38.40
Serum uric acid concentration(mg/dl)								
Mean	3.30 ^d	7.09 ^a	4.70 ^b	4.26 ^{bc}	4.05 ^c	5.30 ^b	5.00 ^b	4.73 ^b
SD	0.22	0.66	0.29	0.3	0.25	0.37	0.34	0.29
% of change	0.00	+114.85	-33.71	-39.92	-42.88	-25.25	-29.48	-33.29

Data are presented as the mean $\pm$ SD for six animals per group (n = 6). Values within the same row that are followed by different superscript letters differ significantly at $p \leq 0.05$. The experimental groups were designated as follows: G1, normal control (healthy untreated rats); G2, model control (cisplatin-induced kidney injury without treatment); GA, gum arabic. G3–G5 were the preventive groups, in which rats received gum arabic at dietary levels of 2, 3, and 4 g/100 g diet, respectively, before cisplatin administration. G6–G8 was the therapeutic groups, in which gum arabic was administered at the same dietary levels after cisplatin treatment. The percentage change (%) for the model control group was calculated relative to the normal control group, whereas the percentage change for the gum arabic-treated groups was calculated relative to the model control group.

The factors responsible for the observed improvement in GA may be multiple. Cisplatin-related generation of reactive oxygen species could cause lipid peroxidation, mitochondrial dysfunction, DNA damage, and inflammatory mediators, which may enhance tubular damage. Studies have shown that GA can inhibit superoxide generation and DNA damage, and improve oxidative and inflammatory defects [55]. Nonetheless, GA is not to be considered only a direct renal antioxidant. Studies by Ali [56] have shown that GA did not affect a number of antioxidant indexes in normal rats, implying that its physiological functions may also include indirect control of inflammation, gastrointestinal metabolism, and physiology [55,56]. The current biochemical improvement may thus result from the preservation of tubular architecture, reduction of inflammatory damage, and enhanced systemic physiological function.

3.5. Effects of Gum Arabic on Renal Antioxidant Enzyme Activities

Table 5 demonstrates a marked disruption of the renal enzymatic antioxidant defense system following cisplatin exposure. Compared with G1, G2 showed significant reductions in GPx, SOD, and CAT activities, with GPx decreasing from 15.90 ± 0.84 to 5.52 ± 0.60 $\mu\text{mol}/\text{min}/\text{mg}$ protein (65.28%), SOD from 4.21 ± 0.45 to 2.40 ± 0.39 IU/mg protein (42.99%), and CAT from 63.30 ± 5.34 to 33.56 ± 3.50 mmol/min/mg protein (46.98%). The different superscript designations confirmed significant differences at $p \leq 0.05$. The greater reduction in GPx suggests particularly marked impairment of peroxide detoxification, while the simultaneous decline in SOD and CAT indicates disruption of sequential antioxidant defenses. This coordinated suppression provides a plausible mechanistic basis for the renal dysfunction observed in Table 4, as cisplatin-induced mitochondrial dysfunction and excessive ROS generation can overwhelm

endogenous antioxidant capacity and promote oxidative injury [62,64].

The current trend is in accordance with past evidence that cisplatin causes interference with the renal antioxidant system. This drug tends to concentrate in renal tubular epithelial cells and brings about mitochondrial dysfunction, production of reactive oxygen species (ROS), DNA damage, inflammation, and death of cells. Too much ROS is able to interfere with SOD-, CAT-, and GPx-based clearance and also cause oxidative stress leading to oxidation of lipids, proteins, and DNA [62,64]. Sugiyama et al. [65] have shown that cisplatin results in reduced respiratory activity of mitochondria, GPx activity and elevated plasma creatinine and blood urea nitrogen levels. Similarly, Badary et al. [66] and Almaghrabi [67] have observed inhibition of renal SOD, CAT, and GPx activity after treatment with cisplatin. The simultaneous reduction of all three enzymes in G2 is, therefore, suggestive of general disruption of the redox balance in kidneys.

GA substantially restored antioxidant enzyme activities, with the magnitude of improvement generally increasing with concentration and being greater after pretreatment. Preventive GA increased GPx activity to 7.98 ± 0.64 , 8.40 ± 0.51 , and 9.28 ± 0.49 $\mu\text{mol}/\text{min}/\text{mg}$ protein in G3, G4, and G5, corresponding to increases of 44.57%, 52.17%, and 68.12%, respectively, relative to G2. SOD increased to 2.72 ± 0.60 , 3.02 ± 0.91 , and 3.82 ± 0.82 IU/mg protein, representing increases of 13.33%, 25.83%, and 59.17%, while CAT increased to 44.20 ± 3.77 , 51.70 ± 5.02 , and 56.90 ± 3.42 mmol/min/mg protein, corresponding to increases of 31.70%, 54.05%, and 69.55%. The statistical classifications indicate that the 3% and 4% preventive concentrations provided significant improvement in SOD, whereas all preventive concentrations significantly improved GPx and CAT. G5 produced the highest activity for all three enzymes and therefore showed the strongest overall restoration within the preventive protocol.

