Hepato-toxic risk of gum arabic during adenine-induced renal toxicity prevention

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ABSTRACT
Objective: Lately, gum arabic (GA) is traditionally used in Middle East countries to ameliorate renal function of patients with chronic renal failure (CRF). This action is controversial and it is still experimentally under evaluation. We aimed to shed more light on the potential effects of GA administration to rats with adenine (AD)-induced CRF through investigating kidney and liver changes.

Material and Methods: Rats were divided into four groups treated for consecutive 28 days. Control group was given normal food and water. GA group was given GA (15% w/v/day) in drinking water. AD group; received AD (50 mg/kg/day, intraperitoneally). GA + AD group received both AD (50 mg/kg/day) and GA (15% w/v/day). On day 29, rats were sacrificed and serum creatinine, urea, uric acid, blood urea nitrogen (BUN), aspartate aminotransferase (AST), alanine aminotransferase (ALT), albumin, bilirubin, cholesterol levels, and renal/hepatic malondialdehyde (MDA), superoxide dismutase (SOD), and catalase were estimated. Kidney/liver histo-pathological studies were performed.

Results: GA supplement efficiency in preventing AD-induced renal toxicity is clearly evident from histo-pathological examination and reduced urea, BUN, and creatinine levels. Also, it is proven that GA supplementation produces harmful effects on the liver as it increases ALT and AST levels.

Conclusion: Liver function tests should be monitored in chronic kidney disease (CKD) patients who utilize GA supplement.

INTRODUCTION
CKD is a real health problem worldwide (Saad et al., 2018; Umekeje et al., 2018). Variable factors affect its onset and development like obesity, dyslipidemia, diabetes (Saad et al., 2015a; 2017a), cancer (Saad et al., 2017b; 2017c; 2017d), and exposure to toxicants (Saad, 2013; Toson et al., 2014). Also, inflammation and oxidative stress contribute to its pathogenesis and progression (Ali et al., 2013).

CRF is an irreversible loss of a great number of functional nephrons originated from an extensive diversity of disorders of glomeruli, tubules, renal interstitium, and blood vessels. It is manifested by structural and functional responses of remainder nephrons that eventually result in glomerulo-sclerosis. Injured kidney has decreased size and broad casts in the urine sediment appear indicating dilated hypertrophied remaining nephrons. Inadequacy of functioning nephrons results in ineffective ride of body toxins, thereby uremic poisoning appears (El-Habibi, 2013). AD-induced CRF model in animal results in complications similar to that produced in human CRF. Thus, this CRF model can be used experimentally for studying different complications related to a persistent uremic state (Ali et al., 2010).

Acacia gum (gum arabic, GA) is a water-soluble polysaccharide fiber produced from the dried gummy exudate of Acacia senegal (L.) Willd. trees, stems, and branches, mostly in Sudan (about 80%). It consists of D-galactose units backbone with branched chains of (1–3) linked β-D-galactopyranosyl units containing α-L-arabinofuranosyl, α-L-rhamnopyranosyl, β-D-glucuronopyranosyl, and 4-O-methyl-β-D-glucuronopyranosyl units, and contains high amounts of Ca2+, K+, and Mg2+ ions. It is

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edible and fermented to short chain fatty acids by colonic bacteria (Nasir, 2013).

GA has long been traditionally used as a pain-reliever base by Egyptians and to treat a wide diversity of diseases by Arabic physicians (Dobelis, 1986). It can offset diarrhea, exhibit anti-microbial activity, and promote teeth re-mineralization. Lately, it is traditionally used in the Middle East countries to ameliorate renal function of patients with CRF. This action of GA is controversial and it is still experimentally under evaluation (Nasir, 2013).

