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Research Article
Effect of Arabic Gum (*Acacia senegal*) on Paracetamol-Induced Chronic Nephrotoxicity in Albino Rats

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Abstract

Background and Objective: Acetaminophen (APAP), is a commonly prescribed analgesic and antipyretic drug in clinical practice. It has been reported that APAP overdose potentially induces hepatorenal damage in experimental animals and humans and in severe cases may lead to death. Acute renal failure has been reported in ~1-2% of patients because of APAP overdose. This study was intended to explore the possible effects of *Acacia senegal*, commonly known as Arabic gum (AG) on paracetamol (N-acetyl-p-aminophenol, APAP)-induced nephrotoxicity in an albino rat model. **Materials and Methods:** Thirty Wistar albino rats were divided into five groups, six rats each. The normal control group was administered ordinary saline orally, the APAP group received APAP intra-peritoneally for 14 days (200 mg kg^{-1}), the N-acetylcysteine (NAC) group received APAP and NAC as a standard drug orally (140 mg kg^{-1}) and the (APAP) and (AG) groups were administered APAP intraperitoneally+AG orally, in two different doses (7.5 and 15 g kg^{-1}) for 14 days. **Results:** Pretreatment with AG diminished urea and creatinine levels in the blood. It additionally decreased the levels of malondialdehyde (MDA) and Kidney Injury Molecule-1 (KIM-1) and compensated for the deficits in the total antioxidant capacity (TAC) and amended the APAP-induced histopathological kidney alterations. Moreover, AG increased the clearance of creatinine from the body and diminished the levels of inflammatory markers CRP, COX-2, IL-6 and IL-17 in kidney tissues induced by APAP administrations. **Conclusion:** Arabic gum showed a promising role in the protection against paracetamol-induced nephrotoxicity in rats.

Key words: Nephrotoxicity, acetaminophen, paracetamol, N-acetyl-p-aminophenol, arabic gum, *Acacia senegal*, anti-inflammatory

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Paracetamol, with the chemical name N-acetyl-p-aminophenol (APAP), is one of the generally utilized pain-relieving antipyretic drugs sold worldwide as over-the-counter (OTC) due to its relative safety to the other NSAIDs such as diclofenac and Ibuprofen. Nonetheless, excessive uncontrolled use of this medication was reported to affect the kidney tissue resulting in nephrotoxicity. Renal insufficiency occurs approximately in 1-2% of patients exposed to paracetamol toxicity[1]. Renal toxicity develops secondary to acute tubular necrosis induced by N-Acetyl-p-benzoquinone (NAPQI), a reactive intermediate formed by the microsomal P-450 enzyme system. NAPQI is detoxified by intracellular glutathione (GSH) in restorative dosages. In most cases, paracetamol-overdosing can result in exhaustion of glutathione stores and a fast increase in the concentration of NAPQI causing kidney necrosis[2].

N-Acetyl-cysteine (NAC) is an antidote currently used clinically for paracetamol toxicity[3]. The NAC is a precursor of L-cysteine that replenishes the intracellular GSH levels[4]. Serum urea and creatinine levels might be pointers to acute tubular necrosis caused by paracetamol[5]. Free radicals are produced by exposure to drug toxicity and oxidative damage plays an important role in paracetamol-initiated hepatorenal injuries[6].

Restorative plants have been utilized in various societies and nations as a prophylactic remedy for renal injuries. Perhaps the most referred-to family is *Acacia senegal*. Arabic gum (AG) is a dried sticky exudate from the stems and branches of *Acacia senegal* trees grown in Sub-Saharan Africa, particularly in Sudan[7]. It consists of dissolvable fibres. The AG is quite possibly the main restorative plant utilized in conventional medication for anti-diabetic, anti-cholesterolemic and anti-ulcerogenic effects[8]. AG in Arab society medication is usually used to decrease both the recurrence and the requirement for hemodialysis in patients with chronic renal failure (CRF)[9].

Hence, herbal treatments such as AG that have cell reinforcement action could be a favoured option of treatment in cases of paracetamol-induced harmful hazardous effects on the kidney.

MATERIALS AND METHODS

Study area: The study was carried out in the animal house, Faculty of Medicine, Cairo University, Egypt during the period from March to August, 2021.

Animals: Thirty adult male wistar Albino rats weighing 200±20 g obtained from the animal house of the Faculty of Medicine, Cairo University were used. All animals were housed in facilities approved by international guidelines. The study was conducted following the Institutional Animal Care and Use Committee (CU-IACUC) at Cairo University under approval number CUIIIF4620.

Drugs and chemicals

Paracetamol: Paracetamol (GlaxoSmithKline, Ireland) suspension was prepared by dissolving paracetamol powder in saline 0.9% then animals were administered a single daily intraperitoneal injection of 200 mg kg^{-1} for 14 days. The paracetamol dose used to induce nephrotoxicity was selected from the values described in the literature[10,11].

N-Acetylcysteine: NAC (200 mg, SEDICO Pharmaceutical Co., Egypt) was prepared in 0.9% saline. Rats in group III were administered 140 mg kg^{-1} of this NAC solution orally for 14 days by gastric tube.

Arabic gum: AG (ELNASR for Food Industries, Khartoum., Sudan). The doses of AG (7.5 and 15 g kg^{-1}) were selected from described values in the literature[12,13]. The yellowish-white powder of AG was emulsified in water and administered to rats in groups IV and V, using oral gavage.

Thiopental sodium: (EIPICO, Egypt) was provided and used for intraperitoneal euthanasia at a 50 mg kg^{-1} dose.