Therapeutic GA also improved the antioxidant profile,

although recovery was generally less pronounced. GPx increased to 6.58 ± 0.40 , 6.86 ± 0.44 , and 7.36 ± 0.53 $\mu\text{mol}/\text{min}/\text{mg}$ protein in G6, G7, and G8, representing increases of 19.20%, 24.28%, and 33.33%, respectively. SOD increased to 2.80 ± 0.42 , 2.93 ± 0.65 , and 3.43 ± 0.81 IU/mg protein, corresponding to increases of 16.67%, 22.08%, and 42.92%, while CAT increased to 38.80 ± 4.42 , 44.31 ± 3.93 , and 49.20 ± 3.34 mmol/min/mg protein, representing increases of 15.61%, 32.03%, and 46.60%. G8 consistently produced the highest activities among the therapeutic groups. Thus, although post-cisplatin GA administration partially restored renal antioxidant defenses, the enzyme activities generally remained below G1, indicating incomplete recovery.

It is also interesting to consider the response pattern of GPx, SOD, and CAT. SOD catalyzes the conversion of superoxide into hydrogen peroxide, while CAT and GPx detoxify hydrogen peroxide and other peroxides. Thus, the concomitant reduction of their activity in group G2 should contribute to an increased ability of reactive oxygen species to survive in cells and cause oxidative damage. The significantly reduced levels of GPx (65.28%) compared to those of CAT (46.98%) and SOD (42.99%) indicate that the process of GPx-mediated peroxide detoxification is particularly sensitive under the current experimental conditions. The restoration of these complementary pathways following GA administration provides a coherent explanation for the improvement in renal function biomarkers observed.

This is another piece of evidence showing how GA 4% proved its efficacy within the tested concentration. The most powerful preventive effects for GPx, SOD, and CAT were observed for G5, and the most powerful therapeutic effects for G8. It is clear that increase in the concentration of GA from 2% to 4% resulted in better preservation of

the antioxidant system of the kidneys. However, because only 2%, 3%, and 4% concentrations were examined, these findings should be interpreted as an observed optimum within the experimental range rather than evidence of a definitive linear dose-response relationship or maximum effective dose.

The greater antioxidant defense after pretreatment is also biologically reasonable. Treatment with GA prior to cisplatin exposure could maintain the baseline redox state during the early stages of cisplatin accumulation and formation of reactive oxygen species. After significant damage to the oxidation, mitochondria, membranes, and DNA has already been done, there may be limited scope for restoration of the enzymatic function by treatment after exposure. Pretreatment would prevent the oxidative stress from the very beginning while treatment would help decrease the ongoing oxidative damage. This explanation is supported by studies that antioxidant pretreatment offers considerable protection against oxidative damage due to cisplatin exposure [66,68].

The positive impact of the activities of the studied antioxidant enzymes is in line with previous findings about GA. As shown by Ali et al. [55], GA lowers the production of superoxide and DNA damage in experimental renal failure and improves the antioxidant parameters. It appears that GA can lower the oxidative stress of renal tissues and thus maintain the activity of antioxidants. However, it cannot be assumed to mean activation of SOD, CAT, or GPx because GA is a rather complex food polysaccharide. Thus, it may act through many processes including inflammatory, gastrointestinal metabolism, redox balance, and other systemic effects. Indeed, Ali, [56] reported that GA did not significantly modify several antioxidant parameters in healthy rats, arguing against a simple direct antioxidant mechanism.

Table 5. Effects of 30 days of gum arabic (GA) treatment and pretreatment on kidney antioxidant enzymes in cisplatin-induced kidney injury

Value	G1 Normal control)	G2 Model control (Nephrotoxicity)	Prevention (GA concentration)			Treatment (GA concentration)		
			G3 (2%)	G4 (3%)	G5 (4%)	G6 (2%)	G7 (3%)	G8 (4%)
Renal Glutathione peroxidase activity (GPx , μmol/min/mg protein)								
Mean	15.90 ^a	5.52 ^d	7.98 ^b	8.40 ^b	9.28 ^b	6.58 ^c	6.86 ^c	7.36 ^{bc}
SD	0.84	0.60	0.64	0.51	0.49	0.40	0.44	0.53
% of change	0.00	-65.28	+44.57	+52.17	+68.12	+19.20	+24.28	+33.33
Renal Super oxide dismutase activity (SOD, IU/mg protein)								
Mean	4.21 ^a	2.40 ^c	2.72 ^c	3.02 ^b	3.82 ^b	2.80 ^c	2.93 ^{bc}	3.43 ^{ab}
SD	0.45	0.39	0.60	0.91	0.82	0.42	0.65	0.81
% of change	0.00	-42.99	+13.33	+25.83	+59.17	+16.67	+22.08	+42.92
Renal Catalase activity (CAT, mmol/min/mg protein)								
Mean	63.30 ^a	33.56 ^f	44.20 ^d	51.70 ^c	56.90 ^b	38.80 ^e	44.31 ^d	49.20 ^c
SD	5.34	3.5	3.77	5.02	3.42	4.42	3.93	3.34
% of change	0.00	-46.98	+31.70	+54.05	+69.55	+15.61	+32.03	+46.60

