Antihyperlipidemic and cardiopreventive properties of Arabic gum in nicotinamide/streptozotocin-induced diabetic rats

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Background/Aim
Diabetes mellitus (DM) and its complications have a negative impact on human health and the economy worldwide. Diabetic patients are at a high risk of dying from cardiovascular diseases. Arabic gum (AG) is a natural product that exhibits potent anti-inflammatory, antioxidant and hypoglycemic properties. The purpose of this study was to scrutinize the antihyperlipidemic and cardiopreventive efficacy and to assess the antioxidant and anti-inflammatory roles of AG in nicotinamide (NA)/streptozotocin (STZ)-induced DM in rats.

Material and methods
Three groups of 18 adult (6 each) male Wistar rats each were used for the experiment. The first group was the normal control group, which received 0.9% NaCl daily by oral gavage for 8 weeks. The rats in the second group were injected with 60 mg/kg b.w. STZ in citrate buffer (pH 4.5) intraperitoneally (IP), after being given intraperitoneally 120 mg/kg b.w. NA. They also received 0.9% NaCl daily by oral gavage for 8 weeks. The third group was treated with 20 mg AG/kg b.w./day suspended in 0.9% NaCl by oral gavage for 8 weeks after inducing DM in the same way as the second group.

Results
Hyperglycemia and hyperlipidemia were observed in DM rats. They also had significantly higher levels ($P<0.05$) of serum creatine kinase (CK), creatine kinase myocardial band (CK-MB), aspartate aminotransferase (AST), and lactate dehydrogenase (LDH), which indicate heart dysfunction. The diabetic heart suffered from oxidative stress, as shown by significant increases ($P<0.05$) of malondialdehyde (MDA) and decreased glutathione (GSH), glutathione peroxidase (GPx), and superoxide dismutase values (SOD). AG treatment improved blood glucose and serum lipid levels, as well as heart function biomarkers in serum. AG also reduced oxidative stress and enhanced antioxidant defenses in the diabetic heart. Immune-inflammatory markers, such as nuclear factor-kappa B and tumor necrosis factor-α and apoptotic protein p53 expressions were elevated in diabetic rats ($P<0.05$) markedly, but the treatment with AG exhibited normal levels for them.

Conclusion
In conclusion, this study demonstrated that AG has a preventive role against heart injury in NA/STZ-induced DM in rats. AG improved the metabolic, oxidative, and inflammatory status as well as apoptosis and their cardiac function in diabetic rats. Moreover, AG improved the histological picture of cardiac myocytes and therefore, it may be a potential natural remedy for diabetic cardiomyopathy.

Keywords:
antioxidant, Arabic gum, diabetes mellitus, hyperglycemia, hyperlipidemia

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Introduction

Cardiovascular problems are a major cause of death and disability among diabetic patients worldwide due to the long-term effects of hyperglycemia [1]. Diabetes mellitus (DM) is caused by a metabolic imbalance of proteins, lipids, and carbohydrates at the homeostasis level. DM is classified into two types: type I diabetes (T1DM), characterized by insufficient insulin production by the pancreas and type II diabetes (T2DM), characterized by insulin resistance of the body tissues [2]. The World Health Organization (WHO) reports that chronic DM is rising rapidly worldwide, with a doubling of cases from 1980 to 2014. Also, about half of the deaths were due to high blood sugar and occurred before the seventh decade of life [3]. Oxidative stress has a key role in DM complications, as it increases the ratio of oxidants to antioxidants [4], which damages biological macromolecules (proteins, carbohydrates, fats, and nucleic acids). This leads to more reactive oxygen species and more cell damage. DM induces

alterations in the cardiac muscle's structure and function, leading to a condition called diabetic cardiomyopathy (DCM). DCM has a complex origin, with many interrelated mechanisms responsible for cardiomyopathy in DM [5]. Oxidative stress and inflammation are thought to play a key role in the worsening of DCM. Oxidative stress is a major factor that leads to the development and deterioration of DCM in the DM heart [6]. DM complications are generally seen as the outcome of oxidative stress. Moreover, DM complications are linked to the inflammatory response and have been found to be faster at high blood sugar levels, which trigger adipocyte acute response factor creation [7].

Arabic acacia gum (AG) is a food additive that has many uses in food production and is also called *Acacia senegal* L [8]. It can act as a carrier for many drugs that treat patients and can also reduce the toxicity of some drugs. Besides, it has antioxidant and anti-inflammatory effects that make AG the subject of interest for studying human diseases that involve inflammation and inflammatory pathways [9–12]. AG is used for its potential therapeutic effects in many diseases, such as metabolic disorders, gastrointestinal disorders, periodontitis, rheumatoid arthritis and sickle cell disease [13].

