Case Study
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NEPHROPROTECTIVE EFFECT OF *ACACIA SENEGAL* (GUM ARABIC) AGAINST GENTAMICIN INDUCED NEPHROTOXICITY IN RATS

Hala E. Ahmed [1], Tarig. A. H. Bilal [2], Sara A. Mohamed [1], Samia H. Abdlrahman [1], Fahad E.B. Elghazali [1], and Samia M. Elbadwi [3]

[1] Central Veterinary Research Laboratory, P. O. Box 8067 (Alamarat), Khartoum, Sudan
[2] College of Dentistry, King Faisal University, Saudi Arabia
[3] Faculty of Veterinary Medicine, University of Khartoum, , Khartoum, Sudan

ABSTRACT

Objective: To explore the effects of Gum Arabic (Acacia Senegal) aqueous extract in contradiction of gentamicin induced nephrotoxicity in Wistar albino rats.
Materials and Methods: Forty rats were randomly separated into 4 groups (n=10). Group A (negative control) received standard diet and water while group B (positive control) received gentamicin 80 mg/kg b. wt. /day via intra peritoneal (**IP**) route for six days. Groups C and D received Gum Arabic extract at 250 and 500 mg/kg b. wt. via oral route respectively for 10 days and concurrently with gentamicin 80 mg/kg b. wt. IP from day 5 for six days. The nephroprotective activity of Gum Arabic extract was evaluated by measuring the serum and urine biochemical parameters (creatinine, urea, total protein, albumin, sodium and potassium) and examining the histopathological sections of kidney specimen. The serum and urine data were subjected to analysis of variance (ANOVA).
Results: In both serum and urine, the biochemical parameters in groups C and D were significantly improved compared to group B. The histopathological analysis of kidneys showed slight necrosis of glomeruli and tubules in group C compared to group B, while group D showed only hemorrhage and congestion in the glomeruli.
Conclusion: These findings suggest that, Gum Arabic extract may possess a nephroprotective activity.

Keywords: Gentamicin, Nephrotoxicity, Acacia Senegal, Gum Arabic

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CorrespondingAuthor

Hala E. Ahmed, Hala.elr@gmail.com

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1. INTRODUCTION

Nephrotoxicity is one of the most frequent kidney issues, that arises when body is exposed to a drug or toxin (Atef et al. (2015)). A numeral therapeutic mediator can harmfully distress the kidney and subsequently lead to acute renal failure, chronic interstitial nephritis and nephritic syndrome, as there is a collective number of forceful therapeutic drugs like aminoglycoside antibiotics, NSAID's. lately, additional chemotherapeutic agents have been enumerated into the therapeutic acting drugs. (Akram et al. (2019)). Revelation to chemical substances like ethylene glycol, carbon tetrachloride, sodium oxalate and heavy metals such as lead, mercury, cadmium and arsenic, similarly persuades nephrotoxicity (Balali-Mood et al. (2021)). Speedy appreciation of the ailment and termination of accountable drugs, are generally the first essential therapy. Nephroprotective mediators are the materials, which own defensive activity in

contradiction of Nephrotoxicity. Medicinal plants have restorative chattels due to the existence of numerous composite chemical ingredients. Initial literatures have prearranged many herbs for the therapy of renal complaints (http://farmacists.blogspot.com). Co-administration of several medicinal plants having nephroprotective activity laterally with diverse nephrotoxic agents which may weaken its toxicity

The term renal failure principally signifies failure of the excretory role of kidney, leading to retaining of the nitrogenous waste products of metabolism in the blood Sivanandham (2015)**,** furthermore, there is a failure of regulation of fluid and electrolyte balance alongside endocrine dysfunction. The renal failure is basically assorted into acute and chronic renal failure Chertow et al. (2019)**.**

Acute renal failure **(ARF),** indicates the unexpected and regularly revocable loss of renal function that progresses over a period of days or weeks. There are several reasons behind the incidence of acute renal failure which primarily consist of, acute tubular necrosis that regularly represent 85% of the recorded cases. Typically, acute tubular necrosis arises either due to ischemia or toxins. The toxins may originate from exterior cause (exogenous) or inside source (endogenous). The exogenous agents are divergence mediators, such as, cyclosporine, antibiotics, chemotherapeutic agents, organic solvents, acetaminophen and prohibited abortifacients**,** Chertow et al. (2019)**.** Chronic renal failure **(CRF)** is a permanent fall in the renal function which naturally progresses over a period of years, instigating loss of excretory metabolic and endocrine functions. Numerous origins of renal failure have been documented like hypertension, diabetes mellitus, anti-neoplastic agents like cyclophosphamide, vincristin and cisplatin etc. Sivanandham (2015)**.**