Data are presented as the mean $\pm$ SD for six animals per group ($n = 6$). Values within the same row that are followed by different superscript letters differ significantly at $p \leq 0.05$. The experimental groups were designated as follows: G1, normal control (healthy untreated rats); G2, model control (cisplatin-induced kidney injury without treatment); GA, gum arabic. G3–G5 were the preventive groups, in which rats received gum arabic at dietary levels of 2, 3, and 4 g/100 g diet, respectively, before cisplatin administration. G6–G8 was the therapeutic groups, in which gum arabic was administered at the same dietary levels after cisplatin treatment. The percentage change (%) for the model control group was calculated relative to the normal control group, whereas the percentage change for the gum arabic-treated groups was calculated relative to the model control group.

Conclusively, therefore, the current results indicate a multifactorial explanation. The accumulation of cisplatin in the cells lining the renal tubules can trigger the onset of mitochondrial dysfunction and elevated levels of ROS production leading to oxidative stress, inflammation, and eventually cell death. The use of GA could possibly prevent such occurrences through the reduction of oxidative and inflammatory stress along with maintaining antioxidant functions within the body. By restoring the activities of SOD, CAT, and GPx, there will be an improvement in the elimination of superoxides and peroxides, preventing any possible damage to the renal lipids, proteins, DNA, and mitochondria [55,62]. This mechanism is compatible with the concurrent reductions in serum urea, creatinine, and uric acid observed in the present study.

3.6. Effects of Gum Arabic Pretreatment and Treatment on Renal Oxidative Stress

The effects of 30 days of gum Arabic (GA) administration before or after cisplatin exposure on renal oxidative stress are presented in Table 6. Cisplatin produced a clear oxidative imbalance, characterized by significant increases in both lipid and protein oxidation. Renal malondialdehyde (MDA) increased from 5.13 ± 0.78 $\mu\text{mol/mg}$ protein in G1 to 10.16 ± 0.90 $\mu\text{mol/mg}$ protein in G2, representing a 98.05% increase. Protein carbonyl (PC) increased from 0.043 ± 0.009 to 0.129 ± 0.011 nmol/mg protein, corresponding to a 200.00% increase. The different superscript letters confirmed significant differences at $p \leq 0.05$. Thus, cisplatin induced coordinated lipid and protein oxidation in the kidney. This finding agrees with the established role of mitochondrial dysfunction, excessive reactive oxygen species (ROS), antioxidant depletion, and macromolecular oxidation in cisplatin nephrotoxicity [9,62,69,70].

An increased level of MDA shows lipid peroxidation, while an increase in PC shows oxidative modification of cellular proteins. MDA is produced during oxidative decomposition of polyunsaturated fatty acids and indicates membrane lipid peroxidation. PC shows relatively stable ROS-induced modifications of proteins. These changes thus act as complementary signs of oxidative injury to kidneys. Cisplatin can interfere with mitochondrial respiratory chain, reduce levels of glutathione, activate ROS-production mechanisms, and disrupt antioxidant defense. Early loss of glutathione content in mitochondria before lipid peroxidation was found after cisplatin treatment, which proves the cause-effect relationship between failure of antioxidant defense and membrane damage [71]. Renal lipid peroxidation and mitochondrial oxidative damage were found in vivo [72]. Likewise, coexistent increases in kidney MDA and PC along with reductions in glutathione content and antioxidant vitamins were observed in experimental cisplatin nephrotoxicity [73].

These changes appear to be of similar size as expected from the tendency of cisplatin to concentrate in renal tubule cells. The intracellular uptake, which occurs by organic cation transporter 2, leads to mitochondrial dysfunction and ROS production. Such oxidative stress can trigger an amplifying feedback loop that includes lipid peroxidation, protein oxidation, mitochondrial impairment,

inflammation, and cell death [9,62,69,70]. Thus, the current MDA and PC changes should be viewed as related aspects of oxidative injury of the tubules.

GA substantially attenuated both markers. Preventive administration reduced MDA from 10.16 $\mu\text{mol/mg}$ protein in G2 to 8.56, 7.74, and 6.89 $\mu\text{mol/mg}$ protein in G3, G4, and G5, corresponding to reductions of 15.75%, 23.82%, and 32.18%, respectively. PC similarly decreased from 0.129 nmol/mg protein in G2 to 0.110, 0.089, and 0.061 nmol/mg protein in G3, G4, and G5. These changes represented reductions of 14.73%, 31.01%, and 52.71%, respectively. Thus, the 4% preventive regimen produced the greatest improvement in both oxidative indices. The reduction in PC exceeded that observed for MDA, suggesting substantial protection against protein oxidation under the present conditions. The overall response is consistent with previous evidence that GA can attenuate cisplatin-induced renal injury and lipid peroxidation [57] and reduce oxidative damage in renal disease models [55].