AG is widely used and considered safe in both folk medicine and pharmaceutical products. It is indigestible by humans or animals, but it can undergo fermentation in the colon to generate short-chain fatty acids, which may have various health benefits. It has a prebiotic effect as it increases the levels of beneficial bacteria such as Bifidobacteria, Lactobacteria, and Bacteroides. Furthermore, it also has anticancer, antioxidant effects and can protect the liver and the heart from damage [14].

Consequently, the purpose of this study was to explore how AG can modulate heart function, antioxidant defense mechanisms and the immunoinflammatory pathway, thus treating DCM in rat models.

Materials and methods

Plant materials

AG was purchased (in powder form) from Qualikems Fine Chem PVT. LTD (India).

Chemicals

Nicotinamide (NA) and streptozotocin (STZ) were purchased from Sigma-Aldrich (St. Louis, MO, USA).

Experimental animals

The present study involved adult male Wistar rats (120–140 g) that were obtained from the Egyptian Organization for Biological Products and Vaccines (VACSERA), Helwan Station, Cairo, Egypt. The animals were observed for 2 weeks before the experiment to ensure they were free of infections. They were housed in the animal facility of the Zoology Department, Faculty of Science, Beni-Suef University, Egypt, in well-ventilated polypropylene cages. They were exposed to a normal light–dark cycle (10–12 h/day), a normal temperature (20–25°C), and had access to food and water at all times.

Ethical consideration

All the experiments were done in compliance with the public health guide for the care and use of laboratory animals and followed the ethical consideration of the Experimental Animal Ethics Committee of the Faculty of Science, Beni-Suef University, Egypt under approval number BSU/FS/2018/26. The number of animals was minimized and all efforts were made to reduce their pain, distress and discomfort.

Induction of diabetes mellitus

T2DM was induced in 16-h-fasted rats according to Aziz *et al.* [15] and Ahmed *et al.* [16] by a single intraperitoneal (i.p.) injection of STZ (60 mg/kg b.w.) dissolved in 0.09 M citrate buffer (pH 4.5), 15 min after the i.p. injection of nicotinamide (120 mg/kg b.w.) prepared in 0.9% saline solution. Rats received 5% glucose in drinking water to overcome the hypoglycemia caused by STZ. Ten days after the STZ injection, overnight fasted animals were given glucose (3 g/kg b.w.) by gastric intubation. After 2 h of oral glucose loading, blood samples were withdrawn from the lateral tail vein, left to coagulate and centrifuged, then the serum glucose concentration was measured. Rats that had a serum glucose of 180–300 mg/dl after 2 h of glucose intake were considered mild DM and were included in the experiment.

Phenolic constituents of Arabic gum by high-performance liquid chromatography (HPLC)

Sample preparation

A sample was prepared by dissolving 20 mg of Arabic gum in 1 ml of 80% methanol (vortex, sonication, filtration and injection).

HPLC condition

HPLC analysis was carried out in Chromatography Lab., Central Labs., National Research Centre using

an Agilent 1260 series. The separation was carried out using a Zorbax Eclipse plus C8 column (4.6 mm×250 mm i.d., 5 µm). The mobile phase consisted of water (A) and 0.05% trifluoroacetic acid in acetonitrile (B) at a flow rate of 0.9 ml/min. The mobile phase was programmed consecutively in a linear gradient as follows: 0 min (82% A), 0–1 min (82% A), 1–11 min (75% A), 11–18 min (60% A), 18–22 min (82% A) and 22–24 min (82% A). The multiwavelength detector was monitored at 280 nm. The injection volume was 5 µl for each of the sample solution. The column temperature was maintained at 40°C.

Experimental design

Experimental animals were allocated into three groups, each comprising six rats, as follows:

(1) Group I (normal control): 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): rats were orally given the equivalent volume of isotonic solution daily through oral gavage for 8 weeks.
(3) Group III (diabetic + AG treated group 'NA/STZ-induced diabetic group treated with Arabic gum') diabetic animals received 20 mg/kg b.w./day AG suspended in 0.9% NaCl by oral gavage for 8 weeks [17].

