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

Osama M. Ahmed[a], Nermeen M. Mosa[b], Howida S. Abou- Seif[c]

[a]Department of Zoology, Experimental Obesity and Diabetes Research Lab, Physiology Division, Faculty of Science, Beni-Suef University, Beni-Suef, [b]Health Insurance Organization, Ministry of Health and Population, Egypt, [c]Department of Medical Physiology, Medical Research and Clinical Studies Institute, the National Research Centre, Cairo, Egypt

Correspondence to Howida S. Abou- Seif, PhD, Assistant Professor, Medical Physiology Department, Medical Research and Clinical, Studies Institute, National Research Centre, Beni Suef Governorate, Beni Suef City, Post/zip code: 2711860, Dokii, Cairo, Egypt. Tel: +0128 846 2008; e-mail: drhoidaabouseif@gmail.com

Received: 21 February 2024
Revised: 15 March 2024
Accepted: 18 March 2024
Published: 25 July 2024

Egyptian Pharmaceutical Journal 2024, 23:643–653

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.

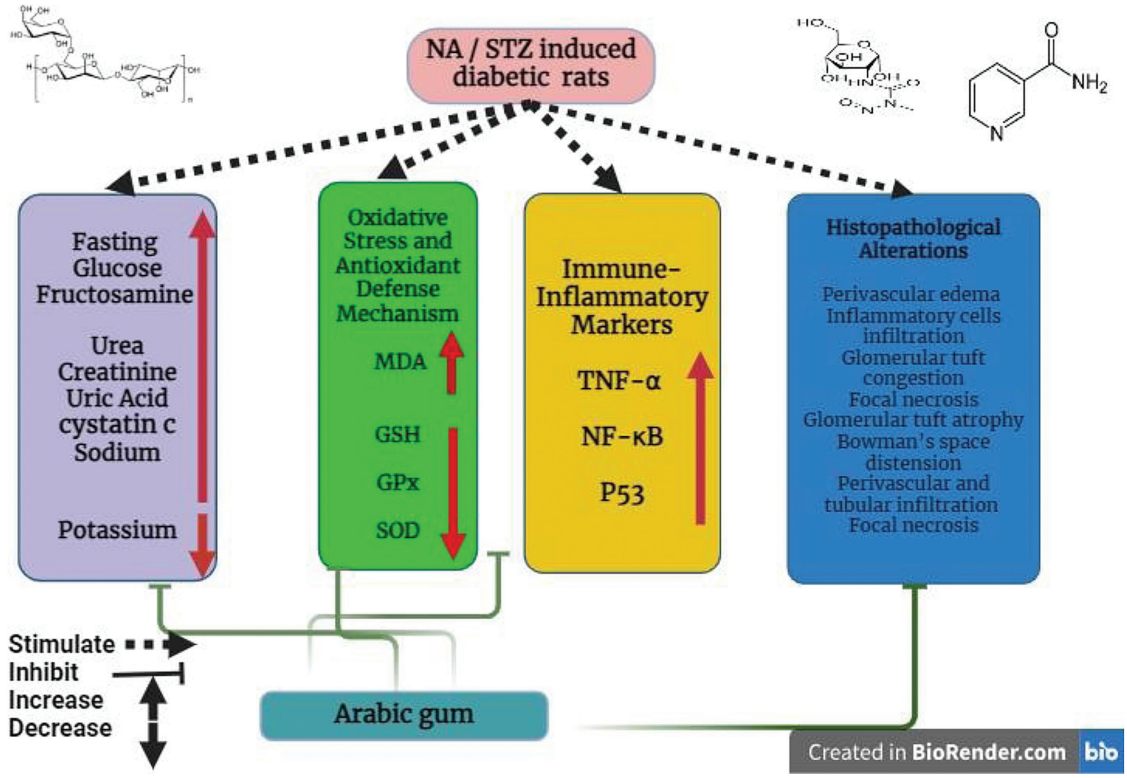
Keywords:
antioxidant defense system, Arabic gum, nephropathy, type 2 diabetes mellitus

Egypt Pharmaceut J 23:643–653

1687-4315

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 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.

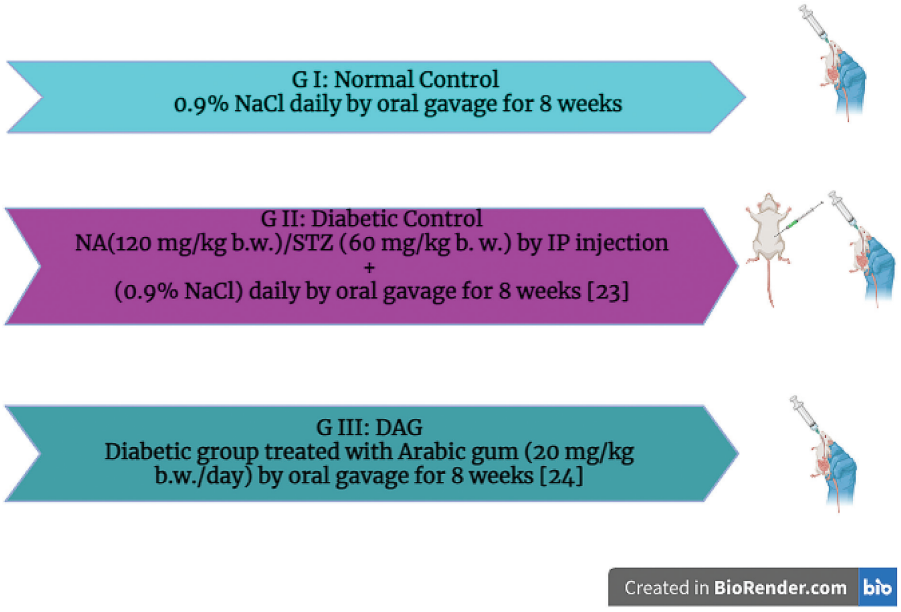
Biochemical analyses

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 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/

Figure 1



Schematic diagram of the animal grouping and the experimental design.

