Protective Role Of Gum Arabic (Acacia Senegal) Against Adenine Induced Nephrotoxicity In Male Albino Rats: Some Histological, Histochemical, And Biochemical Studies

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Abstract
This study was amid to investigate the protective role of Gum Arabic (GA) on Adenine (AD)-induced nephrotoxicity on the final body weight (b.w.), absolute kidney weight, serum concentrations of urea and creatinine with malondialdehyde (MDA), besides histological and histochemical changes in the kidney tissue of male albino rats. Twenty-four adult male albino rats were assigned randomly in to four groups (n=6 of each): Group 1 (Control) take only normal saline, Group 2 (AD group 150 mg/kg b.w.), Group3 (AD +GA 10% w/v), Group 4 (AD +GA 20% w/v). The treatment was given daily via gavage orally for 30 days. AD group showed a significant elevation of final b.w. and absolute kidney weight, urea, creatinine, and MDA level in comparison with the control group. Kidney sections of rats administrated with AD showed dilation of bowman's capsule space, segmentation of glomerulus, necrosis, proteinaceous remnant, hyperplasia, crystallization, and damaged urinary tubules. Histochemical sections of AD group showed depletion of kidney protein and carbohydrates. On the other hand, both groups of GA in combination with AD revealed a significant reduction in the serum urea, creatinine, and MDA level. In conclusion, these results suggest that GA have a noticeable protective and antioxidant effect against AD nephrotoxicity.

Keywords: AD, CKD, Creatinine, GA, MDA, Urea.

Introduction

A serious and growing global health concern is the clinical condition known as chronic kidney disease (CKD), which is defined by progressive renal failure (1, 2). Kidney failure can be brought on by urinary tractemia, complete loss of renal function, Diabetes, stroke, cardiovascular disease, and other conditions (3, 4). Rodent models are used to study the pathophysiology of CKD and to create treatment approaches (5). 500 million people (1 in 10 adults) globally have chronic renal disease, and nearly half of those over 75 have a high risk of morbidity and mortality. Two important elements of the disease's pathophysiological foundations that have an impact on both humans and animals are inflammation and oxidative stress. In CKD patients and experimental animals, inflammatory mediators with high plasma concentrations, including C-reactive protein and tumor necrosis factor, diverse cytokines, and other indicators of oxidative stress were found (6). Our results suggest that apoptosis is essential for the development of CKD (7).

Adenine, a purine nucleobase, is essential for the biochemical and physiological processes that take place inside of cells (8). Under physiological circumstances, xanthine oxidase catalyzes the conversion of adenine to 2, 8-dihydroxyadenine (DHA) in the liver, and DHA is ultimately excreted from urine. However, excessive DHA production will

cause kidney damage because it is poorly soluble under urine pH and crystallizes and deposits in renal tubules or interstitial tissues. Adenine is now frequently utilized to create an experimental mouse model of chronic renal failure (CRF). Thus, oral adenine administration may result in renal tubule congestion, which leads to delays the excretion of nitrogenous substances and results in a biochemical and physiological state likewise CKD in humans (9).

Gum Arabic (*Acacia senegal*), family Fabaceae is a small deciduous Acacia tree from the genus *Senegalia*, obtained from the secretions of the mature GA trees that grow mainly in Sudan. Acacia gum is an edible water-soluble polymer yellow to beige (10). It is employed as an emulsifier in the pharmaceutical, culinary, and cosmetic sectors, as well as a traditional therapy for renal sufferers, as well as antibacterial and antioxidant properties. It is considered an antioxidant because it contains copper, manganese, iron, zinc and positively affects enzymes antioxidants (11). That's why used in the traditional treatment with chronic renal disease in various countries (12).

The aim of the research is to see whether Gum Arabic will alleviate the nephrotoxicity caused by Adenine in male albino rats with histological and histochemical examinations.

Materials and methods

Animals

Twenty-four male albino rats (200-250g) were breeding in the animal house of the University of Salahaddin / College of Education /Department of Biology; Rats were kept in conventional cages at room temperature (RT) of 25±3°C with a 12 hours dark/light cycle. They had allowed to standard laboratory feed and water *ad libitum*. Then they were distributed into four groups, six rats for each (13).

