Therapeutic role of Arabic gum against nicotinamide/ streptozotocin-induced diabetes and nephropathy in Wistar rats

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Background
Chronic kidney disease is mainly caused by diabetic nephropathy and also causes a lot of suffering and death for people with diabetes, as one of the worst long-term complications. Arabic gum (AG) has been reported to have antioxidant, hypolipidemic and hypoglycemic effects.
Objective
The goal of this study was to scrutinize the antioxidant and anti-inflammatory roles of AG against nicotinamide (NA)/streptozotocin (STZ)-induced diabetic nephropathy in Wistar rats.
Materials and methods
The experiment involved three groups of 18 adult male Wistar rats (six each). The normal control group received 0.9% NaCl orally for 8 weeks. The diabetic group received NA intraperitoneal injection (120 mg/kg b.w.) followed by 60 mg/kg body weight (bw) STZ in citrate buffer (pH 4.5) after 15 min. After confirming the induction of diabetes, animals received 0.9% NaCl orally for 8 weeks. The AG-treated diabetic group received 20 mg AG/kg bw/day orally for 8 weeks after diabetes induction.
Results and conclusion
Diabetic rats exhibited hyperglycemia which was confirmed by increased levels of serum fasting glucose and fructosamine. Elevated serum urea, creatinine, uric acid, cystatin c, and sodium levels were noticed in the serum of diabetic rats while potassium levels were markedly reduced reflecting nephropathy. Oxidative stress was evident in the diabetic kidney, as indicated by increased malondialdehyde (MDA) and decreased reduced glutathione (GSH), glutathione peroxidase (GPx) and superoxide dismutase (SOD). AG administration ameliorated elevated fasting blood glucose and serum fructosamine levels as well as the kidney function parameters in serum. AG also attenuated oxidative stress and increased antioxidant capacity in the diabetic kidney. Immune-inflammatory mediators, such as tumor necrosis factor-alpha (TNF-α), nuclear factor kappa B (NF-κB), and tumor suppressor protein (p53) expression were significantly upregulated in diabetic rats, but AG produced a downregulation of them.
Thus, AG possesses an antidiabetic effect and has a nephropreventive effect that was manifested by a decrease of urea, creatinine, uric acid, cystatin c and sodium. AG also has anti-inflammatory and antioxidant effects and minimizes histopathological alterations in the kidneys of diabetic rats. Despite these ameliorative effects, the efficacy and safety of AG as an adjunct drug for diabetic kidney disease needs to be validated by more scientific research.

Keywords:
antioxidant defense system, Arabic gum, nephropathy, type 2 diabetes mellitus

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Introduction

Diabetes mellitus (DM) is a chronic disease with rising prevalence worldwide [1]. DM cause's microvascular and macrovascular complications that increase the risk of death and disability [2]. Diabetic nephropathy is a frequent complication of diabetes and also known as

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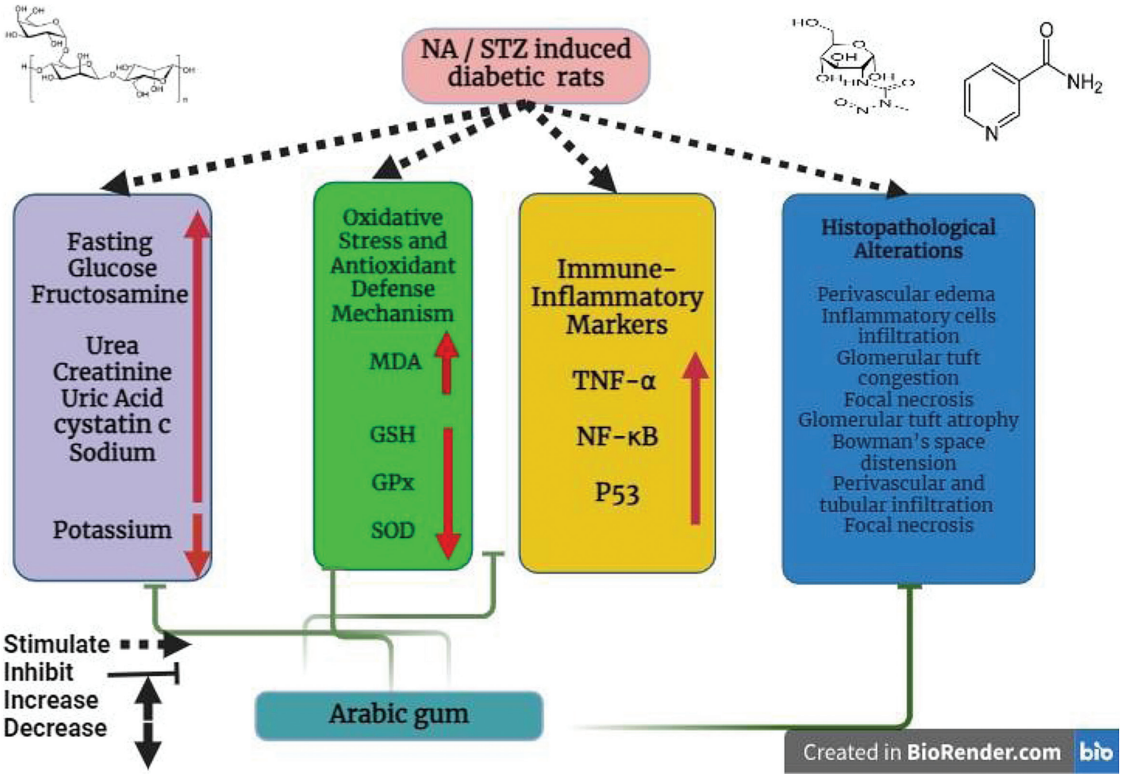