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

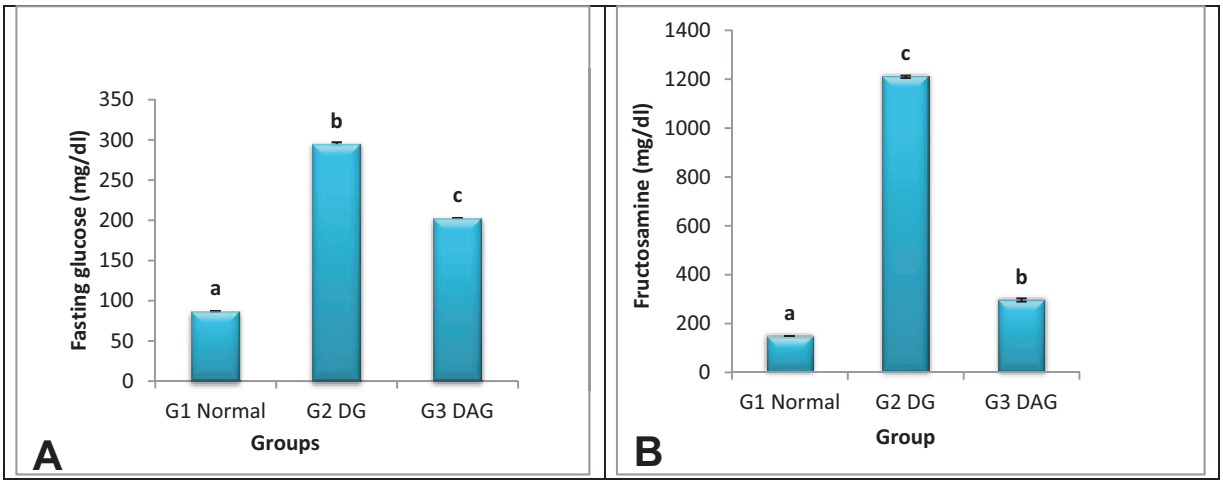
The obtained data were analyzed post hoc by one-way analysis of variance followed by Tukey's methods [37] and presented as mean±standard error. Data were considered statistically significant when P is less than or equal to 0.05.

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 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 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.

Figure 2



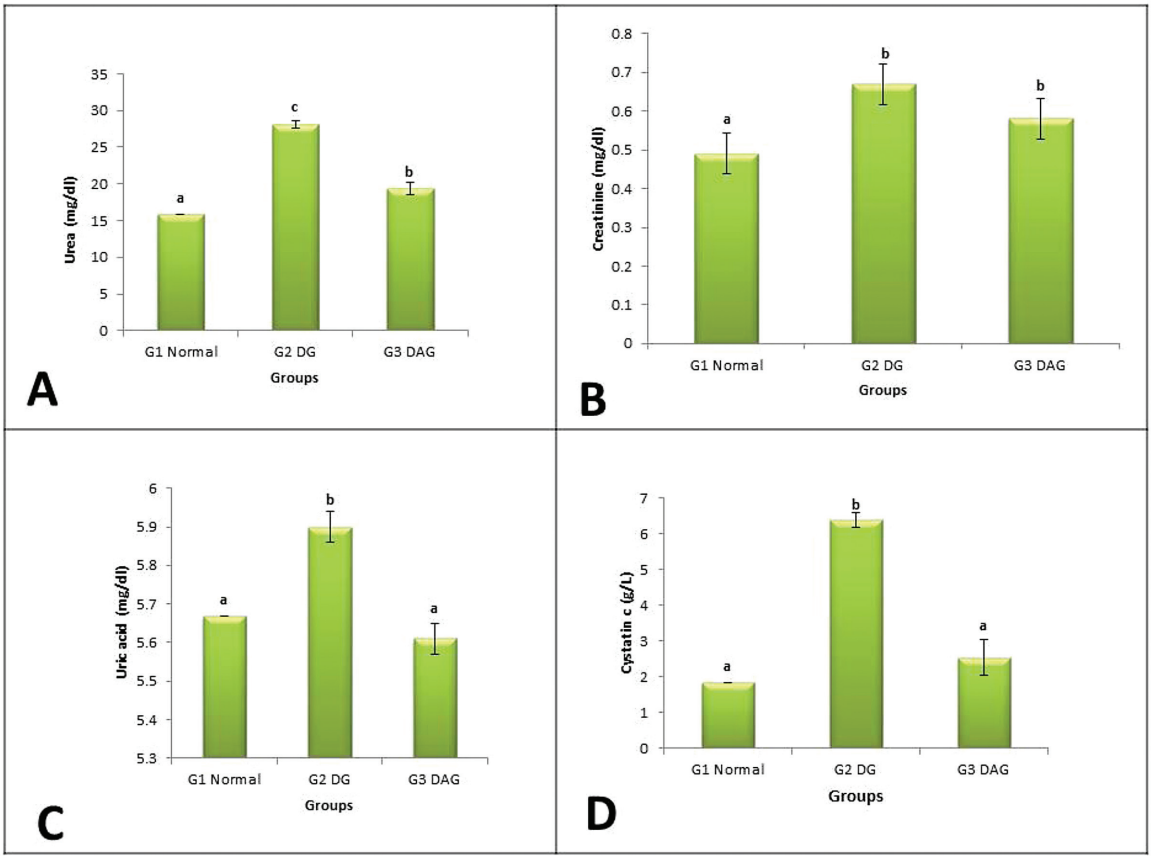
The influence of AG on fasting blood glucose (**A**) and fructosamine (**B**) levels, in normoglycemic and diabetic rats. Letters indicate significant differences at *P* less than or equal to 0.05. Diabetic group versus normal control group and diabetic group with AG treatment versus diabetic group.

