

Assessment of the therapeutic role of Arabic Gum as Antioxidants on Cadmium induced kidney dysfunction in male albino rats

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ABSTRACT: Many industrial emissions and the exhaust of vehicles contain heavy metals. Cadmium, (Cd) is one of these heavy metals and is emitted in the gas and dust remnants of some factories like copper smelters. Cadmium has a half-life of greater than ten years in human and thus accumulates in the body over the time. It is a potentially neurotoxic pollutant and approximately 50% of the body burden of cadmium can be found in the kidney. Cadmium produces proximal tubule dysfunction and tissue injury. This injury may progress to a chronic interstitial nephritis. This study aimed to investigate the effect of Arabic gum on renal disorder induced by cadmium on male rats. The results obtained showed that daily intraperitoneal injection of 2 mg cadmium chloride (CdCl₂) / Kg b. wt / day for ten weeks induced renal toxicity in rats. Serum urea, creatinine, sodium (Na), potassium (K), phosphorus (P) and total calcium (Ca) were evaluated one and two weeks post-cadmium induction. Significant ameliorations were noted in these parameters after daily treatment with a dose 0.5 g/kg of Arabic gum during the experimental period.

KEYWORDS: Cadmium, Arabic gum, Serum renal function, Electrolytes, Kidney dysfunction.

1 INTRODUCTION

Chronic exposure of non-smoking human and animals to cadmium (Cd) is primarily through food and results in hepatorenal toxicity. In the workplace, inhalation of cadmium (Cd) containing dust and fumes is the major route of exposure. Cadmium has a half-life of greater than ten years in human and thus accumulates in the body overtime [1],[2]. The earliest adverse effect of cadmium on the kidney is usually an increased excretion of specific proteins in urine [3],[4]. Approximately, 50 percent of the body burden of cadmium can be found in the kidney. Cadmium produces proximal tubule dysfunction and injury characterized by increases in urinary excretion of glucose, amino acids, calcium and cellular enzymes. This injury may progress to a chronic interstitial nephritis [5].

A very interesting aspect of cadmium nephrotoxicity is the role of metallothionein. Metallothionein is low-molecular weight, cysteine-rich, metal binding protein that has a high affinity for cadmium and other heavy metals. In general, the exposure to CdCl₂, cadmium – metallothionein complex formed and released either from intestinal cells or hepatocytes. The cadmium metallothionein complex is freely filtered by the glomerulus and is reabsorbed by the proximal tubule. Inside the tubular cells it is thought that lysosomal degradation of the cadmium–metallothionein results in the release of "Free" cadmium which in turn induces renal metallothionein production [6].

Arabic gum (AG) is known as acacia gum which is a brittle, odourless and generally tasteless material that contains a number of neutral sugars, acids, calcium, potassium and other electrolytes. It is a dietary fiber derived from the dried gummy exudates of the stems and branches of Acacia Senegal [7]. The molecular weight of the gum is large and estimates suggest the weight lies in the range of 200000 to 600000 Daltons. It is easily soluble in water without increasing viscosity but does not dissolve in alcohol [8]. AG is built upon a backbone of D-galactose units with side chains of D-glucuronic acid with L-

rhamnose or L-arabinose terminal units [9]. It is a branched- chain, complex polysaccharide, either neutral or slightly acidic, found as a mixed calcium, magnesium and potassium salt of a polysaccharidic acid (arabic acid) [10]. Idris et al. reported that AG comprised of 39-42% galactose, 24-27% arabinose, 12-16% rhamnose, 15-16% glucuronic acid, 1.5-2.6% protein, 0.22-0.39% nitrogen, and 12.5-16.0% moisture[11]. The chemical composition of AG can vary with its source, the age of the trees from which it was obtained, climatic conditions and soil environment [12].