DKD (diabetic kidney disease). This problem makes the kidneys work worse over time and affects approximately 20–40% of people with diabetes [3]. The reason for this problem is that high blood sugar, high blood fat, and oxidative stress (OS) damage the blood vessels in the kidneys [4]. Oxidative stress happens when there are too many harmful oxygen molecules and not enough protective antioxidants. Hydroxyl radical (OH-), superoxide (O_2^-), and hydrogen peroxide (H_2O_2) are harmful oxygen molecules called reactive oxygen species (ROS) that are made by healthy cells constantly. These molecules act as signals for many cell processes. However, they can also harm nearby molecules such as proteins, carbohydrates, lipids and DNA by making them oxidized. To prevent this, cells have a group of enzymes called antioxidant enzymes (hemoxygenase, superoxide dismutase, glutathione reductase, catalase, glutathione peroxidase, and others) that can break down ROS and keep the balance between oxidation and reduction [5,6]. Besides the enzymes, the antioxidant defense system also has some compounds that do not need enzymes to work as antioxidants. These are beta-carotene, alpha-tocopherol (vitamin E), glutathione and ascorbate (vitamin C). When the cells make more reactive oxygen species than the antioxidants, these compounds can get rid of the oxidative stress that occurs. As time went by, people realized that more OS damage could cause many diseases and related problems, such as metabolic, degenerative, inflammatory, autoimmune and malignant diseases [7]. Along with these findings, people also tried to stop or cure diseases caused by OS by making the antioxidant defense system stronger. Many studies in humans and animals show that OS plays a key role in causing and worsening diabetic kidney disease [8]. Therefore, scientists have looked into the possible use of antioxidants to treat diabetic kidney disease. Antioxidants can reduce OS and protect the kidneys from damage. Gum Arabic, a dry, sticky dietary fiber, is derived from the stems and branches of Acacia Senegal and Acacia Seyal. It has many applications in the food, pharmaceutical industries and the joint expert Committee for Food Additives (JECFA) approved it as safe to eat [9]. GA has been reported to exert antidiabetic effects in humans and animals. Prediabetic and diabetic subjects experienced significant declines in fasting blood glucose and glycated hemoglobin (HbA1c) levels after taking GA supplements [10]. Taking 30 g of GA for 4 months had a beneficial effect in diabetic patients with poor glycemic control [11]. Al-Nagar [12] demonstrated that by activating or multiplying beta cells that produce insulin and/or stopping the inhibition of the immune receptors of beta cells in the islets of Langerhans, GA decreased blood glucose levels in alloxan-induced diabetic rats. It also alleviated histopathological alterations in injured islets and demonstrated antioxidant and antiapoptotic properties [13,14]. GA lowered plasma glucose and insulin levels by decreasing intestinal glucose uptake in

diabetic mice [14,15]. In addition, gum intake reduced glucose urea and urine volume [15,16]. GA is commonly prescribed for patients in Sudan with renal dysfunction, as it reduces uremia, dialysis frequency and enhances quality of life [17]. Arabic folk medicine used it to lower the need for hemodialysis in patients with chronic renal failure [18] and to treat diabetes [19].

Khojah [20] conducted a study and showed that oral administration of 1 ml/day/Kg bw GA in pomegranate juice given to rats with chronic kidney disease (CKD) for 4 weeks, concomitant with a low potassium, protein and phosphorus diet, led to a remarkable improvement in serum minerals such as calcium, potassium, phosphorus, kidney functions (lower serum creatinine and urea) and nutritional status. The beneficial effect of GA in CKD induced by adenine in rats improved biochemical indicators and the histological characteristics of damaged kidneys [21,22].

The aim of the study was to find out if AG could help recover the kidneys of diabetic rats to reduce renal dysfunction or nephropathy, downregulate oxidative stress and suppress inflammations.

Material and methods

Animal models and housing conditions

Adult male Wistar rats (120–140 g) were obtained from the VACSERA, Helwan Station, Cairo, Egypt. They were infection free after 2 weeks of observation. They stayed in the Zoology Department's animal facility at the Faculty of Science, Beni-Suef University, Egypt, in airy polypropylene cages. They had a normal light–dark cycle (10–12 hr/day), a normal temperature (20–25°C), food and water all the time. The animal care ethics and guidelines were followed and the experiments were approved by the Faculty of Science's Experimental Animal Ethics Committee, Beni-Suef University, Egypt (Ethical Approval Number: BSU/FS/2018/26). We tried to use as few animals as we could and to lower their agony, misery and discomfort.

Protocol and criteria of diabetes induction

Type 2 diabetes mellitus (T2DM) was induced in rats that fasted for 16 h, following Aziz *et al.* [23]. Rats received a single i.p. injection of STZ (60 mg/kg b.w.) in citrate buffer (pH 4.5), 15 min after an i.p. injection of NA (120 mg/kg b.w.). Also, rats were supplied with 5% glucose in drinking water to prevent STZ-induced hypoglycemia. Ten days later, we administered the fasted rats glucose (3 g/kg b.w.) via stomach tube. Blood samples were taken from the lateral tail vein, 2 h after the oral glucose load and let blood clot and spin. Serum glucose levels were measured and rats with serum glucose levels of 180–300 mg/dl 2 h after glucose intake were included, as mild diabetics in the experiment.

Chemicals

STZ and NA were obtained from Sigma-Aldrich (St. Louis, MO, USA). AG was purchased (powder form) from Qualiems Fine Chem Pvt. Ltd, India.

Experimental design

The experimental animals were allocated into three groups, each comprising six rats, as follows (Fig. 1):

(1) Group I (Normal/Control 'NC'): Normal rats were given the equivalent volume of isotonic solution (0.9% NaCl) daily by oral gavage for 8 weeks.
(2) Group II (NA/STZ-induced diabetic control 'DC'): Diabetic rats were orally given an equivalent volume of isotonic solution daily through oral gavage for 8 weeks.
(3) Group II (NA/STZ-induced diabetic group treated with AG 'DAG'): Diabetic rats received 20 mg/kg bw/day AG suspended in 0.9% NaCl by oral gavage for 8 weeks [24].