Sampling

At the end of the treatment period, the rats were deprived of food overnight and were anesthetized by diethyl ether inhalation. Blood samples were collected from the jugular vein and then the rats were killed by sudden cervical decapitation while they were anesthetized. Blood was left at room temperature to coagulate and then centrifuged at 3000 rpm for 15 min. The clear, non-hemolyzed supernatant sera were collected into three Eppendorf tubes for each rat and kept at −80°C until used.

Preparation of tissue homogenates

Tissue homogenates were prepared as follows: rats were killed; heart tissue (5µm) was cut and rinsed with ice-cold (0.01 M, pH=7.4) phosphate-buffered saline (PBS), weighed, minced and then homogenized in PBS (9 ml PBS per gram tissue) with a glass homogenizer on ice. The homogenates were centrifuged at 3000 rpm. for 10 min and the supernatants were removed and frozen at −80°C.

Biochemical analyses

Spectrophotometrically, using kits purchased from SPINREACT serum glucose was estimated according to Valerie [18]. Serum insulin level was measured using sandwich enzyme-linked immunosorbent assay (ELISA) using kits purchased from Linco Research, USA, in accordance with the manufacturer's instructions. Creatine kinase (CK) and creatine kinase myocardial band (CK-MB) were estimated according to Clayton and Thomas [19] and Wu and Bowers [20]. Lactate dehydrogenase (LDH) and aspartate aminotransferase (AST) were estimated following the methods of Young [21] and Reitman and Frankel [22], respectively, using kits purchased from SPINREACT Co. (Barcelona, Spain). Serum total cholesterol, triglycerides (TG), low-density lipoprotein cholesterol (LDL-cholesterol) and high-density lipoprotein cholesterol (HDL-cholesterol) were estimated using kits of SPINREACT Co. (Barcelona, Spain) following the methods of Burtis *et al.* [23], Buccolo *et al.* [24], Armstrong and Seidel [25] and Jacobs *et al.* [26], respectively.

Measurement of oxidative stress and antioxidant biomarkers

Spectrophotometrically, the heart level of reduced glutathione (GSH) was measured according to Beutler *et al.* [27]; lipid peroxidation/malondialdehyde (LPO/MDA) level was measured according to Ohkawa *et al.* [28]; glutathione peroxidase (GPx) activity was determined following the method of Paglia and Valentine [29] and superoxide dismutase (SOD) activity was estimated according to Marklund and Marklund [30] using kits purchased from Biodiagnostic Co. (Egypt).

Estimation of mRNA expression of heart NF-κB, TNF-α, and p53

Total RNA from the liver tissue was extracted according to the method of Chomzynski and Sacchi [31] using the Thermo Scientific GeneJET RNA purification kit obtained from Thermo Fisher Scientific Inc., Rochester, New York, USA. The purified RNA was transcribed into cDNA and then amplified in a PCR reaction using the Thermo Scientific Verso 1-Step real-time polymerase chain reaction Reddy Mix Kit (Thermo Fisher Scientific Inc., Rochester, New York, USA) in the presence of specific primers (Table 1) obtained from Biosearch Technologies, South McDowell Blud and Petaluma, CA, USA [32–35]. Real-time polymerase chain reaction products were electrophoresed on a 1.5% agarose gel and visualized under ultraviolet light after staining with ethidium bromide. The electrophoretic picture was analyzed by the gel documentation system (GelDocu Advanced) and the values of nuclear factor-kappa B (NF-κB) according to Shaker and Sourour [32]. Tumor necrosis factor-α

Table 1 Primer sequences for polymerase chain reaction

mRNA species	Forward primer sequence	Reverse primer sequence	Reference numbers
NF-κB	5′d TACCATGCTGTTTTGGTTAC3′	5′d dTCAAGCTACCAATGACTTTC 3′	[32]
TNF-α	5′d GCTGAGGTTGGACGGATAAA3′	5′d AAAATCCTGCCCTGTCACAC3′	[33]
P53	5′d-GCTGCCCTCCCTTC TCCTAG3′	5′d CCCCGACTTTGGAGTAGTCTGA3′	[34-36]
β-actin	5′d TCACCCTGAAGTACCCCATGGAG3′	5′d TTGGCCTTGGGGTTCAGGGGG 3′	[32]

(TNF-α) and apoptotic protein p53 expression were normalized to the quantity of β-actin [32–36].

Histological examination

After embedding the heart tissues in paraffin blocks, serial sections (4 µm thick) were mounted on glass slides, washed in a water bath and left in an oven for dewaxing. Finally, the sections were stained with hematoxylin and eosin [37]. Histological changes were assessed under an electrical light microscope (Olympus CX 41 RF, TOKYO, JAPAN). Adobe Photoshop version 8.0 was used for processing the photomicrographs.