AG was used primarily in the food industry to modify the physical properties of foods as an emulsifier and stabilizer and as food additive in sodas and candies. Also, it was used in a clinical study of cholesterol reduction at a dose of 15 g per day [13]. In folk medicine, AG has been reported to be used internally for the treatment of inflammation of the intestinal mucosa. At an appropriate dosage, it was used to modify intestinal transport. Externally, it was used to cover inflamed surfaces [14]. AG has been used in pharmaceuticals as a demulcent and soothes irritated mucous membranes. Consequently, it is used widely in topical preparations to promote wound healing and as a component of cough and some gastrointestinal preparations. Also it has been shown to inhibit the growth of periodontics bacteria and the early deposition of plaque [15].

Acacia gum has long been used in traditional medicine and in everyday applications. The Egyptians used the material as glue and as a pain-reliever base. Arabic physicians treated a wide variety of ailments with the gum, resulting in its current name [16]. Today, it is used widely in the pharmaceutical industry as a demulcent and in the cooking industry to give body and texture to processed food products [17].

AG contains a peroxidase enzyme which forms coloured complexes with certain amines and phenols and enhances the destruction of many pharmaceutical products including alkaloids and readily oxidizable compounds and also it has been identified as a trypsin inhibitor [17].

AG is primarily indigestible to both humans and animals and after passing the small intestine it is fermented under the influence of microorganisms in the colon to short chain fatty acids, particularly propionic acid. Such degradation products are absorbed in the human colon and subsequently utilized energetically in metabolism[18].

Either end stage renal failure or end stage renal disease requires renal replacement therapy (RRT) in the form of either dialysis or renal transplantation for survival. However, provision of RRT requires expert teams, working in specialized units, which makes therapy of patients with renal failure expensive. Maintenance peritoneal dialysis and hemodialysis sustain the lives of approximately 250000 uremic patients in developing countries [19]. The number of end-stage renal disease patients requiring renal replacement therapy (RRT) has increased dramatically throughout the world during the last decades [20]. The cost of treating uremia represents a growing demand on the health care systems of both rich and poor countries, the last being affected most. The literature is replete with publications on the impact of nutrition on kidney disease [21]. Most dietary attempts to treat chronic renal failure (CRF) and to decrease uremia use a protein restriction regimen (PRR) [22]. An alternative dietetic approach has relatively recently been proposed, based on fermentable carbohydrate (FC) supplementation of the diet[23]. This has been claimed to result in a similar urea-lowering effect by increasing urea nitrogen (N) excretion in stools, with a concomitant decrease in the total N excreted in urine of adults [24] and children [25].

Sodium Na^+ is the major positive ion (cation) in body fluid outside of cells and potassium K^+ is the major one inside the cells. Many processes in the body require electrical signals for communication. The movement of sodium and potassium is critical in generation of these electrical signals. Therefore variations in these cations level can cause cells to malfunction and can be fatal. Sodium and potassium regulate the total amount of water in the body and work to maintain the body's water balance also they play a role in critical body functions. One possible explanation for potassium's protective effect against hypertension is that increased potassium may increase the amount of sodium excreted from the body [26],[27].

This study aimed to investigate the effect of Arabic gum on some essential renal functions disorder caused by cadmium induction. A daily oral dose of 0.5 g/kg of AG has been administrated to nephrotoxic rats for two weeks post cadmium induction. Renal functions as urea, creatinine and some electrolytes such as Na, K, Ca and P were evaluated in serum.

2 MATERIAL AND METHODS

This study was carried out on male albino rats *Rattus rattus* as an animal model for induction of renal disorder. 40 adult male albino rats were employed in the current study. Animals were allowed ten days pre-experiment period to adapt to laboratory conditions in order to avoid any complications along the course of the experiment. They were housed in metallic cages at $28 \pm 2^\circ\text{C}$ and 50% relative humidity and received food and water ad-libitum with fresh supplies presented daily. The

animals were divided at random into four equal groups (ten rats each) on the base of body weight ($140 \pm 20\text{g}$) and according to the different treatment of the animals:

- 1- The first group received no treatment and represented the control group.
- 2- The second group received AG as a daily oral dose of 0.5 g/kg body weight dissolved in water for 14 days according to [28].
- 3- The third group were daily injected intraperitoneally with cadmium chloride at a dose of 2 mg / kg b.wt. for the same period as described by [29].
- 4- The fourth group received a cadmium chloride at a dose of 2 mg / kg b.wt. then followed by daily oral dose of 0.5 g/kg AG for 14 days.