Blood sampling

After the treatment period, the rats were made to fast overnight and inhaled diethyl ether to anesthetize them. Blood samples were collected from the jugular vein and the rats were killed by quick cervical decapitation while they were still anesthetized. At room temperature, blood samples were left to clot and spun at 3000 rpm for 15 min. The clear, nonhemolyzed sera were collected into three Eppendorf tubes for each rat and stored at −20°C until use.

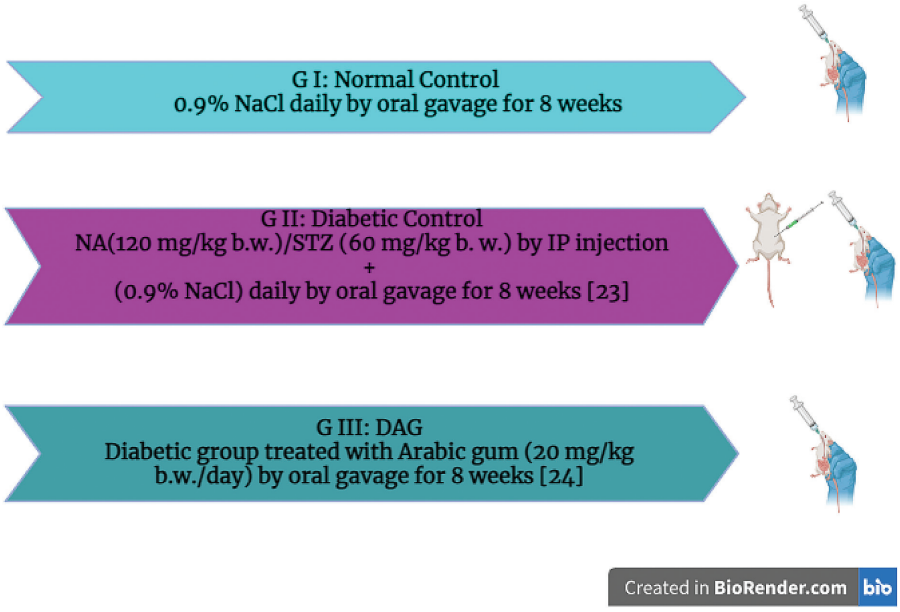
Tissue sampling and homogenate preparation

Rats were killed; kidney tissues (5 μm) were sliced and rinsed with ice-cold PBS (0.01 M, pH=7.4), weighed, diced and then blended in 9 ml PBS per gram tissue with a glass blender on ice. The homogenates were centrifuged at 3000 rpm for 10 min and supernatants were collected and frozen at − 80°C.

Biochemical analyses

Spectrophotometrically, using kits purchased from SPINREACT, serum glucose and fructosamine were estimated according to Trinder [25] and Valerie [26]. Serum urea and creatinine were measured according to Kaplan *et al.* [27] and Murray [28]. Uric acid levels

Figure 1



Schematic diagram of the animal grouping and the experimental design.

were measured according to Fossati *et al.* [29] by SPINREACT kits. The levels of sodium and potassium were estimated using SPINREACT kits, following the methods of Young [30] and Burtis and Ashwood [31], respectively.

Measurement of oxidative stress and antioxidant biomarkers

Using reagent kits obtained from Biodiagnostic (Egypt) and spectrophotometrically, kidney levels of reduced glutathione (GSH) were measured according to Beutler and colleagues [32]. Lipid peroxidation/malondialdehyde (LPO/MDA) level was measured according to Ohkawa and colleagues [33]. GPx (glutathione peroxidase) and SOD (superoxide dismutase) activities were determined following the methods of Paglia and Valentine [34] and Marklund and Marklund [35], respectively.

Estimation of pro-inflammatory cytokines and survival markers

The levels of proinflammatory cytokines and other proteins were measured in kidney homogenates by commercially available ELISA kits (SinoGeneClon Biotech Co., Ltd), including nuclear factor-kappa B (NF-κB), tumor necrosis factor-α (TNF-α), apoptotic protein p53 expression and cystatin c.

Histological examination

Kidney tissues were embedded in paraffin blocks and cut into thin slices (5 μm) that were placed on glass slides [36]. The slides were then rinsed in a water bath and heated in an oven to remove the wax. The slices were colored with hematoxylin and eosin (H and E) to show the tissue structure. An electrical light microscope (Olympus CX 41 RF, TOKYO, JAPAN) was used to examine histological changes. Photomicrographs were edited using Adobe Photoshop version 8.0.

Statistical analysis

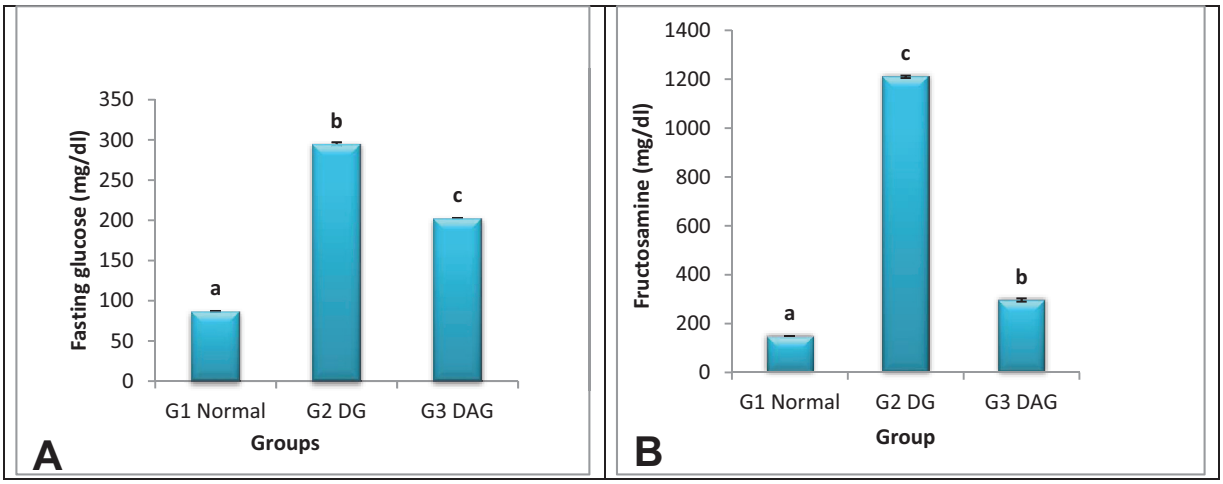
The obtained data were analyzed post hoc by one-way analysis of variance followed by Tukey's methods [37] and presented as mean±standard error. Data were considered statistically significant when P is less than or equal to 0.05.