Statistical analysis

All data were coded, tabulated and statistically analyzed using the Statistical Package for the Social Sciences software, SPSS version 24. All data are presented as mean±standard error. The obtained data were analyzed by post hoc one-way analysis of variance followed by Tukey's methods [38]. Data were considered statistically significant when the *P*-value is less than or equal to 0.05.

Results

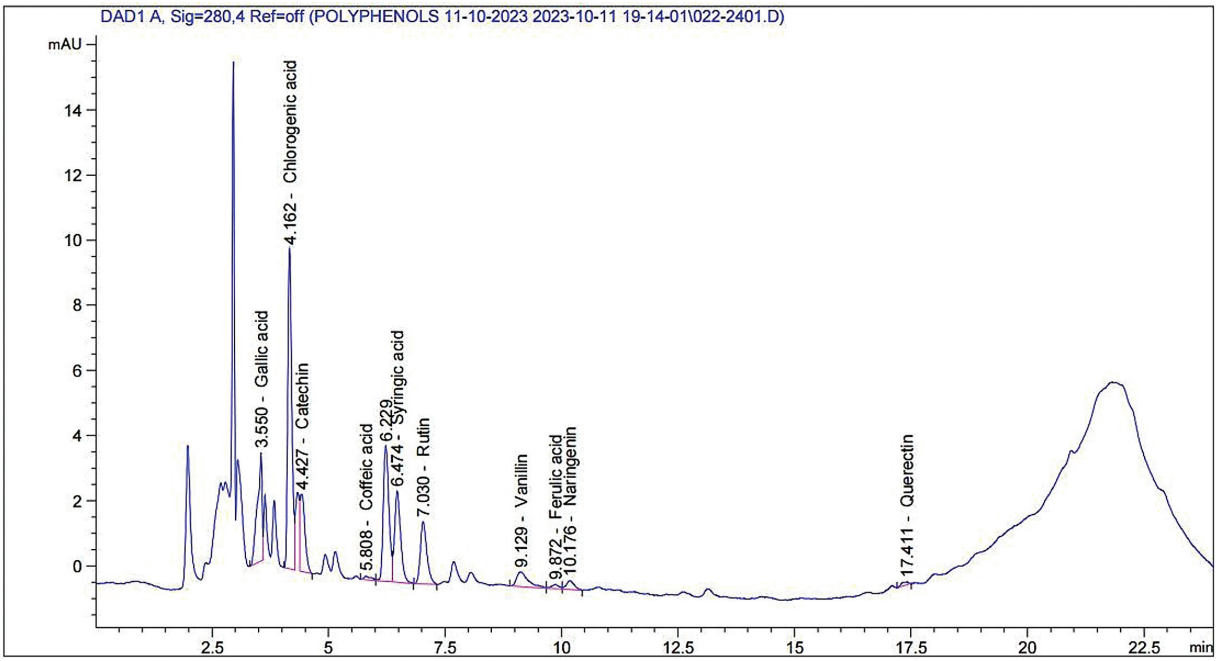
Phenolic profile of Arabic gum by HPLC

HPLC analysis of Arabic gum, illustrated in Table 2 and Fig. 1, revealed 10 phenolic compounds, consisting of six phenolic acids and/or compounds (gallic acid, chlorogenic acid, caffeic acid, syringic acid and vanillin) and four flavonoids (catechin, rutin, naringenin and quercetin). Chlorogenic acid was the most abundant in Arabic gum, followed by catechin, rutin, gallic acid and

Table 2 Phenolic compounds identified in Arabic gum using high performance liquid chromatography

Polyphenols	Area	Conc. (µg/ml)	Conc. (µg/g)
Gallic acid	23.70	2.11	105.50
Chlorogenic acid	59.10	8.00	400.18
Catechin	17.36	3.95	197.41
Caffeic acid	1.18	0.09	4.72
Syringic acid	25.32	1.93	96.59
Rutin	18.42	3.09	154.36
Vanillin	7.88	0.30	14.86
Ferulic acid	1.53	0.09	4.61
Naringenin	3.28	0.31	15.53
Quercetin	1.24	0.17	8.25

Figure 1



Phenolic profile of Arabic gum by high performance liquid chromatography.

syringic acid. However, vanillin, naringenin, quercetin, ferulic acid and caffeic acid were found in minor concentrations.