Venous blood of all the groups was collected from the venous plexus of the eye by standard venipuncture with glass capillary tubes at the end of the 1st and the 2nd weeks post cadmium induction. The Sera were separated using cooling centrifuge and kept frozen at -20°C up to the time of estimation. Serum urea, creatinine and total calcium were measured spectrophotometrically according to [30], serum Na and K were measured by ion selective electrode according to [31] and phosphorus was estimated according to [32].

2.1 STATISTICAL ANALYSIS

All recorded data were expressed as mean \pm standard error and analyzed by applying the following mathematical principles, two-way analysis of variance (ANOVA) test followed by Duncan's multiply range test [33],[34].

The Statistical Package for the Social Sciences (SPSS) version 15 at a statistical significance level of $P < 0.05$ and 95% confidence interval were used.

- Evaluation of significant difference between the different treatments (F1) and also between 1st and 2nd week (F2).
- $\text{Na/K ratio} = [(\text{Na value in mEq/l}) / (\text{K value of the same group in mEq/l})] \times 100$

3 RESULTS AND DISCUSSION

Cadmium is a known human carcinogen and one of the components of tobacco which together with water and food contamination represent the main sources of non – occupational exposure in the general population [35]. Many studies were carried out on the physiological and histological effects of cadmium in human beings [36] and on laboratory animals [37],[38],[39].

Our present findings clearly indicated that exposure to cadmium led to a significant dysfunction in the kidney represented by a significant increment in the concentration of creatinine, urea, of the groups which treated with cadmium chloride at the 1st and 2nd weeks post cadmium induction compared to the control groups. These results are in accordance with the data obtained by [40],[41],[42],[43].

Treatment of the cadmium groups with AG decreased significantly the elevated urea and creatinine levels to be within the control levels. These results agree with [44],[45] who induced chronic renal failure (CRF) by adenine in animal model of human and tested the effect of AG. They found that AG alleviates the adverse effects of chronic renal failure in animal.

Dietary supplementation with AG may be an alternative to renal replacement therapy RRT to improve the quality of life and reduce or eliminate the need for dialysis in children with end stage renal disease (ESRD) in some developing countries [46],[47]. This is based on an increase in bacterial growth rate and activity in the gut. More advanced study has shown that AG is fermented by intestinal bacteria to short chain fatty acids propionate. The dominant bacteria which is most likely to be responsible for fermentation is *Prevotella ruminicola* [48]. Colonic bacteria produce ureases that hydrolyze urea to ammonia and CO_2 . The resultant ammonia can then be incorporated into bacterial proteins, which are subsequently excreted in the bacterial mass fraction of the feces. The net result is increased nitrogen excretion in the feces [49].

Clinically, AG has been tried in patients with chronic renal failure, and it was claimed that it reduce urea and plasma creatinine concentrations and reduces the need for dialysis from 3 to 2 times per week [50].

In Middle Eastern countries, AG is used in the traditional treatment of patients with chronic kidney disease and end stage renal disease. It increases fecal nitrogen excretion, lower serum urea nitrogen concentration in patients with chronic renal failure and decreases production of free oxygen radicals [51].

Intestinal AG fermentation leads to the formation of several degradation products including short-chain fatty acids [52]. Accordingly, AG treatment may enhance serum butyrate concentrations which have potential beneficial effects in renal disease by suppressing both basal and stimulated pro-fibrotic cytokine transforming growth factor-beta1 (TGF-beta1) by renal epithelial cells [53]. In the intestine, AG may modify the function of the reabsorbing epithelial cells [54].