Results and discussion

AG improves diabetic parameters

Serum levels of fasting glucose and fructosamine increased remarkably ($P \leq 0.05$) in diabetic animals relative to the control group (Fig. 2). Conversely, AG-treated animals had a noticeable decrease ($P \leq 0.05$) in fasting glucose and fructosamine in contrast to the diabetic group. These results harmonize with Mohammed *et al.* [38] who examined the impact of gum Arabic on the development of DKD in rats with STZ-induced diabetes. GA has antioxidant effects [39]. In addition, gum Arabic is safe for human consumption and does not alter the properties of food. End-stage renal disease and death Fig. 3 are mainly caused by DKD among diabetic patients [40]. Rats that were

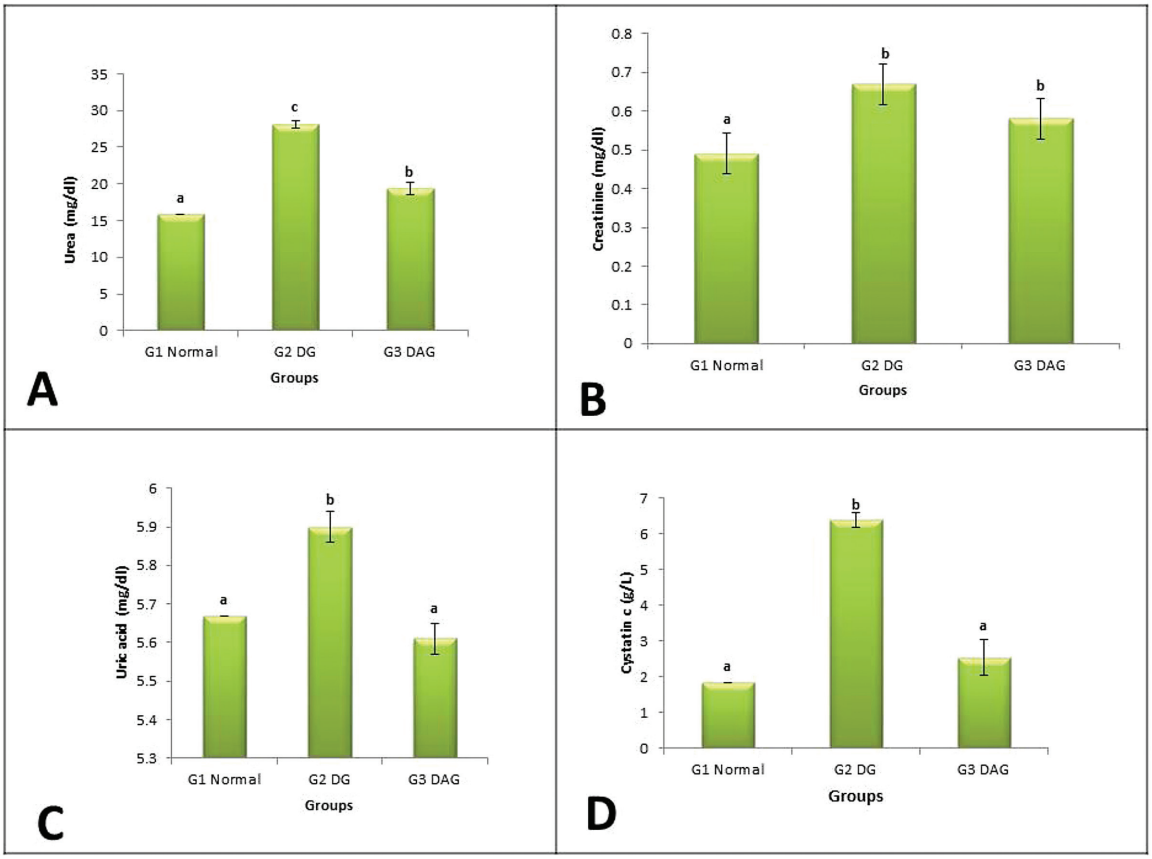
Figure 2



The influence of AG on fasting blood glucose (**A**) and fructosamine (**B**) levels, in normoglycemic and diabetic rats. Letters indicate significant differences at *P* less than or equal to 0.05. Diabetic group versus normal control group and diabetic group with AG treatment versus diabetic group.

administered GA with STZ-induced diabetes reduced the negative metabolic consequences of diabetes and prevented the onset of DKD. GA had hypoglycemic and less oxidative stress than rats that did not receive GA [38]. According to Qureshi *et al.* [41] and El Tobgy [15], GA exhibited antihyperglycemic effects in diabetic rats by reducing intestinal glucose uptake, which in turn lowered plasma glucose and insulin

