https://doi.org/10.18321/ectj1611

Antihyperglycemic, Antihyperlipidemic, and Antioxidant Effects of Morin on Streptozotocin-Induced Diabetic Rats

A. Beyatli[1]*, N. Gül[2], Ş. Coşkun Cevher[3], N. Arı[4]

[1]University of Health Sciences, Department of Medicinal and Aromatic Plants, 34668 Üsküdar, Istanbul, Türkiye
[2]Ankara University, Faculty of Science, Department of Biology, 06100 Tandoğan, Ankara, Türkiye
[3]Gazi University, Faculty of Science, Department of Biology, 06500 Beşevler, Ankara, Türkiye
[4]Ankara University, Faculty of Pharmacy, Department of Pharmacology, 06100 Tandoğan, Ankara, Türkiye

Article info

Received:
10 March 2024

Received in revised form:
12 April 2024

Accepted:
6 June 2024

Keywords:
Morin
Streptozotocin
Diabetes
Pancreas
β cell
Oxidative stress

Abstract

Recently, natural remedies for the management of diabetes observed a rise in interest as a result of the negative impacts of conventional treatment. The present work studies the beneficial effects of morin in normal and streptozotocin-induced diabetic rats on glucose levels, tissue antioxidant state, and lipid peroxidation. Oral delivery of morin (25 and 50 mg/kg body weight/day) for 21 days to normal and diabetic rats could not prevent weight loss, but consumption of food and water (25 mg/kg) was considerably reduced. Morin substantially decreased glucose, total cholesterol, triglycerides, LDL cholesterol, and VLDL cholesterol in the blood of diabetic rats. Additionally, it greatly halted the rise in aspartate aminotransferase and alanine aminotransferase levels as well as the decline in HDL cholesterol levels in diabetic rats. In comparison to normal rats, diabetic rats had higher levels of malondialdehyde, lower levels of nitric oxide, decreased glutathione, and lower levels of superoxide dismutase in their hepatic, renal, and pancreatic tissues. The morin treatments substantially reduced the levels of hepatic and pancreatic reduced glutathione, hepatic and pancreatic reduced nitric oxide, and hepatic, renal, and pancreatic superoxide dismutase. They also prevented the increase of hepatic, renal, and pancreatic malondialdehyde. Histopathological findings revealed a reduction in pancreatic damage in morin-treated rats. Morin exerts antihyperglycemic, antihyperlipidemic, and antioxidant activities in diabetic rats.

1. Introduction

Hyperglycemia caused by defects in insulin secretion, action, or both characterizes a collection of metabolic diseases known as diabetes mellitus (DM). There are two known types of DM: Type 1, which causes a complete absence of insulin secretion, and Type 2, which causes both tolerance to the effects of insulin and a lack of insulin secretion [1]. Free radicals formation particularly reactive oxygen species (ROS) are produced as a result of persistent diabetes. The formation of ROS can be explained by three main mechanisms, glucose auto-oxidation, protein glycation, and polyol pathway activation, additionally accompanied by weakened antioxidant defense systems that cause oxidative stress [2]. DNA, protein, lipid, and carbohydrate molecules can be damaged by oxidative stress [3]. Conventionally DM is treated with insulin and oral hypoglycemic drugs. The limitations of both treatments, in addition to the constraints imposed by their side effects and their inability to restore a regular rhythm of glucose homeostasis [4]. Recently many antioxidant compounds, particularly those derived from plants, were effective at preventing diabetes

*Corresponding author.
E-mail address: ahmet.beyatli@sbu.edu.tr

and its complications [5]. One of the most powerful antioxidants, flavonoids is also employed in the treatment of oxidative stress in diabetes [6]. Morin (2′,3,4′,5,7-pentahydroxyflavone) is a flavonol (Fig. 1), isolated from many plants of Moraceae. *Acridocarpus orientalis*, *Allium cepa*, *Maclura pomifera*, *Maclura tinctoria*, *Malus domestica*, *Prunus dulcis*, and *Psidium guajava* are examples of plant species that contain morin [7].

