IJPSR (2021), Volume 12, Issue 12 (Research Article)

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 18 January 2021; received in revised form, 10 May 2021; accepted, 28 May 2021; published 01 December 2021

ANTITOXIC EFFECTS OF GUM ARABIC (*ACACIA SENEGAL*) AND GUAR GUM (*CYAMOPSIS TETRAGONOLOBUS*) AGAINST HEPATORENAL TOXICITY INDUCED BY MERCURIC CHLORIDE IN RATS

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Keywords:

Mercuric chloride, Gum Arabic, Guar gum, Hepatorenal, Toxicity

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ABSTRACT: Heavy metal accumulates mostly in the liver and kidney as these organs involved in the detoxification and excretion of foreign materials. In the present study, we explored the effect of Gum Arabic (GA) and Guar Gum (GG) on mercuric chloride ($HgCl_2$) induced hepatorenal toxicity. Twenty-eight adult male albino rats "Sprague Dawely" weighing 250-300 g were divided into four equal groups: the first group served as the negative control group, the second group received intraperitoneal (I.P.) injection with $HgCl_2$, the third group received $HgCl_2$ injection followed by GA and the fourth group received $HgCl_2$ injection followed by GG. $HgCl_2$ injection caused a significant increase in serum total bilirubin, aspartate aminotransferase (ALT), alanine aminotransferase (AST), creatinine, urea, and uric acids compared to control. Moreover, there was a significant reduction in tissue-reduced glutathione (GSH) with a marked increase in the tissue hydroxyproline content and TGF-β% in the liver and kidney. Also, hepatorenal intoxication was confirmed by histopathological examination compared with the control group. Treatment with GA or GG showed significant recovery ($p \leq 0.05$) in all previous parameters and histopathological appearance. In contrast, GG showed more powerful improvement than GA. In conclusion, we suggested that GA & GG may have a promising antitoxic property, gives it the applicability to be used as a prophylactic agent against mercury-induced hepatorenal cytotoxicity.

INTRODUCTION: Mercury (Hg) is a global environmental pollutant, accumulating mainly in the kidney and liver inducing hepatorenal toxicity, oxidative stress, and tissue damage [1]. Exposure to any form of mercury from different ways such as water, air, soil, and food poses serious threats to our health and the environment [2].

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.12(12).6353-61

This article can be accessed online on www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.12(12).6353-61

Mercury ions are taken up and accumulate in numerous organs, including the brain, intestine, kidney, liver, and placenta [3]. One reasonable hypothesis of mercury toxicity that it is involves oxidative stress, inflammation, and apoptosis [4].

High Hg exposure can trigger the formation of Reactive Oxygen Species (ROS) and interfere with the body's antioxidant metabolism. A high level of free radicals in the body can be characterized by a low level of an antioxidant enzyme [5]. The uptake, accumulation, and toxicity of inorganic Hg in the liver and kidney have been related to its binding to endogenous thiol-containing molecules. 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 [1].

Gum Arabic (GA) belongs to the "Fabaceae" plant family, also known as gum acacia. GA is a dehydrated sticky exudate gained mainly from the stems and branches of Acacia Senegal, it is water-soluble dietary fibers, consists principally of polysaccharides with high molecular weight and their magnesium, calcium, and potassium salts, the viscosity effect of these fibers relays digestion and absorption of carbohydrates, regulating glycemic index and bodyweight reduction [6]. GA suppresses absorption of glucose in the intestine via interaction with membrane abundance of sodium-glucose transporter-1 (SGLT1) in experimental mice [7]. GA possesses antioxidant, antihyperlipidemic, and antidiabetic effects [8]. Moreover, phenolic compounds, ferric reducing power, and cupric reducing capacity was detected in GA samples [9]. This antioxidative capacity enables GA to exert protective effects on liver and kidney organs [10].