Chemicals

In this study, chronic kidney disease was induced by oral gavage of adenine (150 mg/kg/day: GE7863, Glentham Life Sciences Ltd, UK) the powder was dissolved in 0.9% sodium chloride (2ml for 200g body weight). Fresh solutions were prepared daily for a period of 30 days. Gum Arabic is obtained from *Acacia Senegal* trees, which purchased from the local market of the Erbil city, Iraq. It is ground into a powder and then dissolved in sterile distilled water at a concentration of 10% and 20% w/v and given to rats instead of orally by stomach gavage for 30 days.

Experimental Protocol

After two weeks of acclimation, before starting the experiment. The animals were separated in to four equal groups, each with six animals, and were handled as follows: The first group of control rats was taken orally normal saline (0.9% NaCl). The second group was administered orally for 30 consecutive days with AD (150 mg/kg,b.w) . The third group: was treated orally with GA (10%, w/v) plus AD (150 mg/kg,b.w) for 30 days. The fourth group: was treated orally with GA (20%, w/v) plus AD (150 mg/kg,b.w) for 30 days. At the end of the scheduled 30th day of the experiment, all the animals were sacrificed.

Blood samples collection

At the end of the experiment, all the animals were fasted overnight and weighed. Blood samples were collected direct cardiac puncture after ketamine (75 mg/kg i.p.) and xylazine (5 mg/kg i.p.) was used to anaesthetize fasting animals then transformed to tubes without ethylene diamine trichloroacetic acid (EDTA) and left for clotting. Blood samples were centrifuged at 3000 g for 15min. Serum were collected and stored at - 20°C to evaluate serum urea, creatinine which measured by kits purchased from Cobas Roche co. (Mannheim, Germany) and for determination of Malondialdehyde (MDA) by Colorimetric method/ (Elabscience, Cat. No. E-BC-K025-S, TBA method) according to (13).

Tissues preparation

After sacrificing the animals, a longitudinal incision was made from the ventral side of the

rat, and the kidneys were taken from the rats, they were fixed in 10% neutral buffered formalin for 48 hours, purified with xylol, embedded in paraffin, paraffinized kidney tissue blocks were processed and cut by a microtome at 5 μm thickness, then deparaffinized, and counterstained by staining.

Histopathological Examination

Hematoxylin and eosin dye (H&E) used, and after being prepared, they are examined under a microscope to study histological changes. Alcian blue-periodic acid Schiff (AB-PAS) (pH2.5) staining kit (Solarbio co., Beijing, China) was used to detect polysaccharides such as glycogen, and muco-substances such as glycoproteins, glycolipids, and acidic mucins. Essential protein in kidney tissue sections was determined by bromophenol blue (Himedia Laboratories, Mumbai, India) staining technique, according to (13).

Statistical Analysis

Statistical analyses were conducted using the Statical Product for Service Solution version 28 (Spss Gmbh, Munich, Germany). Data are presented as means and standard errors of the means (mean SEM). Before performing an ANOVA, the data's normality and homogeneity were determined by one-way direction (ANOVA), and Tukey's test was used to see whether there were any differences between the experimental groups. A probability level of $P<0.01$ and $P<0.05$ were considered as statistically significant.

Results

Table (1) shows the final body weight in Adenine administrated groups was reduced significantly ($P<0.05$) when compared with the control group, while Gum Arabic treated groups (10%,20%) w/v shows increase statically non-significant in the final body weight when compared with the AD group, but still lower than the average value when compared with the control group. The obtained results (Table1) revealed that absolute kidney weight in AD administrated group had the strongest significant ($P<0.05$) increase in comparison with the control group. While, in both doses treated groups of GA, there were a non-significant reduced in kidney weight respectively when compared with AD group but still near to control group.

In addition, there were significant increase ($P<0.01$) in urea and creatinine levels of AD group when compared with control group. On the other hand, in both doses treated groups of Arabic gum, there were a non-significant decrease in both urea and creatinine levels when compared with AD treated group. The best lowering effect was seen in high dose of AG treated group which have significant ($P<0.01$) obvious decreasing in urea level when compared with AD group.