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

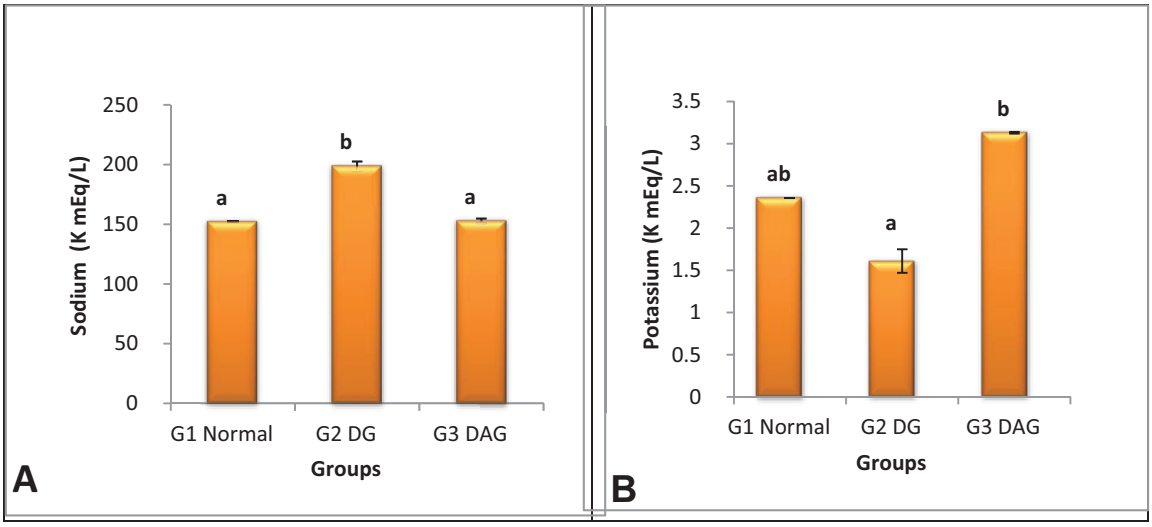
Figure 3



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.

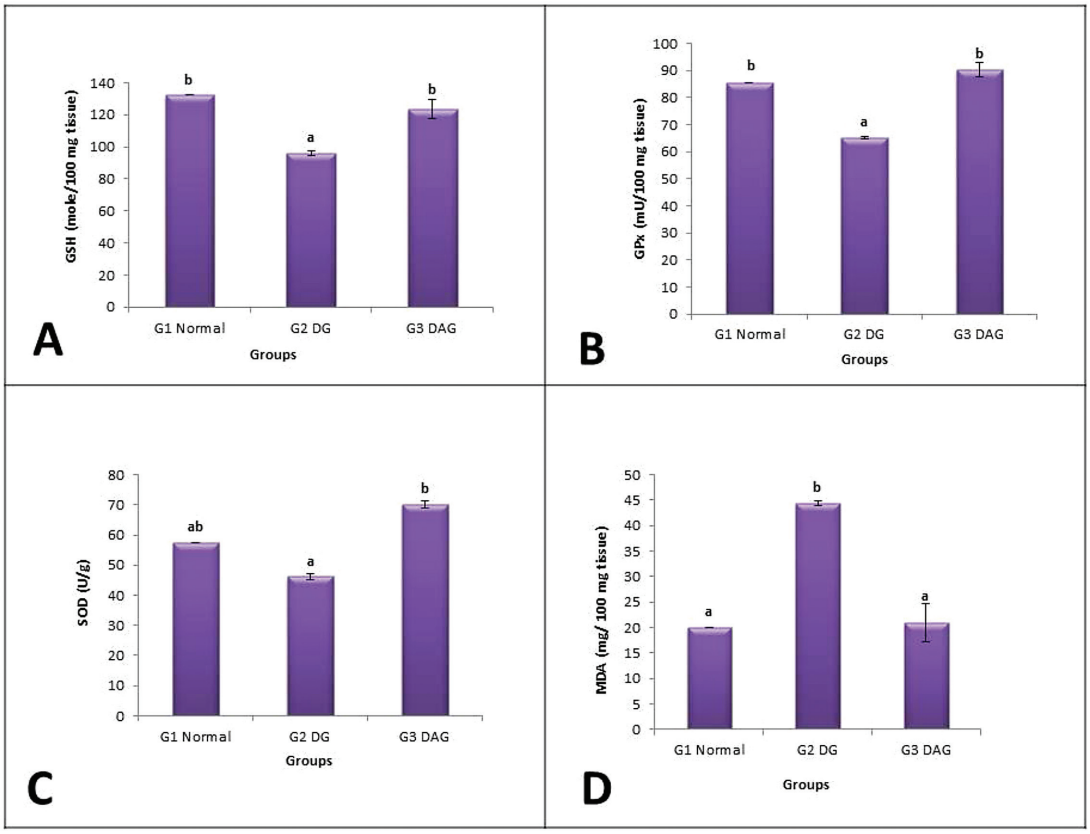
($P \leq 0.05$) versus the control group, while they were reduced in the AG-treated group below the normal level as opposed to the diabetic group. Serum potassium level has the opposite effect in diabetic rats (Fig. 4), which decreased remarkably ($P \leq 0.05$) relative to the normal group. Following 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 [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].