Fecal bacterial mass and fecal nitrogen content were significantly increased during supplementation with AG compared with the baseline low protein diet (LPD) or supplementation with pectin. Serum urea nitrogen was significantly decreased during supplementation with Arabic gum compared with the baseline LPD or supplementation with pectin. Chronic renal failure (CRF) patients consuming a LPD supplemented with 50 g Arabic gum/d had greater fecal bacterial masses, greater fecal nitrogen excretion, and lower serum urea nitrogen than those consumed the LPD alone or supplemented with 1 g pectin/d. Because elevated concentrations of serum urea nitrogen have been associated with adverse clinical symptoms of CRF, the results suggest that Arabic gum may be a useful adjunct to a LPD for increasing excretion of nitrogenous wastes in feces [49]. Other study by Ali et al. [55] on rat models of acute renal failure showed that Arabic gum may also improve renal function independently of its action on fecal bacterial ammonia metabolism, but its effect is attributed to a decrease in the generation of free oxygen radicals.

Table 1. Mean and standard error of urea and creatinine after 1st and 2nd weeks post-cadmium treatment.

Renal functions	Treatments	1 st week	2 nd week	D.T.1 (treatment)
Urea (mg/dl) F1 = 7.102 * F2 = 3.342 *	Control	21.21± 0.20	21.18± 0.17	A
	Arabic gum	21.11± 0.19	20.69± 0.31	A
	Cd treatment	54.36±1.82	51.36±1.77	B
	Cd treatment + AG	25.11± 1.02	23.37± 1.13	A
D.T.2 (time) Urea		B	A	
Creatinine (mg/dl) F1 = 12.037 * F2 = 04.213 *	Control	0.50±0.02	0.47±0.03	A
	Arabic gum	0.48±0.03	0.51±0.02	A
	Cd treatment	1.79±0.06	1.71±0.05	B
	Cd treatment + AG	0.88±0.05	0.79±0.04	A
D.T.2 (time) Creatinine		B	A	

* Significant and no asterisks means non-significant.

- $P < 0.05$, F1 and F2 are the values of two ways ANOVA test.
- D.T.1 and D.T.2 are Duncan test symbols, (1) for different treatments and (2) for different times.
- Different letters in the same column indicated significant difference between different treatments.
- Different letters in the same row indicated significant difference between 1st and 2nd weeks.
- Letters in columns and rows are independent.

Pharmacologically, AG has been claimed to act as an anti-oxidant, and to protect against experimental hepatic, renal and cardiac toxicities in rats. Also, AG has been claimed to alleviate the adverse effects of chronic renal failure in humans. Reports on the effects of AG on lipid metabolism in humans and rats are at variance, but mostly suggest that AG ingestion can reduce plasma cholesterol concentrations in rats. AG has pro-absorptive properties and can be used in diarrhea. Previous studies have suggested an association between a low fiber intake and subsequent cardiovascular risk and very few studies have examined therapeutic intervention by Arabic gum supplementation of the diet [56].

According to Duncan test, the results in table (2) showed significant increase in serum K of the Cd treated groups as compared to the control group at the 1st and 2nd week post-cadmium induction. These results could be explained as those of Seifter (2011) [57] who reported that kidneys normally remove excess potassium from the body. High potassium levels are more likely to occur when the kidneys are not working properly and are less able to get rid of potassium.

The elevated level of K decreased significantly to be close to the control level when treated with AG. This can be explained as a result of kidney amelioration after treatment with AG.

According to Duncan test, table (2) showed significant decrease in serum Na levels of the Cd treated group compared to the control group in the 1st and 2nd week post-cadmium induction. The explanation for the decreased serum sodium (Na) level of the Cd group is that the increased potassium level due to kidney malfunction may increase the amount of sodium

excreted from the body [58]. Treatment of the Cd treated group with AG increased significantly the reduced Na levels to be close to the control level. Studies performed in healthy mice have suggested that Arabic gum decreases urinary sodium excretion and it could be the reason that raised serum Na in Cd treated group decreased significantly after AG treatment [54].