Experimental design and animal grouping: Before starting our experiment, all rats were allowed to be fed a standard diet and fresh water ad libitum for 1 week under standard constant conditions for acclimatization.

Animals were randomly divided into five groups (6 rats each) as shown in Table 1 as follows: (Group I): [Normal control]: Animals of this group received normal saline (2 mL/rat) daily for 14 days. (Group II): [Disease model, untreated control]: Rats in this group received a single daily intraperitoneal dose of 200 mg kg^{-1} of APAP for 14 days. (Group III): [Disease model, treated with the standard drug N-acetyl cysteine]: Rats received NAC in a dose of 140 mg kg^{-1} orally[14] as a standard drug and APAP intra-peritoneally as in group II. (Group IV, V): [Disease model treated with 2 different doses of AG]: Rats were pretreated with AG in two different doses (7.5 and 15 g kg^{-1}), respectively. The AG was dissolved in a volume of 2 mL saline and given as a single daily dose for 14 days. APAP was administered intra-peritoneally in group IV and V as in group II.

Table 1: Description of animal grouping

Groups	Medications
I: Normal	Normal saline orally
II: APAP	Paracetamol (APAP) 200 mg kg^{-1} intra-peritoneally for 14 days
III: APAP+NAC	Paracetamol (APAP) 200 mg kg^{-1} intra-peritoneally for 14 days+NAC 140 mg kg^{-1} orally for 14 days
IV: APAP+AG 7.5	Paracetamol (APAP) 200 mg kg^{-1} intra-peritoneally for 14 days+AG 7.5 g kg^{-1} orally for 14 days
V: APAP+AG 15	Paracetamol (APAP) 200 mg kg^{-1} intra-peritoneally for 14 days+AG 15 g kg^{-1} orally for 14 days

Urine collection: Animals were kept separately in rat metabolic cages for roughly 15-16 hrs while urine samples were being collected. Food was not allowed during the urine collection period, although the water was available at all times. Throughout the collection period, urine was collected in conical polypropylene tubes that were 25 mL in size and maintained refrigerated in an ice container. Multiple aliquots of the supernatant urine were produced and kept in polypropylene tubes at -80°C until analysis after low-speed centrifugation (400 g) at 4°C for 5 min. Before being used in the experiment, urine samples were centrifuged to eliminate particles after being thoroughly thawed, mixed by vortexing and used. Two freeze/thaw cycles at most were used.

Blood sample collection: After 24 hrs from the last doses (i.e., on day 15), blood samples were collected from the rat tail veins, centrifuged at 3500 rpm for 15 min and the sera were obtained and stored at -80 until analyzed to measure serum levels of urea and creatinine. Subsequently, all animals were sacrificed by injecting thiopental sodium intraperitoneally at a 50 mg kg^{-1} dose.

Kidneys were rapidly removed and washed in ice-cold saline in all groups. The right kidneys were labelled and stored at -80°C until the biochemical analyses to measure MDA, TAC, KIM-1, CRP, IL-6 and IL-17 were conducted while the left kidneys were used for histopathological examination.

Biochemical studies

Estimation of serum urea and creatinine: Serum levels of urea and creatinine (mg dL^{-1}) were measured using the commercial kits Biochemical Enterprise (BEN), Milano, Italy, BK 151 and CR280 in an automatic biochemical analyzer (ChemWell, Palm City, FL) at 340 nm and 510 nm, respectively. The results are expressed as mg dL^{-1}.

Estimation of tissue MDA, TAC, KIM-1, CRP, IL-6 and IL-17: Renal tissue samples from each rat were first perfused with phosphate-buffered saline (PBS) /heparin and then ground in liquid nitrogen using a tissue laser II grinding Jar Set. 0.1 g was weighed and then treated with 4.5 mL of an appropriate buffer. This mixture was homogenized on ice using an ULTRA-URRAX homogenizer for 5 min. Homogenates were filtered and centrifuged using a refrigerator centrifuge at 4°C.

These supernatants then were used to determine MDA, TAC, KIM-1, CRP, IL-6 and IL-17 levels with highly sensitive ELISA kits. Measurements were performed according to the manufacturer's instructions. The average absorbance of each sample and standard were calculated. A standard curve was plotted and an equation was obtained from the absorbance of standards.

All assays were carried out at room temperature in duplicate. Linear MDA, TAC, KIM-1, CRP, IL-6 and IL-17 concentrations were calculated according to this equation. The results of the MDA, TAC and KIM-1, CRP, IL-6 and IL-17 levels in the tissues were expressed as mmol g^{-1} and nmol g^{-1} tissue, pg mL^{-1}, ng mL^{-1}, pg mg^{-1} protein, respectively. All data were presented as the Mean±Standard Deviation (SD).

Detection of COX-2 by western blot technique: The protein levels of COX-2 were detected by western blot analysis with the corresponding antibodies. Specific primary antibodies for COX-2 and beta-actin were obtained from Thermo Fisher Scientific, Rockford, Illinois, USA. ChemiDoc TM Imaging system was used to analyze band intensity with Image LabTM software version 5.1 (Bio-Rad Laboratories Inc., Hercules, CA, USA). The results were shown as arbitrary units following normalization for the expression of B-actin protein. B-actin expression was used as a control for normalizing the protein of interest.

Estimation of urine creatinine: Urine samples were analyzed for creatinine using Rx Daytona (Randox Laboratories Limited).

By looking at the corresponding quality controls conducted before sample analysis, the effectiveness of the various analyzers employed in the study was confirmed. In the test buffer that was included in the kit, urine samples were diluted to 1:5000.