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

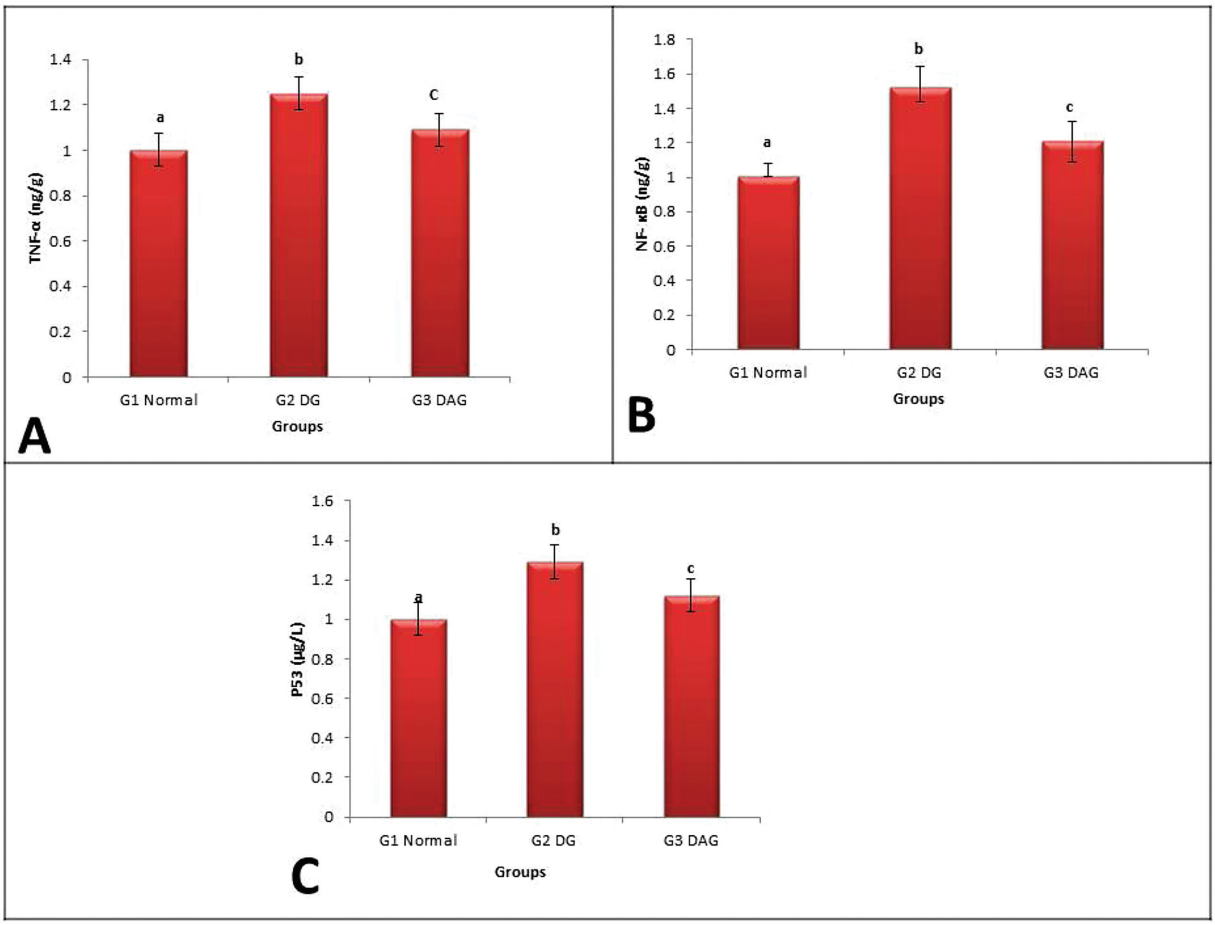


The influence of AG on GSH (**A**), GPx (**B**), SOD (**C**) and MDA (**D**) levels in kidney homogenate in normoglycemic and diabetic rats. Letters indicate significant differences at $P \leq 0.05$. Diabetic group versus normal control group and diabetic group with AG treatment versus diabetic group.