Table 2. Mean and standard error of some electrolytes (Na, K, Ca and P) after 1st and 2nd weeks post- cadmium induction.

Renal functions	Treatments	1 st week	2 nd week	D.T.1 (treatment)
Sodium (Na) (mEq/l) F1 = 6.732* F2 = 12.723*	Control	151.6±0.58	150.9±0.54	B
	Arabic gum	149.7±0.67	148.5±0.59	B
	Cd treatment	138.0±0.73	139.4±0.71	A
	Cd treatment + AG	148.2 ±0.88	148.9±0.79	B
D.T.2 (time) Na		B	A	
Potassium (K) (mEq/l) F1 = 4.332* F2 = 3.527*	Control	5.4±0.19	5.2±0.21	A
	Arabic gum	5.3±0.26	5.1±0.28	A
	Cd treatment	7.7±0.28	7.2±0.23	B
	Cd treatment + AG	6.5±0.38	5.8±0.24	A
D.T.2 (time) K		B	A	
Calcium (Ca) (mg/dl) F1 = 1.078 F2 = 0.012	Control	10.7±0.12	10.5±0.16	A
	Arabic gum	10.4±0.07	10.2±0.23	A
	Cd treatment	09.8±0.09	10.1±0.07	A
	Cd treatment + AG	10.4±0.17	10.6±0.22	A
D.T.2 (time) Ca		A	A	
Phosphorus (P) (mg/dl) F1 = 3.163* F2 = 6.546*	Control	5.1±0.11	4.8±0.13	B
	Arabic gum	4.8±0.19	4.7±0.16	B
	Cd treatment	3.9±0.10	4.4±0.05	A
	Cd treatment + AG	4.7±0.25	4.8±0.21	B
D.T.2 (time) P		A	B	

* Significant and no asterisks means non-significant.

- $P < 0.05$, F1 and F2 are the values of two ways ANOVA test.
- D.T.1 and D.T.2 are Duncan test symbols, (1) for different treatments and (2) for different times.
- Different letters in the same column indicated significant difference between different treatments.
- Different letters in the same row indicated significant difference between 1st and 2nd weeks.
- Letters in columns and rows are independent.

Table (2) also shows, according to Duncan test, that serum P was decreased significantly in the Cd treated group. Although most publications reported an increase in P level in CKD, Rubin explained that the levels of serum phosphorus in patients with CKD remain within the normal range or may even be modestly below the normal range, since the re-absorption of phosphorus from the renal tubules is reduced, thereby increases P excretion and decreases its serum level. As the glomerular filtrate rate (GFR) declines (stage 4 of CKD) the serum P increases [59].

Goldman and Schafer reported that in case of CRF serum sodium and P usually be normal but may be low, serum potassium raised and serum calcium: may be normal, low or high [60]. In this study, results of serum Ca in table (2) show non-significant difference either between different treatments or different times.

AG exhibits pharmacological effects related to interference with gastro- intestinal absorption of nutrients. Nasir et al. showed that AG blunted intestinal absorption of Na⁺ and water in healthy mice while enhanced calcium and magnesium uptake [54]. In a rat model of chronic osmotic diarrhea, AG exerted pro-absorptive properties by increased sodium and water absorption [61].

It is particularly important that the signs and symptoms of changes in plasma potassium concentrations should be particularly recognized and quickly treated, because the changes are potentially life threatening [62], so, it was helpful to evaluate Na/K ratio different groups.

