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Antioxidant effect of Arabic gum against mercuric chloride-induced nephrotoxicity

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Abstract: The effects of Arabic gum (AG) against nephrotoxicity of mercury (Hg), an oxidative-stress inducing substance, in rats were investigated. A single dose of mercuric chloride (5 mg/kg intraperitoneal injection) induced renal toxicity, manifested biochemically by a significant increase in serum creatinine, blood urea nitrogen, thiobarbituric acid reactive substances, and total nitrate/nitrite production in kidney tissues. In addition, reduced glutathione, glutathione peroxidase, and catalase enzymes in renal tissues were significantly decreased. Pretreatment of rats with AG (7.5 g/kg/day per oral administration), starting 5 days before mercuric chloride injection and continuing through the experimental period, resulted in a complete reversal of Hg-induced increase in creatinine, blood urea nitrogen, thiobarbituric acid reactive substances, and total nitrate/nitrite to control values. Histopathologic examination of kidney tissues confirmed the biochemical data; pretreatment of AG prevented Hg-induced degenerative changes of kidney tissues. These results indicate that AG is an efficient cytoprotective agent against Hg-induced nephrotoxicity by a mechanism related at least in part to its ability to decrease oxidative and nitrosative stress and preserve the activity of antioxidant enzymes in kidney tissues.

Keywords: mercury, acacia gum, oxidative stress, lipid per oxidation, kidney toxicity

Introduction

Mercury (Hg) is a hazardous environmental and industrial pollutant which induces severe alterations in the body tissues of both humans and animals.^{1,2} The toxicity of Hg depends on the form of the Hg compounds (elemental, inorganic, and organic). Inorganic Hg accumulates predominantly in the kidneys, causing acute renal failure.^{3,4} The uptake, accumulation, and toxicity of inorganic Hg in the kidney have been related to it binding to endogenous thiol-containing molecules.⁵ Thiol-containing enzymes have been recognized as the targets of inorganic Hg.^{5,6} Moreover, binding of mercuric ions to thiol groups may cause decreased glutathione (GSH) levels, leading to increases in levels of reactive oxygen species (ROS), such as superoxide anion radicals, hydrogen peroxide, and hydroxyl radicals, which provoke lipid, protein, deoxyribonucleic acid (DNA), and ribonucleic acid (RNA) oxidation.^{7,8} Considering that oxidative stress and endogenous thiol depletion are involved in inorganic Hg toxicity, it has been suggested that antioxidants could contribute to the treatment of Hg poisoning.^{9,10} In this way, melatonin, curcumin, and vitamin E have been found to play a protective effect against mercuric chloride (HgCl₂)-induced acute renal toxicity.^{2,11–13} Similarly, a number of plant extracts with antioxidant properties have been shown to inhibit HgCl₂-induced renal toxicity.^{14–16}

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Arabic gum (AG) is a dried, gummy exudate from the stems and branches of *Acacia senegal* (Leguminosae), composed of calcium, magnesium, and potassium salts of the polysaccharide Arabic gum acid.¹⁷ AG has been used in Arabic folk medicine to reduce both the frequency and the need for hemodialysis in chronic renal failure patients.¹⁸ AG also has been shown to reduce urinary nitrogen excretion by increasing urea disposal in the cecum and lowering serum urea concentration in rats and humans.^{19,20} Additionally, we have recently reported that AG prevented gentamicin-induced nephrotoxicity. Co-treatment of AG significantly prevented gentamicin-induced lipid peroxidation in the kidney tissue, which was closely associated with protection of renal function and histological changes.¹⁸

To the best of our knowledge, there are no studies concerning the nephroprotective effect of AG against Hg intoxication. Therefore, the present study was carried out to investigate: 1) the adverse effect of acute Hg intoxication on the kidneys based on serum biochemical parameters, oxidative stress, and histopathologic alterations; and 2) the possible mitigating effect of AG against acute Hg intoxication in rats.

Materials and methods

Chemicals

Hg in the form of HgCl_2 was purchased from CHEMA TEC CO (Alexandria, Egypt). AG was purchased from Sigma-Aldrich (St Louis, MO, USA), and thiobarbituric acid was a product of Sigma-Aldrich. All other chemicals were of the highest grade commercially available.