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 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

Figure 6

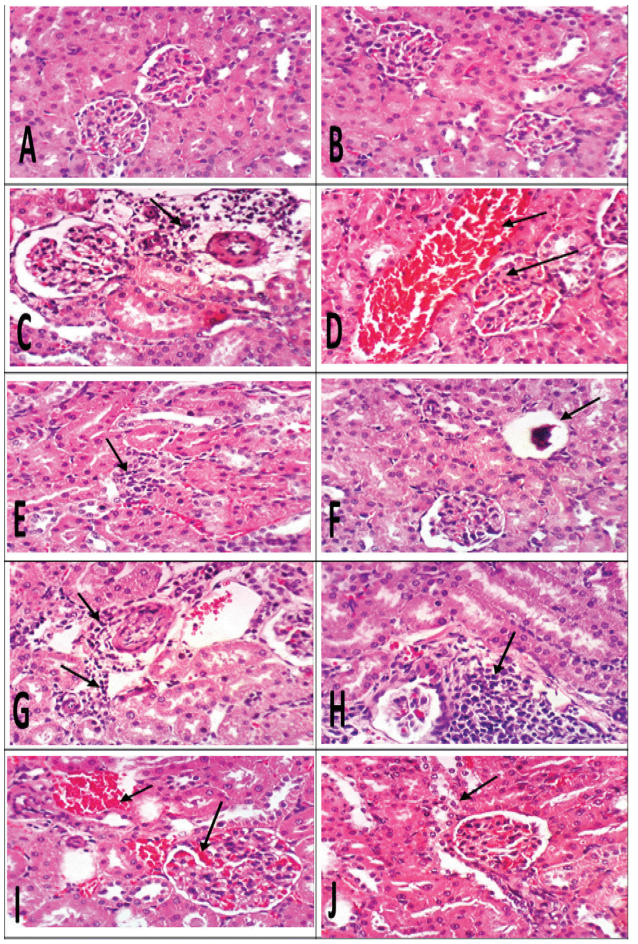


The influence of AG on TNF-α (**A**), NF- κB (**B**) and p53 (**C**) concentrations in kidney homogenate in normoglycemic and diabetic rats. Letters indicate significant differences at $P \leq 0.05$. Diabetic group versus normal control group and diabetic group with AG treatment versus diabetic group.

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 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].

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).

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.

Authors' contributions

AOM designed the study, participated in the practical part, data collection and analyses and revised the manuscript in the final form for publication. MNM participated in the practical part and participated in the data collection and analyses. HAS is the corresponding author who participated in the practical part, data collection and analyses, performed the statistical analysis, viewed the results, wrote the manuscript and prepared it in the final form for publication. All authors read and approved the submitted version.

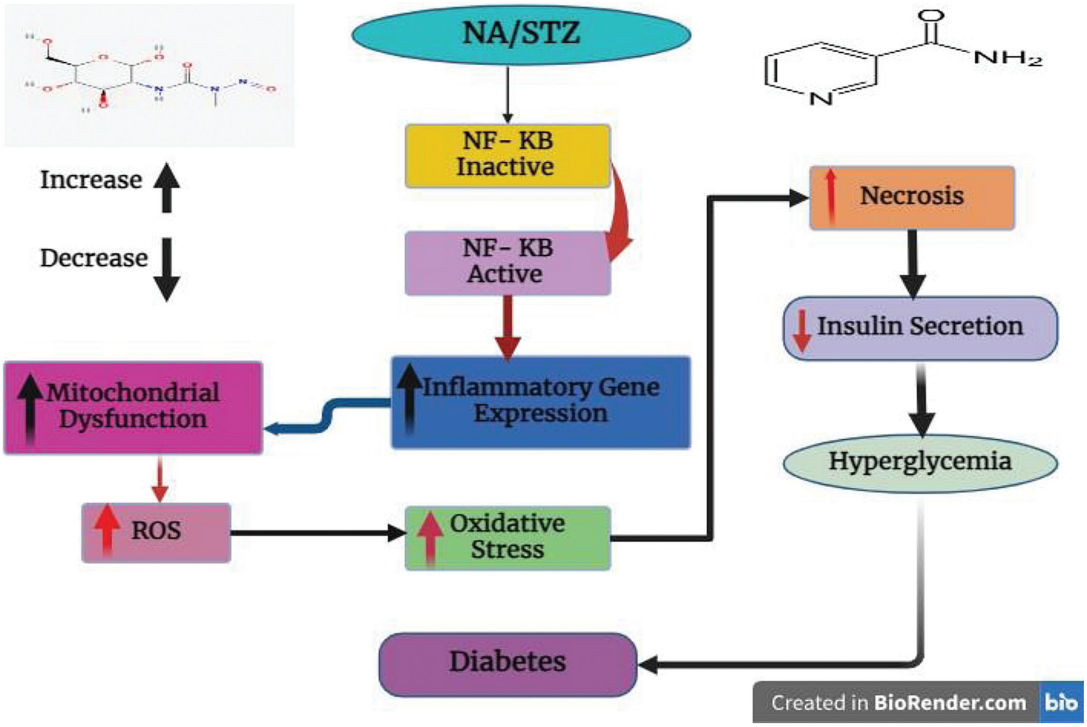
Abbreviations

AG, Arabic gum; CKD, Chronic kidney disease; DAG, Diabetic acacia group; DG, Diabetic group; DKD, Diabetic kidney disease; DM, Diabetes mellitus; DN, Diabetic nephropathy; DNA, Deoxyribonucleic acid; GPx, Glutathione peroxidase; GSH, Reduced glutathione; H and E, Hematoxylin, and eosin; HbA1c, Glycated hemoglobin; iNOS, Nitric oxide synthase 2; LPS, Lipopolysaccharides; MDA/ LPO, Malonaldialdehyde/ Lipid peroxidation; NA, Nicotinamide; NF-κB, Nuclear factor kappa B; OS, Oxidative stress; P53, Tumor suppressor protein; PBS, Phosphate-buffered saline; ROS, Reactive oxygen species; SOD, Superoxide dismutase; STZ, Streptozotocin; TNF-α, Tumor necrosis factor alpha.