To our knowledge, GA is considered non-toxic when taken in food or medications; however, certain side effects may result, including cholesterol levels increase and allergic reactions in some people as well as uncoupling of oxidative phosphorylation in the heart and liver (Babiker et al., 2017). Until now, there are no enough investigations to find out all of the GA benefits/potential adverse effects, particularly during CRF treatment, the most common traditional use now among Arabs, especially Egyptians; therefore, more research concerning this issue is of interest. This will help to evaluate GA utilization as a supplement at the clinical level for patients with kidney disease and could help in how to avoid/control or prevent its undesirable effects if present aiming to maximize the benefit of its clinical use in such patients in the future.

The aim of this work was to investigate the hepatic and renal effects of GA administration to healthy rats and to rats with AD-induced CRF. Kidney and liver function changes were studied on both biochemical and histological levels, and oxidative stress state in both organs was also monitored.

MATERIALS AND METHODS

Chemicals, kits, and plant material

AD was obtained from Sigma Chemicals (St. Louis, MO), while AST and ALT kits were obtained from ELITech clinical systems, France. Albumin, cholesterol, total protein, and bilirubin kits were purchased from BIOMED, Cairo, Egypt. Creatinine, urea, and uric acid kits were purchased from Diamond Diagnostics, USA. MDA, SOD, and catalase were purchased from Biodiagnostic Company, Cairo, Egypt.

GA (Sudanese) was purchased from a Saudi Arabian local market, representing the type and source that were most commonly and traditionally used by Egyptians in particular. Dried gum was grounded into fine powder, kept in air tight plastic containers, and stored at 5°C until used. Voucher specimen will be kept at Herbarium of Botany Department, Faculty of Science, Damietta University, Egypt.

Gum extract (15% w/v, the most common traditionally used concentration) was made by soaking 15 g in 100 ml of distilled water, settled for 24 hours and then filtered. It was prepared freshly for every use.

Animals

Adult male Sprague-Dawley rats (170–190 g) brought from Urology and Nephrology Centre, Mansoura University, Egypt were used. According to the National Institute of Health (1996), rats were housed for 10 days prior to experimental use in cages (four in each) under controlled conditions; temperature of 25°C, relative humidity of 60%–70%, and a 12/12 hours light/dark cycle. Normal food and water ad libitum were allowed. Our study was approved by the Animal House of Biochemistry, Chemistry Department, Faculty of Science, Damietta University, Egypt.

Experimental design

Rats were gathered into four groups of 10 rats for each. AD group; injected intraperitoneally (ip) with AD (50 mg/kg/day) for 28 successive days. AD-induced CRF was confirmed via detection of serum creatinine and urea every week. GA + AD group; received GA (15% w/v) orally in drinking water daily concomitant with AD (50 mg/kg/day) injection for 28 successive days. GA group; received GA (15% w/v) orally in drinking water daily for successive 28 days. Normal control group; received only the respective vehicles.

Biochemical analysis

On day 29, all animals were fasted for 12 hours, then sacrificed under diethyl ether anesthesia and blood samples were collected, left to clot and the sera were separated and stored at −20°C until used for estimation of AST, ALT, albumin, cholesterol, total protein, total bilirubin, creatinine, urea, uric acid, and BUN levels. MDA, SOD, and catalase levels were estimated in kidney/liver tissue homogenate (10%) according to kits instructions.

Histo-pathological analysis

Residual washed liver and kidney, obtained after decapitation, were fixed in 10% formalin, processed, embedded in paraffin wax, cut into 5-μm thick sections, stained with hematoxylin and eosin (H&E) dye and examined.

Statistical analysis

Results are introduced as mean ± SD. Student’s t-test was used for statistical analysis between two groups. p < 0.05 was considered as significant. InStat statistical software version 3.10 (GraphPad, USA) was used for statistical calculations.

RESULTS

Body weight changes

Table 1 illustrates that the healthy control rats normally continued to gain weight gradually. Final body weight showed a significant reduction by 25% following daily injection of AD, while when AD injection was combined with oral administration of GA it showed significant regain; body weight loss changed from −25% in AD group to −3.5% in GA + AD group. Moreover, administration of GA alone firstly reduced body weight during the first week, then rats’ body weight started to increase from the third week and go on.

