Research Article

# Gum Arabic Mitigates AlCl3-Induced Nephrotoxicity by Upregulating the XRCC1 Gene and Downregulating Ki67 and P53 Expressions


## Abstract

The kidney is an important organ for the elimination of waste products. However, insults to the kidney arising from the effects of reactive oxygen species could limit its functions. This study evaluated the nephroprotective effects of Gum Arabic, an FDA-approved edible fiber against aluminum chloride (AlCl3)-induced nephrotoxicity in rats and its impact on XRCC1 gene expression and Ki67 and p53 immunoreactivity. Twenty male Wistar rats were divided into four groups of five (n = 20). In Group 1, there was no intervention for the control group. A 5-mg/kg intraperitoneal (IP) $AlCl_3$ dosage was administered to Group 2 throughout a 2-week period. Gum Arabic (GA) extract was administered orally to Group 3 for 4 weeks at a dose of 500 mg/kg body weight. Group 4 received an IP dose of $AlCl_3$ at 5mg/kg body weight for 2 weeks followed by a 500 mg/ kg body weight oral dose of GA extract for 4 weeks. The following variables were evaluated: body weight, relative kidney weight, serum urea, uric acid, tissue oxidative stress, ERCC1 gene expression, kidney histology, and Ki67 and p53 immunoreactivity. The findings demonstrated that giving rats AlCl3 reduced the amount of SOD, and GSH in their kidneys and caused alteration in the kidney tissue histoarchitecture, while also increasing the serum levels of urea, tissue lipid peroxidation, and Ki67 and p53 positive immunoreactivity. Interestingly, GA treatment following AlCl3 administration to rats mitigated these changes. Taken together, this study showed the capacity of Gum Arabic as a nephroprotective agent against AlCl3-induced nephrotoxicity.


**Keywords:** *Nephrotoxicity, Immunoreactivity, Reactive oxygen species, Medicinal plant, Nephrotoxicants*


**Dalia Mostafa Mohammed Domiaty[1*]**

*[1]Department of Biology, College of Science, University of Jeddah, Jeddah, Saudi Arabia.*


## Introduction

The kidney is a pair of complex bean-shaped organs that is a part of the renal system. The kidney is made up of millions of functional cells called nephron that helps in the filtration of blood, elimination of metabolic waste products, production of hormones, and maintenance of the homeostasis of body fluids.[1-4] However, nephrotoxicity sets in when there is a fast deterioration in the function of the kidney as a result of medications (drugs), chemicals, and industrial or environmental toxic agents known as nephrotoxicants or nephrotoxins.[5, 6] Some of these nephrotoxicants could be aminoglycoside antibiotics, for example. Others include moulds, fungi, cisplatin, lead, arsenic, mercury, and cocaine.[7] Changes in the concentration of several parameters such as urine output, glomerular filtration rate, blood urea nitrogen, and serum creatinine are utilized as indicators for nephrotoxicity. However, some nephrotoxicants can cause kidney injury without changing some of these listed biomarkers.[7] Since kidney damage can occur without any changes in the previously established biomarkers, other studies on nephrotoxicity have concentrated on the biochemical and molecular causes of kidney toxicity, oxidant-induced injury, transporters, and bioactivation.[8-10]

Aluminum Chloride is a yellowish, crystalline powder that is used as a chemical intermediate for Aluminium compounds. It is one of the chemicals listed as a risky substance by the Agency for Toxic Substances and Disease Registry.[8]

Humans are exposed to Al regularly because of their presence in the environment. Aluminum is present in foods like yellow cheese, corn, grain products, and vegetables; it can also be found in cosmetics, cooking utensils, and containers. It is also used for the purification of water.[11] Aluminum and its compound ($AlCl_3$) are also used in pharmaceutical companies in the production of drugs like



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***Address for correspondence:***
*Dalia Mostafa Mohammed Domiaty,*
*Department of Biology, College of Science, University of Jeddah, Jeddah, Saudi Arabia.*
*E-mail: ddomiaty@uj.edu.sa*

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vaccines, injectable allergens, phosphate binders, aspirin, and antacids.[11, 12] Al gets into the body through the gastrointestinal and respiratory tracts and is excreted through the urine and when consumed, it can lead to retention in the kidney and induce nephrotoxicity.[11] $AlCl_3$ toxicity has been reported to cause degeneration of the renal tubular cells by increasing the production of ROS thereby causing oxidative stress to cells, lowering the concentration of GSH in cells, and DNA oxidative deterioration.[11, 12] Some of the toxic effects of aluminum and its compounds include microcytic hypochromic anemia, hepatotoxicity, genotoxicity, and Alzheimer's disease.[12]