The therapeutic groups showed a similar but less pronounced pattern. MDA values were 9.04, 8.10, and 7.68 $\mu\text{mol/mg}$ protein in the corresponding 2%, 3%, and 4% GA groups, whereas PC values were 0.114, 0.093, and 0.071 nmol/mg protein. Compared with G2, preventive administration therefore produced greater reductions in MDA at every concentration. The same trend was observed for PC. At 4% GA, PC reduction reached 52.71% with prevention compared with 44.96% with treatment. These findings indicate that GA was more effective when present before the cisplatin challenge. The temporal difference is biologically plausible because cisplatin-induced oxidative injury begins rapidly, with early glutathione depletion and mitochondrial dysfunction preceding extensive macromolecular oxidation. Pretreatment may therefore preserve the cellular redox environment before irreversible damage develops, whereas post-treatment must act after oxidative injury has already occurred [9,71].

The response associated with concentration further proves that there is a gradual increase in protection with the tested concentrations. Increase in GA concentrations from 2% to 4% gradually caused a reduction in the levels of MDA and PC. The most significant results were obtained at the 4% concentration level. The findings agree with earlier findings on the effect of GA in the attenuation of oxidative and inflammatory injuries in renal disease. In the adenine-induced chronic renal failure model, GA has been found to reduce oxidative and inflammatory injuries and improve renal injury markers [55]. GA has also been linked to a reduction in plasma MDA levels and increased total antioxidant capacity [26,33]. In the present study, the stronger response of the 4% groups should nevertheless be regarded as the best observed response within the tested range rather than proof of a linear dose-response relationship.

The mechanism of protection mediated by GA most likely cannot be limited to direct ROS neutralization alone. GA is a complex polysaccharide which contains fractions of arabinogalactan and arabinogalactan-protein and which possesses antioxidant, anti-inflammatory, and cytoprotective properties [26]. The mechanism of renal protection by GA is most likely associated with maintenance of endogenous antioxidant system and

suppression of inflammatory amplification process. Contribution of the gut-kidney axis to the beneficial effect of GA cannot be excluded. Being an indigestible soluble polysaccharide, GA is capable of being fermented in the intestine and affecting short-chain fatty acids synthesis, composition of intestinal microflora, integrity of intestinal barrier and systemic redox balance [74]. These mechanisms have not been directly investigated in the current experiment.

The results of oxidative damage are also in agreement with the effects of antioxidant enzymes shown in this study. The increased levels of MDA and PC along with

the decrease in the activities of GPx, SOD, and CAT following cisplatin administration indicate that oxidative stress occurs due to excess production of ROS along with decreased endogenous antioxidant defense. The results of the decreased levels of MDA and PC due to GA treatment show a biological effect of improved antioxidant status seen in Table 5. Similarly, the reduced oxidative damage is in line with the improvement in the markers of renal functions shown in Table 4. This concordance among oxidative damage, antioxidant defenses, and renal function supports a coherent renoprotective response rather than an isolated change in a single biochemical marker.

Table 6. Effects of 30 days of gum arabic (GA) treatment and pretreatment on renal oxidative stress in cisplatin-induced kidney injury

Value	G1 Normal control)	G2 Model control (Nephrotoxicity)	Prevention (GA concentration)			Treatment (GA concentration)		
			G3 (2%)	G4 (3%)	G5 (4%)	G6 (2%)	G7 (3%)	G8 (4%)
			Renal malondialdehyde (MDA, $\mu\text{mol}/\text{mg}$ protein)					
Mean	5.13 ^d	10.16 ^a	8.56 ^{ab}	7.74 ^{bc}	6.89	9.04 ^a	8.10 ^b	7.68 ^c
SD	0.78	0.90	0.39	0.44	0.66	0.55	0.71	0.76
% of change	0.00	+98.05	-15.75	-23.82	-32.18	-11.02	-20.28	-24.41
			Renal protein carbonyl (PC, nmol/mg protein)					
Mean	0.043 ^e	0.129 ^a	0.110 ^{ab}	0.089 ^{bc}	0.061 ^d	0.114 ^a	0.093 ^b	0.071 ^{cd}
SD	0.009	0.011	0.005	0.003	0.008	0.007	0.009	0.006
% of change	0.00	+200.00	-14.73	-31.01	-52.71	-11.63	-27.91	-44.96

Data are presented as the mean $\pm$ SD for six animals per group ($n = 6$). Values within the same row that are followed by different superscript letters differ significantly at $p \leq 0.05$. The experimental groups were designated as follows: G1, normal control (healthy untreated rats); G2, model control (cisplatin-induced kidney injury without treatment); GA, gum arabic. G3–G5 were the preventive groups, in which rats received gum arabic at dietary levels of 2, 3, and 4 g/100 g diet, respectively, before cisplatin administration. G6–G8 were the therapeutic groups, in which gum arabic was administered at the same dietary levels after cisplatin treatment. The percentage change (%) for the model control group was calculated relative to the normal control group, whereas the percentage change for the gum arabic-treated groups was calculated relative to the model control group.