Morin has a molecular weight of 302.2357 g/mol, an exact mass of 302.042653 g/mol, monoisotopic mass of 302.042653 g/mol. The solubility of morin in methanol is 50 mg/ml. Additionally, it has an intense yellow color that turns brown when exposed to air, and it is soluble in aqueous alkaline solutions, freely soluble in alcohol, and mildly soluble in ether and acetic acid. It is soluble in water (0.25 mg/ml, 20 °C; 0.94 mg/ml, 100 °C) [8]. Morin has been known to have several biological and pharmacological activities, such as antioxidant [9], antiallergic, anti-inflammatory, antimutagenic [10], anticarcinogenic [11], hepatoprotective [12] and anti-atherosclerotic [13]. In a study carried out by Wang and colleagues, in rat insulinoma cell line (RINm5F pancreatic cells), morin demonstrated protective benefits against streptozotocin (STZ)-induced cell damage through triggering the phosphorylation of 5′ adenosine monophosphate-activated protein kinase [14]. Additionally, even at large doses, it had no toxic impacts on laboratory animals [15]. The present study was undertaken to evaluate the hypoglycemic, hypolipidemic, and antioxidant activity of morin in STZ diabetic rats. Additionally, a histopathological study was conducted on normal and diabetic rats to evaluate the impact of morin on pancreatic tissue.

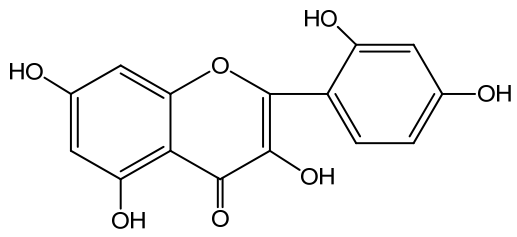

Fig. 1. Chemical structure of morin.

2. Experimental

Morin and all the analytical-grade chemicals and solvents were purchased from Sigma Chemical Co. (St. Louis MO, USA), TEKKİM (Bursa, Turkey), Merck, or AppliChem (Darmstadt, Germany).

Refik Saydam Central Institute of Health (Ankara, Turkey) provided adult male Wister albino rats (2–3 months, 180–230 g), which were kept in standard laboratory conditions (12 h light/dark cycle, 22 °C) and fed a standard pellet diet (Bil-Yem, Ankara) and water ad libitum, and were acclimated for 3 days. The Institutional Animal Ethics Committee's approved guidelines and protocol were followed for all animal experiments, Gazi University (G.Ü ET-10.084).

A single intraperitoneal dose of freshly made STZ (45 mg/kg BW) in 0.1 M cold sodium citrate solution was used to induce diabetes in overnight fasted male rats. (pH. 4.5). Rats were administered 5% glucose solution for 24 h after receiving STZ injections to prevent hypoglycemia. Normal rats were injected with sodium citrate buffer alone. After 72 h fasting, blood glucose levels were determined. Animals with blood glucose levels higher than 200 mg/dL were considered diabetic and were included in the research.

The rats were randomly divided into seven groups of six animals each: Group I: normal rats administered vehicle alone (carboxy methyl cellulose CMC 0.5%; 1 mL/kg, p.o.) for 21 days and considered as control. The rats were separated randomly into seven groups of six each, Group I: Vehicle alone (carboxy methyl cellulose CMC 0.5%; 1 mL/kg, p.o.) was given to healthy rats for 21 days and was regarded as the control group. Group II: normal rats were administered morin (25 mg/kg, p.o.) for 21 days. Group III: normal rats were administered morin (50 mg/kg, p.o.) for 21 days. Group IV: diabetic control rats administered vehicle alone for 21 days. Group V: diabetic rats were administered morin (25 mg/kg, p.o.) for 21 days. Group VI: diabetic rats were administered morin (50 mg/kg, p.o.) for 21 days. Group VII: diabetic rats were administered tolbutamide (100 mg/kg, p.o.) for 21 days.