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,

Figure 8



NA/STZ induce diabetes in rat model.

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.

References

1 Nasir O, Babiker S, Salim AM. Protective effect of gum Arabic supplementation for type 2 diabetes mellitus and its complications. International Journal of Multidisciplinary and Current Research 2016; 4:288–294.

2 Mohamed RE, Gadour MO, Adam I. The lowering effect of Gum Arabic on hyperlipidemia in Sudanese patients. Front Physiol 2015; 6:160.

3 Gheith O, Farouk N, Nampoory N, Halim MA, Al-Otaibi T. Diabetic kidney disease: worldwide difference of prevalence and risk factors. J Nephropharmacol 2016; 5:49–56.

4 Cade WT. Diabetes-related microvascular and macrovascular diseases in the physical therapy setting. Phys Ther 2008; 88:1322–1335.

5 Dröge W. Free radicals in the physiological control of cell function. Physiol 2002; 82:47–95.

6 Valko M, Leibfritz D, Moncol J, Cronin MT, Mazur M, Telser J. Free radicals and antioxidants in normal physiological functions and human disease. Int J Biochem Cell Biol 2007; 39:44–84.

7 Ghezzi P, Jaquet V, Marcucci F, Schmidt HW. The oxidative stress theory of disease: levels of evidence and epistemological aspects. Br J Pharmacol 2017; 174:1784–1796.

8 Miranda-Diaz AG, Pazarín-Villaseñor L, Yanowsky-Escatell FG, Andrade-Sierra J. Oxidative stress in diabetic nephropathy with early chronic kidney disease. J Diabetes Res 2016; 2016:7047238.

9 Phillips GO. Acacia gum (Gum Arabic): a nutritional fibre; metabolism and calorific value. Food Addit Contam 1998; 15:251–264.

10 Nasir O, Umbach AT, Rexhepaj R, Ackermann TF, Bhandaru M, Ebrahim A, *et al.* Effects of Gum Arabic (Acacia senegal) on Renal Function in Diabetic Mice. Kidney Blood Press Res 2012; 35:365–372.

11 Babiker M, Abbas T, Elimam M, Mohammed A. Effect of gum Arabic on liver function and antioxidant enzymes of Sprague-Dawley Rats. IOSR-JPBS 2017; 12:29–33.

12 El-Nagar DM. Pancrease-protective effects of Gum Arabicon diabetic type2 streptozotocin-induced in albino mice. Res J Pharm Biol Chem Sci 2017; 8:1263–1270.

13 Abd El Fatah SM. Biological Study on the Beneficial Effects of Gum Arabicon Biological Parameters of Hyperglycemic Albino Rats. Life Sci J 2013; 10:3570–3579.

14 Nasir O. Effect of gum Arabic (Acacia Senegal) on glucose metabolism and body weight gain in mice. J Bio Agrict Healt 2014; 4:34–41.

15 El Tobgy K. Protective role of Gum Arabic (Acacia senegal) on oxidative stress in diabetic and adenine-induced chronic renal failure in rats. Int J Chem Tech Research 2019; 12:223–234.

16 Tabassum K, Mohammad Nasar K. Scope of Unani Herbal Medicine in the Management of Obesity – A Review. Int J Herb Med 2014; 2:121–125.

17 Ahmed AA, Ali XX, Eltom AK, Eigani FA, Eltahir KK. The effects of gum Arabic oral treatment on the metabolic profile of chronic renal failure patients under regular hemodialysis in central Sudan. Nat Prod Res 2008; 22:12–21.

18 Obaid SS. The medical uses of Gum Acacia-Gum Arabic (GA) in human. Academic Journal of Research and Scientific Publishing 2020; 1:1–10.

19 Ahmed AA, Fedail JS, Musa HHd, Musa TH, Sifaldin AZ, *et al.* Gum Arabic supplementation improved antioxidant status and alters expression of oxidative stress gene in ovary of mice fed high fat diet. Middle East Fertil Soc J 2016; 21:101–108.

20 Khojah EY. Biological effects of low protein diet with gum Arabic on rat's chronic kidney disease. Adv Environ Biol 2017; 11:60–69.

21 Al Za'abi M, Al Salam S, Al Suleimani Y, Manoj P, Nemmar A, Ali BH, *et al.* Gum acacia improves renal function and ameliorates systemic inflammation, oxidative and nitrosative stress in streptozotocin-induced

diabetes in rats with adenine-induced chronic kidney disease. Cell Physiol Biochem 2018; 45:2293–2304.