Biochemical effects of GA administration to healthy rats

Renal function

When orally administered to healthy rats, GA non-significantly increased the concentrations of urea, BUN, and creatinine by 30%, 29%, and 25%, respectively, while non-significantly decreased uric acid concentration by 18% (Table 2).
Hepatic function

Figure 1 shows that by GA administration in drinking water, the concentration of total bilirubin was decreased by 23% \( (p < 0.05) \), total protein by 13% \( (p < 0.05) \), and albumin by 8% \( (p < 0.05) \), while ALT activity was increased by 32% \( (p < 0.01) \), AST activity by 54% \( (p < 0.001) \), and cholesterol level by 33% \( (p < 0.001) \).

Oxidative stress

Table 3 shows that by GA administration, the concentration of MDA was significantly increased by 40% associated with significant elevation in SOD activity by 33% and a significant decrease in catalase activity by 10% in kidney tissues. Whereas, MDA was non-significantly increased in liver tissues by 20% associated with a significant decrease in SOD activity by 26% and a significant increase in catalase activity by 42%.

Biochemical effects of GA co-administration to rats with AD-induced CRF

Renal function

Table 2 shows that AD causes significant \( (p < 0.001) \) increase in the concentrations of urea by 326%, BUN by 326%, creatinine by 67%, and uric acid by 95% compared with the control group. Co-administration of GA significantly \( (p < 0.001) \) reduced the concentrations of urea by 256%, BUN by 270%, creatinine by 21%, and uric acid by 53% when compared with those of the AD group. Comparing AD + GA group with the control group, levels of urea, BUN, uric acid, and creatinine are still higher by 19%, 15%, 27%, and 38%, respectively, than their corresponding values in the control group.

Hepatic function

Figure 1 shows that AD causes significant \( (p < 0.001) \) increases in the concentration of total bilirubin by 431%, ALT by 126%, AST by 154%, and cholesterol by 45% associated with significant \( (p < 0.001) \) decreases in total protein by 25% and in albumin concentration by 45%. Comparing AD group with GA + AD group, GA significantly \( (p < 0.01–p < 0.001) \) reduced the concentrations of total bilirubin by 25%, ALT by 46%, AST by 115%, and cholesterol by 33%, while the concentration of albumin was significantly \( (p < 0.01) \) increased by 24% and total protein was significantly \( (p < 0.05) \) increased by 11%. Comparing GA + AD group with the control group, these parameters were improved but still away from the values in the control group.

Oxidative stress

Table 3 shows that AD causes significant \( (p < 0.001) \) increase in the concentration of MDA in kidney by 70% and in liver tissues by 201%, while it causes significant \( (p < 0.001) \) decreases in the SOD activity by 35% in kidney and by 67% in liver and in catalase activity in kidney by 28% and in liver by 22%. Comparing AD group with GA + AD group, GA significantly \( (p < 0.001) \) reduced the concentration of MDA in kidney by 52% and in liver by 73%, while SOD activity in kidney was significantly increased by 123% \( (p < 0.001) \) and in liver by 178% \( (p < 0.001) \). Also, the catalase activity in kidney was significantly increased by 57% \( (p < 0.001) \) and in liver by 98% \( (p < 0.001) \).

Histo-pathological changes

Administration of GA to normal rats did not cause any harm to renal/hepatic tissues normal architecture, while AD injection caused congestion and necrosis of renal glomeruli with necrosis of renal tubular epithelium lining renal tubules besides lymphohistiocytic infiltration in hepatic tissue with coagulative necrosis of hepatocytes. In GA + AD group, little improvements in renal and hepatic tissues had been observed (Figures 2 and 3; Table 4).