Arabic gum improves lipid profile

As far as we know, the current study investigates the effect of Arabic gum (AG) on heart damage in T2DM. DM caused significant increases in serum levels of total cholesterol, triglycerides, LDL cholesterol and the ratios of total cholesterol to HDL-cholesterol and LDL cholesterol ($P<0.05$), while HDL-cholesterol levels decreased significantly compared with the control group. However, these changes were reversed when the DM rats received AG treatment, as the serum levels of the above parameters decreased significantly ($P<0.05$) except for HDL-cholesterol, which increased significantly compared with the DM group (Table 3).

Arabic gum enhances glucose control and heart efficacy

Back to the present results, fasting blood glucose levels and cardiac damage markers (serum CK, CK-MB, LDH and AST) were higher ($P\leq0.05$) in DM rats than in the control group. AG treatment significantly ($P\leq0.05$) reduced fasting glucose and cardiac damage markers levels of CK-MB, LDH and AST in the blood relative to the DM group (Table 4).

Arabic gum attenuates oxidative stress and enhances the antioxidant defense system

DM significantly ($P\leq0.05$) decreased heart values of GSH, GPx and SOD, which are antioxidants, relative to the control group. However, AG treatment significantly increased the heart values of these antioxidants, compared with the diabetic group. Diabetic rats also increased markedly ($P\leq0.05$) the heart level of MDA, which is a marker of oxidative stress, in contrast to the control group. However, AG treatment significantly reduced the heart level of MDA, relative to the diabetic group (Table 5).

Arabic gum reduces heart inflammation

Diabetes elevated heart mRNA expressions of NF-κB and TNF-α, which are inflammatory factors, above normal ($P\leq0.05$), in contrast to the control group. However, AG treatment lowered the mRNA expression of NF-κB and TNF-α below normal ($P\leq0.05$), relative to the DM group. Meanwhile,

Table 3 Influence of Arabic gum on serum lipid profile in normal and diabetic rats

Group parameters	G1 (negative control)	G2 (diabetic control)	G3 (diabetic+AG treated)
Total cholesterol (mg/dl)	49.1±0.9[a]	101.2±2.0[b]	57.02±0.6[a]
Triglycerides (mg/dl)	58.3±2.9[a]	97.8±2.9[b]	62.08±3.1[a]
HDL-cholesterol (mg/dl)	28.5±1.1[a]	11.4±0.4[b]	28.1±1.8 [a]
LDL-cholesterol (mg/dl)	7.0±1.7[a]	39.0±1.1[b]	18.9±1.1[c]
Total chol/HDL-cholesterol	1.7±0.5[a]	8.9±0.4[b]	2.03±0.1[a]
Total chol/LDL-cholesterol	7.01±0.4[a]	2.3±0.4[b]	3.02±0.08[a]

All data are presented as mean±SE. All means with different superscript letters (a, b, c) within the same row are significantly different at *P* less than 0.05.

Table 4 Influence of Arabic gum on serum glucose level and cardiac function markers in normal and diabetic rats

Group parameters	G1 (negative control)	G2 (diabetic control)	G3 (diabetic+AG treated)
Fasting glucose (mg/dl)	81.3±3.2[a]	472.5±3.9[b]	102.2±0.6[c]
Creatine kinase (IU/l)	47.0±4.3[a]	544.2±6.2[b]	69.5±4.5[c]
Creatine kinase-MB (IU/l)	82.3±0.3[a]	276.5±0.9[b]	95.5±0.6[c]
LDH (IU/l)	477.6±4.2[a]	1558.5± 8.4[b]	493.3±5.3[a]
AST (IU/l)	22.7±4.8[a]	149.0±9.0[b]	42.1±4.8[c]

All data are presented as mean±SE. All means with different superscript letters (a, b, c) within the same row are significantly different at *P* less than 0.05.

Table 5 Influence of Arabic gum on the heart oxidative stress (MDA) and antioxidant defense (GSH, GPx and SOD) in normal and diabetic rats

Group parameters	G1 (negative control)	G2 (diabetic control)	G3 (diabetic+AG treated)
GSH (mol/100 mg tissue)	121.7±0.57[a]	88.9±4.7[b]	116.9±5.1[a]
GPx (mU/100 mg tissue)	86.2±0.10[a]	71.8±2.1[b]	85.0±0.25[a]
SOD (U/g)	63.6±1.8[a]	33.7±0.79[b]	59.2±2.1[a]
MDA (nmol/ 100 mg tissue/h)	25.8±2.6[a]	139.3±2.7[b]	25.1±1.3[a]

All data are presented as mean±SE. All means with different superscript letters (a, b, c) within the same row are significantly different at *P* less than 0.05.