Gum Arabic (Acacia Gum) is an ingestible biopolymer that is gotten from the stems of the Acacia trees (*Acacia Senegal, Acacia seyal, and Acacia nilotica*).[13] The leguminous tree is widely distributed in Africa and Asia[14] and is safe for consumption by the United States, Food and Drug Administration.[15] The phytochemical content of Gum Arabic includes carbohydrates, tannins, alkaloids, saponins, flavonoids, cardiac glycosides, and terpenoids.[14] Gum Arabic has always been applied in the treatment of numerous medical conditions. Gum Arabic has been used to alleviate the negative effects of nephrotoxicity by increasing creatinine clearance, improving renal excretion, and decreasing plasma urea and phosphate, proteinuria, and glucosuria. Its extract has been reported to help in the reduction of blood pressure and plasma cholesterol. It has antioxidant properties that protect against ROS, and it is used as a medication for diarrhea.[13]

The X-ray repair cross-complementing 1 (XRCC1) is a gene located on chromosome 19 that encodes a protein that helps in the repairing of single-strand breaks and oxidative DNA damage as a result of exposure to ionizing radiation and alkylating agents.[16] Polymorphisms in ERCC1 have been associated with modifications in the DNA repair pathway that have been shown to impact nephron healing following injury.[17, 18] Studies have demonstrated that nucleotide excision repair genes aid in the removal of lesions that alter the DNA helix structure and that DNA repair mechanisms play a function in renal cells during cisplatin-induced nephrotoxicity.[19] In this study, we assessed the nephrotoxicity of $AlCl_3$ in rats and its impact on the DNA repair potentials of XRCC1. In addition, we evaluated the ameliorative potentials and Gum Arabic mode of action on $AlCl_3$-induced nephrotoxicity in rats.

## Materials and Methods

### Plant material

Gum Arabic was purchased from a market for herbal and traditional medicines in Jeddah, Saudi Arabia, and then ground into powder form using a blender. In order to make gum Arabic extract, 10 g of this material was dissolved in 100 ml of distilled water. Filtered, concentrated to 8.5 mg/ml of Gum Arabic extract, and stored at 4 °C until use.

### Animals

Male Wistar rats weighing between 150 and 250 grams were bought from the King Fahd Medical Research Center at King Abdulaziz University in Jeddah, Saudi Arabia. The animals were given a lab animal food and free access to water while they adjusted to the environment for one week (12hr/12hr light on/off). This animal experiment was approved by the ethics committee of King Abdulaziz University College of Medicine.

### Chemicals

Aluminum chloride (AlCl3) was from Sigma-Aldrich in the USA. The highest grades were used for all other compounds.

### Experimental design

Following acclimation, rats were divided into four groups (n = 5) at random and treated as follows:

**Group 1 (Control):** the control group was untreated.

**Group 2 ($AlCl_3$):** This group received an intraperitoneal (IP) dose of $AlCl_3$ at 5mg/kg body weight for two weeks.

**Group 3 (GA):** For four weeks, animals in this group were given an oral dose of an extract of Gum Arabic (GA) at a dose level of 500 mg/kg body weight.

**Group IV ($AlCl_3$ + GA):** In this group, GA extract was administered orally for four weeks after receiving an IP dosage of $AlCl_3$ at a dose level of 5 mg/kg body weight for two weeks.

Following the experimentation time, the animals had their food withheld overnight, and they were then put to sleep while being given diethyl ether anesthesia. The kidneys were then taken out, cleaned in regular saline, and weighed. Blood was then taken from the aorta in the abdomen. Parts of the kidney were either preserved at -80 C for RNA extraction or stored in 10% buffered formalin for histology and immunochemistry studies. The remaining half was homogenized at 14,000 rpm for 30 min in 100 mM phosphate buffer, pH 7.4.

### Quantification of serum kidney function biomarkers

Using a commercial kit from (Diagnostic System Laboratories Inc., USA), the serum concentrations of urea and uric acid were measured according to the manufacturer's guidelines.

### Quantification of kidney tissue antioxidant level

The supernatant obtained after centrifugation was used to assess the amounts of catalase (CAT) and superoxide dismutase (SOD) in the kidney tissues using a commercial kit (MyBioSource, Califonia, USA), according to the manufacturer's instructions.