Guar gum (GG) bean is found mostly in India, Pakistan, U.S., Australia and Africa. It is a high molecular weight polysaccharide that is chemically composed of sugar galactose and mannose. The backbone of this polysaccharide is a linear chain of β 1,4-linked mannose residue while the galactose residues are 1,6-linked at every second mannose, giving short side branch [11]. Guar gum has been widely used in the food industry as a thickener and/or emulsion stabilizer based on its excellent solution properties [12]. However, a highly viscous GG solution can interfere with digestion and absorption of nutrients, resulting in reduced protein efficacy and lipid utilization [13]. Guar gum (GG) acts frequently as water-soluble and bulk-forming laxative fiber. It is effective in promoting regular bowel movements, relieving constipation, Crohn's disease, diverticulosis, irritable bowel syndrome and colitis, *etc.* Guar gum and its derivatives can be employed for physiological disorders [14]. The intake of partially hydrolyzed guar gum (PHGG) reduces the postprandial blood glucose absorption in the small intestine and glucose level in the systemic circulation [15]. Moreover, extremely high viscosity restricts the incorporation of GG into enteral formulas or food products at a physiologically effective concentration to show positive health benefits [16]. This study aimed to evaluate the antitoxic effects of GA and GG against hepatorenal toxicity induced by mercuric chloride in rats.

MATERIALS AND METHODS:

Materials: Gum Arabic and Guar Gum were purchased from the Agriculture Research Center, (Giza, Egypt). They were purified and screened out from any impurities. The water solution was prepared by adding distilled water to the powder of GG and GA to achieve a dose of (500 mg/kg body weight) [10].

Chemicals: Mercuric chloride was obtained from El Gomhoreya Company for Drugs Trade& Medical supplies, Cairo, Egypt.

Animals: Twenty-eight adult male albino rats "Sprague Dawely" weighing 250-300 g were kept in stainless steel cages in the well-ventilated animal house of the Medical Ain Shams Research institute (MASRI), Faculty of Medicine, Ain Shams University. All rats had been kept in the room for 1 week before the beginning of the experiment for acclimatization. All experiments were conducted in accordance with the guide for the care and use of experimental animals for maintenance, treatment, and killing of the animals. Animals were housed in stainless cages and provided a commercial diet and water *ad-libitum*.

The experiment was designed and conducted according to bioethics approved by the animal care use committee (IACUC) of Faculty of Science, Cairo University No: 1607 on 3/7/2020.

Induction of Hepatorenal Toxicity: Rats were injected I.P. by 4 mg/kg $HgCl_2$ as a single dose 1.

Experimental Design: The animals were divided into four groups 7 rats in each group. Group 1: (control group) rats were injected I.P. by normal saline as a single dose then received 1ml distilled water daily using oral gavage for 2 weeks. Group 2: ($HgCl_2$ group) served as positive control injected by $Hgcl_2$ as mentioned before for induction of hepatorenal toxicity then received 1 ml distal water using oral gavage daily for 2 weeks. Group 3 ($HgCl_2$+GA) & Group 4 ($HgCl_2$+GG) rats were injected by HgCl2 as group 2 followed by 1ml oral dose of GA or GG water solution respectively at a

dose of (500 mg/kg body weight) 12using oral gavage daily for 2 weeks.

Sample Collection: At the end of the experimental period (2 weeks), all animals were sacrificed by cervical decapitation and blood samples were collected from the hepatic portal vein. Blood was left to clot and serum was separated by centrifugation at 3000 r.p.m. for 10 min at 4 °C where the clear serum was obtained for biochemical analysis. Liver and kidney were removed, washed with saline solution, dried then part of tissue samples was and kept in 10% formalin solution for microscopic examination, and another part used for determination of reduced glutathione, hydroxyproline content and $TGF\beta^{-1}$.

Biochemical Analysis: Liver function tests such as serum ALT, AST enzyme activities, and serum total bilirubin were determined. Also, serum urea, uric acid, and creatinine levels were determined to assess kidney functions using colorimetric Bio-Systemskits (BioSystems S. A. Costa Btava, Spain) according to the manufacturer's instructions.

Liver and kidney tissue homogenate were prepared by rapidly homogenizing (Use Dounce Tissue Homogenizer Cat. No.PK-CA577-1998) and used for determination of GSH level, using colorimetric assay PromoKine kits IC at. No. PK-CA577-K464 (Sickingenstr. Hiedelberg, Germany). Also, tissue TGFβ-1% was measured by sandwich ELISA assay for quantitative measurement using BioVision $TGF\beta^{-1}$ (Rat) ELISA Kit Cat. No. #E4510-100 (Milpitas Blvd., Milpitas USA).