Figure 3



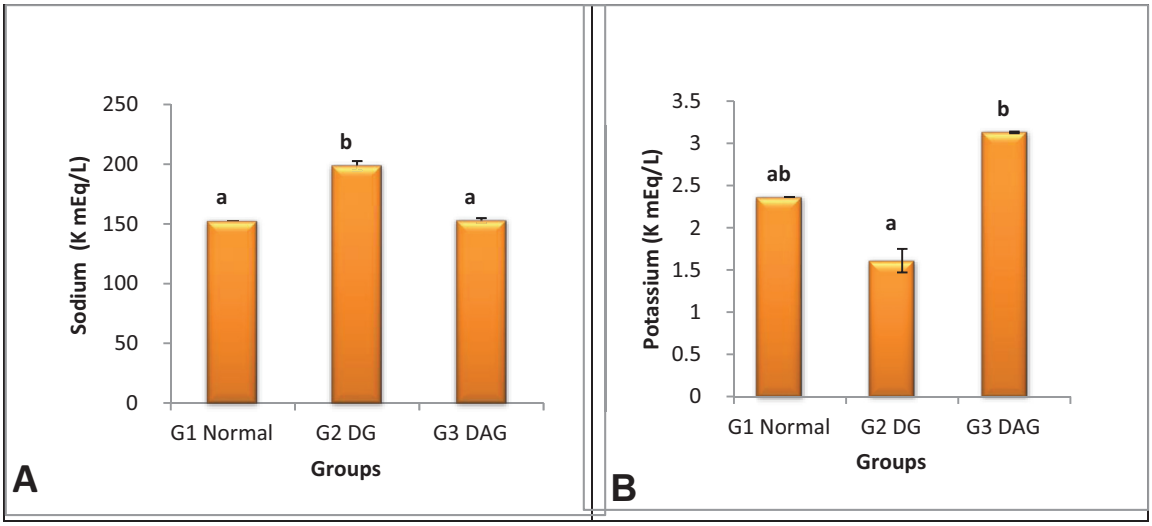
The influence of AG on serum urea (**A**), creatinine (**B**), uric acid (**C**) and cystatin c (**D**) levels in normoglycemic and diabetic rats. Letters indicate significant differences at $P \leq 0.05$. Diabetic group versus normal control group and diabetic group with AG treatment versus diabetic group.

levels. GA also reduced urinary output and glucose excretion. The beneficial effects of GA on diabetic complications were demonstrated by its improvement of neuropathy [42], nephropathy [43] and albuminuria. Furthermore, GA significantly decreased serum phosphate, proteinuria and enhanced glomerular filtration rate, leading to better renal functions [38].

AG ameliorates kidney potency and impaired kidney oxidative stress

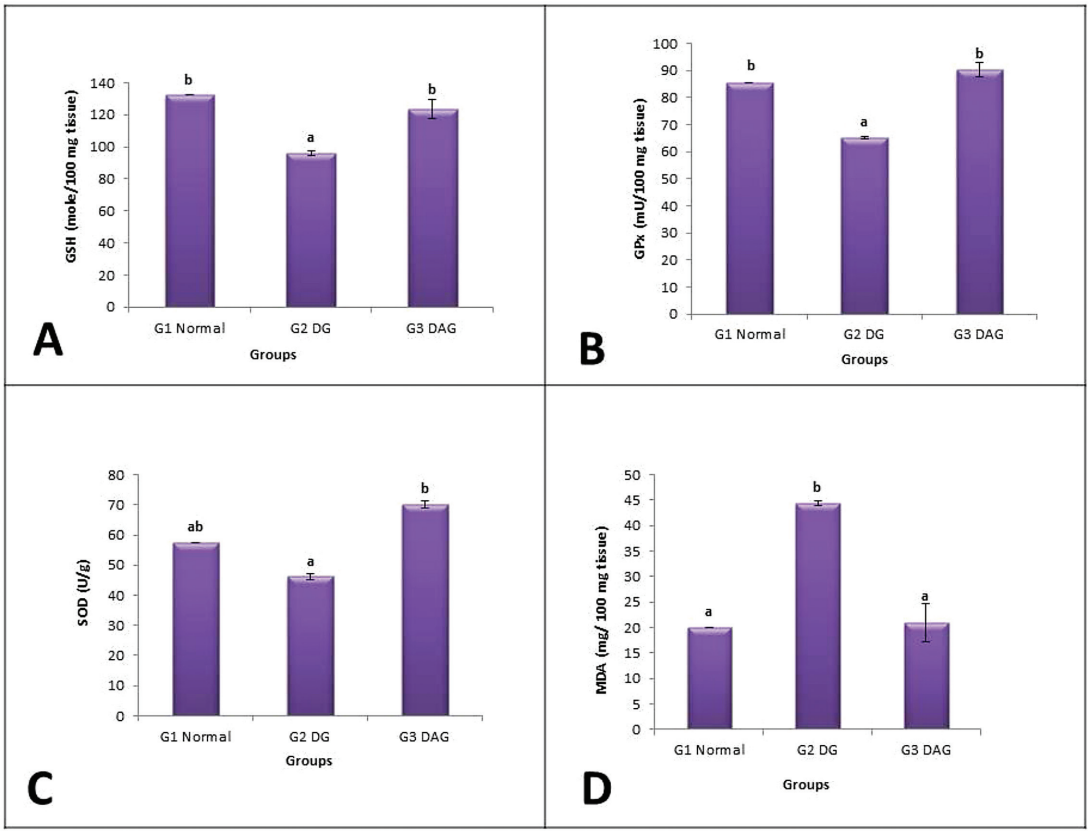
Serum urea, creatinine, uric acid, sodium and cystatin c Fig. 3 levels in the diabetic group were obviously raised ($P \leq 0.05$) versus the control group, while they were reduced in the AG-treated group below the normal level as opposed to the diabetic group. Serum potassium level has the opposite effect in diabetic rats (Fig. 4), which decreased remarkably ($P \leq 0.05$) relative to the normal group. Following AG treatment, animals amplify potassium above normal levels, in contrast to the diabetic group. Compared with the normal group, the diabetic group disturbs (Fig. 5) or reduces the levels of renal antioxidant parameters (GSH, GPx and SOD) ($P \leq 0.05$). The current results are consistent with other studies [44,45], which demonstrated that Arabic gum possesses potent antioxidant activity [46,47], which may be related to its amino acid composition [48]. A rich source of amino acids, GA has aspartic acid and serine as the main ones and Acacia senegal and Acacia seyal gums also have lysine, histidine, glycine, tyrosine, and others [49]. Experimental data showed that the antioxidant effect of GA is correlated with the protein fraction, especially the amino acid residues such as histidine, tyrosine and lysine, which are known to have antioxidant properties [50]. GA enhances the levels of antioxidant enzymes and reduces the levels of oxidizing agents in various organs [10]. AG enhances the antioxidant defense system, which raises these parameters markedly relative to the diabetic group. Currently, diabetic rats elevate kidney oxidative stress, which elevates MDA levels (Fig. 5) more than in the normal or negative control group ($P \leq 0.001$). However, the rats who received AG restored their MDA level in contrast with the diabetic rats ($P \leq 0.001$). These results coincide with Kashihara *et al.* [51] who illustrated that oxidative stress mediates the main mechanisms of diabetic micro- and macrovascular complications. OS in the renal tissue impairs cellular function by altering the structure of proteins, lipids, carbohydrates and DNA. Moreover, reactive oxygen species (ROS) induce inflammatory and fibrotic responses in renal tissue by activating redox-sensitive pathways that cause the morphological changes typical of DKD [52]. Diabetes induction enhanced OS, as indicated by the increased MDA and decreased GSH, CAT and SOD levels. Consequently, untreated diabetic rats exhibited impaired renal function and increased blood urea and serum creatinine levels [38]. Antioxidant effects of GA could be attributed to several factors such as direct antioxidant, hypoglycemic effect and a lipid-lowering effect. Previous studies have reported that GA had a direct antioxidant effect. It prevented kidney damage from gentamicin and mercuric chloride, two substances that cause renal impairment by enhancing OS mechanisms