### Quantification of kidney levels of glutathione and tissue antioxidant level

For this, a commercial kit (MyBioSource, California, USA) was used to measure the concentrations of glutathione (GSH) and malondialdehyde (MDA) in the supernatant obtained following centrifugation at 14,000 rpm.

### RNA: Extraction and Real-time quantitative PCR (RT-qPCR)

First, using a (QIAgen RNeasy mini kit, cat # 74104), total

RNA was extracted from the kidneys in accordance with the manufacturer's instructions. The M-MLV Reverse Transcriptase System (Promega, USA) was used to create cDNA from 200ng of the isolated RNA, and the following components were added to the qPCR reaction: 3 mL cDNA, 0.5 mL (500 nM) right and left primers, 1 mL filtered water, and 3 mL SYBR Green Master Mix (Applied Biosystems, USA). **Table 1** below lists the primer sequences that were employed. The 2 $^{-\Delta\Delta CT}$ method was used to measure the relative mRNA expression and was normalized to the expression of (GAPDH).

**Table 1. Primer sequences**

| Primers | Primers sequence (5`-3`) |
|---|---|
| XRCC1 - left | 5'-TTCACAGCCCTCCAGACAAAG-3' |
| XRCC1 right | 5'-CGGAACTGGCCGAGCTT-3' |
| GAPDH - left | 5'-GAT GGT GAA GGT CGG TGT G-3' |
| GAPDH -right | 5'-ATG AAG GGG TCG TTG ATG G-3' |

### Histopathology

The kidney tissue was fixed in 10% buffered formalin and then embedded in paraffin wax after being dried out in graded ethanol for a day at room temperature. Hematoxylin and eosin (H&E) were used to stain the thin sections of tissue blocks that had been sliced into tissue blocks in order to assess histopathological changes. 400x magnification light microscope photographs of stained kidney slices were obtained.

### Immunohistochemistry analysis

Immunohistochemical analysis was done for anti-Ki67 and p53 antibodies using streptavidin-biotin. The kidney sections of a thickness of 5 µm and at room temperature were deparaffinized followed by incubation in hydrogen peroxide (0.3%) prepared in methanol for half an hour. The kidney sections were incubated with anti-Ki67 and anti-p53 antibodies at a dilution of 1:100 respectively followed by counterstaining with hematoxylin and eosin.

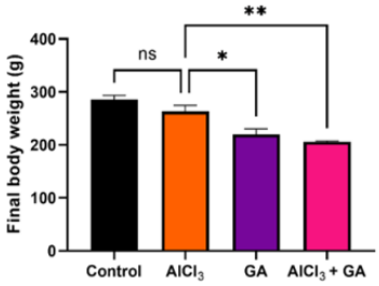
### Statistical analysis

One-way ANOVA was used for the statistical analysis for this study, and the data are shown as mean SEM. Dunnett's multiple comparisons test was used to compare means, and a significance level of $p < 0.05$ was chosen.

## Results and Discussion

### Effects of $AlCl_3$ and GA on final body weight and relative kidney weight

Several previous studies have shown that $AlCl_3$ is a toxic compound. Firstly, we examined the effect of this compound and the corresponding treatment with GA on the final body weight and relative kidney weight of rats. The findings from this study demonstrated that the administration of $AlCl_3$ to rats did not significantly alter their weight in comparison to the control group **(Figure 1a)**. In contrast to the animals given $AlCl_3$, rats given GA displayed a substantial ($p < 0.05$) change in body weight. Additionally, when animals were given GA after being given $AlCl_3$, their body weights were significantly reduced ($p < 0.01$) in comparison to rats who just received $AlCl_3$ **(Figure 1a)**. Furthermore, our findings demonstrated that relative kidney weights were similar across all experimental groups **(Figure 1b)**.

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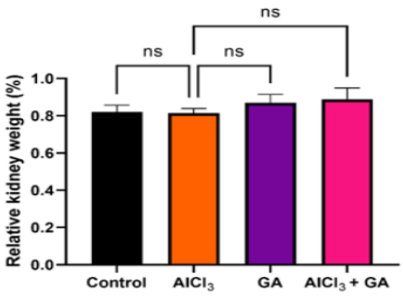