Histopathological examination: Kidney tissue specimens were fixed in 10% neutral buffered formalin. The fixed specimens were then trimmed, washed and dehydrated in ascending grades of alcohol, cleared in xylene, embedded in

Table 2: Grading system for renal lesions

Scores	Lesion
0	Normal histology
1	Tubular epithelial cell degeneration, without significant necrosis or apoptosis
2	Tubular epithelial cell necrosis and apoptosis <25%
3	Tubular epithelial cell necrosis and apoptosis <50%
4	Tubular epithelial cell necrosis and apoptosis <75%
5	Tubular epithelial cell necrosis and apoptosis ≥75%

paraffin, sectioned at 4-6 U thickness and stained by hematoxylin and eosin according to Bancroft and Gamble[15]. Histological grading of renal damage with special reference to renal tubules was done[16] as shown in Table 2.

Evaluation of P53 labelling index expression: Immunohistochemistry staining was performed using the Ventana Benchmark automated immunostainer following the protocols provided by the manufacturer. The antibody used was DO-7 for wild-type p53. The selected paraffin blocks for immunohistochemical staining were sectioned at 5 µm and stained with monoclonal antibodies P53 according to the method described previously by Hsia *et al.*[17].

The extent of positivity ("extent of distribution" of positive cells) was estimated on a scale of 0 to 4, in which 0 = negative, 1 = positive staining in 1-25% of cells, 2 = positive staining in 26-50%, 3 = positive staining in 51-75% and 4 = positive staining in 76-100%. The combined staining score (extension+intensity) ≥3 was considered positive staining. The tissue section was examined by light microscopy at power 200X[18].

Statistical analysis: Data were coded and entered using the statistical package for the Social Sciences (SPSS) version 26 (IBM Corp., Armonk, NY, USA). Data were summarized using mean and standard deviation. Comparisons between groups were done using Analysis of Variance (ANOVA) with multiple comparisons *post hoc* test in normally distributed quantitative variables while, non-parametric Kruskal-Wallis Test and Mann-Whitney Test were used for non-normally distributed quantitative variables[19]. The $p<0.05$ were considered statistically significant.

RESULTS

Effects on serum urea and creatinine levels: As shown in Fig. 1, In the APAP group, serum urea (Fig. 1a) and creatinine levels (Fig. 1b) were significantly increased in comparison to the normal group. Treatment with GUM 7.5 g kg^{-1} showed a significant decrease in serum urea levels compared to the APAP group. Treatment with GUM 15 g kg^{-1} showed a significant decrease in serum urea levels compared to APAP, NAC and GUM 7.5 groups.

Effect on tissue MDA levels: As shown in Fig. 2a, In the APAP group, tissue MDA levels were significantly increased in comparison to the normal group. Treatment with GUM 7.5 g kg^{-1} showed a significant decrease in tissue MDA levels compared to the APAP group. Treatment with GUM 15 g kg^{-1} showed a significant decrease in tissue MDA levels compared to APAP, NAC and GUM 7.5 groups.

Effects on total antioxidant capacity: In the APAP group, TAC levels were significantly decreased in comparison to the normal group. Treatment with GUM 7.5 showed a significant increase in TAC levels compared to the APAP group. Treatment with GUM 15 showed a significant increase in TAC levels compared to APAP, NAC and GUM 7.5 groups (Fig. 2b).

Effects on tissue kidney injury molecule 1: The KIM levels were significantly increased in the APAP group, compared to the normal group. Treatment with GUM 7.5 showed a significant decrease in tissue KIM levels compared to the APAP group. Treatment with NAC, GUM 7.5 and GUM 15 g kg^{-1} showed a significant decrease in tissue KIM levels compared to the APAP group (Fig. 2c).

Effects on tissue CRP: In the APAP group, tissue CRP levels were significantly increased in comparison to the normal group. Treatment with GUM 7.5 showed a significant decrease in tissue CRP levels compared to the APAP group. Treatment with GUM 15 g kg^{-1} showed a significant decrease in tissue CRP levels compared to the APAP group (Fig. 2d).

Effect on tissue IL-6 and IL-17: In the APAP group, tissue IL-6 (Fig. 3a) and IL-17 (Fig. 3b) were significantly increased in comparison to the normal group. Treatment with GUM 7.5 showed a significant decrease in tissue IL-6 and IL-17 levels compared to the APAP group. Treatment with GUM 15 g kg^{-1} showed a significant decrease in tissue IL-6 and IL-17 levels compared to APAP, NAC and GUM 7.5 groups.

Effects on urine creatinine: In the APAP group, urine creatinine levels were significantly decreased in comparison to the normal group. Treatment with NAC showed a significant increase in urine creatinine levels compared to the