Furthermore, Hydroxyproline in liver and kidney tissue was determined by colorimetric assay using BioVision hydroxyproline Kit (Perchlorate-Free) Cat. No. #NBP2-59747) USA.

Histopathological Examination: Formalin-embedded liver and kidney tissues were cut into 4 μm thick sections, and then, the slides were stained with hematoxylin and eosin (H&E) for histological. Sections were examined and photographed using an Olympus light microscope (Olympus BX51, Tokyo, Japan).

Statistical Analysis: Data were statistically analyzed by Statistical Package for Social Science (SPSS) version 16.0 statistical packages. Values were presented as mean ± standard deviation (S. D). Statistical differences between groups were performed using one-way ANOVA; the mean difference was significant at the level ($p<0.05$) level [17].

RESULTS:

Antitoxic Effects of Gum Arabic (Acacia Senegal) and Guar Gum (*Cyamopsis tetragonolobus*) on live status: From the results tabulated in **Table 1** it was clear that I.P. injection with $HgCl_2$ caused acute liver toxicity that appeared as a significant increase in serum total bilirubin level that recorded 0.541±0.178mg/dl while the normal control group recorded mean value 0.116±0.010mg/dl. Also, liver enzymes ALT and AST showed a significant increase as the mean values were 77.37±15.530 U/L and104.11±4.70 U/L, respectively.

TABLE 1: ANTITOXIC EFFECTS OF GUM ARABIC (*ACACIA SENEGAL*) AND GUAR GUM (*CYAMOPSIS TETRAGONOLOBUS*) ON LIVER STATUS

	Total bilirubin (mg/dl)	ALT (U/L)	AST (U/L)	L-GSH (nmol/mg)	L-HRP (µg/mg)	L-TGFβ-1 (pg/mg)
Normal control	0.116±0.010[a]	21.63±5.030[a]	42.39±1.35[a]	0.495±0.050[a]	0.69±0.054[a]	4.65±1.65[a]
$Hgcl_2$ group	0.541±0.178[b]	77.37±15.530[b]	104.11±4.70[b]	0.271±0.029[b]	3.06±0.147[b]	9.99±0.96[b]
Gum Arabic group ($Hgcl_2$ + GA)	0.257±0.029[c]	37.52±0.325[c]	90.05±1.35[c]	0.883±0.029[c]	1.98±0.047[c]	5.96±0.40[c]
Guar Gum group ($Hgcl_2$+GG)	0.220±0.026[a,c]	30.57±0.975[a,c]	77.46±2.41[c]	0.709±0.014[d]	1.80±0.010[d]	5.50±0.28[a,c]

Values are represented as mean ±SD., (n=7) There was no significant difference between means that have the same letter in the same column ($P< 0.05$)

While their corresponding controls were 21.63 ± 5.030 U/L and 42.39 ±1 .35U/L, respectively. The oral administration of water solution of GA showed a significant decrease in serum total bilirubin level and liver enzyme activities ALT and AST by about 52.5%, 51.5%, and 13.5%, respectively as

compared with $HgCl_2$ group. Meanwhile, the oral administration of water solution of GG caused a more significant decreased in serum total bilirubin level and liver enzymes ALT and AST activities by about 59.33%, 60.5%, and 25.6%, respectively, as compared with the HgCl2 group.

The results of liver homogenate analysis for GSH level showed a significant decrease in$HgCl_2$ group that recorded 0.271 ± 0.029 nmol/mg while the corresponding normal control mean value was 0.495 ± 0.050 nmol/mg. Treatment with GA and GG caused a significant increase of reduced glutathione level where the mean values were 0.883 ± 0.029 nmol/mg and 0.709 ± 0.014 nmol/mg respectively. With respect to the result of hydroxyl-proline (HPR) in liver homogenate, the normal control group recorded 0.69 ± 0.054 µg/mg while I.P. injection with $HgCl_2$caused a significant increase that recoded 3.06 ± 0.147 µg/mg. Oral administration of GA and GG decreased significantly the mean values of HPR by about 35.29% and 41.18%, respectively, as compared with $HgCl_2$ group. The results of $TGF\beta^{-1}$ showed the normal control level was 4.65±1.65 pg/mg while $HgCl_2$ injection caused a significant increase that recoded 9.99 ± 0.96 pg/mg. Moreover, treatment with GA and GG caused a significant decrease in $TGF\beta^{-1}$ level in liver homogenate by about 40.34% and 44.94 %, respectively, as compared with $HgCl_2$ group.