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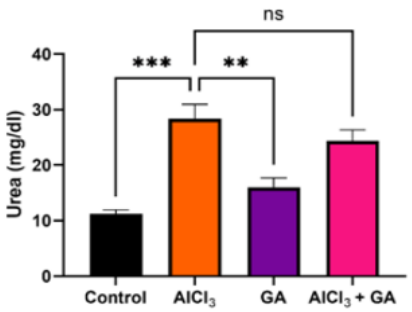
**Figure 1. Effects of $AlCl_3$ and GA on the final body weight and relative kidney weight. a) final body weight. b) relative kidney weight**

### Effects of $AlCl_3$ and GA on serum kidney function biomarkers

Next, this study examined the effects of $AlCl_3$ and GA on urea and uric acid, two serum kidney function biomarkers. Rats treated with $AlCl_3$ have considerably greater urea contents than untreated rats in the control group ($p < 0.001$). A similar outcome was seen in the urea content of the animals in the GA-only treated group, who had considerably ($p < 0.01$) lower urea content than those who had received $AlCl_3$ **(Figure 2a)**. Additionally, although not significantly lower than the rats treated with $AlCl_3$ alone, the animals treated with $AlCl_3$ after receiving $CCl_4$ demonstrated a 14% reduction in serum urea levels **(Figure 2a)**. Additionally, our findings showed that the serum uric acid levels of all the animals were essentially the same **(Figure 2b)**.

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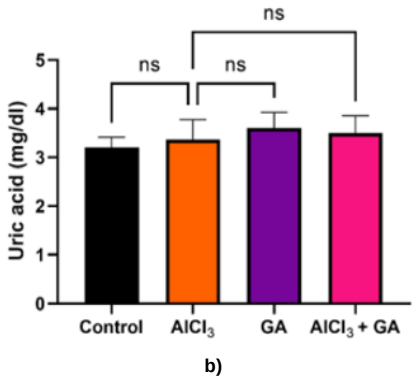


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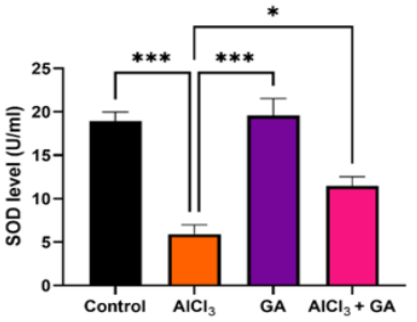
**Figure 2. Effects of $AlCl_3$ and GA on serum kidney function biomarkers. a) Urea, b) uric acid**

## Effects of $AlCl_3$ and GA on kidney tissue antioxidant level

Next, the activity of the kidney's enzymes of catalase (CAT) and superoxide dismutase (SOD) was investigated in this study in relation to $AlCl_3$ and GA. As can be shown in **Figure 3a**, and as was predicted, animals given $AlCl_3$ have considerably lower SOD activity than the control group's untreated animals and the animals given GA, respectively ($p < 0.001$). Interestingly, the treatment of animals with GA following $AlCl_3$ administration, resulted in a significant rise in the SOD activity when compared with $AlCl_3$-only administered animals **(Figure 3a)**. Furthermore, our results revealed that the catalase activity in all the experimental groups was similar **(Figure 3b)**.

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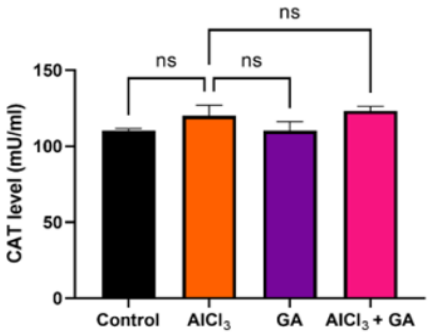


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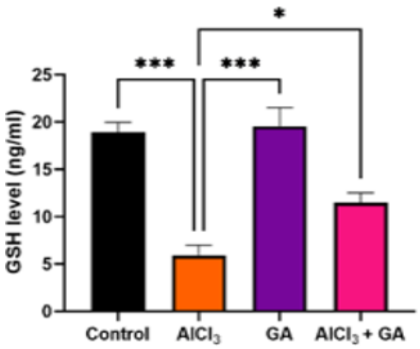
**Figure 3. Effects of $AlCl_3$ and GA on kidney tissue antioxidant level. a) superoxide dismutase, b) catalase**