Table 6 Influence of Arabic gum on the heart mRNA expression of inflammatory markers (NF-κB and TNF-α) and apoptotic protein (P53) in diabetic rats

Groups Parameters	G1 (negative control)	G2 (diabetic control)	G3 (diabetic +AG treated)
NF-κB (fold change)	1.05±0.01[a]	4.26±0.03[b]	1.9±0.04[c]
TNF-α (fold change)	1.01±0.01[a]	6.22±0.005[b]	1.12±0.004[c]
P53 (fold change)	1.11±0.01[a]	7.11±0.003[b]	1.7±0.003[c]

All data are presented as mean±SE. All means with different superscript letters (a, b, c) within the same row are significantly different at *P* less than 0.05.

there was no significant difference in heart mRNA expression of P53, which is a tumor suppressor and apoptotic protein, among the control, DM and AG-treated groups (Table 6).

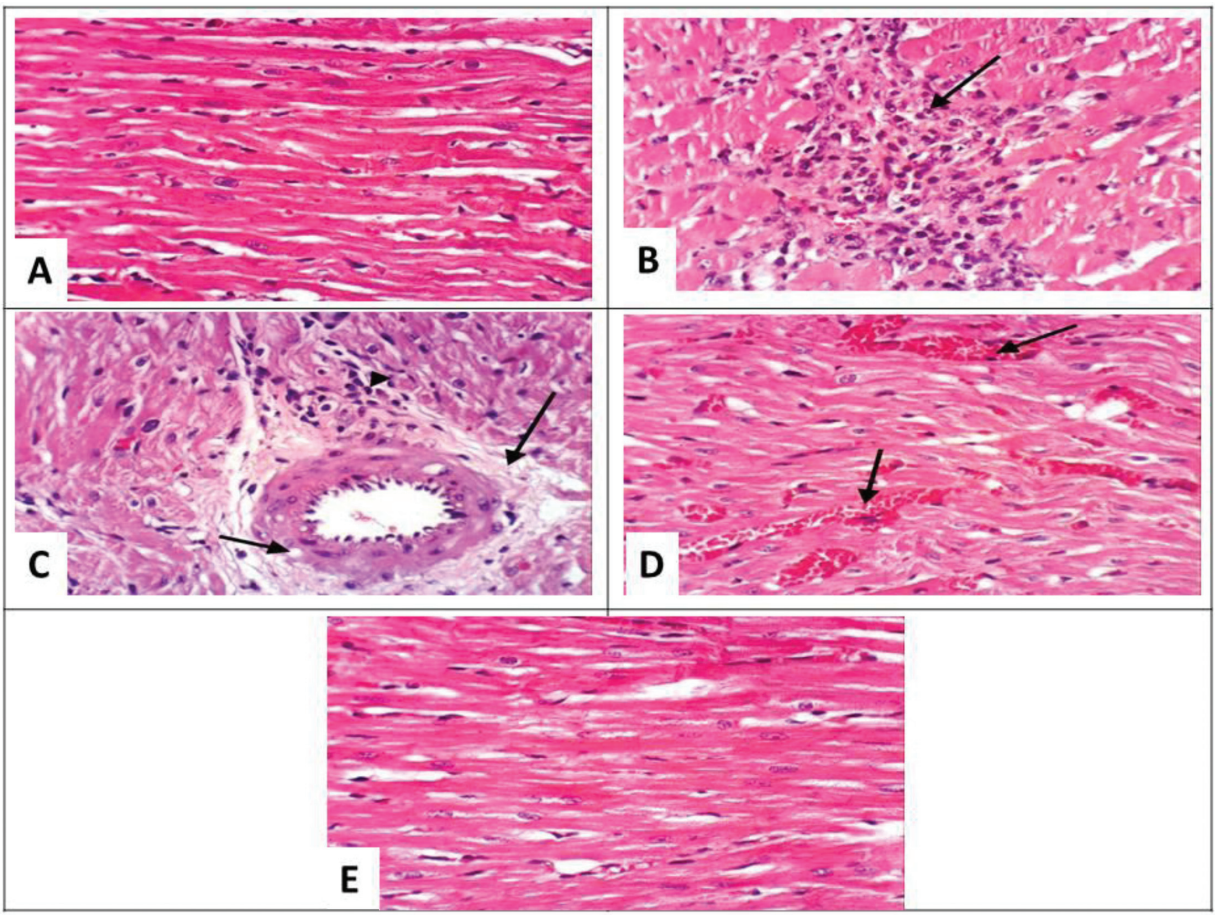
Histopathological findings

The heart sections of normal control depicted normal histological structure of the heart as the cardiac muscle fibers are aligned with each other with an oval central nucleus (Fig. 2a). The heart section of diabetic rats, however, depicted focal necrosis of cardiac myocytes associated with inflammatory cell infiltration (Fig. 2b) and vacuolation of the wall of blood vessel associated with perivascular edema and inflammatory cell infiltration (Fig. 2c). The diabetic rats treated with AG extract exhibited mild congestion of myocardial blood vessels in the heart of some animals and near-normal histological structures in others (Fig. 2d and e).

Discussion

One of the main causes of death among DM patients in developing countries is damage to the cardiovascular system caused by long-term high blood sugar levels,

Figure 2



Heart of a rat from a normal control (A) showing the normal histological structure of cardiac myocytes. In the heart of a diabetic rat (B), focal necrosis of cardiac myocytes was associated with inflammatory cells infiltration (black arrows). In addition to vacuolation (C) of the wall of the blood vessel associated with perivascular edema and inflammatory cell infiltration (black arrows). The heart section of a rat from the diabetic group treated with Arabic gum showed congestion (D) of myocardial blood vessels (black arrows). However, no pathological alterations were observed (E) in the heart tissue of a diabetic rat treated with Arabic gum (H and E ×400).