Figure 4



The influence of AG on serum sodium (**A**) and potassium (**B**) concentrations in normoglycemic and diabetic rats. Letters indicate significant differences at $P \leq 0.05$. Diabetic group versus normal control group and diabetic group with AG treatment versus diabetic group.

Figure 5



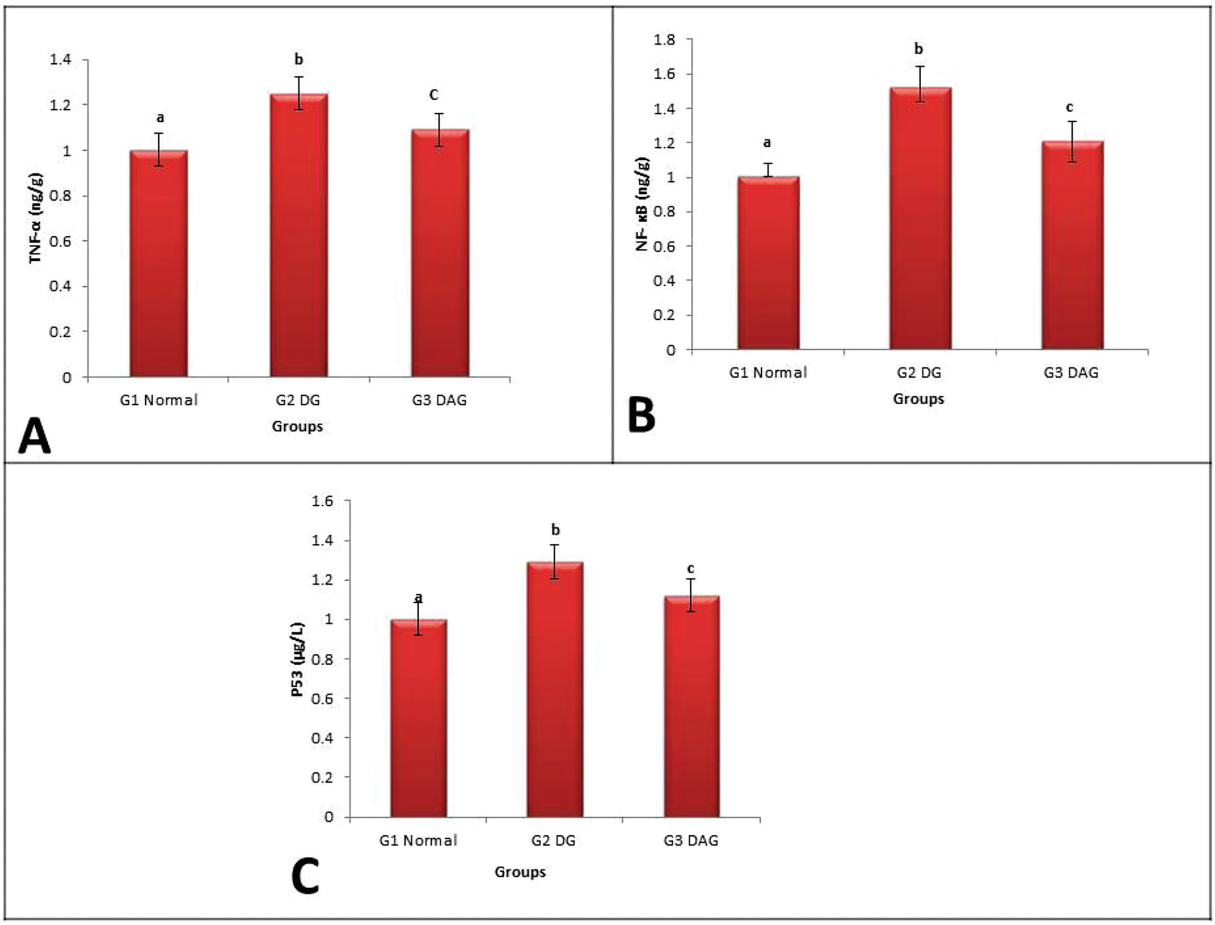
The influence of AG on GSH (**A**), GPx (**B**), SOD (**C**) and MDA (**D**) levels in kidney homogenate in normoglycemic and diabetic rats. Letters indicate significant differences at $P \leq 0.05$. Diabetic group versus normal control group and diabetic group with AG treatment versus diabetic group.