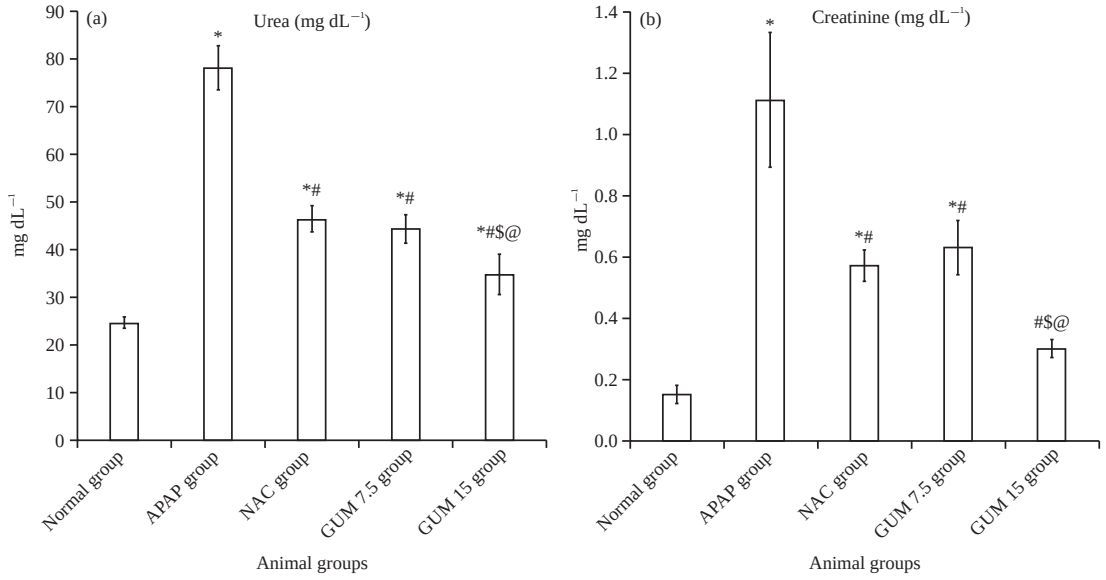

Fig. 1(a-b): Effect of AG on serum (a) Urea and (b) Creatinine in rats

Values were represented as Mean+SD, APAP: Acetyl para amino phenol, NAC: N acetylcysteine, *Statistically significant compared to corresponding values in the normal group, #Statistically significant compared to corresponding values in the APAP group, $Statistically significant compared to corresponding values in the NAC group and @Statistically significant compared to corresponding values in the GUM 7.5 group

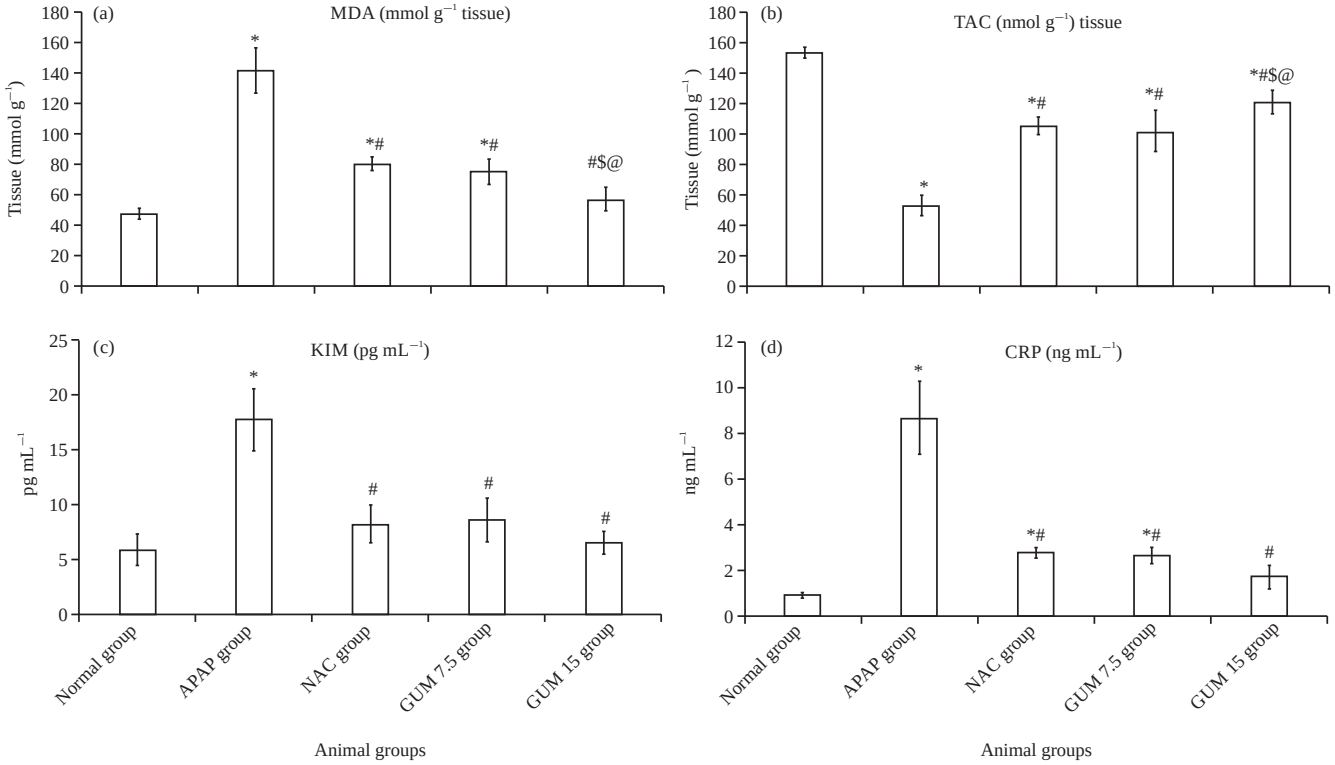

Fig. 2(a-d): Mean±SD of tissue (a) MDA, (b) TAC, (c) KIM and (d) CRP of rats in the different studied groups

APAP: Acetyl para amino phenol, NAC: N acetylcysteine *Statistically significant compared to corresponding values in the normal group, #Statistically significant compared to corresponding values in the APAP group, $statistically significant compared to corresponding values in the NAC group and @Statistically significant compared to corresponding values in the GUM 7.5 group