Antitoxic Effects of Gum Arabic (*Acacia Senegal*) and Guar Gum (*Cyamopsis tetragonolobus*) on Kidney Status: The present results tabulated in **Table 2** showed that the I.P. injection with HgCl2 caused acute kidney toxicity that appeared as a significant increase in serum levels of NPN components creatinine, urea, and uric acid that recorded mean values 3.74 ± 0.132 mg/dl, 81.45 ± 6.50 mg/dl and 2.24 ± 0.163 mg/dl respectively while, their corresponding normal control mean values were 0.39 ± 0.045mg/dl, 34.61 ± 0.05 mg/dl and 1.14 ± 0.107mg/dl respectively.

TABLE 2: ANTITOXIC EFFECTS OF GUM ARABIC (*ACACIA SENEGAL*) AND GUAR GUM (*CYAMOPSIS TETRAGONOLOBUS*) ON KIDNEY STATUS

	Creatinine (mg/dl)	Urea (mg/dl)	Uric Acid (mg/dl)	K-GSH (nmol/mg)	K-HRP (µg/mg)	K- TGFβ-1 (Pg/mg)
Normal control	0.39±0.045[a]	34.61±0.05[a]	1.14±0.107[a]	0.42±0.036[a]	1.42±0.021[a]	10.84±0.370[a]
$Hgcl_2$ group	3.74±0.132[b]	81.45±6.50[b]	2.24±0.163[b]	0.33±0.013[b]	4.79±0.264[b]	24.45±4.400[b]
Gum Arabic group ($Hgcl_2$+ GA)	1.88±0.021[c]	51.84±2.34[c]	1.12±0.083[a]	0.65±0.018[c]	3.86±0.144[c]	11.49±0.169[a]
Guar Gum group ($Hgcl_2$+GG)	1.98±0.538[c]	38.29±5.22[a]	1.20±0.067[a]	0.79±0.018[d]	4.03±0.072[c]	11.17±0.502[a]

Values are represented as mean ±SD., (n=7) There was no significant difference between means that have the same letter in the same column (P< 0.05)

The oral administration of GA showed a significant decrease in serum levels of creatinine, urea, and uric acid by about 49.73%, 36.35%, and 50 % respectively as compared with $HgCl_2$ group. Whereas, oral administration of GG significantly reduced their serum levels by about 47.06%, 52.90%, and 46.43%, respectively as compared with $HgCl_2$ group. The results of kidney homogenate analysis for reduced glutathione level were 0.42 ± 0.036 nmol/mg in the normal control group while injection with $HgCl_2$ significantly reduced the level to 0.33 ± 0.013 nmol/mg. Treatment with GA and GG caused a significant increase of reduced glutathione level in kidney homogenate and mean values were 0.65 ± 0.018 nmol/mg and 0.79 ± 0.018 nmol/mg, respectively. As noticed GG was more effective than GA on GSH level. Concerning the result of HPR level in kidney homogenate, the normal control group recorded 1.42 ± 0.021 µg/mg while $HgCl_2$ group significantly increased the level to 4.79±0.264 µg/mg. Oral administration of GA and GG significantly decreased the mean values of HPR that recorded 3.86 ± 0.144 µg/mg and 4.03 ± 0.072 µg/mg, respectively. The results of $TGF\beta^{-1}$ in kidney homogenate showed that the normal control level was 10.84 ± 0.370pg/mg while injection with $HgCl_2$ caused a significant increase that recoded 24.45 ± 4.400pg/mg. Moreover, treatment with GA and GG caused a significant decrease in $TGF\beta^{-1}$ level by about 53.17% and 54.31%, respectively, as compared with $HgCl_2$ group.