Animals

Male Swiss albino rats (Animal house of College of Pharmacy, King Saud University, Riyadh, Saudi Arabia) weighing 150–200 g were used in all experiments. Animals were maintained under standard conditions of temperature and humidity with regular light/dark cycles and allowed free access to food (Purina Chow, Gray Summit, MO, USA) and water. All animal experiments were conducted according to the regulations of the Committee on Bioethics for Animal Experiments of Riyadh Colleges of Dentistry and Pharmacy.

Animal treatment

The animals were divided at random into four groups of ten animals each. The first group (control) received vehicles used for Hg (physiological saline solution, intraperitoneal injection [IP]). The second group received AG by oral gavage (7.5 g/kg/day) for 1 week.²¹ The third group was injected with HgCl_2 (5 mg/kg IP).²² The fourth group, received Ag

per oral route (os) (7.5 g/kg/day) for 5 days, then injected with HgCl_2 (5 mg/kg IP) and continued on Ag daily until the end of the experiment (1 week). Blood samples were taken by cardiac puncture, under light ether anesthesia, into non-heparinized tubes. Serum was separated by centrifugation for 5 minutes at 1,000 \times g and stored at -20°C until analysis. Animals were sacrificed by cervical dislocation and the kidneys were quickly isolated, washed with saline, blotted dry on filter paper, and weighed, and 10% (% weight per volume [w/v]) homogenate of the left kidney was made in ice-cold saline.

Measurement of serum biochemical parameters

Serum creatinine and blood urea nitrogen (BUN) concentrations were determined colorimetrically as described by Bonsnes and Taussky, and Hallet and Cook, respectively, using commercially available diagnostic kits (bioMérieux-RCS, Lyon, France).^{23,24}

Determination of lipid peroxides, GSH content, and enzyme activities of GSH peroxidase and catalase in kidney homogenate

GSH content and lipid peroxidation (malondialdehyde production) in the kidney tissues were determined according to Ellman, and Ohkawa et al, respectively.^{25,26} The enzyme activity of glutathione peroxidase (GSH-Px) and catalase were measured in the kidney homogenates according to Kraus and Ganther, and Higgins et al, respectively.^{27,28}

Determination of total nitrate/nitrite concentrations in renal tissues

Total nitrate/nitrite (NO_x) was measured as stable end product, nitrite, according to the method of Miranda et al.²⁹ The assay is based on the reduction of nitrate by vanadium trichloride combined with detection by the acidic Griess reaction. The diazotization of sulfanilic acid with nitrite at acidic pH and subsequent coupling with N-(10 naphthyl)-ethylenediamine produced an intensely colored product that is measured spectrophotometrically at 540 nm. The levels of total NO_x were expressed as mol g^{-1} wet tissue.

Histopathology

Histopathologic examination was performed on the animals of each group. Right kidney samples were taken. The tissue samples were fixed for at least 48 hours in 10% formalin in phosphate buffer (pH 7). The samples were then embedded in paraffin

wax, cut into 5 μm sections, and stained with hematoxylin and eosin. The slides were coded and were examined by a histopathologist who was unaware of the treated groups.

Statistical analysis

Data are expressed as mean \pm standard error. Statistical comparison between different groups was conducted using one-way analysis of variance (ANOVA) followed by a Tukey–Kramer multiple comparison test to judge the difference between various groups. Significance was accepted at $P < 0.05$.

Results

Effects of AG on Hg-induced changes in serum biochemical parameters

Serum creatinine and blood urea nitrogen (BUN) were significantly increased after injection of Hg as compared with the control group ($P < 0.001$) (Figures 1 and 2). Pretreatment of animals with AG (7.5 g/kg/day per os) 5 days before and concomitantly with Hg significantly reduced the rise in the level of BUN and creatinine.