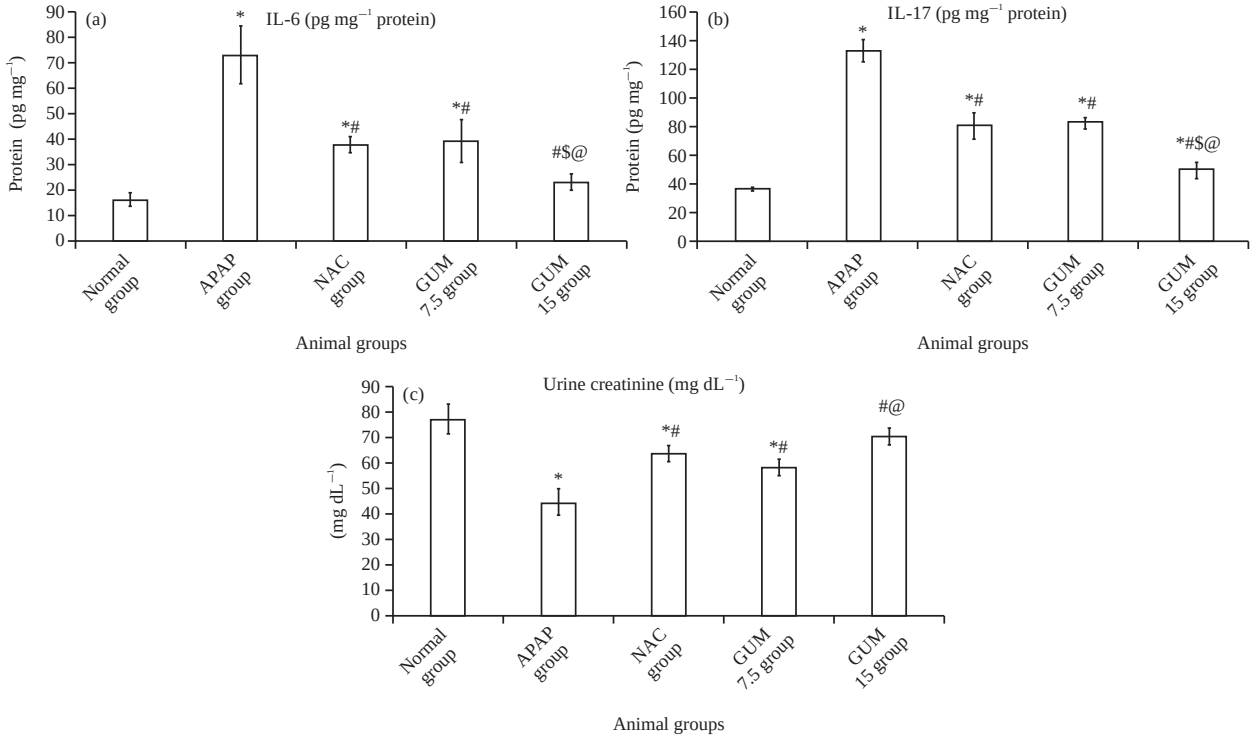

Fig. 3(a-c): Mean±SD, (a) IL-6, (b) IL-17, (c) COX-2 and (d) Urine creatinine of rats in the different studied groups

APAP: Acetyl-para-amino-phenol, NAC: Acetylcysteine, *Statistically significant compared to corresponding values in the normal group, #Statistically significant compared to corresponding values in the APAP group, $statistically significant compared to corresponding values in the NAC group and @Statistically significant compared to corresponding values in GUM 7.5 group

APAP group. Treatment with GUM 7.5 g kg^{-1} showed a significant increase in urine creatinine levels compared to the APAP group. Treatment with GUM 15 g kg^{-1} showed a significant increase in urine creatinine levels compared to APAP and GUM 7.5 groups (Fig. 3c).

Effects on tissue COX-2: In the APAP group, tissue COX-2 levels were significantly increased in comparison to the normal group. Treatment with GUM 7.5 g kg^{-1} showed a significant decrease in COX-2 levels compared to the APAP group. Treatment with GUM 15 g kg^{-1} showed a significant decrease in tissue COX-2 levels compared to APAP, NAC and GUM 7.5 groups (Fig. 4a). The COX-2 protein levels were detected by western blot (Fig. 4b) as described earlier.

Histopathological results: The kidney tissue section of Group I (The normal control group) showed circumscribes glomeruli with the normal structure of capillary tufts and Bowman's capsule. The renal tubules of both proximal and distal convoluted tubules showed intact epithelial lining and regular arrangement grade (0) Fig. 5a-b. On the other side, the kidney tissue section of animals in Group II (APAP) revealed shrinkage of capillary tufts with a widening of Bowman's space of some glomeruli. Interstitial oedema is characterized by widening spaces in between the renal tubules. Few mononuclear cell infiltrations mainly lymphocytes and macrophages were noticed. The renal tubules showed epithelial cell degeneration with marked swelling of tubular epithelial lining accompanied by narrowing and occlusion of tubular lumen by albuminous and cellular casts. Tubular epithelial cell necrosis and apoptosis <50% grade 3 were seen in Fig. 6a-b.

The kidney tissue section of animals Group III (APAP+NAC) revealed moderate improvement when compared with Paracetamol alone in Group II which was characterized by tubular epithelial cell degeneration with intra-luminal albuminous eosinophilic droplets. Marked dilatation and congestion of glomerular tufts and interstitial oedema were noticed. Tubular epithelial cells revealed necrosis and apoptosis of its epithelial lining <25% grade 2 (Fig. 6c-d).