[53,54]. Moreover, GA treatment decreased the generation of superoxide radicals, increased kidney glutathione levels and superoxide dismutase activity in rats with chronic renal failure caused by adenine [55]. Hyperglycemia is the main source of increased OS in diabetes. Lipid peroxidation products, such as MDA, correlated directly with hyperglycemia levels [56]. Hyperglycemia chronically induced oxidative stress and inflammation, which accelerated cell damage and end-stage renal disease [10,57].

AG reduces kidney inflammation

Compared with the normal control group, diabetic group upregulated kidney inflammatory marker and mediator (NF-κB, TNF-α and p53) levels above the normal average ($P \leq 0.05$). Compared with the diabetic group, AG alternatively significantly downregulated ($P \leq 0.05$) these markers (Fig. 6). These results support the hypothesis that diabetes involves the activation of protein complex called NF-κB by various inflammatory molecules that affect the life and death of β-cells. These are the cells that produce insulin in the pancreas [58]. The expression of a gene called iNOS (nitric oxide synthase 2) and the subsequent production of NO lead to the destruction of β-cells. In type-1 diabetes, IL-1β triggers the activation of NF-κB, which causes β-cells to undergo programmed cell death or apoptosis. In T2DM, NF-κB activation also induces apoptosis as well as insulin resistance. NF-κB is further enhanced by the interaction of advanced glycation end products and their receptors. The continuous activation of NF-κB causes a systemic inflammation, which contributes to the development of various diabetic complications such as cardiomyopathy, retinopathy, nephropathy and neuropathy. This indicates the need for treatment strategy that targets NF-κB. The damage to cells, tissues, organs and harmful inflammation process can be diminished by inhibiting NF-κB actions [59]. NF-κB activity was induced by TNF, interleukin 1-β (IL-1β), reactive oxygen species (ROS), osteoprotegerin, isoproterenol, bacterial lipopolysaccharides (LPS), cocaine and ionizing radiation. NF-κB activity influenced inflammatory responses and the activation, differentiation and function of inflammatory T-cells. NF-κB pathway controlled the production of pro-inflammatory cytokines and the recruitment of leukocytes, which

Figure 6

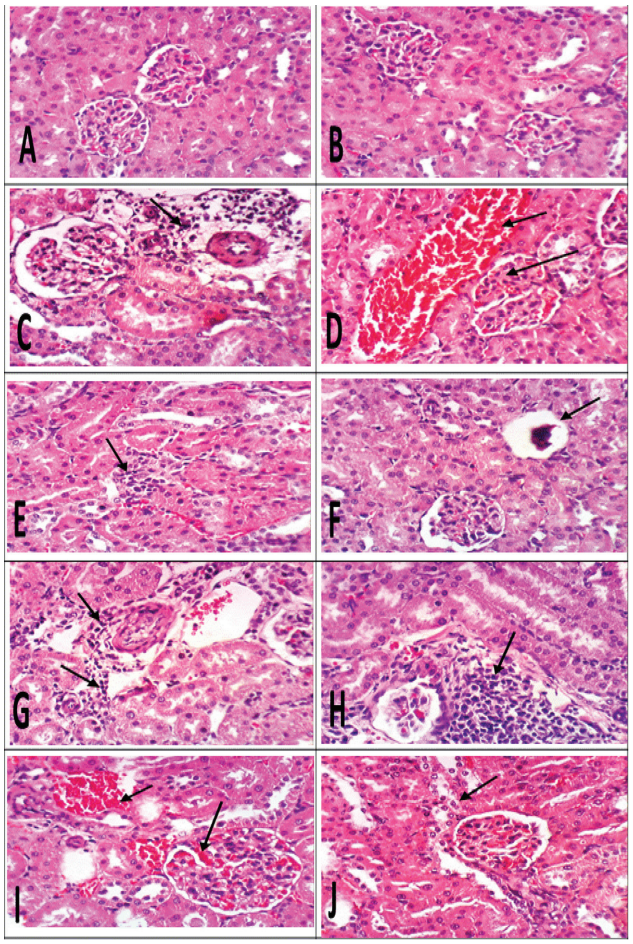


The influence of AG on TNF-α (**A**), NF- κB (**B**) and p53 (**C**) concentrations in kidney homogenate in normoglycemic and diabetic rats. Letters indicate significant differences at $P \leq 0.05$. Diabetic group versus normal control group and diabetic group with AG treatment versus diabetic group.

were the main factors in inflammation. By reducing NF-κB, multiple inflammatory mechanisms can be controlled and the severity and duration of inflammation can be diminished. The NF-κB-signaling system, which can be prevented or inhibited by plant- and animal-derived substances, has therapeutic effects for inflammatory diseases, including cancer [60]. NF-κB is a key protein complex that regulates the internal immune response and is activated to protect the host. However, long-term inflammation can cause cancer and the activities of inflammatory mediators can be blocked to reduce tumor growth and spread. NF-κB-activation has two distinct pathways: canonical pathway and noncanonical (alternative) pathway. Multiple signaling pathways, including NF-κB-and p53, are targeted by several natural secondary metabolites and small synthetic molecules. Fruits, vegetables and natural supplements contain a number of natural substances that can lower or avoid chronic inflammation and its related diseases [61].