Oxidative and nitrosative stress biomarkers

Figures 3 and 4 show the effects of AG, Hg, and their combination on oxidative stress biomarkers in renal tissues, namely

thiobarbituric acid reactive substance (TBARS) and reduced GSH, respectively. Hg resulted in a significant decrease in GSH content to reach only 75% of control group. Also, it leads to a significant 73% increase in TBARS as compared to the control group. Combined AG treatment with Hg significantly decreased TBARS ($P < 0.001$) and restored GSH level in renal tissues compared to the control values. Figure 5 shows the effects of AG, Hg, and their combination on the level of NOx levels in rat renal tissues. Hg resulted in a significant 91% increase of NOx in renal tissues as compared to the control group. Combined AG treatment with Hg significantly decreased NOx in renal tissues ($P < 0.05$) compared to the control values.

Antioxidant enzymes activities

Figures 6 and 7 show the effects of AG, Hg, and their combination on the activity of antioxidant enzymes GSH-Px and catalase in renal tissues, respectively. Hg resulted in a significant decrease in both GSH-Px and catalase enzyme activities as compared to the control group ($P < 0.001$ and $P < 0.001$, respectively). Combined AG treatment with Hg significantly improved both enzymes' activity ($P < 0.001$) in renal tissues compared to the control values.

Kidney pathology

Pathological examination of the kidneys of control and AG groups showed normal morphology of the renal parenchyma

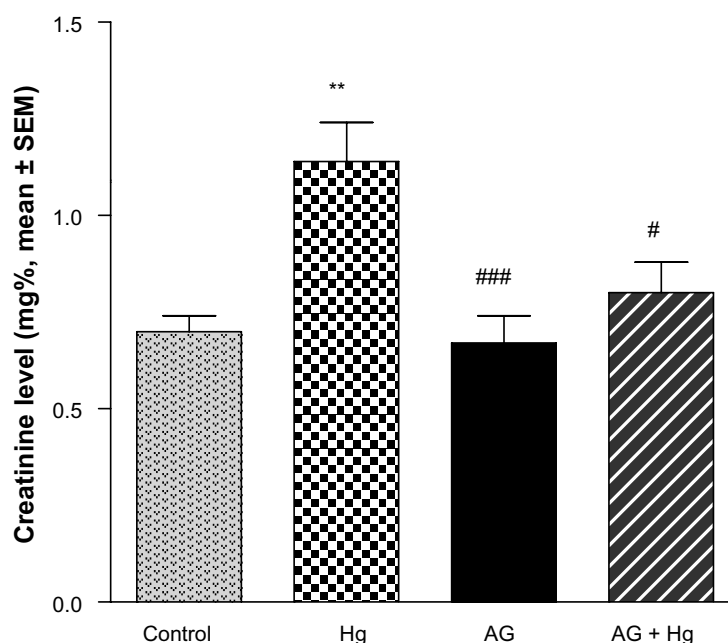


Figure 1 Effects of AG on elevated levels of serum creatinine induced by Hg.

Notes: AG (7.5 g/kg/day po) was given for 5 days before and concomitant with Hg. Significantly different from control group, ** $P < 0.01$. Significantly different from Hg, # $P < 0.05$, ### $P < 0.001$.

Abbreviations: AG, Arabic gum; Hg, mercury; SEM, standard error of the mean; po, per oral.

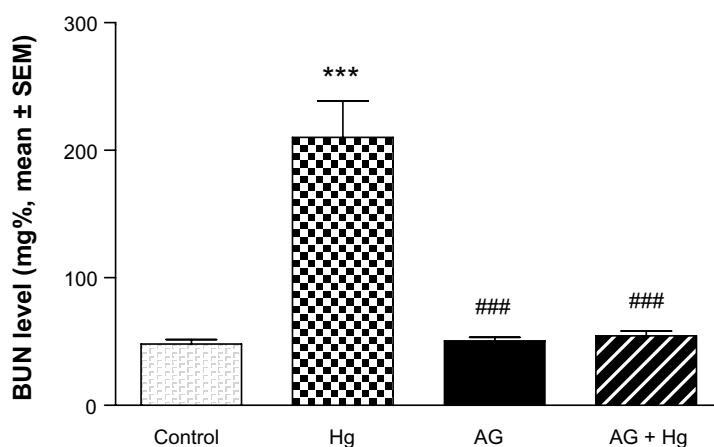


Figure 2 Effects of AG on elevated levels of BUN induced by Hg.