The kidney tissue section of animals in Group IV (APAP+AG 7.5 g) showed mild histological damage to renal tubular epithelial lining in the form of mild swelling of cell lining with narrowing of its lumen. Tubular epithelial cell

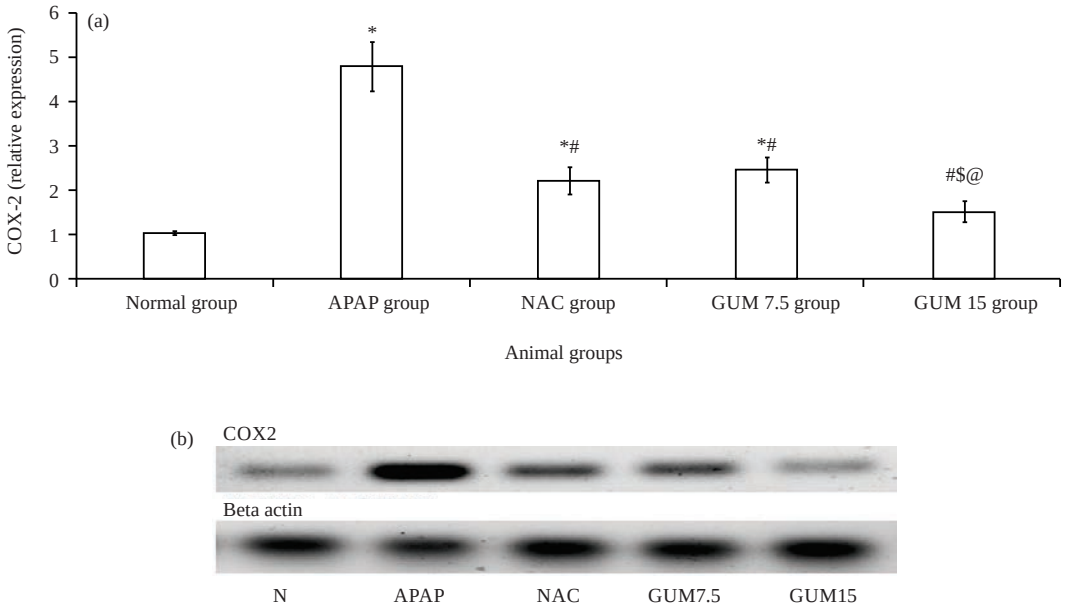

Fig. 4(a-b): Effect of APAP, NAC and gum in the two different doses on levels of COX-2 protein level

Lane1: Group 1 control group), Lane 2: Group II (APAP group), Lane III: Group III (NAC), Lane 4: Group IV (gum 7.5) and Lane 5: Group (gum 15) and (a, b) COX-2 protein levels were detected by western blot analysis with the corresponding antibodies

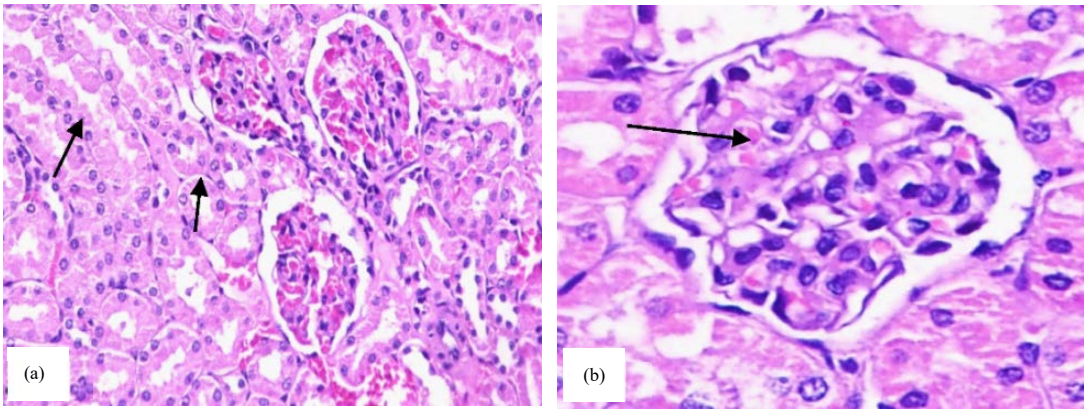

Fig. 5(a-b): Photomicrograph of kidney tissue section showing (a) Intact tubular epithelial lining in black arrow (x200) and (b) Normal histological structure of glomerulus in black arrow (x400)

degeneration, without significant necrosis or apoptosis, was observed. The glomeruli showed a mild degree of glomerular tufts congestion grade (1) Fig. 6e-f. More improvement was recorded in the kidney tissue section of animals in Group V (APAP+AG 15 g) than in the previous group. Circumscribed glomeruli with the normal architecture of capillary tufts and Bowman's capsule were seen. Renal tubules showed intact epithelial lining grade (0) Fig. 6g-h.

Immunohistopathological findings: Kidney expressions of P53 have been shown in plate B, respectively. The control group showed a negative immune stain (0) (Fig. 7a). On the other side, the kidney tissue section of animals group II (Paracetamol alone) revealed a positive immunostained grade (3) (Fig. 7b). The kidney tissue section of animals group III (Paracetamol and N acetylcysteine) showed a positive immunostained grade (2) (Fig. 7c). The kidney tissue section of animals group IV (Paracetamol and Arabic gum 7.5 g) showed a positive immunostained grade (2) (Fig. 7d). Complete improvement was seen in animals of group V (Paracetamol and Arabic gum 15 g) showing a negative immunostained grade (0) (Fig. 7e).