Histopathological Examination of Liver and Kidney Tissues: According to the results of histo-pathological examination of liver and kidney tissues that were illustrated in **Fig. 1** & **2**, there were no abnormalities or histological changes observed in the livers of normal rats as illustrated in **Fig. 1A** that showed normal central vein in some of the hepatic lobules. In addition, unremarkable hepatocytes and portal tract concluded unremarkable changes in liver tissue.

While $HgCl_2$ injection caused severe hepatic necrosis with disappearance and dis-arrangement of hepatic lobules structures. Extensive granular and vesicular degeneration, vacuolation, and inflammatory cell infiltrations in the portal region in the liver were also observed **Fig. 1B**, **1C** & **1D** illustrated that treatment with GA, and GG showed some regions of recovery and restored the normal architecture of the hepatic lobules and the hepatocytes.

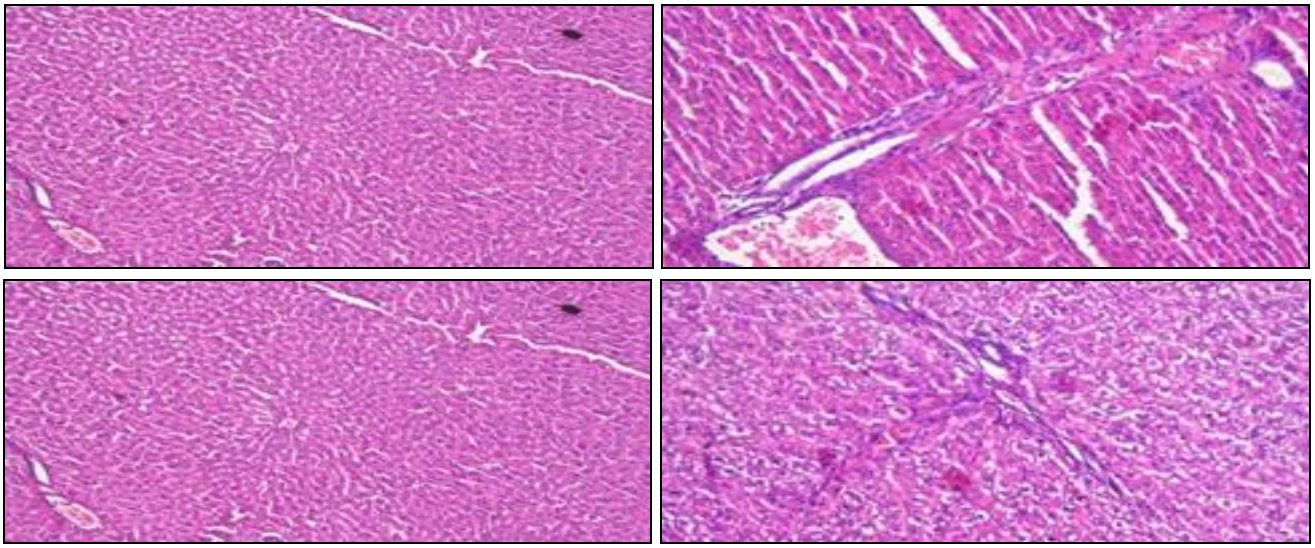

FIG. 1: HISTOPATHOLOGICAL FINDINGS IN THE LIVER. (A) HEPATIC HISTOLOGY OF THE CONTROL GROUP, SHOWING NORMAL HEPATIC LOBULAR ARCHITECTURE. (B) HEPATIC DEGENERATIVE CHANGES WITH EXTENSIVE CELL NECROSIS WERE OBSERVED INHGCL2 INJURED RATS. (C) GA TREATED GROUP SHOWED MILD CHRONIC NECROSIS (D) GG TREATED GROUP SHOWED A SIGNIFICANT MODULATION IN THE HEPATIC HISTOLOGY