Further, in AD administrated group, MDA level was caused a significant ($P<0.01$) increase when compared with the control group. In contrast, there were high significant ($P<0.01$) decrease in MDA level in both AG treated groups when compared with the AD administered group and near to the control group. **Table 1:** Shows (mean ± SEM) effect of different treatments on final body weight, absolute kidney weight, urea, creatinine, and MDA levels in the serum.

The different capital letters mean significant differences ($p<0.05$)
The different small letters mean significant differences ($p<0.01$)

Histological examination of Kidney

Histologically, Adenine affected on the kidney tissue which caused dilation of bowman’s capsule space, and segmentation with degeneration of glomerulus in the cortex. AD was also infarcted in the medulla layer, caused necrosis in some uriniferous tubules, proteinaceous remnant inside some uriniferous tubule, hemorrhage, hyperplasia of uriniferous tubules epithelium with crystallization and urinary tubules damaged as shown in (Fig. 1).

Histochemical results revealed that AD group caused depletion in the essential proteins which appeared from faint blue color, while basement membrane stained strongly with bromophenol blue and mucopolysaccharides by thickness of bowman’s capsule parietal

membrane and thickness of uriniferous tubules (Fig. 2). Treatment with Gum Arabic in both dose levels accompanied by AD ameliorated the adverse effects of AD in kidney tissue and retained the healthy protein by showing high protein content in the glomeruli with urinary tubules as well as retained polysaccharides content which shows normal distribution of mucopolysaccharides in the glomeruli and urinary tubules when compared with AD group tissue sections (Fig. 2).

Discussion

According to table (1) from this study, treatment with AD caused the treated rats' body weight to drop dramatically while their absolute kidney weight increased significantly. According to (14), this may be because after oral administration, adenine is converted to 2,8-dihydroxyadenine, which precipitates and produces tubular crystals that harm the renal tissues. Adenine (100 mg/rat) and methylcellulose were given daily for 12 days by (15), which was followed by a considerable loss in body mass as compared to solvent control treated rats. (15), body mass loss following adenine feeding is correlated with decreased food intake (about 50% less than controls), and azotemia, which is described here. Previous research has demonstrated that administering adenine orally or through food can cause reproducible renal impairment (16; 17; 18; 19). According to various research, animals administered adenine lost body weight (20), and adenine-induced chronic renal failure in rats mirrors the clinical symptoms of human chronic kidney failure.

Besides to. In this investigation, we discovered that rats given 150 mg/kg/day of adenine had considerably higher serum levels of creatinine and urea, as well as significant changes to relevant biochemical markers, as shown in Table (1). One indication of renal illness is a high amount of urea and creatinine in the blood (21). Adenine is a commonly used model medicine that degenerates renal tubule and interstitial, leading to kidney failure and inhibiting the excretion of nitrogen molecules like creatinine and urea in a manner likewise (22) findings. The metabolic byproduct of creatine, phosphocreatine, and urea is creatinine, which is produced in the liver from ammonia. Both metabolites are carried to the kidney through glomerular filtration for excretion, and damage to the glomerulus will cause hazardous metabolites to build up and eventually cause kidney failure (23).

Also, in table (1), the MDA level was significantly higher in the Adenine-administered group compared to the control group. Similar findings from earlier research showed that the kidney's lipid peroxidation levels increased. Excessive quantities of free radicals and other oxidants cause oxidative stress, which damages DNA, proteins, lipids, and lipoproteins as well as genetic material (24). It is well-known that oxidative stress is brought on by an imbalance between rising reactive oxygen species (ROS) production and a corresponding decline in the body's natural antioxidant defenses (25). More and more health issues are being linked to the image (26).

In our study, Adenine administration altered the biochemical composition of the kidney by causing noticeable histological changes in the glomerulus and kidney tubules and led to the depletion of protein and neutral polysaccharides in the kidney of the treated rats which deterioration of creatinine liquidation in blood and urea, as well as noted an increase in inflammatory cells because of damage to the epithelial cells of the kidney in a similar way with (27).