Notes: AG (7.5 g/kg/day po) was given for 5 days before and concomitant with Hg. Significantly different from control group, *** $P < 0.001$. Significantly different from Hg, ### $P < 0.001$.

Abbreviations: AG, Arabic gum; BUN, blood urea nitrogen; Hg, mercury; SEM, standard error of the mean; po, per oral.

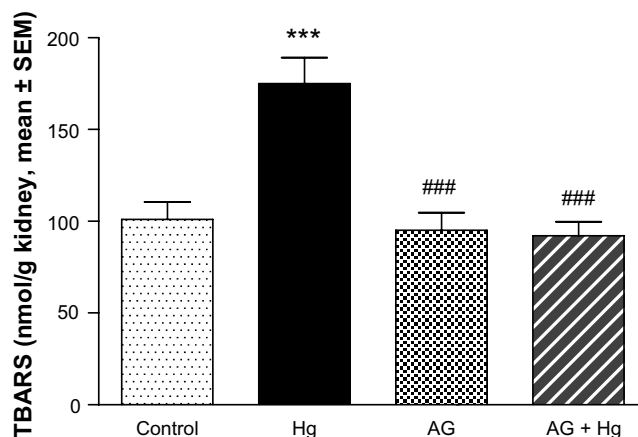


Figure 3 Effect of Hg, AG, and their combination on the levels of TBARS in rat renal tissues.

Notes: AG (7.5 g/kg/day po) was given for 5 days before and concomitant with Hg. Significantly different from control group, *** $P < 0.001$. Significantly different from Hg, ### $P < 0.001$.

Abbreviations: AG, Arabic gum; Hg, mercury; SEM, standard error of the mean; TBARS, thiobarbituric acid reactive substances; po, per oral.

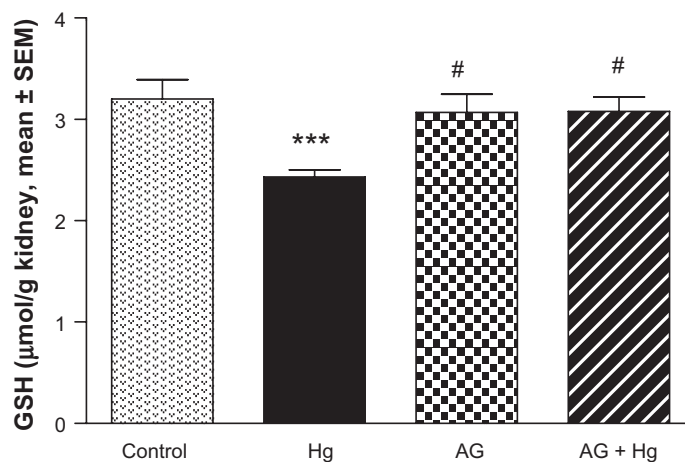


Figure 4 Effect of Hg, AG, and their combination on the levels of reduced GSH in rat renal tissues.

Notes: AG (7.5 g/kg/day po) was given for 5 days before and concomitant with Hg. Significantly different from control group, *** $P < 0.001$. Significantly different from Hg, # $P < 0.05$.

Abbreviations: AG, Arabic gum; GSH, glutathione; Hg, mercury; SEM, standard error of the mean; po, per oral.

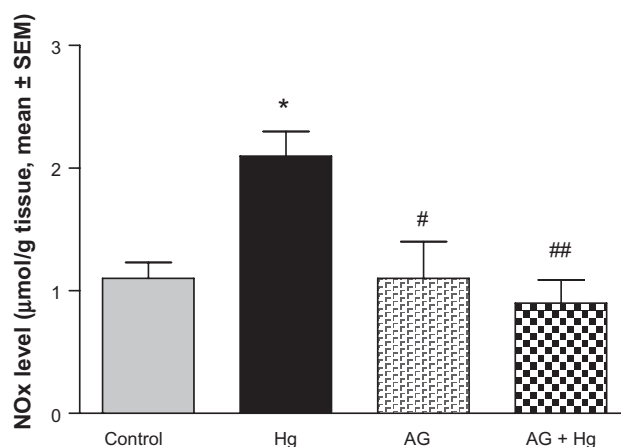


Figure 5 Effect of Hg, AG, and their combination on total NOx levels in rat renal tissues.