which leads to a condition called cardiomyopathy [39]. According to Jia *et al.* [40], high blood sugar levels are linked to an enlargement of the heart due to problems in the small blood vessels. This happens because long-term DM makes the heart less responsive to insulin [41], increases oxidative stress and impairs the calcium transport in the mitochondria, which produces energy in the cells [42]. A recent study suggested that GA could slow down the progression of DCM by improving high blood sugar levels, high blood lipid levels and oxidative stress. This implies that GA might have the potential to treat DCM in humans [43]. DCM is a condition where the heart muscle and function are abnormal in people with DM, even when they do not have other factors that can affect the heart, such as blocked arteries, high blood pressure, or significant valve problems [39]. Early management and treatment of high blood sugar can improve the quality of life of diabetic patients and prevent complications. GA lowers blood sugar by increasing the amount of stool, decreasing its water content, trapping bile acids and improving the body's functions [44].

DM raised serum levels of total cholesterol, triglycerides, LDL cholesterol, and their ratios and lowered HDL-cholesterol levels, compared with the control group. AG treatment reversed these changes, except HDL-cholesterol increased, in contrast to the DM group. The present study was in line with Fouda *et al.* [43], who reported that broiler chickens had lower serum cholesterol and triglycerides when fed diets with 5% and 7.5% AG, which has a hypolipidemic effect. Mice that had a fat-rich diet and 7% GA for about four-and-a-half months also had lower serum cholesterol and triglycerides. Different mechanisms have been proposed for the hypolipidemic action of AG. One way is that GA increases bile salt excretion in the stool, which makes the liver use more cholesterol to make new bile salts and reduces body fat and serum cholesterol [45,46]. Another way is that GA changes the expression of genes that are related to cholesterol formation and fat oxidation in mice [47]. Jangra *et al.* [48] also suggested that GA increases the expression of the fasting-induced adipose factor gene in the mice, which helps break down fat and prevent fat accumulation. The role of the fasting-induced adipose factor gene in regulating lipid metabolism in T2DM has been confirmed by other studies [49,50]. Some studies indicated that AG increases the viscosity of the intestinal content and therefore, prevents intestinal lipid absorption [51]. Another mechanism indicated that AG acts by interrupting the enterohepatic circulation of bile acids, resulting in increased bile acid excretion and subsequently decreasing plasma cholesterol concentrations, in addition to enhancing the numbers of lipoprotein receptors in the liver and lowering plasma cholesterol concentrations [52]. Arabic gum lowered blood sugar levels significantly by stimulating the production of insulin from β cells. It did this by getting rid of free radicals and preventing the oxidation of lipids [53,54].