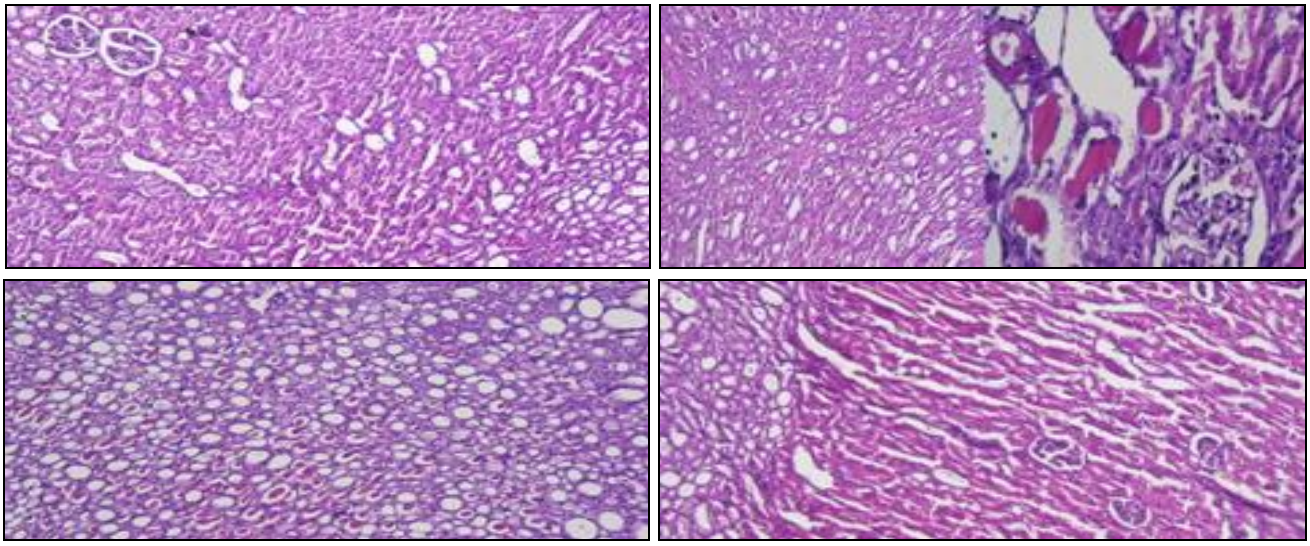

FIG. 2: HISTOPATHOLOGICAL FINDINGS IN THE KIDNEY. (A) CONTROL GROUP REVEALS NORMAL TISSUE ARCHITECTURE. (B) HGCL2 TREATED GROUP, NEPHROPATHIES ARE CHARACTERIZED BY CHRONIC TUBULE-INTERSTITIAL NEPHRITIS (C) HGCL2+ GA TREATED GROUP, THERE IS PRONOUNCED PRESERVATION OF TUBULAR INTERSTITIAL NEPHRITIS WITH MILD DECREASES IN THE DEGENERATIVE (D) HGCL2+GG TREATED GROUP, SIGNIFICANT REDUCTION IN LESIONS WERE OBSERVED ONLY IN THE RATS THAT WERE CONTINUOUSLY TREATED WITH GG AFTER HG INTOXICATION

Fig. 2 H&E histopathological stain in the control group showed normal kidney morphology **Fig. 2A**, **2B** showed the gross change of kidney was characterized by swelling, paleness of kidney, and congestion in $HgCl_2$ treated groups with chronic tubular interstitial nephritis, and many degenerated signs. Microscopic lesions with variable severity were noticed in the kidney. The lesions were characterized as various degrees of hemorrhage, necrobiotic changes, degenerative changes in tubular epithelium, hypercellularity of glomeruli, degeneration, and intratubular hemorrhage, with prominent nuclei as seen in **Fig. 2B**. Atrophic lining with intraluminal hyaline casts was also observed in GA treated group **Fig. 2C**. Meanwhile, GG administration after $HgCl_2$ showed mild mesangial hypercellularity in some of the glomeruli **Fig. 2D**. Dramatically, GA and GG treatment improved Hg nephrotoxicity, and less histological damage was observed in renal corpuscles and renal tubules.