## Effects of $AlCl_3$ and GA on tissue GSH and MDA levels and the expression of XRCC1 gene

The study then looked at how $AlCl_3$ and GA affected tissue antioxidant levels and XRCC1 gene expression levels. Rats that received $AlCl_3$ were much less likely to have GSH in their kidneys than untreated animals in the control group or rats that received GA alone ($p < 0.001$) **(Figure 4a)**. Also, the administration of GA to rats after they had been treated with $AlCl_3$, resulted in a considerable rise in the kidney's GSH concentration in comparison to the animals administered with $AlCl_3$. Additionally, compared to the animals in the control group that weren't given any treatment, the MDA level increased noticeably ($p < 0.01$) after $AlCl_3$ treatment to rats **(Figure 4b)**. Animals administered with only GA and those treated with GA following $AlCl_3$ administration showed a 39% and 15% reduction respectively in the MDA content in the kidney in comparison with the $AlCl_3$-only administrated rats. Furthermore, the administration of $AlCl_3$ to rats resulted in a significant downregulation in the XRCC1 gene in comparison to the untreated animals in the control group ($p < 0.005$) and ($p < 0.0001$) when compared to the animals administered with GA only **(Figure 4c)**. Also, the treatment of animals with GA following $AlCl_3$ administration, revealed noticeable overexpression of the XRCC1 gene compared to $AlCl_3$-only administered animals **(Figure 4c)**.

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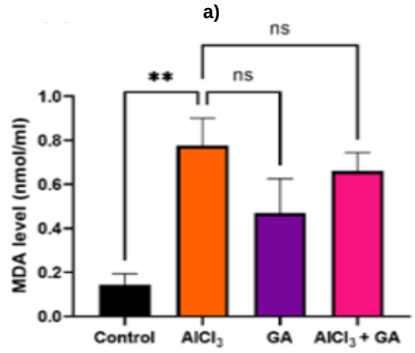


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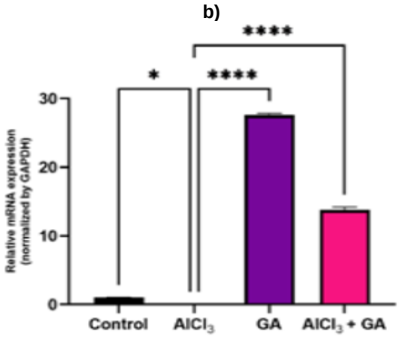


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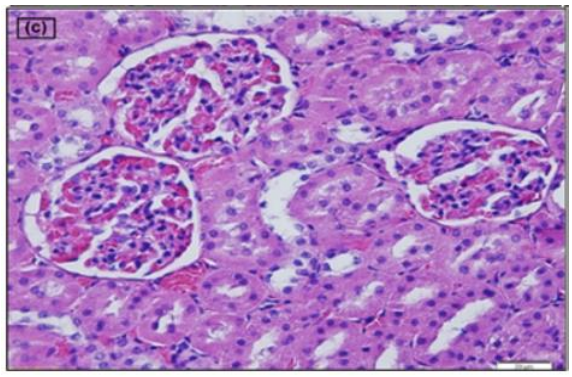
**Figure 4. Effects of $AlCl_3$ and GA on tissue GSH and MDA levels and the expression of XRCC1 gene. a) Tissue glutathione (GSH) level. b) Tissue malondialdehyde (MDA) level. c) Relative XRCC1 gene expression**

### Effects of $AlCl_3$ and GA on the histology of the kidney

On the kidneys' histological architecture, this study looked at how GA therapy and $AlCl_3$ injection impacted it. As shown in **Figure 5** below, rats in the control and the GA-administered groups showed normal kidney architecture devoid of any structural alterations or macrophage infiltration **(Figure 5a and 5c)**. However, the histological examination of the kidney of rats administered with $AlCl_3$ showed mild necrosis, which was accompanied by an increased bowman's space, glomerular capillary degeneration, macrophage infiltration, and thickening of the outer kidney membrane **(Figure 5b)**. After administering $AlCl_3$, treating the rats with GA reduced all structural alterations caused by $AlCl_3$ and returned the kidney histology to normal **(Figure 5d)**.

### Effects of $AlCl_3$ and GA against Ki67 and p53 immunoreactivity

Finally, we examined the effect of $AlCl_3$ and the treatment with GA against the immunoreactivity of markers of active proliferation and apoptosis, Ki67 and p53 respectively. The administration of $AlCl_3$ to rats elicited increased brown positive cells for Ki67 and p53 in the kidney of rats **(Figure 6b and Figure 6c)**. However, the kidney of rats from the control and those administered with GA showed no reactivity against the two markers tested. Interestingly, the rats treated with GA after $AlCl_3$ administration revealed an attenuation of the immunostaining against Ki67 and p53 in comparison to the rats administered with only $AlCl_3$ **(Figure 6d and Figure 6h)**. This demonstrates that GA administration has the potential to decrease proliferation and apoptosis in kidney cells.