Returning to the current results, diabetic rats had higher fasting glucose levels and cardiac damage markers (CK, CK-MB, LDH, and AST) reflecting cardiomyopathy. AG treatment significantly lowered fasting blood glucose and cardiac damage markers, which were increased by DM. Heart section of diabetic rats, depicted focal necrosis of cardiac myocytes associated with inflammatory cell infiltration and vacuolation of the wall of blood vessels associated with perivascular edema and inflammatory cell infiltration. The diabetic rats treated with AG extract exhibited mild congestion of myocardial blood vessels in the heart of some animals and near-normal histological structures in others. The NA/STZ-induced histological changes were consistent with the biochemical evidence of enhanced oxidative stress manifested by lipid peroxidation and inflammation. These results are consistent with Upaganlawar and Balaraman [55], who reported that creatine kinase-MB, is a well-known indicator of cardiomyocyte damage and that there is a positive association between the degradation of muscle filaments and increased serum levels of CK-MB. Al-Rasheed *et al.* [56] proved that serum CK-MB and AST were elevated in rats with experimentally induced DCM. Interestingly, AG treatment significantly lowered the levels of CK-MB, LDH and AST in the blood and prevented hyperglycemia-induced cardiomyocyte damage, demonstrating its cardioprotective benefit of AG. Fouda *et al.* [43] showed that rats with STZ-induced DM had significantly higher levels of hyperglycemia and hypoinsulinemia. This might be because STZ was selectively taken up by β cells through the glucose transporter GLUT2 and destroyed β-cells by damaging their nuclear DNA. STZ injection did not affect non-β endocrine cells in pancreatic islets, suggesting that STZ was specific to beta cells [57]. Pal *et al.* [54] demonstrated that Arabic gum had a significant hypoglycemic effect by stimulating the secretion of insulin from pancreatic beta cells by eliminating free radicals and suppressing lipid peroxidation.

DM lowered heart levels of antioxidants (GSH, GPx, and SOD) and raised oxidative stress markers (MDA)

significantly, compared with the control group. AG reversed these effects, boosted the immune system by increasing GSH level, GPx and SOD activities and inhibited oxidative stress by reducing MDA level, compared with the DM group. These results align with Fouda *et al.* [43], who proved that STZ-induced DM, reduced SOD activities and increased MDA levels, indicating oxidative stress. This could be a reflection of impaired antioxidant defense potential, as hyperglycemia and hyperlipidaemia are linked to increased ROS production [58]. Arabic gum improved MDA and SOD values because it contains four antioxidant minerals: copper, iron, manganese and zinc, or because it positively influenced the expression of antioxidant enzymes [59]. The high blood lipid levels seen in STZ-induced DM rats might be caused by oxidative stress due to chronic hyperglycemia [60] or by insulin resistance, as insulin resistance is linked to hyperglycemia and changes in lipid metabolism [61].

DM increased heart mRNA expressions of inflammatory factors (NF-κB and TNF-α) above normal, but AG treatment reduced them below normal, compared with the control group. Heart mRNA expression of P53, a tumor suppressor and apoptotic protein, was not significantly different among the groups. These results are in agreement with Nemmar *et al.* [62], who stated that Arabic gum reduced cardiotoxicity caused by water-pipe smoke exposure in mice by a mechanism that involved activating the nuclear factor-like 2 signaling pathway. Nuclear factor-like is an important transcription factor that has a key role in activating antioxidant enzymes to cope with oxidative stress [63]. Indira and Abhilash [64] illustrated that DM causes the activation of a protein called NF-κB in β-cells, which are the cells that produce insulin. NF-κB is triggered by different substances that cause inflammation and damage β-cells. When NF-κB is activated, it turns on a gene called inducible nitric oxide synthase, which makes a molecule called NO that kills β-cells. In T1DM, a substance called IL-1β activates NF-κB and causes the death of β-cells in the pancreas. In T2DM, NF-κB not only kills β-cells, but also makes them resistant to insulin. NF-κB also interacts with other substances, which increases its activity and causes more inflammation throughout the body. This inflammation leads to many complications of DM, such as the heart, eye, kidney and nerve problems. Therefore, blocking NF-κB could be a way to treat DM. When NF-κB is activated repeatedly, it blocks the action of inflammatory mediators, which helps the tumor grow. Many small molecules from natural or synthetic sources can affect different signalling pathways, including those involving NF-κB and p53, a protein that controls cell growth. These molecules have changed the way cancer is treated and managed. Some of the NF-κB inhibitors can fight cancer by making the cancer cells produce more p53 [65].

Conclusion

These results suggest that Arabic gum has antihyperlipidemic and cardiopreventive properties in NA/STZ-induced DM rats and prevents cardiomyopathy by increasing antioxidants, decreasing oxidative stress, apoptosis and stopping the harmful effects of pro-inflammatory cytokines.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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