3.7. Association of Oxidative Stress with Hepatic and Renal Dysfunction

Table 7 shows a consistent association between oxidative stress and hepatorenal dysfunction after cisplatin exposure. MDA correlated positively with AST ($r = +0.6058$), ALT ($r = +0.6499$, $P \leq 0.05$), ALP ($r = +0.6638$, $P \leq 0.05$), urea ($r = +0.8150$, $P \leq 0.01$), and creatinine ($r = +0.7737$, $P \leq 0.01$), but negatively with albumin ($r = -0.7134$, $P \leq 0.05$). Similarly, PC correlated positively with AST ($r = +0.5884$), ALT ($r = +0.6138$), ALP ($r = +0.6097$), urea ($r = +0.7804$, $P \leq 0.01$), and creatinine ($r = +0.7640$, $P \leq 0.05$), but negatively with albumin ($r = -0.6275$). In contrast, MDA/uric acid ($r = +0.6211$) and PC/uric acid ($r = +0.5723$) were weaker and non-significant. These findings indicate that lipid and protein oxidation closely accompany hepatic and renal dysfunction, consistent with cisplatin-induced ROS generation, mitochondrial injury, membrane damage, and apoptosis [59,60,69,75,76,77].

The strongest associations were inverse correlations of MDA with GPx ($r = -0.8623$, $P \leq 0.01$), SOD ($r = -0.8217$, $P \leq 0.01$), and CAT ($r = -0.7946$, $P \leq 0.05$), and of PC with GPx ($r = -0.8233$, $P \leq 0.01$), SOD ($r = -0.8340$, $P \leq 0.01$), and CAT ($r = -0.7521$, $P \leq 0.05$). This pattern indicates that increasing oxidative damage was accompanied by depletion of antioxidant defenses, supporting a redox imbalance caused by excessive ROS

production [76,78]. The particularly strong MDA–GPx and PC–GPx relationships further emphasize the role of glutathione-dependent detoxification in controlling lipid and protein oxidation.

Table 7. Association of oxidative biomarkers, liver function, enzymatic antioxidant and kidney function in cisplatin-induced kidney injury rats following treatment and pretreatment with gum arabic (GA)

Parameters	<i>R</i>	Parameters	<i>r</i>
MDA/ AST	+ 0.6058	PC/ AST	+ 0.5884
MDA/ ALT	+ 0.6499*	PC/ ALT	+ 0.6138
MDA/ ALP	+ 0.6638*	PC/ ALP	+ 0.6097
MDA / Alb	- 0.7134*	PC / Alb	- 0.6275
MDA/GPx	- 0.8623**	PC/GPx	- 0.8233**
MDA/SOD	- 0.8217**	PC/SOD	- 0.8340**
MDA/CAT	- 0.7946*	PC/CAT	- 0.7521*
MDA/Urea	+ 0.8150**	PC/Urea	+ 0.7804**
MDA/Creatinine	+ 0.7737**	PC/Creatinine	+ 0.7640*
MDA/ Uric acid	+ 0.6211	PC/ Uric acid	+ 0.5723

* $P \leq 0.05$ ** $P \leq 0.01$

These correlations, in total, demonstrate the interconnectedness of an oxidative mechanism involved in the pathophysiology of cisplatin-induced hepatorenal damage. Pretreatment and treatment with GA could interrupt this cascade due to the preservation of endogenous antioxidant defense systems and minimization

of oxidative and inflammatory insult. GA has been shown to enhance SOD, CAT, and GPx activities, decrease the level of MDA, and improve hepatic markers as well as decrease the levels of urea and creatinine and protect kidneys from oxidative damage [79]. In addition, the protection from cisplatin toxicity provided by GA has been demonstrated through the restoration of antioxidant system and lowering the level of MDA [80]. GA may exert its protective effects not through the direct scavenging of radicals, but via a more complex regulation of redox reactions and inflammatory responses [55,56]. Thus, pretreatment may provide additional protection by maintaining antioxidant capacity before cisplatin-induced ROS generation [80].