Notes: AG (7.5 g/kg/day po) was given for 5 days before and concomitant with Hg. Significantly different from control group, * $P < 0.05$. Significantly different from Hg, # $P < 0.05$, ## $P < 0.01$.

Abbreviations: AG, Arabic gum; Hg, mercury; NOx, nitrate/nitrite; SEM, standard error of the mean; po, per oral.

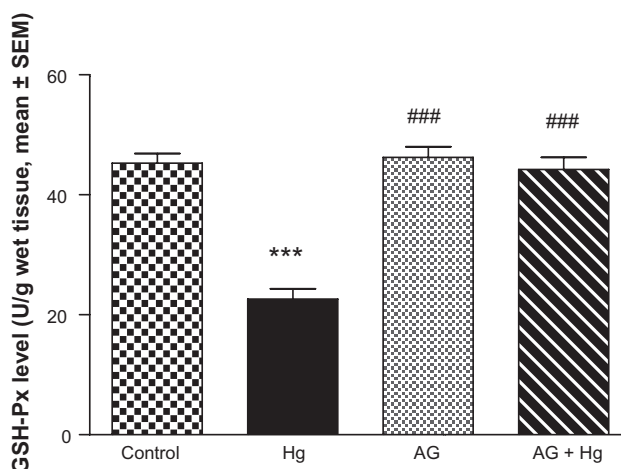


Figure 6 Effects of AG on changes in GSH-Px enzyme activities induced by Hg.

Notes: AG (7.5 g/kg/day po) was given for 5 days before and concomitant with Hg. Significantly different from control group, *** $P < 0.001$. Significantly different from Hg, ### $P < 0.001$.

Abbreviations: AG, Arabic gum; GSH-Px, glutathione peroxidase; Hg, mercury; SEM, standard error of the mean; po, per oral.

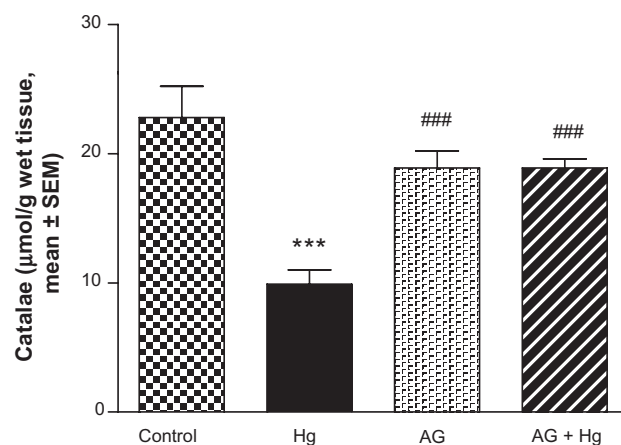


Figure 7 Effect of Hg, AG, and their combination on the catalase activity in rat renal tissues.

Notes: AG (7.5 g/kg/day po) was given for 5 days before and concomitant with Hg. Significantly different from control group, *** $P < 0.001$. Significantly different from Hg, ### $P < 0.001$.

Abbreviations: AG, Arabic gum; Hg, mercury; SEM, standard error of the mean; po, per oral.

with well-defined glomeruli and tubules with non-significant changes (Figures 8 and 9). However, animals treated with Hg showed clear signs of glomerular and tubular necrosis, interstitial nephritis, and desquamation of the tubular epithelial cells in the renal cortex (Figure 10). Interestingly, kidney specimens from rats treated with AG and Hg revealed significant improvement in glomeruli and renal tubules, evidenced by less vacuolization and more preservation of tubular histology (Figure 11).