Aminoglycoside antibiotics have been extensively used for gram-negative bacterial infections. Though, their nephrotoxicity and ototoxicity are the key confines in clinical practice. Amongst some aminoglycoside antibiotics, the score of nephrotoxicity has been described to be in the subsequent order as, neomycin > gentamicin > tobramycin McWilliam (2015)**.** Gentamycin Nephrotoxicity happens in about 15-30% of treated subjects, is demonstrated clinically as non-oliguric renal failure, with a slow escalation in serum creatinine and hyperosmolar urinary yield evolving after several days of treatment Abdel-Zaher et al. (2008)**.** Gentamicin is filtered through glomeruli into tubular urine, that binds with anionic phospholipids, such as phosphatidylinositol or phosphatidylserine, in brush border membrane of proximal tubular cells reabsorbed actively via pinocytosis process into tubular cells, reserved up by lysosomes and afterward produces phospholipidosis, McWilliam (2015)**.** The drug passes into the cells by adsorptive/receptor mediated endocytosis after binding to acidic phospholipids and megalin and is located essentially in lysosomes. Animals treated with low, therapeutically pertinent doses of aminoglycosides show both lysosomal phospholipidosis and apoptosis in proximal tubular cells Randjelovic et al. (2017)**.**

The goal of this study, is to explore the properties of Gum Arabic aqueous extract against gentamicin induced nephrotoxicity in Wistar albino rats.

2. MATERIALS AND METHODS

Animals

Forty grown Wistar albino rats of either sexes weighing (100–120 g) were attained from the experimental animal residence at the Central Veterinary Research Laboratory (CVRL) and from the Faculty of Pharmacy (University of Khartoum). The rats were kept at the experimental animal house at the Faculty of Pharmacy

(University of Khartoum), isolated and observed for 7 days before the experiment. All animals reserved in aluminum laboratory cages, fed the standard pellet feedstuff and fresh water *ad libitum.*

Preparation of Gum Arabic extract

The Gum Arabic was gotten from Elobied (North Kordofan State, Sudan) as fine powder. Extraction of plant material was achieved using water according to the method described by Sukhdev et al. (2008)**.** Briefly, eighty grams of Gum Arabic was macerated in 500 ml hot distilled water, left till cooled down with unceasing stirring at room temperature, filtered, deep-frozen and then freeze-dried previously to calculating the yield percentage.

Assessment of nephroprotective activity against gentamicin-induced nephrotoxicity

Gentamicin (80 mg/kg) was inoculated by intra peritoneal **(IP)** route concurrently with Gum Arabic extract which administered orally. Blood samples from ocular vein were collected under light diethyl ether anesthesia into a sterile plain vacutainer tube at day 0 and day 10. Serum was separated from blood by centrifugation for 15 minutes at 3000 rpm and stored at −20º C until tested for renal function. Urine samples were collected by mean of metabolic cages in day 0 and 10 in sterile container. Biochemical profile determined using ***BIOSYSTEM BTS-350*** Apparatus.

Histopathological study

Kidney specimens were handled in the Department of Pathology (Faculty of Veterinary Medicine, University of Khartoum) and the slides were examined under microscope in the Department of pathology (CVRL). Kidney tissue samples perceived in 10% formaldehyde for two days then placed into automatic tissue processor (Histos5, rapid microwave processor, Milestone-USA) and monitored for 12 hours. The samples were blocked with molten paraffin at 56-58 0C and those paraffin blocks froze at -10^{0} C in a refrigerator. After 4-5µ thick sections were sliced the paraffin blocks were stained with hematoxylin eosin. The stained sections were inspected under a light microscope.

Experimental design

The forty rats were alienated into four groups, each of ten rats. Group A (negative control) did not receive neither gentamycin nor aqueous extract of Gum Arabic. Group B (positive control) received gentamicin (80 mg/kg b. wt) IP for initiation of nephrotoxicity (6 days). Group C parallelly received, the aqueous extract of Gum Arabic (250 mg/kg b. wt) orally for 10 day and gentamicin (80 mg/kg b. wt) for 6 days. Group D concomitantly received the aqueous extract of Gum Arabic (500 mg/kg) orally for 10 days with gentamicin (80 mg/kg b.wt) IP for 6 days.

Statistical analysis

Analysis of Variance (ANOVA) was used to analyses the data using SPSS software (IBM, Version 16). A probability of $p<0.05$ was considered as significant. All results were expressed as mean ± standard error of means SE.