3.8. Effects of Gum Arabic on the Histopathological Examination of Kidneys in Cisplatin-Induced Kidney Injury

The effects of gum arabic (GA) on the histopathological changes in cisplatin-induced kidney injury are presented in Figure 1. The kidneys of G1 showed normal renal architecture, with preserved cortical and medullary structures (Photo 1). In contrast, G2 showed severe renal lesions, including tubular necrosis, extensive inflammatory-cell infiltration, focal interstitial nephritis, vascular congestion, and tubular epithelial vacuolar degeneration (Photos 2–4). These findings confirm the successful induction of marked cisplatin-associated renal injury. Cisplatin preferentially damages renal tubular epithelial cells through intracellular accumulation, mitochondrial dysfunction, oxidative stress, DNA damage, and inflammatory activation [9,52,54,81].

The extensive tubular and interstitial lesions in G2 also indicate a strong inflammatory component. Tubular injury can release damage-associated signals that activate inflammatory pathways and promote cytokine production and inflammatory-cell recruitment. Oxidative stress can further amplify this response through redox-sensitive signaling. Vascular congestion may reflect associated microvascular dysfunction and impaired renal perfusion, which can aggravate tubular hypoxia and cellular injury [52,70,81]. Thus, the combined lesions observed in G2 are consistent with the complex interaction between oxidative, inflammatory, mitochondrial, and vascular mechanisms in cisplatin nephrotoxicity.

The effects of GA administration on these pathological changes were clearly seen as attenuation. The preventive groups fed with 2, 3, and 4 g/100 g diet (G3–G5) exhibited primarily tubular vacuolar degradation, with a few instances of focal necrosis and inflammatory-cell infiltration being most apparent in G3 (Photos 5–7). The therapeutic groups that were fed the same dose of diet both before and after exposure to cisplatin (G6–G8)

exhibited further improvement in structure. G6 had a few tubules with necrosis in a focal area, while G7 had a few tubules with necrosis and a few regenerated tubules with vacuolation in the area, and G8 had only focal tubular epithelial vacuolar degeneration (Photos 8–10). Overall, the results suggest a transition from a broad necroinflammatory injury and into tubular preservation and repair following the administration of GA.

The observed improvement is in line with the antioxidant and anti-inflammatory effects of GA reported. Cisplatin nephrotoxicity is known to be linked to increased ROS generation and is involved in lipid peroxidation, mitochondrial dysfunction, damage to the membranes and damage to the DNA and tubular cell death. So, limiting oxidative stress may help prevent it from progressing from reversible epithelial injury to irreversible necrosis [52,54,81]. GA has been reported to exert beneficial effect on the oxidative balance and inflammatory responses in experimental renal injury and hence is suggested to aid in maintaining tubular integrity under nephrotoxic conditions [26,55,82].

The present results are in line with those of Al-Majed et al., [57] who directly studied the effect of oral Arabic gum in cisplatin-induced nephrotoxicity in rats. They found that they decreased the cisplatin-induced lipid peroxidation. This suggests a plausible mechanism as to why less tubular damage occurred in the present study. Notably, their findings did not suggest 'total' prevention of all changes associated with cisplatin. Therefore, the main effect of GA is likely to be in decreasing the downstream oxidative injury, not to stop the primary effects of cisplatin. This interpretation is supported by the remaining vacuolar degeneration seen in some treated groups [57].

Evidence from other renal injury models further supports this interpretation. Al-Majed et al., [83] reported protective effects of oral Arabic gum against gentamicin-induced nephrotoxicity. Ali et al. [55] also demonstrated reduced oxidative stress and inflammation following GA administration in adenine-induced chronic renal failure. These findings suggest that the renoprotective activity of GA is not limited to a single nephrotoxic model. Rather, it may involve broader modulation of oxidative and inflammatory processes [55,83].

Additional morphological evidence of recovery is provided by the appearance of regenerated tubules in G6, G7. Acute tubular injury can cause the remaining epithelial cells to regenerate and rebuild defective portions of the tubule if the tissue architecture is preserved. Consequently, the predominance of necrosis in G2 and predominantly degenerative/regenerative changes in the treated groups may suggest a shift from active necrosis to repair [52,81]. This is of special therapeutic interest as it indicated that GA could be useful for renal recovery after cisplatin exposure.

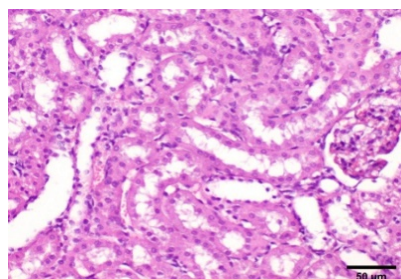


Photo 1. Group 1 showing the normal histological structure of renal parenchyma.

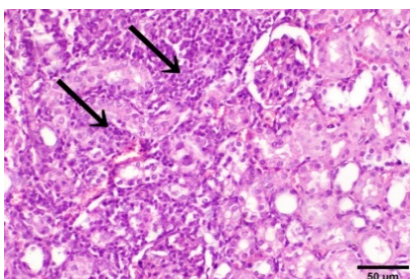


Photo 2. Group 2 showing necrosis of renal tubules associated with massive inflammatory cells infiltration (black arrow).