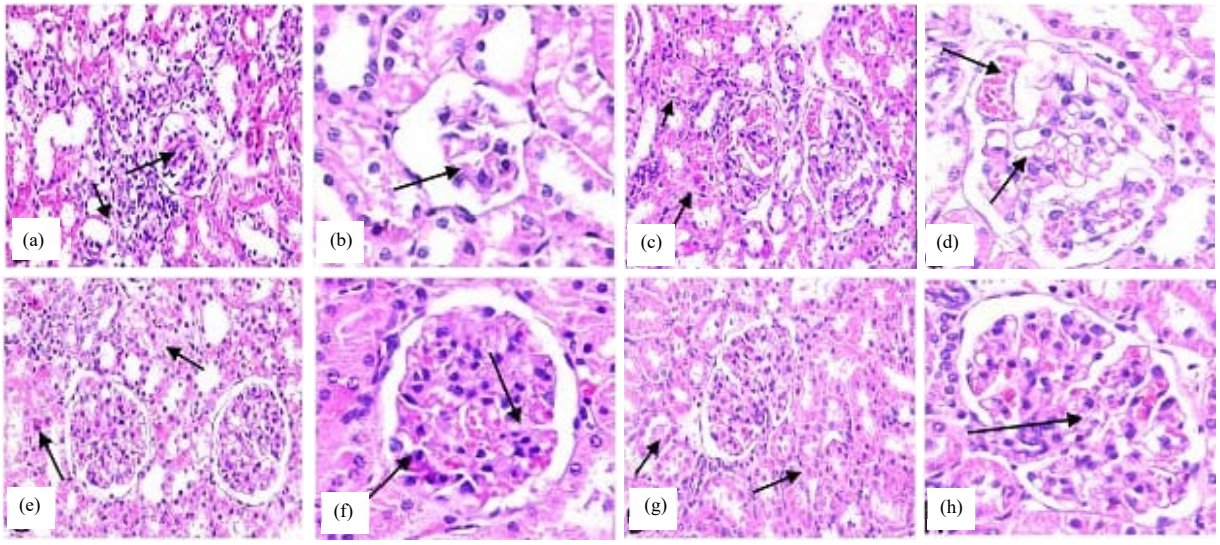

Fig. 6(a-h): Photomicrograph of kidney tissue section, (a) Tubular epithelial cell necrosis and apoptosis <50% and Few mononuclear cells infiltration arrow (x200), (b) Shrinkage of glomerular capillary tufts arrow (x400), (c) Tubular epithelial cell necrosis and apoptosis <25% arrow (x200), (d) Dilatation and congestion of glomerular tufts arrow (x400), (e) Mild swelling of cell lining arrow (x200), (f) Mild degree of glomerular tufts congestion arrow (x400) (g) Intact tubular epithelial lining arrow (x200) and (h) Circumscribe glomeruli with the normal architecture of capillary tufts arrow (x400)

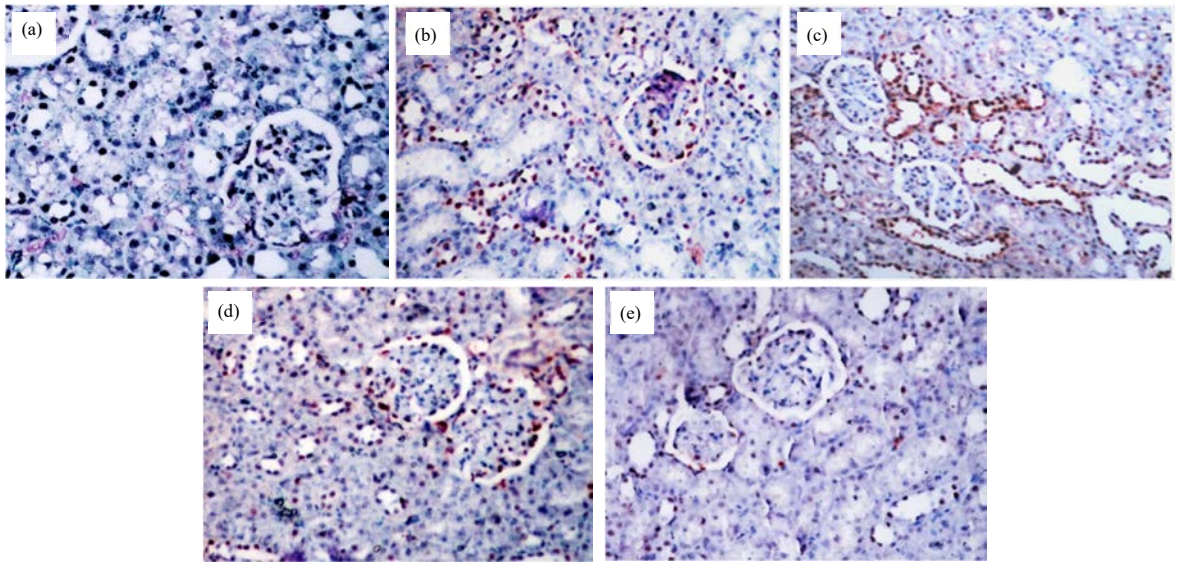

Fig. 7(a-e): Photomicrograph of kidney tissue section, (a) Negative stain (0), (b) Positive immunostained grade (3), (c) Positive immunostained grade (2), (d) Positive immunostained grade (2) and (e) Negative stain immunostained grade (0) (P53 x200)

DISCUSSION

In this study, paracetamol administration altered serum urea and creatinine levels, indicating nephrotoxicity. These outcomes were as per past studies[20,21]. The administration of AG diminished these altered values. Indeed, the most elevated serum urea and creatinine decreases were noticed when utilizing AG (15 g/kg/day) and this decrease was statistically

higher than that of NAC administration. This finding was following a recent finding conducted on a patient with rheumatoid arthritis suffering from renal affection to find that AG was able to decrease levels of urea in those patients[22]. What's more the creatinine clearance in urine improved essentially with Arabic gum administration, this was following[23].