On the other hand, there are improving in the body weight, kidney parameters and MDA levels in serum by Gum Arabic as well as shown in table (1), may be related to the presence of antioxidant compounds. Recent reports suggest GA exerts anti-inflammatory, antioxidant and anti-apoptotic roles in mitigating renal injury in numerous animal models of renal injury, this is a similar way with the documentation with (28). Data is also emerging that oral administration of GA ameliorates renal injury in models of chronic renal disease by similar anti-inflammatory and

antioxidant mechanisms, agreed with (29) and (30). Recent studies in both patients with CKD stage 3–4 (31), and hemodialysis patients (32), suggests that daily supplementation with GA reduces measures of oxidative stress and inflammatory markers. GA, given orally, has been used in the treatment of CKD in several developing countries such as Iraq and Sudan (33; 34). The supplement of GA had a median lethal dose (LD50) >16 g/kg for rats (35; 36). Details about toxicological indexes were published by (37). GA is thought to act primarily via increasing the fecal nitrogen excretion which in turn lowers serum urea nitrogen concentration. Furthermore, previous *in vitro* studies showed that GA dose dependently scavenged generated superoxide radicals (38). Consequently, both doses of Gum Arabic typically architecture of renal glomeruli and renal tubules, appears few infiltrations of a mononuclear inflammatory cell. GA abrogated the histopathological findings seen in the adenine administered groups likewise with (29). These beneficial effects suggest that the antioxidative and anti-inflammatory properties possessed by oral GA are the main mechanism for its salutary action in adenine-induced kidney failure.

Conclusions. We concluded that Gum Arabic could be improved kidney failure in rats administrated Adenine by minimizing several biochemical and histological changes.