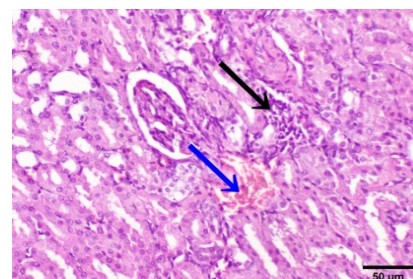


Photo 3. Group 2 showing focal interstitial nephritis (black arrow) and congestion of renal blood vessel (blue arrow).

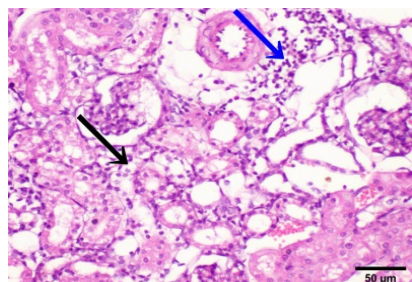


Photo 4. Group 2 showing vacuolar degeneration of epithelial lining renal tubules (black arrow) associated with focal inflammatory cells infiltration (blue arrow).

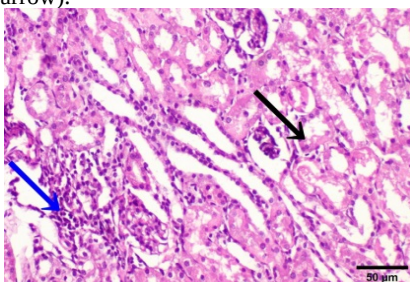


Photo 5. Group 3 showing vacuolar degeneration of epithelial lining some renal tubules (black arrow) and focal necrosis of renal tubules associated with inflammatory cells infiltration (blue arrow).

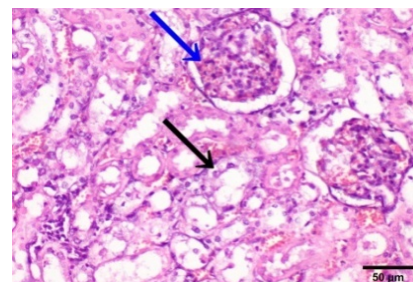


Photo 6. Group 4 showing vacuolar degeneration of epithelial lining some renal tubules (black arrow) and congestion of glomerular tuft (blue arrow).

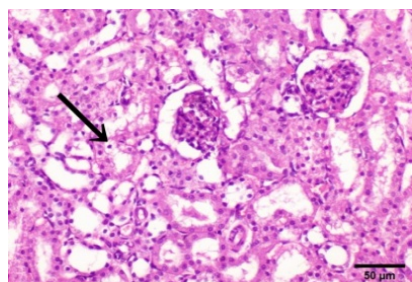


Photo 7. Group 5 showing vacuolar degeneration of epithelial lining some renal tubules (black arrow).

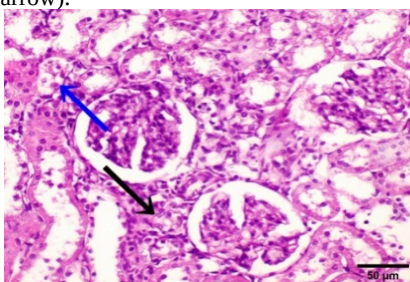


Photo 8. Group 6 showing focal vacuolated regenerated renal tubules (black arrow) and necrosis of sparsely renal tubule (blue arrow).

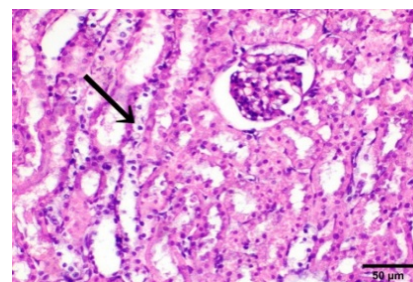


Photo 9. Group 7 showing vacuolar degeneration of epithelial lining some renal tubules (black arrow).

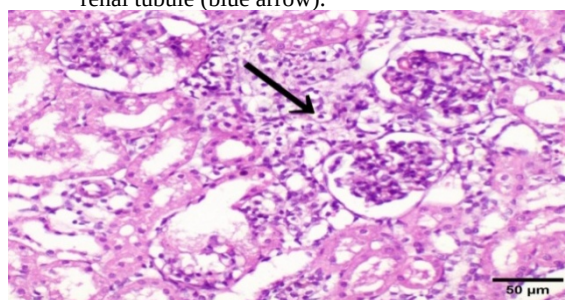


Photo 10. Group 8 showing focal vacuolated regenerated renal tubules (black arrow).

Figure 1. Effects of gum arabic on Histopathological examination of kidneys in cisplatin-induced kidney injury (H & E stain, scale bar 50μm).

The experimental groups were designated as follows: G1, normal control (healthy untreated rats); G2, model control (cisplatin-induced kidney injury without treatment); GA, gum arabic. G3–G5 were the preventive groups, in which rats received gum arabic at dietary levels of 2, 3, and 4 g/100 g diet, respectively, before cisplatin administration. G6–G8 was the therapeutic groups, in which gum arabic was administered at the same dietary levels after cisplatin treatment.