Also, our result was supported by Ali *et al.*[24] which found that Arabic gum improved creatinine clearance in adenine-induced chronic kidney disease.

Paracetamol is commonly used for the relief of pain and fever. Many specialists have zeroed in essentially on paracetamol (APAP) initiated hepatotoxicity[25], Unfortunately, logical investigations have archived APAP acute toxicity on kidneys in enormous doses[26,27].

Although, paracetamol has an overall security profile, its excessive use for a long time has been found as of late to influence kidney work[28] resulting in acute tubular necrosis[29]. Free radicals produced by exposure to the drug in toxicity result in oxidative damage in renal tissues[30,31]. These free radicals can initiate lipid peroxidation which brings about a rise in MDA levels[32]. In addition to the previously mentioned mechanism of tissue toxicity, numerous inflammatory mediators are released by various pathways, these inflammatory cytokines can magnify the toxicity[27,33].

N-Acetyl cysteine has for some time been utilized as a powerful antidote to paracetamol toxicity. It gives cysteine to stimulate the replenishment of GSH which detoxifies NAPQI[34]. In this study, Arabic gum (AG) exhibited a protective effect on chronic paracetamol-induced nephrotoxicity. For assessment of kidney function, levels of urea and creatinine in serum were initially measured. These markers are utilized in the diagnosis of kidney damage. Serum urea and creatinine levels might be a pointer to acute tubular necrosis caused by paracetamol toxicity[5].

The intestine acts as a "substitute kidney," increasing urea nitrogen (N) excretion in stools and concurrently decreasing total (N) excreted in the urine, which is likely the basis of AG's favourable effect on renal function[35-37]. Sorbents (such as resins) can augment hemodialysis systems by adsorbing/ eliminating conventional uremic toxins such as urea and creatinine and also other toxins[37]. Since serum urea and creatinine can be impacted by many factors independent of kidney function, so we estimated kidney injury molecule-1 which is a biomarker released by the injured kidney and is analogous to the troponin release by injured myocardial cells after myocardial ischemia or infarction[38].

Patients with acute tubular necrosis (ATN) can be identified by Kidney Injury Molecule (KIM-1), which may be a useful biomarker for renal proximal tubule injury[39]. It was found that KIM-1 is up-regulated in renal disease and is associated with renal fibrosis and inflammation and that urinary KIM-1 can be utilized as a non-invasive biomarker of tubular injury in different renal diseases[39]. APAP was found to induce significant height in a degree of KIM-1 which was diminished by treating rats either by NAC or AG.

Notably, total antioxidant capacity (TAC) and malondialdehyde (MDA) are significant pointers to the antioxidant capacity of the body against oxidative stress. In the present study, we have investigated alterations in the tissue MDA levels after the administration of paracetamol. This outcome was as per past investigations[40,41]. The increase in lipid peroxidation induced by APAP decreased altogether with AG in a dose-dependent manner to reach normal values in group V (15 g/kg/day). As TAC reflects the antioxidant defense system in the body and the power for removal of free-radical species, such as hydrogen peroxide and superoxide radicals, so we measure its level to establish that TAC level significantly increased in AG groups in contrast to the APAP group.

These outcomes were upheld by histopathological findings that were distinguished by H&E which delighted shrinkage of capillary tufts with a widening of Bowman's space of certain glomeruli as well as interstitial oedema. The renal tubules showed epithelial cell degeneration with marked swelling of tubular epithelial lining accompanied by narrowing and obstruction of the tubular lumen by albuminous and cellular casts, every one of these findings was amended by administration of Arabic gum.

Similarly, current findings were supported by immunohistochemical staining for the detection of p53 protein as a parameter for DNA damage, which can be used as a reliable marker of cellular damage to aid in the diagnosis of ATN[35]. The administration of AG significantly reduced the nephrotoxicity of paracetamol in a dose-dependent manner, this finding was in agreement with a previous study[12] that concluded the effectiveness of AG in the remedy of histopathological alterations in kidney tissues induced by mercuric chloride.

The resulting outcome showed the capacity of AG to diminish fundamentally the raised levels of CRP, COX-2, IL-6 and IL-17 that have been raised in the APAP group. This can be clarified by the fact that AG fermentation by colonic bacteria increases serum butyrate concentrations which have an

anti-inflammatory effect and act as prebiotics. This outcome was as per an ongoing study[42] that recorded the capacity of AG to diminish the level of CRP in patients with sickle cell anaemia due to its anti-inflammatory effect. Kamal *et al*.[43] found that AG was able to decrease the level of ESR and TNF-alpha in a patient with rheumatoid arthritis and modulate the hepatic and renal profile in a patient with rheumatoid arthritis.

CONCLUSION

The nephroprotective properties of AG might be identified by its beneficial outcomes on the antioxidant system as shown by improving the antioxidant parameters as TAC and MDA as well as its anti-inflammatory effect which was detected from readjusting the tissue levels of IL-6, IL-17 and CRP and COX-2 expression. It is concluded that Arabic gum can protect kidneys from the damage caused by paracetamol excessive use as illustrated by restoring the kidney function tests as urea and creatinine and reducing the tissue KIM levels, the biomarker for human renal injury and therefore, maybe a likely tissue injury-limiting agent against paracetamol-induced nephrotoxicity.

SIGNIFICANCE STATEMENT

Excessive paracetamol use can result in severe kidney damage which may be extensive, irreversible and in rare cases, require organ transplantation. To the best of our knowledge, the potential protective effect of Arabic gum in chronic paracetamol toxicity was not investigated. A current study showed the renoprotective effect of Arabic gum as a safe herbal remedy in protection against chronic paracetamol toxicity.

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