DISCUSSION

Comparing to healthy control, GA administration to healthy rats for consecutive 4 weeks reduced body weight during

### Table 1. Body weight (g) changes of rats in different groups throughout the experimental period.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Day 0</th>
<th>First week</th>
<th>Second week</th>
<th>Third week</th>
<th>Fourth week</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>178.1 ± 7.8</td>
<td>186.60 ± 8.26</td>
<td>192.20 ± 6.77</td>
<td>209.40 ± 8.56</td>
<td>221.60 ± 8.28</td>
</tr>
<tr>
<td>AD</td>
<td></td>
<td></td>
<td>203.3 ± 9.2</td>
<td>190.62 ± 6.54</td>
<td>194.50 ± 3.62</td>
</tr>
<tr>
<td>GA</td>
<td></td>
<td>189.9 ± 4.45</td>
<td>190.60 ± 3.80</td>
<td>186.13 ± 6.51</td>
<td>190.80 ± 2.97</td>
</tr>
<tr>
<td>GA + AD</td>
<td>208.5 ± 3.17</td>
<td>198.60 ± 2.11</td>
<td>203.3 ± 9.2</td>
<td>194.50 ± 3.62</td>
<td>201.20 ± 5.26</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Groups</th>
<th>% Change from day 0</th>
<th>% Change from day 0</th>
<th>% Change from day 0</th>
<th>% Change from day 0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>0.0%</td>
<td>0.0%</td>
<td>0.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td>AD</td>
<td>0.0%</td>
<td>0.0%</td>
<td>0.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td>GA</td>
<td>0.0%</td>
<td>0.0%</td>
<td>0.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td>GA + AD</td>
<td>0.0%</td>
<td>0.0%</td>
<td>0.0%</td>
<td>0.0%</td>
</tr>
</tbody>
</table>

**AD = adenine, GA = gum arabic. Data are expressed as mean ± SD (n = 10 rats in each group).**

### Table 2. Urea, blood urea nitrogen (BUN), creatinine, and uric acid levels in different groups.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Urea (mg/dl)</th>
<th>Creatinine (mg/dl)</th>
<th>BUN (mg/dl)</th>
<th>Uric acid (mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>26.6 ± 2.21</td>
<td>0.63 ± 0.08</td>
<td>12.42 ± 1.04</td>
<td>2.14 ± 0.40</td>
</tr>
<tr>
<td>AD</td>
<td>113.3 ± 12.7</td>
<td>1.05 ± 0.107</td>
<td>52.93 ± 5.95</td>
<td>4.17 ± 0.46</td>
</tr>
<tr>
<td>GA</td>
<td>34.5 ± 4.32</td>
<td>0.73 ± 0.13</td>
<td>16.05 ± 2.01</td>
<td>1.75 ± 0.32</td>
</tr>
<tr>
<td>GA + AD</td>
<td>31.8 ± 5.37</td>
<td>0.87 ± 0.105</td>
<td>14.32 ± 2.52</td>
<td>2.72 ± 0.56</td>
</tr>
</tbody>
</table>

**AD = adenine, GA = gum arabic. Data are expressed as mean ± SD (n = 10 rats in each group).**

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Figure 1. Bilirubin, protein, albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), and cholesterol levels in different groups. Each column represents the mean ± SD (n = 10 rats in each group). $$ and $$$$: p < 0.01 and p < 0.001, respectively, versus control group. *, ** and ***: p < 0.05, p < 0.01 and p < 0.001, respectively, versus AD group.

Table 3. Malondialdehyde (MDA), superoxide dismutase (SOD), and catalase levels in kidney and liver tissues.

<table>
<thead>
<tr>
<th>Groups</th>
<th>MDA (nmol/g tissue)</th>
<th>SOD (U/g tissue)</th>
<th>Catalase (K Unit/g tissue)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Kidney</td>
<td>Liver</td>
<td>Kidney</td>
</tr>
<tr>
<td>Control</td>
<td>215.34 ± 54.72</td>
<td>148.60 ± 38.57</td>
<td>1468.40 ± 390.19</td>
</tr>
<tr>
<td>AD</td>
<td>366.86 ± 31.03$$$$</td>
<td>447.04 ± 86.34$$$$</td>
<td>952.25 ± 181.71$$$$</td>
</tr>
<tr>
<td>GA</td>
<td>301.20 ± 14.53$$$$</td>
<td>186.18 ± 58.96</td>
<td>1948.20 ± 55.15$$$$</td>
</tr>
<tr>
<td>GA + AD</td>
<td>177.13 ± 60.77***</td>
<td>121.20 ± 13.70***</td>
<td>2126.05 ± 345.85$$$$***</td>
</tr>
</tbody>
</table>