3. RESULTS

Biochemical parameters in sera samples

The biochemical parameters in sera samples are expressed in Table 1**.** The creatinine showed significant (P< 0.05) rise in group B compared to groups A, C and D, concurrently, nonsignificant variation observed between groups C and D. The urea exposed significant elevation in group B compared to groups A, C and D, whereas nonsignificant variance between groups A, C and D was documented. The total protein displayed significant reduction in group B compared to group A. A significant increase in groups C and D compared to group B was noted, while the difference between groups C and D was nonsignificant. The albumin showed significant decrease in group B compared to groups A, C and D. whereas the difference between groups A, C and D was not pronounced. The sodium showed remarkable increase in group B compared to groups A, C and D. A significant reduction of sodium concentration distinguished in groups C and D compared to group B. A substantial decrease in group D compared to group C, was observed. Serum potassium levels, showed important decrease in groups B, C and D compared to group A, and nonsignificant variance between groups B, C and D was recognized.

Table 1 The effect of Gum Arabic aqueous extract administered for 10 days on biochemical parameters in sera samples

Group	Creatinine (mg/dl)		Urea (mg/dl)		Total protein (g/dl)		Albumin (g/dl)		Sodium (mmol/l)		Potassium (mmol/l)	
	D0	D10	D0	D10	D0	D10	D0	D10	D0	D10	D0	D10
A	0.31± 0.03a	0.34± 0.03a	40.33± 1.68a	47.88± 0.27a	5.46± 0.24a	5.69± 0.15b	2.88± 0.10c	2.90± 0.01b	81.38± 3.33a	85.00± 3.14a	3.58± 0.26b	3.86± 0.15b
B	0.32± 0.04a	3.71± 0.41b	38.70± 1.23a	59.70± 2.38b	6.14± 0.21a	4.90± 0.10a	2.69± 0.12bc	2.41± 0.05a	76.56± 3.11a	102.50 ± 2.20b	3.12± 0.10ab	2.25± 0.20a
C	0.29 ± 0.02a	1.24 ± 0.26a	38.38± 1.63a	53.01 ± 3.73ab	5.81± 0.91a	5.56 ±0.05 ab	2.51 ± 0.17ab	2.80 ± 0.06b	73.15 ± 5.58a	94.72 ± 9.77a	2.43 ± 0.19a	2.38± 0.26a
D	0.30 ± 0.03a	1.14 ± 0.19a	40.37± 1.58a	51.71 ± 3.92ab	5.49± 0.31a	5.56 ± 0.16 ab	2.32 ± 0.14a	2.89 ± 0.09b	72.1± 3.91a	90.38± 8.99a	3.21± 0.16b	2.50± 0.24a

***Data are means ± SE. A** = Negative control; **B** = Positive control (Gentamicin 80mg/kg b. wt); **C** = Gum Arabic 250 mg/kg b. wt. + Gentamicin 80 mg/kg b. wt; **D** = Gum Arabic 500 mg/kg b. wt+Gentamicin 80 mg/kg b.wt.*

Biochemical parameters in urine samples

The biochemical parameters in urine samples are expressed in Table 2**.** The creatinine levels, showed significant (P< 0.05) increase in groups B and C compared to group A. Meanwhile nonsignificant difference between groups A and D was noted. Urea concentrations, revealed significant rise in group B compared to groups A, C and D. Nonsignificant difference between groups A, C and D. The sodium displayed significant decrease in group B compared to groups A, C and D, while the difference was nonsignificant between groups A, C and D. The potassium showed significant reduction in groups B, C and D compared to group A, whereas, significant increase

in groups C and D compared to group B was observed. A nonsignificant different level of potassium between groups C and D was obtained.

Table 2 The effect of Gum Arabic aqueous extract administered for 10 days on biochemical parameters in urine samples

Group	Creatinine (mg/dl)		Urea (mg/dl)		Sodium (mmol/l)		Potassium (mmol/l)	
	D0	D10	D0	D10	D0	D10	D0	D10
A	65.20± 12.60a	67.41± 11.30a	920± 23.09a	918± 0.03a	113.77± 5.05a	106.80± 17.18b	27.50± 0.62a	29.29± 2.06b
B	73.90± 0.003a	91.26± 7.51b	846± 6.58a	1219± 36.49b	113.75± 5.05a	52.50± 10.10a	29.64± 0.62b	11.79± 0.62a
C	82.60± 0.12a	88.90± 16.20a	875± 68.52a	951± 173.0a	108.50± 14.14a	103.25± 22.80b	30.36± 1.03b	20.36± 2.27b
D	65.22± 0.20a	69.38± 0.19a	927± 140.50a	941± 87.33a	101.5± 2.02a	94.83± 6.07b	22.50± 0.62a	20.72± 3.71b