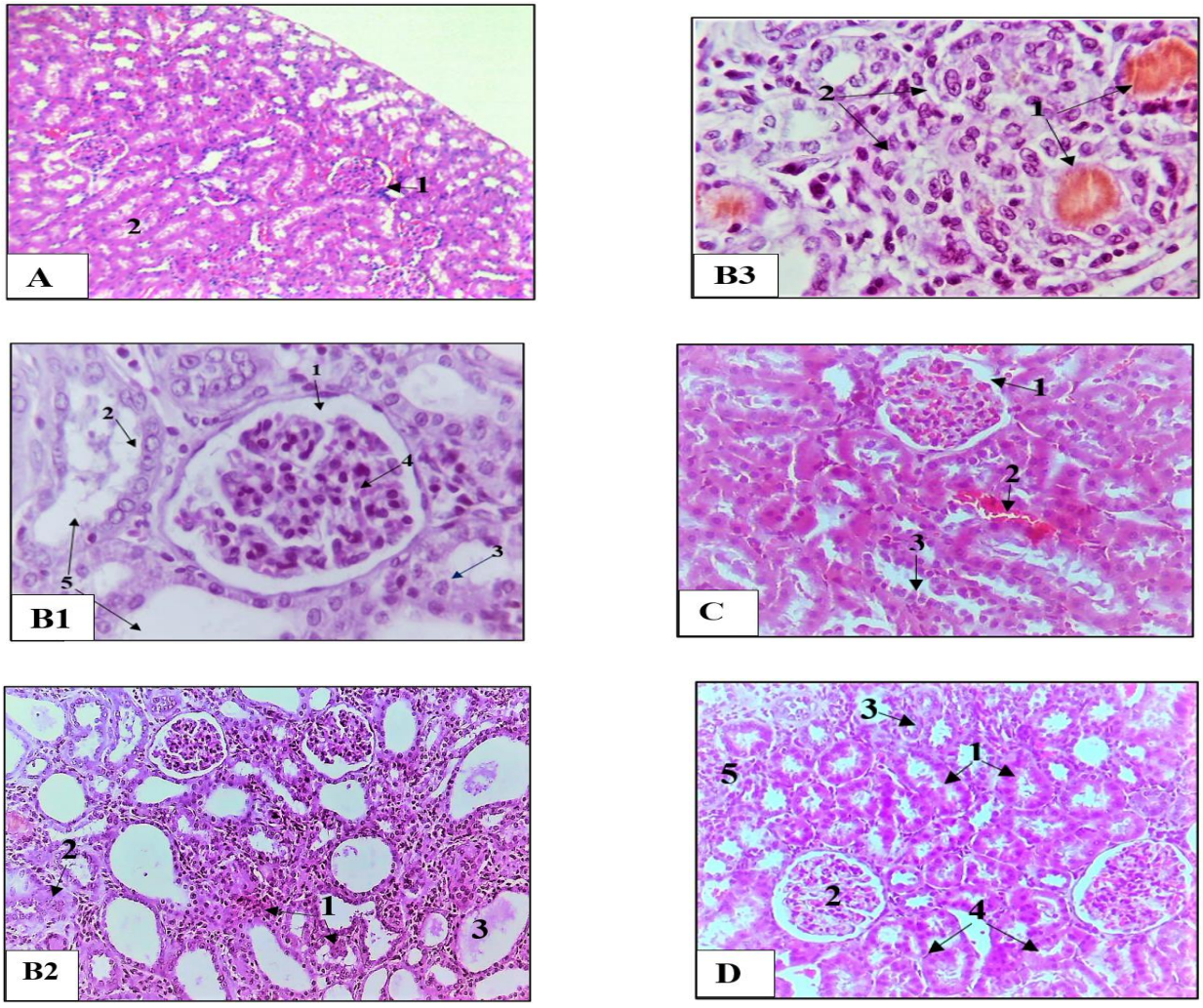

Figure 1. Cross section in the kidney of the treated groups:**(A)** Control group Shows: **1.** Normal structure glomerulus **2.** Healthy urinary tubules. **(B 1,2,3)** Adenine treated group revealed: **(B1)** shows:**1.** Dilation of Bowmans Capsule space. **2.** Degeneration of Uriniferous tubules. **3.** Sloughing of lining epithelium of uriniferous tubules. **4.** Segmentation and degeneration of glomerulus and Dilation of uriniferous tubules. **(B2)**

Shows: **1.** Hemorrhage inside uriniferous tubules in the medulla. **2.** Necrosis of some Uriniferous tubules. **3.** Proteinaceous remnant inside some uriniferous tubule. **(B3)** Shows: **1.** Hyperplasia of uriniferous tubules epithelium with crystallization. **2.** Urinary tubules damaged. **(C)** Adenine (150 mg/kg) + Arabic gum (10% w/v) treated group shows moderate improvement in kidney tissue with: **1.** More normal glomeruli and Bowman's Capsule space. **2.** Hemorrhage. **3.** Some uriniferous tubules degeneration. **(D)** Adenine (150 mg/kg) + Arabic gum (20% w/v) treated group revealed nearly normal tissue with:**1.** Interstitial tissue fibrosis. **2.** More normal renal glomeruli. **3.** Eosinophilia of epithelium for some uriniferous tubules and sloughing the epithelium. **4.** Damage of some uriniferous tubules. **5.** Appear few infiltrations of inflammatory cells. (100,400X), H&E