AD = adenine, GA = gum arabic. Data are expressed as mean ± SD (n = 10 rats in each group). $$, $$, $$$: p < 0.05, p < 0.01, and p < 0.001, respectively, versus control group. ***, ***: p < 0.001 versus AD group.
the first week, then rats’ body weight started to increase, with a rate lower than that in the control group, from the third week and go on. This may be due to GA ability to slow intestinal glucose transport as previously reported by Nasir (2013). In addition, it did not significantly change levels of bilirubin, protein, and albumin; however, they were slightly decreased, while it significantly \( p < 0.01 \)– \( p < 0.001 \) increased ALT activity by 32% and AST activity by 54%. Observed elevation in liver enzymes may be related to weight loss or due to fatty infiltration attributed to increased hepatic fats evidenced by the observed increase in cholesterol level. Despite GA dose, route, and treatment duration as well as experimental animal used, our findings are in harmony with Babiker et al. (2017) who showed ALT increase with AST decrease \( (p > 0.05) \) in healthy rats administered GA (dose of 500 ml 10%/5 rats/day orally for 12 weeks) indicating GA cytotoxic effect on hepatocytes. Another more recent study of Eyibo et al. (2018) concluded that healthy rats administered GA (at doses of 200 mg/kg or 400 mg/kg or 600 mg/kg orally for 2 weeks) had distorted normal body chemistry reflected in body weight reduction, significant ALT and AST increases, lipid profile alterations, and other biochemical levels. On contrary to our

**Figure 2.** Kidney histo-pathology. Kidney of control rats (A) and kidney of rats administered gum arabic (B) show normal renal glomeruli (arrow) with normal renal tubules lined by normal renal tubular epithelium (arrow head). Kidney of rats injected with adenine (C) shows congestion and necrosis of the renal glomeruli (arrow) with degenerative changes and necrosis of the normal renal tubular epithelium lining renal tubules (arrow head). Kidney of rats injected with adenine in concomitant with gum arabic administration (D) shows normal renal glomeruli with degenerative changes and necrosis of the normal renal tubular epithelium lining renal tubules (arrow) (hematoxylin and eosin, 100×).

**Figure 3.** Liver histo-pathology. Liver of control rats (A) and liver of rats administered gum arabic (B) show normal hepatocytes (arrow) and normal radial arrangement around the central vein (CV). Liver of rats injected with adenine (C) shows lympho-histocytic infiltration in hepatic tissue (arrow) and coagulative necrosis of hepatocytes (arrow head). Liver of rats injected with adenine in concomitant with gum arabic administration (D) shows focal hemorrhage in hepatic tissue (arrow) and coagulative necrosis of hepatocytes (arrow head) (hematoxylin and eosin, 100×).
Incidence of CKD is rising and renal replacement therapy admission by either transplantation or dialysis is limited due to lack of financial and medical resources (Ashuntantang et al., 2017). Entrance of strategies based on dietary supplements seeks to delay the onset of dialysis or to ameliorate uremia (Bellizzi et al., 2016).

Metabolically AD is converted to 2,8-dihydroxyadenine (DHA) which deposits in renal tubules resulting in interstitial inflammation, tubular injury, and fibrosis inducing CKD (Boon et al., 2015). In the present study, kidney patho-histological examination exhibited that the administration of GA alone to normal rats did not cause any harm to renal tissues normal architecture and it confirmed congestion and necrosis of renal glomeruli with necrosis of renal epithelium lining renal tubules induced by AD injection to healthy rats and reflected little amelioration of renal tissues damage by concomitant oral administration of GA with AD. These data indicate that GA can protect kidney tissue against induced CRF to a little extent at the histological level.