22 Al-Jubori Y, Ahmed NTB, Albusaidi R, Madden J, Das S, Sirasanagandla SR. The Efficacy of Gum Arabic in Managing Diseases: A Systematic Review of Evidence-Based Clinical Trials. Biomolecules 2023; 13:138.

23 Aziz SMA, Ahmed OM, El-Twab SMA, Al-Muzafar HM, Amin KA, Abdel-Gabbar M. Antihyperglycemic Effects and Mode of Actions of Musa paradisiaca Leaf and Fruit Peel Hydroethanolic Extracts in Nicotinamide/ Streptozotocin-Induced Diabetic Rats. Evid-Based Complement Altern Med 2020; 2020:9276343.

24 Sayed HM, Awaad AS, Abdel Rahman FES, Al-Dossari M, Abd El-Gawaad NS, Ahmed OM. Combinatory Effect and Modes of Action of Chrysin and Bone Marrow-Derived Mesenchymal Stem Cells on Streptozotocin/ Nicotinamide-Induced Diabetic Rats. Pharmaceuticals (Basel) 2022; 16:34.

25 Trinder P. Enzymatic determination of glucose in blood serum. Ann Clin Biochem 1969; 6:24.

26 Valerie Ng. Effects of disease on clinical laboratory tests, 4th ed, Vol. 1 and 2. D.S. Young and R.B. Friedman, eds. Washington, DC: AACC Press, 2001.

27 Kaplan A, Glucose K. ClinChem. St Louis, Toronto, Princeton: The CV Mosby Co. 1984. 436.

28 Murray RL. Creatinine. In: Kaplan LA, Pesce AJ (Eds.) Clinical Chemistry; Theory, Analysis and Correlation. St. Louis: CV Mosby Co. 1984. 1247–1253

29 Fossati P, Prencipe L, Berti G. Use of 3,5-dichloro-2-hydroxybenzenesulfonic acid/4-aminophenazone chromogenic system in direct enzymic assay of uric acid in serum and urin. Clin Chem 1980; 26:227–231.

30 Young DS. Effects of disease on Clinical Lab. Tests, 4th ed AACC 2001

31 Burtis CA, Ashwood ER. Tietz Textbook of Clinical Chemistry. 3rd Edition Philadelphia: W. B. Saunders Co 1999. 29–150

32 Beutler E, Duron O, Kelly BM. Improved method for the determination of blood glutathione. J Lab Clin Med 1963; 61:882–888.

33 Ohkawa H, Ohishi N, Yagi K. Assay for lipid peroxides in animal tissues by thiobarbituric acid reaction. Anal Biochem 1979; 95:351–358.

34 Paglia DE, Valentine WN. Studies on the quantitative and qualitative characterization of erythrocyte glutathione peroxidase. J Lab Clin Med 1967; 70:158–169.

35 Marklund S, Marklund G. Involvement of the superoxide anion radical in the autoxidation of pyrogallol and a convenient assay for superoxide dismutase. Eur J Biochem 1974; 47:469–474.

36 Banchroft JD, Stevens A, Turner DR. Theory and Practic of Histologixal Techniques. 4th edn. New York, London, San Francisco, Tokyo: Churchil Livingstone 1996.

37 Tukey J. Comparing Individual Means in the Analysis of Variance. Biometrics 1949; 5:99–114.

38 Mohammed ME, Badi RM, Osman OM, Morsy MD, Abbas AM, Bashir SO, Saeed AM. Preventive Role of Gum Arabic Administration on STZ Induced Diabetic Kidney Disease in Rats; Renal Antioxidant and Histopathological Evidence. Int J Morphol 2020; 38:1003–1009.

39 Ahmed AA, Fedail JS, Musa HH, Sifaldin AZ, Musa TH. Gum Arabic extracts protect against hepatic oxidative stress in alloxan induced diabetes in rats. Pathophysiology 2015; 22:189–194.

40 Almohaimeed HM, Amin HA, Abd El-Aziz GS, Saleh HA. Arabic gum acacia improves diabetic peripheral neuropathy in rats: a biochemical and histopathological evidence. International Journal of Basic & Clinical Pharmacology 2018; 7:1065–1071.

41 Qureshi JA, Memon Z, Mirza KM, Saher F. Herbal approach towards the cure of diabetes mellitus—a review. Asian Journal of Medicine and Health 2018; 12:1–12.

42 Ali BH, Ziada A, Blunden G. Biological effects of gum arabic: a review of some recent research. Food Chem Toxicol 2009; 47:1–8.

43 Reidy K, Kang HM, Hostetter T, Susztak K. Molecular mechanisms of diabetic kidney disease. J Clin Invest 2014; 124:2333–2340.

44 Abd-El-Hafez SM, Ismael AB, Soliman MM, Mohamed EH, Kafaween IK, Mohamed HH. Effect of gum Arabic and Nigella sativa on T-helper1 and T-helper2 immune response in Wistar rats infected with methicillin-resistant Staphylococcus aureus. Natl J Physiol Pharm Pharmacol 2017; 7: 1410–1416.

45 Abd-Allah AR, Al-Majed AA, Mostafa AM, Al-Shabanah OA, Din AG, Nagi MN. Protective effect of arabic gum against cardiotoxicity induced by doxorubicin in mice: a possible mechanism of protection. J Biochem Mol Toxicol 2002; 16:254–259.