The figure (1) shows the variation in Na/K ratio in different treated groups at 1st and 2nd weeks post-Cd induction. From the figure (1), it is clear that the Na/K ratio decreased in the Cd-treated groups about 16.0% compared with the control group. These results agree with Roth and Tyler who evaluated the low Na/K ratio in dogs suffering from different diseases including renal failure [63]. Also from the figure (1), it is clear that Na/K ratio of AG treated group decreased only about 4.0% compared with the control group. This implies that the treatment of the Cd-treated group with AG improved the decreased Na/K ratio by about 12.0%.

According to Earlbaum and Quinton, the Na/K ratio was significantly decreased with renal failures [64]. The serum Na/K ratios were more closely related to serum potassium concentrations than serum sodium concentrations. There is close correlation between progression of renal disease and blood pressure and furthermore, there is a large body of evidence which suggests that management of hypertension has profound beneficial effects delaying progression of renal disease.

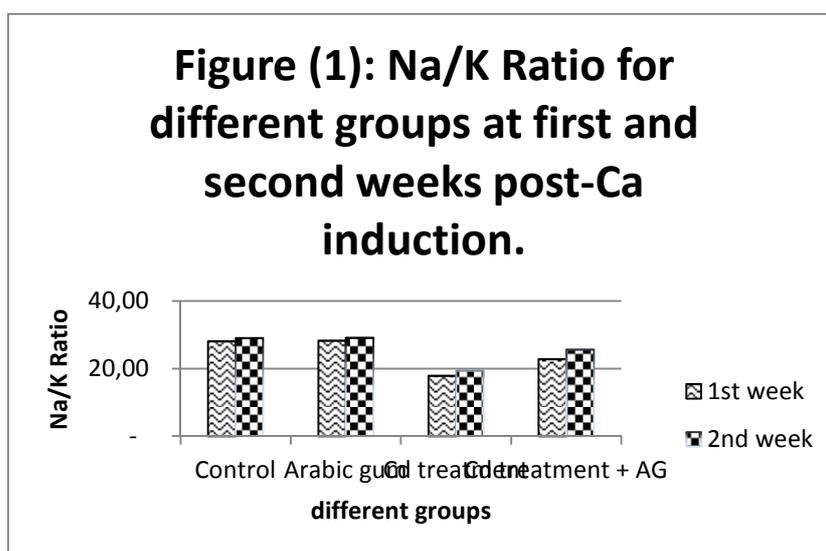


Figure (1): Na/K Ratio for different groups at first and second weeks post-Ca induction.

The alterations in blood pressure were occurred over a relatively short time and will translated into marked improvement in renal outcome [65]. The most striking finding in David et al. study is the reduction of blood pressure in all the groups supplemented with AG [66]. The lack of alteration in serum electrolytes and fluid balance in the patient cohort with significant renal failure can be added to the previous data on the safety and tolerance of AG in humans [67]. Cd-induced nephropathy and chronic oxidative renal damage and Arabic gum may reduce Cd-induced nephropathy by inhibiting chronic oxidative stress [68].

4 RECOMMENDATION

Results in tables (1) and (2) show significant enhancement in the level of urea, creatinine, K, Na and P at the 2nd week as compared to the 1st week post- Cd induction. This enhancement recommended the beneficial supplementation of daily diet intake with AG due to their effective roles in building the general body resistance parameters and immunity system. It also aid in decreasing the destructive and harmful effects caused by Cd in the kidney function. This correction was dependent on time of treatment.

5 CONCLUSION

In conclusion, AG which sometimes used in medications, has been claimed to alleviate the adverse effects of chronic renal failure. The current study showed significant amelioration of the studied kidney parameters after daily treatment with a dose of 0.5 g/kg of AG, hence, it can be used as a potent therapeutic in the treatment of renal disorder (urea, creatinine and

some electrolytes) resulted from cadmium toxication. The data support the dietary fiber hypothesis which states that there is a relationship between dietary fiber consumption and the improvement in renal malfunction. Since it is used till now as food supplement, so, further studies are needed to utilize AG pharmacologically in therapy.

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