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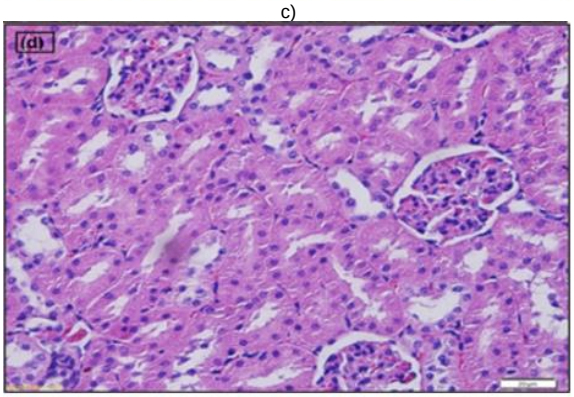
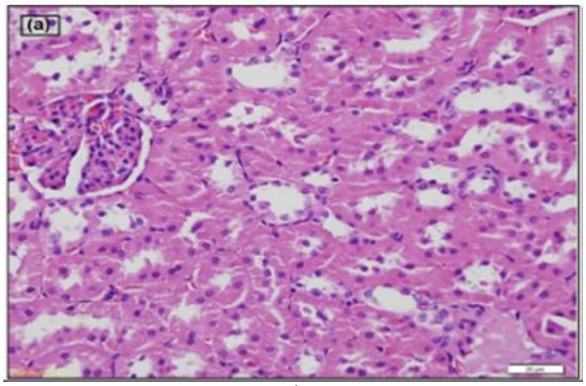



d)

**Figure 5. Effects of $AlCl_3$ and GA on the histological appearance of the kidney. a) Kidney histology from the healthy control group demonstrates normal kidney architecture. b) The kidney of the animals in the group that received $AlCl_3$ revealed mild necrosis and macrophage infiltration. c) The kidney histology of the animals administered with GA showed normal histology. d) The kidney architecture of the $AlCl_3$ + GA treatment group showed improved kidney histology.**

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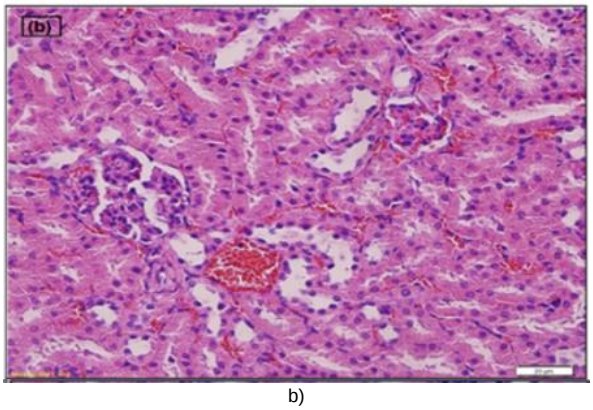


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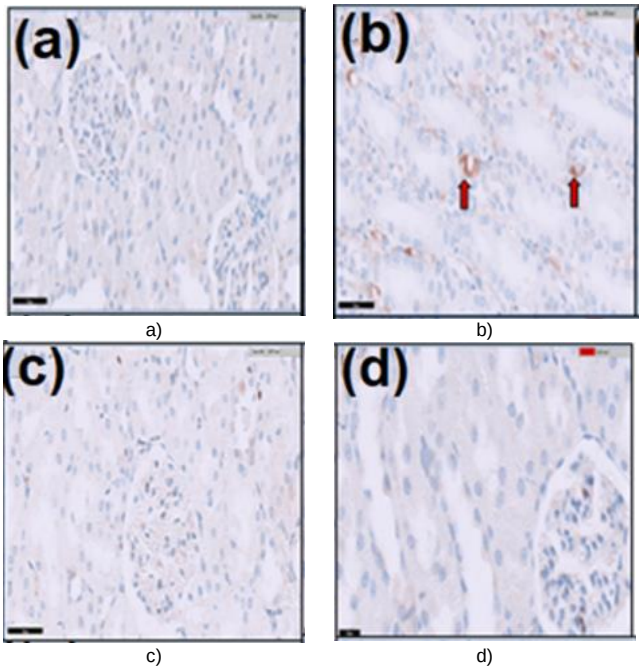