46 Nezu M, Suzuki N, Yamamoto M. Targeting the KEAP1- NRF2 system to prevent kidney disease progression. Am J Nephrol 2017; 45:473–483.

47 Zheng H, Whitman SA, Wu W, Wondrak GT, Wong PK, Fang D, Zhang DD. Therapeutic potential of Nrf2 activators in streptozotocin-induced diabetic nephropathy. Diabetes 2011; 60:3055–3066.

48 Dashtdar M, Kardi K. Benefits of gum Arabic for a solitary kidney under adverse condition. A case study Chin Med Cult 2018; 81:88–96.

49 Naima ES, Ali NES, Elkarim AMA, Fageer ASHM, Nour AAM. Physicochemical Characteristics of Some Acacia Gums. Int J Agric Res 2012; 7:406–413.

50 Lee HB, Yu MR, Yang Y, Jiang Z, Ha H. Reactive oxygen species regulated signaling pathways in diabetic nephropathy. J Am Soc Nephrol 2003; 14: S241–S245.

51 Kashihara N, Haruna Y, Kondeti VK, Kanwar YS. Oxidative stress in diabetic nephropathy. Curr Med Chem 2010; 17:4256–4269.

52 Al-Majed AA, Mostafa AM, Al-Rikabi AC, Al-Shabanah OA. Protective effects of oral arabic gum administration on gentamicin-induced nephrotoxicity in rats. Pharmacol Res 2002; 46:445–451.

53 Gado AM, Aldahmash BA. Antioxidant effect of Arabic gum against mercuric chloride-induced nephrotoxicity. Drug Des Devel Ther 2013; 7:1245–1252.

54 Ali BH, Al-Husseni I, Beegam S, Al-Shukaili A, Nemmar A, Schierling S, *et al.* Effect of gum arabic on oxidative stress and inflammation in adenine induced chronic renal failure in rats. PLoS ONE 2013; 8:e55242.

55 Manohar SM, Vaikasuvu SR, Deepthi K, Sachan A, Narasimha SR. An association of hyperglycemia with plasma malondialdehyde and atherogenic lipid risk factors in newly diagnosed Type 2 diabetic patients. J Res Med Sci 2013; 18:89–93.

56 Amorim RG, Guedes GDS, Vasconcelos SML, Santos JCF. Kidney disease in diabetes mellitus: cross-linking between hyperglycemia, redox imbalance and inflammation. Arq Bras Cardiol 2019; 112:577–587.

57 Stefanson AL, Bakovic M. Dietary regulation of Keap1/ Nrf-2/ARE pathway: focus on plant-derived compounds and trace minerals. Nutrients 2014; 6:3777–3801.

58 Indira M, Abhilash PA. Role of NF-Kappa B (NF-κB) in diabetes. For Immunopathol Dis Therap 2013; 4:111–132.

59 Vlahopoulos SA, Cen O, Hengen N, Agan J, Moschovi M, Critselis E, *et al.* Dynamic aberrant NF-κB spurs tumorigenesis: A new model encompassing the microenvironment. Cytokine Growth Factor Rev 2015; 26:389–403.

60 Lawrence T. The nuclear factor NF-kappa B pathway in inflammation. Cold Spring Harb Perspect Biol 2009; 1:a001651.

61 Vadapalli J, Vanam A, Motohashi N, Gollapudi R. Chronic Inflammation: Prospective Prevention and/or Control by the Regulation of Nuclear Factor Kappa B with Natural Products as Dietary Supplements. Journal of Community and Preventive Medicine 2018; 1:1–12.

62 Cui W, Bai Y, Miao X, Luo P, Chen Q, Tan Y, *et al.* Prevention of diabetic nephropathy by sulforaphane: possible role of Nrf2 upregulation and activation. Oxid Med Cell Longev 2012; 2012:1–12.

63 Shin S, Wakabayashi J, Yates MS, Wakabayashi N, Dolan PM, Aja S, *et al.* Role of Nrf2 in prevention of high-fat diet-induced obesity by synthetic triterpenoid CDDO-imidazolide. Eur J Pharmacol 2009; 620:138–144.

64 Wardyn JD, Ponsford AH, Sanderson CM. Dissecting molecular cross-talk between Nrf2 and NF-κB response pathways. Biochem Soc Trans 2015; 43:621–626.

65 Li W, Khor TO, Xu C, Shen G, Jeong WS, Yu S, Kong AN. Activation of Nrf2-antioxidant signaling attenuates NFκB inflammatory response and elicits apoptosis. Biochem Pharmacol 2008; 76:1485–1489.

66 Bnuyan IA, Hindi NK, Jebur MH, Mahdi MA. In Vitro antimicrobial activity of gum Arabic (Al Manna and Tayebat) prebiotics against Infectious pathogens. Ijppr 2015; 3:77–85.

67 Saleh MA, Awad AM, Ibrahim TM, Abu-Elsaad NM. Small-Dose Sunitinib Modulates p53, Bcl-2, STAT3, and ERK1/2 Pathways and Protects against Adenine-Induced Nephrotoxicity. Pharmaceuticals (Basel) 2020; 13:397.

68 Derbalaa SA, Gouida MS. Impact of Gum acacia on oxidative stress and apoptosis in Adenine-induced CKD animal model. Biochemistry Letters 2022; 18:73–84.