Data are means ± SE*. Means in the same row followed by the same letters are not significantly different at ($p \leq 0.05$).* ***A*** *= Negative control;* ***B*** *= Positive control (Gentamicin 80 mg/kg b. wt);* ***C*** *= Gum Arabic 250 mg/kg b. wt. + Gentamicin 80 mg/kg b. wt.;* ***D*** *= Gum Arabic 500 mg/kg b. wt. + Gentamicin 80 mg/kg b. wt.*

Histopathological changes in kidney

The kidney of group B rats exhibited immense necrosis of cortical tubules and glomeruli with hemorrhage Figure 1**.** The kidney of group C rats exposed mild necrosis of glomeruli and tubules Figure 2**.** The kidney of group D rats showed hemorrhage and congestion in the glomeruli Figure 3**.**

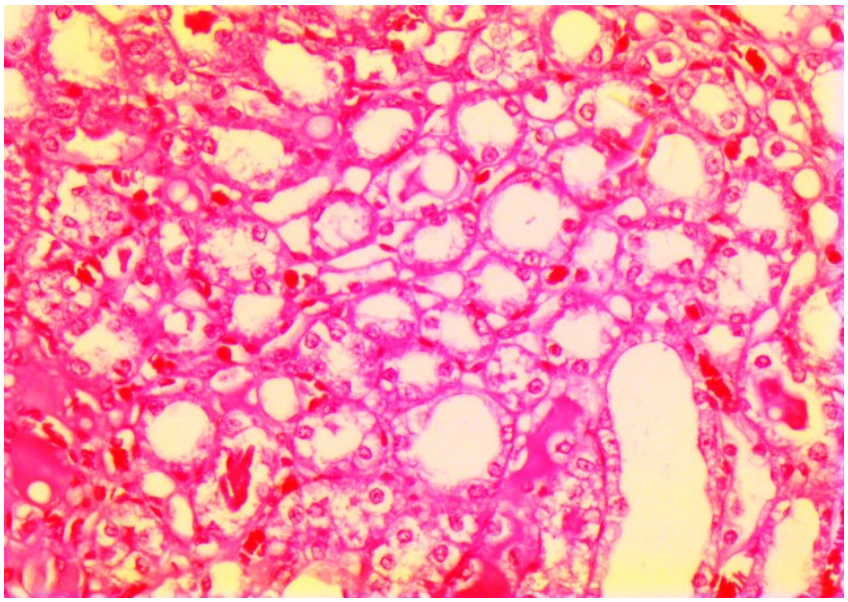

Figure 1 Section of kidney of group B rats.