The preventive and therapeutic findings should, however, be interpreted without assuming a definitive dose-response relationship. Although GA was administered at 2, 3, and 4 g/100 g diet, the present histopathological observations are qualitative. Therefore, the apparent differences among dose levels cannot establish superiority of one dose without a standardized histopathological score and statistical analysis. Nevertheless, the overall reduction in necrosis and

inflammatory changes, together with the appearance of regenerated tubules, supports a beneficial morphological effect of GA.

The proposed mechanism may involve coordinated antioxidant and anti-inflammatory actions. GA may reduce oxidative damage and thereby decrease redox-sensitive inflammatory signaling. This could limit secondary tissue injury and facilitate tubular repair. Recent evidence has linked GA-mediated renoprotection

with improved cellular redox balance and modulation of inflammatory pathways, including NF- κ B-related signaling and kidney injury molecule-1[84] (Habashy and Abu-Serie, 2024). Although that study used carbon tetrachloride rather than cisplatin, its findings provide mechanistic support for the present interpretation.

In general, severe tubular and interstitial damage was observed in G2 animals following cisplatin treatment, while GA at 2, 3 and 4 g/100 g diet resulted in significantly less damage in both preventive and therapeutic groups. The transition from tubular necrosis, inflammation and vascular congestion to limited vacuolar degeneration and tubular regeneration suggests the reduction of renal injury and progression towards tissue recovery. The results of this study are in agreement with previous evidence which demonstrated antioxidant and anti-inflammatory properties of GA, such as the direct study of Al-Majed et al., [57]. But the continued vacuolar degeneration suggests that only partial protection has been afforded by GA. A quantitative histopathological rating, along with renal function, oxidative-stress, inflammatory and kidney injury biomarkers, will further elucidate the extent and underlying mechanisms of this protective effect.

4. Conclusion

The present study demonstrated that cisplatin induced marked acute kidney injury in rats, as evidenced by impaired growth performance, increased kidney weight, elevated serum urea, creatinine, and uric acid, reduced renal GPx, SOD, and CAT activities, and increased lipid and protein oxidation. Cisplatin exposure also caused hepatic biochemical disturbances, anemia, thrombocytopenia, and severe renal histopathological lesions, including tubular necrosis, inflammatory-cell infiltration, vascular congestion, and tubular degeneration. Gum Arabic (GA) administration significantly attenuated most of these abnormalities, improving renal function, antioxidant defenses, oxidative-stress status and hepatic biomarkers, while markedly reducing renal tissue damage. The protective effects were generally more pronounced with preventive administration than with therapeutic treatment, suggesting that GA is more effective when present before cisplatin-induced injury develops. Among the tested concentrations, 4% GA showed the most consistent overall protective response, particularly in renal-function biomarkers, antioxidant enzymes, oxidative-stress markers and histopathological findings. The observed correlations between oxidative stress, renal dysfunction and hepatic alterations, and further support the important role of oxidative imbalance in cisplatin-induced toxicity. Overall, the findings indicate that GA possesses promising preventive and therapeutic renoprotective properties, likely through complementary antioxidant, anti-inflammatory, metabolic and systemic mechanisms. Further studies are recommended to clarify its molecular mechanisms, determine the optimal dose and treatment duration, assess additional inflammatory and molecular biomarkers, and confirm its safety and efficacy in clinical settings as a complementary approach for reducing cisplatin-induced nephrotoxicity.

Conflict of Interest

The authors declare that they have no financial, personal, or professional conflicts of interest related to this research. They further confirm that no competing interests exist that could have influenced the conduct of the study or the publication of this manuscript.

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Authors' Contribution

Yousif Elhassaneen was responsible for developing the study design and methodology, supervising the experimental work, and ensuring the reliability and accuracy of the collected data. He contributed to drafting the manuscript, critically reviewing and revising its content to strengthen its scientific quality and coherence, and approving the final version for submission and publication. Asmaa Bioumy contributed to the supervision and monitoring of the experimental activities. She participated in reviewing the relevant scientific literature, developing and refining the research concept, and contributing to the preparation of the initial manuscript draft. Esraa Badawy conducted the experimental procedures and was responsible for collecting, organizing, analyzing, and presenting the resulting data. She also contributed to the literature review, conceptualization of the research, and preparation of the initial manuscript draft.

Abbreviations

AA, antioxidant activity; Abs, absorbance; AKI, acute kidney injury; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BWG, body weight gain; CAT, catalase; CKD, chronic kidney disease; FI, FER, feed efficiency ratio; fed intake; GPx, glutathione peroxidase; MDA, malonaldehyde; PC, protein carbonyl; ROS, reactive oxygen species; SOD, super oxide dismutase ; TBA, thiobarbituric acid.

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