Physically, treatment of rats with AD significantly caused a gradual dramatic decrease in rats’ body weight. This reduction could be attributed to a reduction in food intake due to uremia (Johari et al., 2008), as a compensatory response increased glycogen, lipid, and protein degradation takes place leading to continued weight loss. Actually, concomitant oral administration of GA with AD did not normalize rat body weight but it just lowered its reduction from −25% to −3.5% indicating that GA administration did not significantly alter food intake alternatively it slowed intestinal glucose transport.

On biochemical level and in the same line with (Saad et al., 2018; Nasir, 2013; Poudel et al., 2011), significant elevations of circulated urea, creatinine, BUN, and uric acid in AD treated animals are indicators of impaired kidney function. These data are in consistency with other studies (Ali et al., 2010; Saad, 2013; Saad et al., 2017c; 2017d; Toson et al., 2014). Together with the reductions in body weight, they suggest catabolic prominence existence. GA administration to AD feeding rats caused significant dramatic reductions in serum concentrations of urea, creatinine, BUN, and uric acid, compared to AD group, to near normal ranges indicating high appreciated improvement in renal function on the biochemical level. These improvements may be attributed to GA ability to reduce the uric acid level and other purine metabolites (Osman et al., 2011), to increase both creatinine clearance and fecal nitrogen excretion, and to induce inhibition of generation of colonic bacterial ammonia (Nasir, 2013), thereby it reduces hepatic urea production rate.

Oxidative stress is the increase in oxidants at the expense of antioxidants resulting in cellular damage (Habib et al., 2015). Commonly, free radicals are scavenged by antioxidants like SOD, catalase, etc., thereby avoiding the oxidative stress (Saad, 2012; Saad and Habib, 2013). Antioxidant effect of GA is still a matter of argument and it has not been resolved; some studies confirmed it and others not (Hamid et al., 2018; Nasir, 2013). Moustafa et al. (2014) observed MDA elevations in GA group (injected once with a dose of 0.2 mg/100 μl/mice) (p > 0.05) and GA plus laser group as well as hepatic hyperplasia groups treated with GA plus laser (p < 0.05) compared with control. While Al-Kenanny et al. (2012) observed a significant decrease in MDA in mice with liver injury induced by gentamycin treated with GA (dose of 10 g/kg orally for 8 days).

Results of the current study showed that when fed to healthy rats, GA elevates MDA by 40% and by 20% in kidney and in liver tissues, respectively. Moreover, it significantly (p > 0.001) increases SOD activity by 33%, while it significantly (p > 0.01) reduces catalase activity by 10% in kidney tissues. The situation was reversed in liver tissues as it significantly (p < 0.001) reduces SOD activity by 26%, while it significantly (p < 0.001) increases catalase activity by 42%. These alterations in antioxidant enzymes (SOD and catalase) may be attributed to renal and hepatic tissues efforts to face oxidative stress. AD injection to healthy rats triggered lipid peroxidation as it caused significant increases in MDA levels either in the kidney or liver. This may be due to precipitation of DHA crystals that could enhance free radicals production such as peroxides and superoxide anion radicals (Veena et al., 2006) resulting in oxidative stress which ultimately causes renal/hepatic cell death. These findings are correlated well with the observed renal and liver histological examination as well as the observed reductions in the activities of antioxidant enzymes SOD and catalase indicating weakened antioxidants scavenging power in AD-induced oxidative stress. Similar results were also observed by others (Ali et al., 2013; Boon et al., 2015). Oral administration of GA to AD treated rats offered protection against lipid peroxidation and kidney/liver cell damage revealed by decreases in MDA levels associated with increases in antioxidant enzymes activities, which can protect proteins and lipids from...
oxidation by oxidants. This result was in agreement with other studies (Nasir, 2013). The mechanism of this protective effect may be at least in part due to the antioxidant effect of GA.