DISCUSSION: Serum levels of total bilirubin, ALT, and AST are sensitive liver function indexes and are usually employed for the diagnosis of liver diseases. When serious liver damage occurs, these parameters are leaked out from hepatocytes into the blood. Moreover, the significant increase of serum urea and creatinine after exposure to $HgCl_2$ indicating its marked nephrotoxic effect and is assumed to be related to the fact that the kidney accumulates more mercury than other organs in the body with serious kidney damage caused these parameters to be elevated in serum. In the present study, liver and renal functions were detrimentally altered after $HgCl_2$ administration causing hepatorenal dysfunction evidenced by a significant elevation in total bilirubin, ALT and AST, enzyme activities, and urea, uric acid, and creatinine levels. Liver and kidney are the target metabolic and excretory organs for numerous harmful compounds and the major sites for Hg accumulation, which can alter their structure and function [18]. The current results come in agreement with the previous work of Oriquat *et al.,* [19] who revealed that $HgCl_2$ at a dose of 3.75 mg/kg body weight increased the AST and ALT, activities significantly than the control group. This study also indicates that mercury increases the levels of serum urea and creatinine; and decreases the iron level. Furthermore, Salman *et al.,* [20] who reported a significant increase in serum ALT, AST, creatinine, and urea levels in rats, received HgCl2 (0.5 mg/kg.BW) intraperitoneal daily for 2 weeks. Additionally, Abd Elghani *et al.,* [21] observed a significant increase in serum values of ALT, AST, and GGT in the HgCl2 group. This could be attributed to severe damage in liver cells which releasing the hepatic enzyme into the serum. Treatment with GA and GG showed a marked improvement that was clear in the previously listed parameters, and these findings agreed with those of Nasir *et al.,* 7 study who reveals several effects of GA treatment, which may delay the progression to renal failure in diabetic rats. Moreover, hung and suzuki, 22 reported that supplemental feeding with GG or PHGG might be effective for the prevention or management of adenine-induced chronic kidney disease symptoms in mice and attenuated the elevation of urea and creatinine levels. Also, Elblehi, *et al.,* [23] reported that GA may possess hepatoprotective effects [28].

Since mercuric administration generates free radicals and subsequently increases oxidative stress, which leads to hepatotoxicity and accelerates nephrotoxicity, this adverse effect of $HgCl_2$ could be eliminated by GA and GG treatment probably because of their strong free radical scavenging activity through the electron donation pathway, protecting cells from oxidation and necrosis. Changes in oxidant-antioxidant balance, inhibition of antioxidant defense system, and enhanced production of reactive oxygen species (ROS) are considered to play a key role in Hg-induced toxicity [24]. Mercuric affects the cell physiology and integrity due to decreased GSH and GSH depending enzyme activity, leading to an increase of ROS such as superoxide anion radicals, hydrogen peroxide, and hydroxyl radicals, which stimulate lipid, protein, and DNA oxidation [25]. $HgCl_2$ administration initiates the formation of highly reactive substances such as ROS in addition to the stimulation of oxidative stress [26] consequently, decreased the reduced glutathione level. This in turn led to cell degeneration, loss of membrane integrity, and cellular necrosis. These results come in accordance with Elblehi *et al.,* [23] who provoked a significant decrease in GSH and a significant increase in the level of malondialdehyde MDA were observed in hepatic and renal tissues of rats received $HgCl_2$ (5 mg/kg B.wt., intragastrical daily) for 30 days.

In the present study, we found that $HgCl_2$ significantly diminishes the level of GSH in kidney and liver tissues. Conversely, co-administration of GG with $HgCl_2$ showed a significant modulation in the level of GSH hepatorenal protective activity of GG was observed in the previous study [27]. This antitoxic effect of GA and GG could be attributed to the ability of their active components to reduce oxidative stress and preserve the structural integrity of hepatocellular and nephrotic cell membranes by the destruction of H_2O_2 and lipid hydroperoxides via elevating GSH and other antioxidants or direct scavenging activity against free radicals. Lui *et al.,* [28] partially hydrolyzed GG significantly elevated the activities of antioxidant enzymes and decreased the content of MDA in rat's serum and brain tissue. Enhanced the activity of antioxidant enzymes and repaired the histopathological damage caused by free radicals.