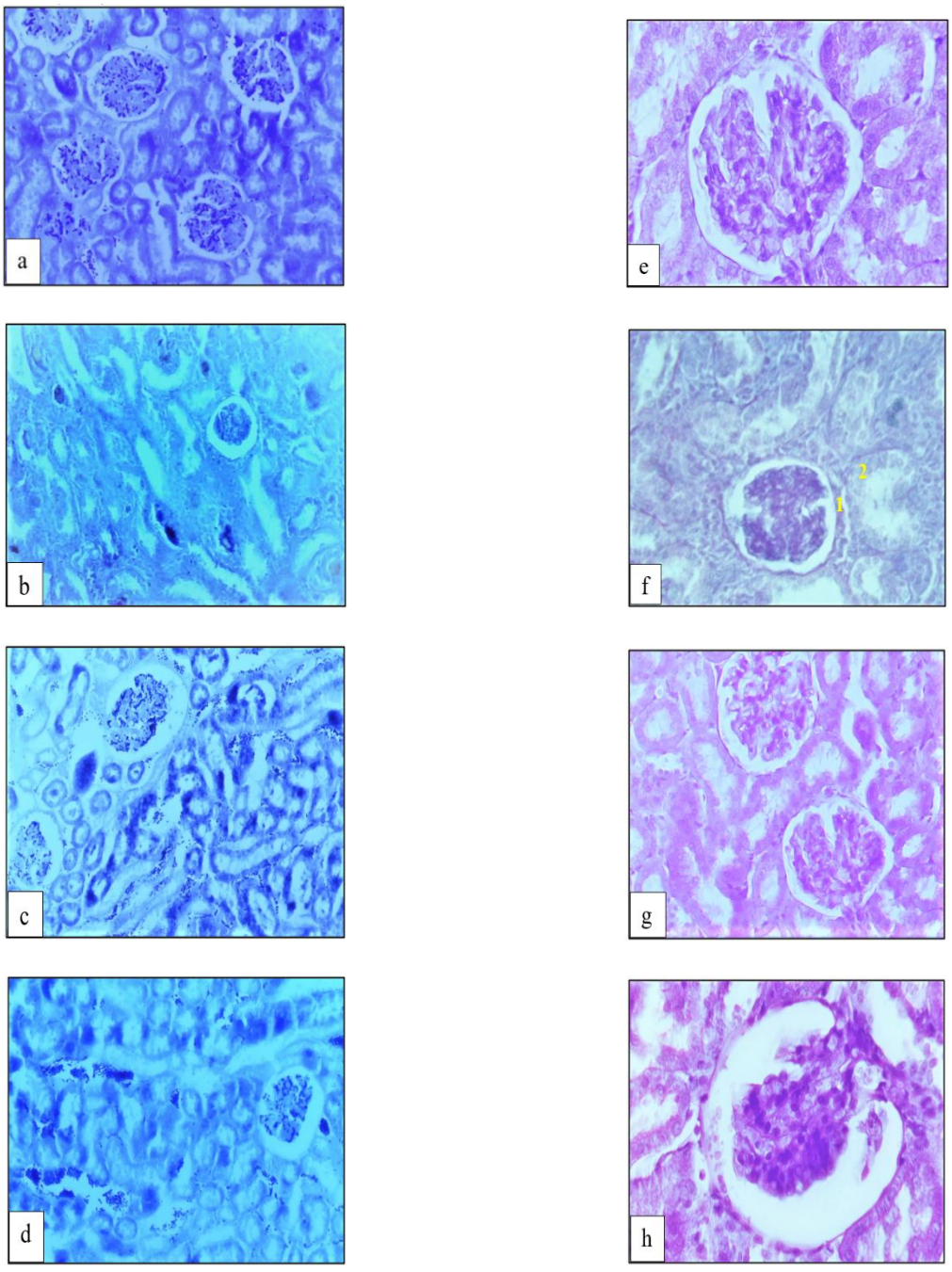

Figure 2. Kidney section (a,b,c,d) stained with bromophenol blue technique to detect protein content. a: Normal protein content in the control group revealed high protein content in the glomeruli and urinary tubules with intense blue color, b:AD treated group

showed protein depletion appeared from faint blue color, while basement membrane stained strongly with Bromophenol blue. c: AD+GA10% showing moderate protein retention. d: AD+GA20% group showing high protein content in the glomeruli and urinary tubules. H&E (100X). (e, f, g, h) stained with PAS-alcian blue for the detection of neutral mucins (PAS) and acidic mucins (alcian blue) e: control group normal distribution of neutral and acidic mucins (magenta). f: AD group showing weak response to PAS stain in the glomerulus and urinary tubule, appeared in weak red magenta color and increased acidic mucin (blue color) over neutral mucin. 1. Thickness of bowman's capsule parietal membrane. 2. Thickness of uriniferous tubules basement membrane. g: AD+GA10% group showing moderate retention of the mucopolysaccharides, the faint color represents degenerated urinary tubules. h: AD+GA20% revealed for normal distribution of mucopolysaccharides in the glomeruli and urinary tubules. H&E(400X.)

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