In this study, kidney has a normal histology of the renal parenchyma (Fig. 7). In the diabetic group (DG) and in the normal control group, the rat kidney shows perivascular edema and inflammatory cells in the tissue, as well as renal blood vessel and glomerular tuft congestion. Renal tubules of DG rats have inflammatory cells causing focal necrosis, glomerular tuft atrophy and Bowman's space distension. Moreover, the kidney of DG has perivascular and tubular infiltration of inflammatory cells with focal necrosis. In the diabetic AG group, the kidney of rat has renal blood vessel and glomerular tuft congestion and some renal tubules exhibit vacuolar degeneration of the epithelial cytoplasm. Chronic hyperglycemia disrupts the glucose–glycogen balance in the body, causing cellular damage and oxidative stress. This imbalance also induces endothelial dysfunction and necrosis, especially in the microvasculature, impairing the blood supply and function of the affected organs. In the renal system, chronic hyperglycemia can cause nephropathy, due to

Figure 7



The renal parenchyma of the rat kidney in the normal control group (G1) has a normal histological appearance (**A** & **B**). The kidney of a rat in the diabetic group (DG) has perivascular edema and inflammatory cells invading the tissue (**C**), congestion of the renal blood vessel and a glomerular tuft (**D**). The renal tubules of rats in the DG group have focal necrosis due to infiltration of inflammatory cells (**E**), atrophy of the glomerular tuft and distension of Bowman's space (**F**). Furthermore, the kidney of DG show perivascular inflammatory cell's infiltration (**G**) and focal necrosis of renal tubules associated with inflammatory cell's infiltration (**H**). The kidney of a rat in the diabetic Arabic gum (DAG) has renal blood vessel and glomerular tuft congestion (**I**) and shows vacuolar degeneration (**J**) in some renal tubules of the epithelial lining (H & E X 400).

hypertension-induced damage to the glomeruli, tubules and excessive glucose load on the kidney [62]. Diabetic nephropathy (DN) is a severe complication of diabetes that is characterized by reduced glomerular filtration rate, increased proteinuria and renal dysfunction. End-stage renal disease and reduced quality of life of diabetic patients are mainly caused by diabetic nephropathy. Oxidative stress and inflammation play a role in the development of DN [63].

NF-κB and Nrf-2 are key pathways that regulate cellular redox homeostasis (Figure 8) in response to oxidative, electrophilic and inflammatory stress. Complex molecular interactions that regulate various cellular functions are involved in the crosstalk between these pathways. The mechanism is controlled by both transcriptional and posttranslational regulation [64,65]. They also play a crucial role in immune responses, where they are activated by stress (internal or external), cytokines and reactive oxygen species. NF-κB consists of five protein subunits, which are classified into two groups: Class I and Class II. Class I comprises NF-κB 1 and NF-κB 2. Class II comprises transcription factors (RelA, RelB, and c-Rel). NF-κB and Nrf-2 are transcription factors that regulate the expression of genes involved in oxidative stress and inflammation. They interact in a feedback loop, where NF-κB activation is inhibited by Nrf-2 and Nrf-2 expression is induced by NF-κB. Cytokine production increases due to increased NF-κB activity in the absence of Nrf-2 [66]. Nrf-2 deficiency results in NF-κB activation and increased cytokine production. NF-κB and Nrf-2 regulate each other's expression and activity in a feedback loop, modulating the cellular response to oxidative and inflammatory stress [67]. Hence, GA can modulate apoptotic pathways, prevent renal tissue damage and inhibit fibrosis progression [68].

Conclusion

The study concluded that AG can alleviate diabetic nephropathy in NA/STZ-induced diabetic Wistar rats through the attenuation of oxidative stress, inflammation and apoptosis.

Acknowledgments

Not applicable.

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Ethics considerations: The animal care ethics and guidelines were followed and the experiments were approved by the Faculty of Science's Experimental Animal Ethics Committee, Beni-Suef University, Egypt (Ethical Approval Number: BSU/FS/2018/26).

Availability of data and materials: All data generated or analyzed during this study are included in this published article.

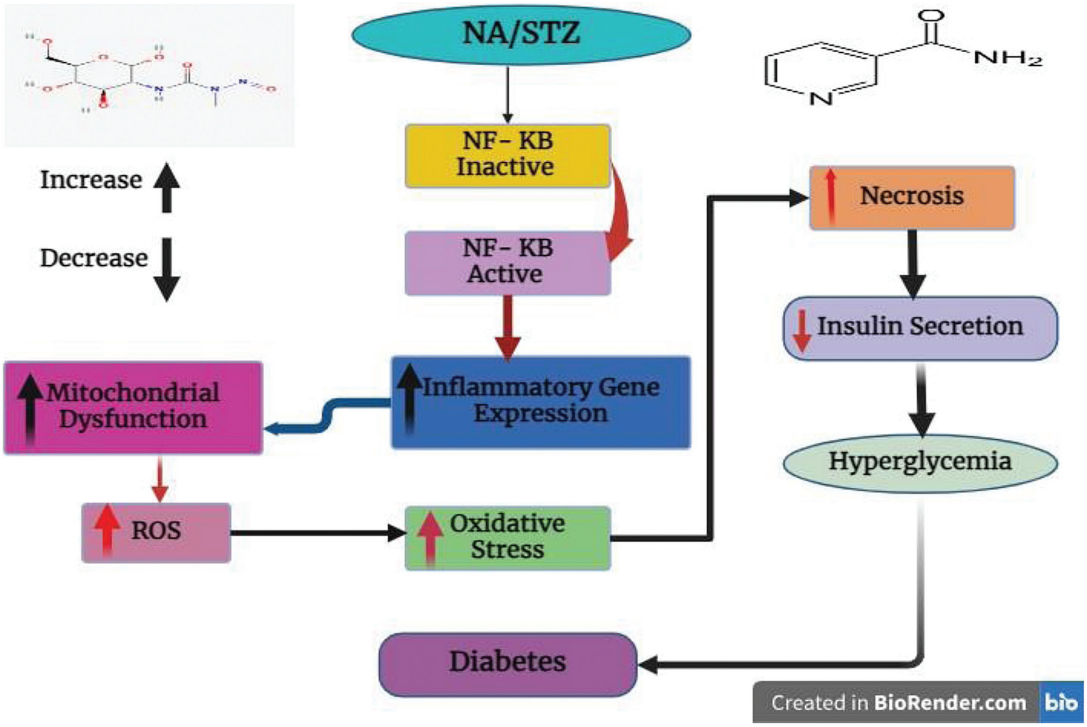
Financial support and sponsorship

Nil.

Conflicts of interest

The authors declare there are no conflicts of interest.

Figure 8



NA/STZ induce diabetes in rat model.

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