Discussion

Mercuric ion, one of the strongest thiol-binding agents, increases the intracellular levels of ROS and induces oxidative stress, resulting in tissue damage.^{30–32} Hg toxicity is associated with superoxide radical generation and GSH reduction.^{33,34} Our study demonstrates that the treatment of rats with HgCl_2 revealed a significant enhancement in TBARS levels, indicative of the generation of lipid peroxides. Enhanced lipid peroxidation levels were also reported in Hg toxicity by Agarwal et al and Sener et al.^{13,35} HgCl_2 is known to increase the production of many ROS, such as superoxide and H_2O_2 , which cause lipid peroxidation and subsequently oxidative tissue damage.^{36–38} Endogenous GSH has a specific role in protecting the body from Hg toxicity due to its function as a carrier of Hg and its antioxidant properties. GSH binds with Hg and forms a complex that prevents Hg from binding to cellular proteins and subsequently causing damage to both enzymes and tissue.³⁹ Hg poisoning leads to a reduction of intracellular GSH content and decreases the antioxidant potential of the cells. The present study revealed that Hg-treated rats showed a significant depletion of serum GSH levels. Agarwal et al reported a significant reduction of GSH levels in liver, kidney and brain tissues.^{12,13}

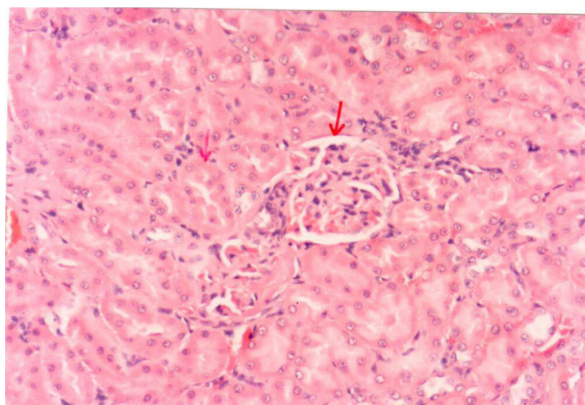


Figure 8 A photomicrograph of the renal cortex of a control rat. The red arrows showing parenchyma with normal glomeruli and tubules, $\times 200$ magnification.

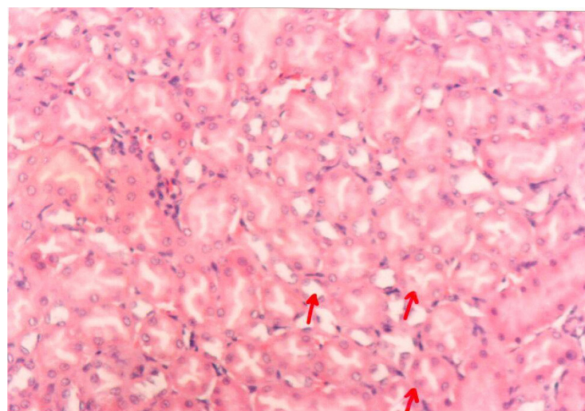


Figure 9 A photomicrograph of kidney of an Arabic gum-treated rat. The red arrows showing cortical tubules and peritubular capillaries with no pathogenic changes, $\times 200$ magnification.

Alterations observed in the activity of GSH-Px and catalase in kidney tissues of Hg-exposed animals indicate the generation of ROS (O_2^- or H_2O_2). Inhibition in the activity of renal antioxidant enzymes, such as superoxide dismutase (SOD), GSH-Px, and catalase, in addition to depletion of GSH levels was also reported earlier.^{40,41} Enhanced creatinine and BUN levels indicate nephrotoxicity, as reported by Rumbeiha et al.⁴² Histopathologic alterations in kidney tissues after Hg exposure were revealed. Rumbeiha et al, Al-Saleh et al, Sarwar Alam et al, and Augusti et al have also reported similar histopathologic alterations in Hg-induced nephrotoxicity.^{42–45}

Pretreatment with AG attenuated the Hg-induced oxidative damage. Hence, pretreatment with AG significantly restored the increased TBARS and decreased GSH levels to the normal values. This could be attributed to the excellent antioxidant properties of AG.⁴⁶ These properties seem to