Hydroxyproline is used for the estimation of the collagen content, considering that collagen contained 12.7% hydroxyproline by weigh [29]. Our results were parallel to those of Yadav *et al.,* [30] who concluded that renal and liver fibrosis is induced by $HgCl_2$, demonstrated by a significant elevation ($p \leq 0.05$) of the hydroxyproline content in liver and kidney tissues compared to control. Whereas GA and GG treatment act as a rescue agent against the toxic effects of inorganic mercury when it is administered shortly after exposure to $HgCl_2$ indicated by alternation in Hydroxyproline content [31].

Our results reported a significant increase in both hepatic and renal TGFβ-1% in HgCl2-treated rats compared to normal control, as a result of mercuric toxicity induction including an increase in TGFβ-1 cytokine production cause collagen deposition. As confirmed by previous work of, Schon and Weiskirchen, [32] who reported a significant increase in hepatic and renal TGFβ-1% in $HgCl_2$-treated rats compared to control. Also, Gewin *et al.,* [33] reported that $TGF\beta^{-1}$ signaling had been shown to alter numerous cellular processes in vitro that may be detrimental to the tubular response to chronic kidney diseases. $TGF\beta^{-1}$ stimulates epithelial de-differentiation; thus, it may facilitate proximal tubule repair by accelerating de-differentiation of surviving epithelial cells, an important initial step in the repair [34]. Moreover, Nabil *et al.,* 1 observed that $HgCl_2$ without treatment showing a significant increase in serum AST, ALT, urea, creatinine, and uric acids compared to control. Furthermore, there was a significant reduction in the activity of the antioxidant enzymes and GSH in addition to a marked increase in the TGFβ-1% in kidney and liver tissues compared with the control group. There is now overwhelming evidence that the pro-fibrotic cytokine TGFβ-1 is a key mediator of progressive renal injury [34]. GA fermentation by colonic bacteria increases serum butyrate concentrations, so it is considered a prebiotic agent. GA has anti-inflammatory activity through its derivative butyrate [35]. GA had a favorable immune-modulator effect that was observed by previous work of Matsumoto *et al.,* [34] who revealed that treatment with GA, has a potential beneficial effect in renal disease by suppression of TGFβ-1 activity. Additionally, Hammad *et al.,* [36] showed that GA significantly attenuated the ureteric obstruction-induced increase in the tissue level of MDA and SOD and the rise in the gene expression of TNF-α and $TGF\beta^{-1}$. Meanwhile, data from the current results reported that rats treated with GG showed a much more significant decrease in TGFβ-1%.

In the present study, we performed a histo-pathological examination to further support the biochemical evidence. We compared the morphological structure among each group using H&E stain. $HgCl_2$ intoxication caused liver necrosis, swelling, and structure changes **Fig. 1B** in addition to renal tissue damage, collagen formation, and atrophy in the normal tubular architecture **Fig. 2B**. The liver is a major site of metabolism for mercury hence, severely affected by mercury. Previous studies also revealed that $HgCl_2$ caused histo-pathological and ultra-structural lesions evidenced by fatty degeneration and cell necrosis in the liver. The hepatic damage is usually observed as a rise in serum levels of liver enzymes such as ALT. Therefore, the elevation of these enzymes in serum may be attributed to their liberation from the cells into the circulation, indicating damage of the cell membrane or bile duct problems due to oxidative stress and the resulting lipid and protein oxidation [36, 38, 39]. Treatment with GA and GG significantly attenuated the pathological changes in both liver **Fig. 1C** & **1D** and kidney **Fig. 2C** & **2D** tissues as described by 4,30 in earlier studies that agreed with

our results. Even though GG treatment showed much less histopathological changes than GA.

CONCLUSION: Finally, we conclude that GA and GG can ameliorate the toxic effect and retard the progression of hepatorenal fibrosis and tissue damage induced by $HgCl_2$. Moreover, GG exhibited more efficiency than GA.

ACKNOWLEDGEMENT: Nil

CONFLICTS OF INTEREST: All authors declare that there are no conflicts of interest.

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How to cite this article:
El-Rhman AA and Shosha NNH: Antitoxic effects of gum Arabic (*Acacia senegal*) and guar gum (*Cyamopsis tetragonolobus*) against hepatorenal toxicity induced by mercuric chloride in rats. Int J Pharm Sci & Res 2021; 12(12): 6353-61. doi: 10.13040/IJPSR.0975-8232. 12(12).6353-61.