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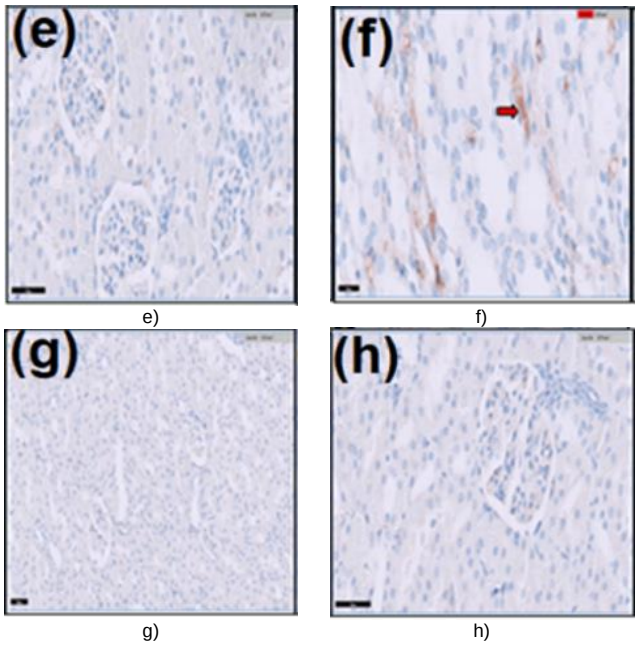


**Figure 6. Effects of $AlCl_3$ and GA against Ki67 and p53 immunoreactivity. a) Immunohistochemistry against Ki67 in the kidney sections of rats in the normal control group showed negative reactivity. b) Immunohistochemistry against Ki67 in the kidney sections of rats administered with $AlCl_3$ showed positive reactivity. c) Immunohistochemistry against Ki 67 for rats administered with GA only showed negative reactivity. d) Immunohistochemistry against Ki67 for $AlCl_3$ + GA group showed negative reactivity. e) Immunohistochemistry against p53 in the kidney section in the normal control group showed negative reactivity. f) Immunohistochemistry against p53 in the kidney sections of the animals in the $AlCl_3$-administered group showed positive reactivity. g) Immunohistochemistry against p53 for GA-only administered group showed no reactivity. h) Immunohistochemistry against p53 for $AlCl_3$ + GA group showing negative reactivity**

Since the kidney is responsible for the excretion of Al and its compound ($AlCl_3$), it is prone to Al toxicity due to the retention of the compound in the kidney.[20] Aluminum is excreted by the kidneys by a variety of mechanisms, such as tubular reabsorption, glomerular filtration, and excretion in the distal tubules.[12]

This present study is aimed at evaluating the nephroprotective effect of Gum Arabic (GA) on $AlCl_3$-induced nephrotoxicity. Our results showed that $AlCl_3$ had no impact on the body and kidney weight of $AlCl_3$-administered rats compared to the control group. These results agree with a similar study by Belaid-Nouira *et. al*.[20] The animals' body weight was significantly reduced by GA in addition to causing a further decrease when administered to the animals previously treated with $AlCl_3$ **(Figure 1)**. This might be due to its potential as a dietary fiber in helping to mediate satiety and improve fat metabolism.[21]

In this study, the serum urea and uric acid levels were assessed as biomarkers for renal damage. The glomerulus filters urea, which is a nitrogenous by-product of amino acids, and the renal tubules reabsorb it before excreting it in urine.[22] Uric acid on the other hand is an end-product of purine metabolism and is usually produced endogenously in the liver, kidneys, intestines, and muscles.[23] A high concentration or production of these biomarkers has been proven to be a sign of renal damage and possibly diseases.[22, 24] According to our results, the $AlCl_3$-treated group's serum urea level rose significantly which was reduced by 14% when GA was administered to the rats. However, the serum uric acid content remained the same in all experimental groups which agree with the study of Al-Kahtani[25] who reported a substantial rise in urea level, and the $AlCl_3$-treated group's uric acid level increased but not significantly.

To further determine the effects of $AlCl_3$ and GA on the kidney, the antioxidant level was assessed since one of the main causes of kidney damage is oxidative stress. The biomarkers that were evaluated included the SOD, CAT, GSH, and MDA.