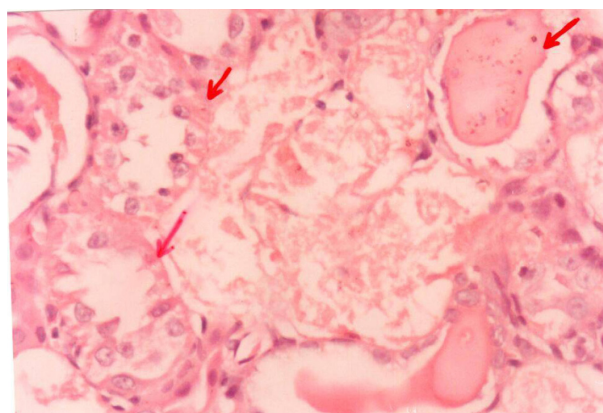


Figure 10 A photomicrograph of the kidney of a mercury-treated rat. The red arrows showing necrotic changes of the renal tubular cells and some tubules contain casts, $\times 400$ magnification.

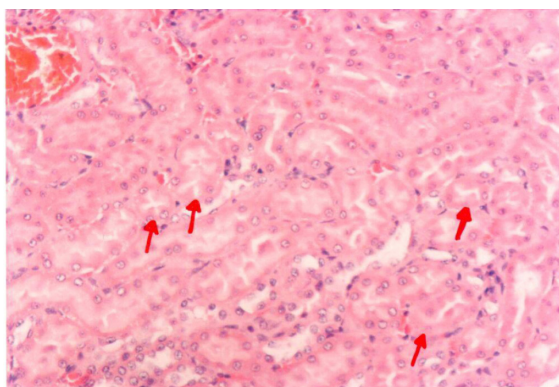


Figure 1 A photomicrograph of the kidney of an Arabic gum- and mercury-treated rat. The red arrows showing insignificant tubular epithelial changes in the form of cloudy swelling, $\times 200$ magnification.

be due to its ability to scavenge free radicals. The kidneys are the primary target organ for accumulation and toxicity of inorganic Hg.⁵ In fact, in as little as 1 hour, 50% of an administered dose of inorganic Hg is present in the kidney.⁴⁷ Within the kidney, the majority of mercuric ions were detected in the cortex and outer stripe of the outer medulla. This finding was expected considering that the proximal tubule, which spans these two renal zones, is the primary site of accumulation of mercuric ions.⁵ The histopathologic findings in the kidney tissue of Hg-treated rats include severe diffuse acute necrosis of the tubular epithelium, fragmentation and shedding of tubular epithelium in the lumina of the renal tubules, and interstitial edema as a result of tubular leakage. The interaction of Hg with protein thiol groups is thought to play an important role in nephrotoxicity induced by Hg at the cellular level.⁵ The results of this study indicate that AG improved Hg-induced nephrotoxicity, manifested by a decrease in both serum creatinine and urea levels, and minimized the intensity of the renal lesions. The nephroprotective effect of AG against many nephrotoxic agents was noted in several reports.^{18,21,48–53} The antioxidation induced by AG might be one of the most likely mechanisms contributing to its beneficial effect against renal injury. This antioxidant effect of AG was confirmed previously by *in vitro* studies, which showed that AG had a dose-dependent scavenging of superoxide radicals generated enzymatically and nonenzymatically.⁵⁴ It could be suggested that AG scavenges Hg free-radical generation and, in turn, inhibits lipid peroxidation-induced injury in renal tissues, which has been suggested to protect renal structure and function. Therefore, the protective effect is provided by AG on renal tissue through antioxidants as well as by scavenging free radicals *in vivo*.

Conclusion

In summary, our data indicate that Hg-induced nephrotoxicity is related to lipid peroxidation. Co-administration of AG provided protection against HG-induced nephrotoxicity, possibly by inhibiting the free radical mediated process. These protective effects of AG on renal injury induced by Hg might have a considerable impact on developing clinically feasible strategies to treat patients with toxin-induced renal failure.

Disclosure

The authors report no conflicts of interest in this work.

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