As far as we know, there is no enough information about GA effect on the liver in renal diseases as very few investigations have been conducted to study this issue. It has long been known that extensive renal damage would also result in hepatic dysfunction due to the interaction of cellular membranes with free radicals mediated by the generation of uremic toxins. Regularly, liver function tests are used to monitor the influences of prospectively hepatotoxic agents or drugs (Saad et al., 2015b; 2017c). Besides, elevated serum cholesterol is considered as a sign for worsening of renal disease (Pandak et al., 1994). In the present study and in agreement with (Boon et al., 2015), animals treated with AD significantly showed 431%, 126%, 154%, and 45% increase in total bilirubin, ALT, AST, and cholesterol, respectively, associated with 45% and 25% decrease in albumin and total protein, respectively. These results introduce evidence of severe liver injury with cellular infiltration. AST value was greatly higher than that of ALT; this may be due to increased release of mitochondrial AST and AST diminished clearance related to aggressive liver damage (Saad, 2014). Observed total bilirubin increase could be attributed to chronic hemolysis as a result of uremic toxins accumulation in the blood (Yavuz et al., 2005). Reductions in albumin and total protein may be due to impaired synthesis by hepatocytes, as a result of hepatic inflammation and oxidative stress, along with increased protein degradation and renal loss. Elevated cholesterol level may be due to alteration in feedback regulation of 3-hydroxy-3-methylglutaryl CoA reductase enzyme (Pandak et al., 1994) as a result of changes in protein synthesis and degradation.

In the present study, concomitant feeding of GA turned levels of liver function tests toward normal but still far from the normal ranges in the control group. Similarly, the results of Al-Kenanny et al. (2012) showed significant decreases in ALT and AST in mice with liver injury induced by gentamycin treated with GA but they did not reach normal levels. These results were parallel with the histo-pathological examination findings. Together, indicate that GA mildly antagonizes hepatic injury following AD-induced CRF. This may be explained on the basis of GA antioxidant effect that protects against cellular leakage and loss of functional integrity of hepatocytes cell membranes. In addition to Babiker et al. (2017) and Eyibo et al. (2018), our results regarding GA effect on liver were in the same line with Moustafa et al. (2014) who observed that GA did not protect or repair hepatocytes deterioration induced by diethylnitrosamine/CCl4 and did not induce cellular apoptosis. Besides, even liver histology of healthy mice treated with GA alone in Al-Kenanny et al. (2012) study showed many pathological changes in hepatic architecture. On contrary to our findings, Gamal el-din et al. (2003) concluded that pretreatment with GA was able to protect mice against acetaminophen-induced liver damage. Alubaidy (2013) reported GA improved oxidative injury and raised liver regeneration and repair capacity. In addition, Ayaz et al. (2017) showed significant decreases in ALT, AST, ALP, and bilirubin along with increases in albumin and total protein to near normal in rats with liver injury induced by trichloroacetate pretreated with GA indicating hepatoprotective effect against subsequent trichloroacetate hepatotoxicity.

CONCLUSION
In conclusion, this study clearly revealed GA supplement pronounced ability to ameliorate renal damage induced by AD in rats. Its amelioration of AD-induced renal toxicity is evident through reductions in levels of urea, BUN, and creatinine, and restored albumin and total protein levels as well as reductions in cholesterol level and oxidative stress. GA, when co-administered to AD feeding rats, reversed levels of routine liver function tests toward normal but their levels still far from the normal ranges in control healthy rats indicating mild antagonistic ability against hepatic injury following AD-induced CRF. On the other hand, GA supplementation to healthy rats elevated ALT and AST activities and cholesterol level indicating harmful effects on the liver. We conclude that GA supplement utilization to treat CKD patients must be done under medical supervision and liver function tests should be monitored during the treatment course. It would be more benefit for such patients to use a hepato-protective supplement in addition to GA supplement for better outcomes.

CONFICT OF INTEREST
There are no conflicts of interest.

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Nil.

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