Superoxide dismutase (SOD) and catalase (CAT) are enzymes that serve as a major form of antioxidant defense against reactive oxidative stress in the body.[26] The inactivity in SOD has been shown to lead to increased kidney dysfunction and apoptosis.[27] In our investigation, we found that $AlCl_3$ significantly decreases the SOD level in the kidney tissue which agreed with the results reported by Al-Kahtani,[25] and Al Dera.[12] However, this decrease in SOD was ameliorated when GA was administered to the $AlCl_3$-treated group. However, there was no significant effect of $AlCl_3$, and GA on the CAT level observed in this study. This study hypothesizes that this may be because of the brief treatment period used in this investigation.

Furthermore, by drastically lowering the GSH content in the kidney tissues and raising the levels of MDA, two crucial oxidative stress biomarkers, $AlCl_3$ produced oxidative stress in the kidney tissue. Glutathione (GSH) is important in reducing the harm caused by ROS and protects biomolecules including DNA from potential cellular damage.[28] An increase in malondialdehyde (MDA) in the kidney, on the other hand, implies an increase in the degradation of kidney tissue phospholipids. However, the changes caused by the treatment with $AlCl_3$ were significantly reversed when GA was administered to the $AlCl_3$-treated group. Additionally, MDA levels were found to be higher and GSH levels to be lower by Al Dera,[12] and Othman *et al*.,[29] and Ahmed *et al*.[30] The results on the effects of GA on SOD, GSH, and MDA provided more understanding of the antioxidant potentials of GA reported in several previous studies.[27, 31]

Base excision repair and the repair of a single-strand break in DNA are both carried out by the X-ray repair cross-complementing 1 (XRCC1) gene. Previous research has demonstrated that numerous kidney illnesses are associated with a reduction in the DNA repair machinery caused by the downregulation of important DNA repair genes.[32] In this study, the administration of $AlCl_3$ caused a significant downregulation of the XRCC1 gene expression, leading to $AlCl_3$ toxicity and ultimately resulting in oxidative DNA damage and impairing the repair of damaged DNA.[33] The upregulation of the XRCC1 gene expression by the administration of GA showed its potential in counteracting the effect of DNA damage by ROS and the subsequent DNA repair of the single-strand break or base excision repair.

Furthermore, the examination of the kidney tissue histology showed that $AlCl_3$ caused necrosis and increased bowman's space, glomerular capillary degeneration, macrophage infiltration, and thickening of the outer kidney membrane. These observations concur with the ones made by Al-Kahtani[25] and Al Dera[12] when they examined the histology of the kidney of animals treated with $AlCl_3$. Interestingly, our assessment of the histology revealed that the administration of GA to $AlCl_3$-treated animals resulted in the amelioration of all the changes caused by the $AlCl_3$ toxicity and further showed the nephroprotective effects of GA.

Ki67 is an antigen (nuclear protein) that is present in all the active phases of the cell cycle. When expressed, it is usually linked with cell proliferation, making it one of the most widely used tumors and cancer markers.[34-36] The p53 gene is a tumor suppressor and plays a critical role in inducing apoptosis.[37] p53 is a recognized marker for DNA damage and cell death in a variety of circumstances. When the kidney cells are subjected to chemical and drug-induced cellular stress, elevated expression of p53 is observed.[38] In this study, we observed an increase in the brown positive cells for Ki67 and p53 because of the toxic effect of $AlCl_3$ on the kidney. This shows that $AlCl_3$ toxicity can lead to the proliferation of kidney cells which might lead to renal cancer. Interestingly, the administration of GA attenuated the effects of $AlCl_3$ on the Kidney tissues.

## Conclusion

This study evaluated the nephroprotective effects of Gum Arabic against AlCl3-induced toxicity in rats and its impact on the XRCC1 gene's expression. The results showed that rats administered with $AlCl_3$ showed no noticeable changes in the relative kidney weight and body weight. Intriguingly, $AlCl_3$ administration to rats caused a reduction in kidney SOD, and GSH levels, and alteration in kidney tissue histoarchitecture, while also increasing the serum levels of urea, tissue lipid peroxidation, and Ki67 and p53 immunoreactivity. Interestingly, GA treatment following $AlCl_3$ administration to rats resulted in an increase in SOD activity, elevation in GSH content, decrease in the urea and lipid peroxidation, increased expression of XRCC1 gene, and abrogation of Ki67 and p53 immunoreactivity in kidney cells. Taken together, this study showed the capacity of Gum Arabic to be used as a nephroprotective agent against $AlCl_3$-induced nephrotoxicity.

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## Conflict of interest
None.

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None.

## Ethics statement
Declaration by the Bioethics Committee of Scientific and Medical Research approved this animal experiment with No. HAP-02-J-094.

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