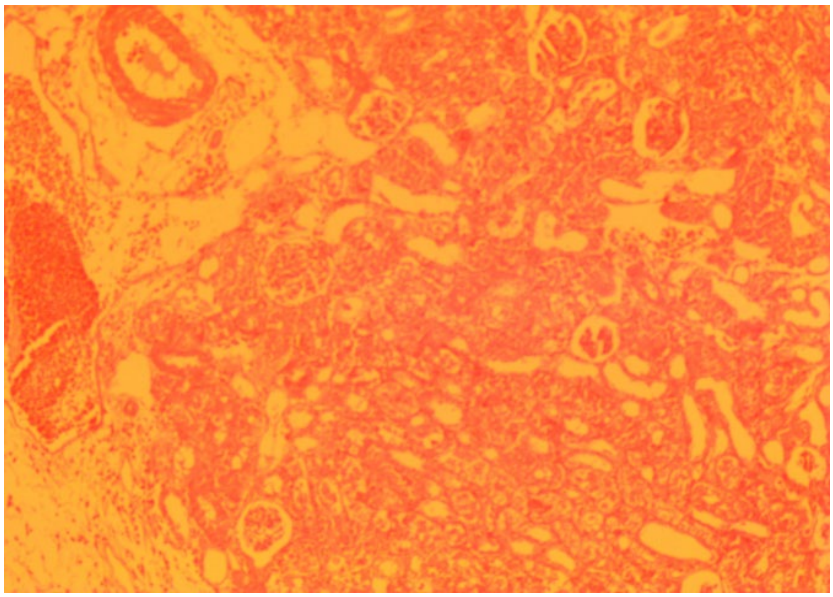

Figure 2 Section of kidney of group C rats

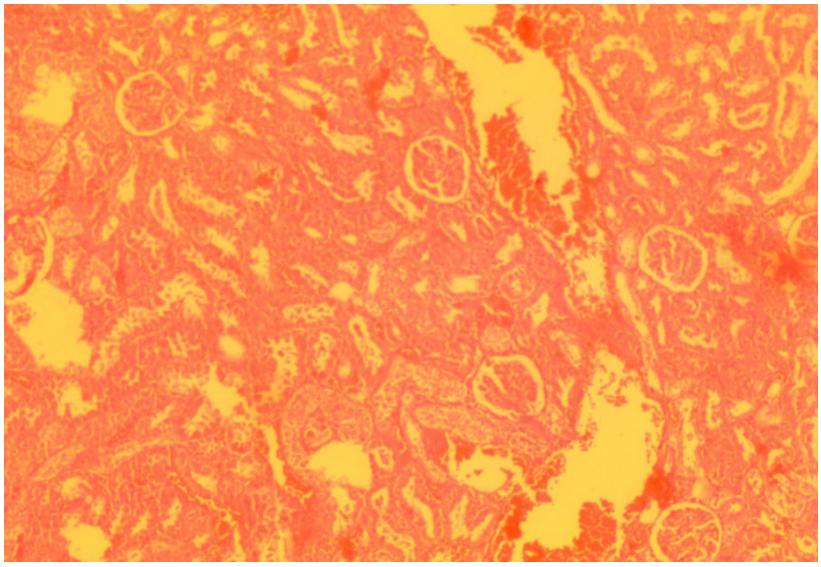

Figure 3 Section of kidney of group D rats

4. DISCUSSION

In this model of acute renal failure induced by gentamycin; rats given Gum Arabic showed values near the normal in creatinine and sodium while they are increased significantly in sera of the intoxicated rats. No significant difference in serum total protein, urea and potassium. Analogous findings were obtained by; El Tahir et al. (2016) and Ali et al. (2013) using the acute renal failure model. The administration of Gum Arabic aqueous extract followed by gentamicin improved the activity of albumin towards the normal values in extract treated groups while it was reduced significantly in the group given only gentamicin. In urine there was a significant elevation in urea and creatinine levels in gentamicin group whereas

there was a significant reduction in urea and creatinine levels in the treated group which given Gum Arabic at 250 and 500 mg/kg.

Mahmoud et al. (2012), studied Gum Arabic on acute and chronic renal failure and they found that Gum Arabic owns anti-inflammatory possessions that seem to ameliorate the renal injury caused by gentamicin. They found Gum Arabic attenuated C - reactive protein levels and increased renal superoxide dismutase activity.

The current study, oral administration of Gum Arabic to rats with renal toxicity induced by gentamicin, showed a marked decrease in level of creatinine. In another study Gum Arabic was found to attenuate renal dysfunction in adenine induced chronic renal failure Ali et al. (2010).

El Tahir et al. (2016); found in a model of acute renal failure induced by gentamicin that Gum Arabic produced mild reduction in urea and creatinine serum levels. This reduction was statistically significant for urea but not for creatinine.

There are many suggestions that explain how dietary fibers such as Gum Arabic declines serum urea nitrogen. It has been declared that colonic bacteria ferment dietary fibers to deliver them with energy for growth and nitrogen excretion Muhamad et al. (2021). Another suggestion in animal replicas of experimental chronic renal failure showed that ingesting of feedstuff containing fermentable carbohydrates consequences in a greater rate of urea nitrogen transfer from blood to the cercal lumen, where it hydrolyzed by bacterial urease before following microflora metabolism and propagation Therefore, this results in a greater faecal nitrogen excretion, joined with a reduction in urinary nitrogen excretion and plasma urea concentration Snelson et al. (2019). However, Mohammed et al. (2018), assumed that the nephroprotective value of Gum Arabic seen in rats treated with gentamicin was due to reduced lipid oxidation and antioxidant effect. The reduction in the markers shows that the extracts having the potential to improve the impairment which produced by gentamicin administration Kuatsienu et al. (2017).

The histopathological finding for the effect of Gum Arabic rehabilitation of kidney tissue was week. This may be attributed to the short length of the trial.

Ali et al. (2013); examined an animal model of chronic renal failure (feeding adenine for four weeks to assess the consequence of Gum Arabic on chronic renal failure and they found that Gum Arabic 6% and 12% (W/V) in drinking water for four uninterrupted weeks, expressively ameliorate the contrary biochemical alterations symptomatic of renal failure and reduced glomerular and interstitial lesions induced by adenine. The mechanism(s) of this nephroprotection was undefined but might include anti-oxidant and /or anti-inflammatory actions. El Tahir et al. (2016); found that Gum Arabic diminished the impairment caused by gentamicin; as coagulative necrosis, hemorrhage and reduced cellularity.

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