Weekly records were kept of changes in body weight and fasting blood sugar levels using a glucometer (Accu-Chek Active, Roche, Germany), while food and water intake were monitored daily during the experimental period. The rats were sacrificed on day 21 under ether anesthesia and blood was collected by heart puncture blood was allowed to clot for approximately 20 min at room temperature and then centrifuged for 10 min at 3500 rpm and the serum was collected. The liver, kidney, and pancreas were dissected out and washed immediately with ice-cold 0.9% saline solution to remove blood, dried on filter paper, and serum and tissue samples stored at −80 °C for further biochemical analysis. In addition, pancreas samples were fixed in 10% buffered neutral formal saline for light microscopic observations.

Aspartate aminotransferase (AST), alanine aminotransferase (ALT), high-density lipoprotein cholesterol (HDL-cholesterol), and triglyceride (TG) amounts were all tested using an analyzer. (Roche Diagnostic). While very-low-density lipoprotein-cholesterol (VLDL-cholesterol) and low-density lipoprotein-cholesterol (LDL-cholesterol) concentrations were calculated by using Friedewald's equation as follows: VLDL-cholesterol = TG/5 and LDL-cholesterol = TC - HDL-cholesterol - VLDL-cholesterol respectively. Lipid peroxidation was estimated by measuring malondialdehyde (MDA) levels in liver, kidney, and pancreas tissues [16]. In summary, 1 mL of tissue lysate was deproteinized by treating it with 0.5 mL of 15% TCA before centrifuging it for 10 min at 2000 x g at 4 °C. To avoid further lipid peroxidation, 0.5 mL of 0.67% TBA and 10 L of 1% BHT were added to the residue. The absorption was then recorded against a blank at 535 nm after being put in a water bath for 10 min. MDA levels were reported in nmol/g of tissue. NO concentrations are determined using the Griess assay, which entails reducing nitrate with vanadium (III) chloride and then detecting the result using the acidic Griess reaction. After being homogenized (1:9) in 0.1 M phosphate solution (pH 7.0), tissue samples were spun at 3500 x g for 15 min at 4 °C. To 0.5 mL of the supernatants, 0.25 mL of 0.3 M NaOH was added. For deproteinization, 0.25 mL of 5% (w/v) $ZnSO_4$ was added after the mixture had been incubated for 5 min at ambient temperature. Following a 20-minute centrifugation at 3000 x g of this combination, the supernatants were used in the Griess assay [17]. NO concentrations were expressed as µmol/g tissue. The tissues GSH were measured by the method of Ellman [18]. In a nutshell, 0.75 mL of deproteinization solution (NaCl, metaphosphoric acid, and EDTA) was combined with 0.5 mL of tissue homogenate before being spun at 4000 x g for 20 min. DTNB (5,5'-dithio-bis-2-nitrobenzoic acid) solution was then added to 0.5 mL of supernatant along with 2 mL of 0.3 M NaH_2PO_4 and 0.2 mL of supernatant. At 412 nm, the absorbance was recorded in comparison to a blank. GSH concentrations were expressed as µmol/g tissue. The activity of SOD was determined by the method of Sun et al. [19]. The principle of the method is based on the inhibition of NBT (nitroblue tetrazolium) reduction to formazan by superoxide which is generated through a xanthine-xanthine oxidase system. 1 mL tissue homogenate was mixed with 1 mL ethanol-chloroform (3:5 v/v) mixture and spun at 7000 x g for 60 min at 4 °C. 0.5 mL of supernatant was mixed with 2.45 mL of (3 mM xanthine, 0.6 mM EDTA, 150 µM NBT, 400 mM Na_2CO_3, 1 g/L BSA) and then 50 µL xanthine oxidase was added. After incubation at room temperature for 20 min the reaction was stopped by the addition of 1 mL of 0.8 mM $CuCl_2$. The absorbance of samples was measured against a blank at 560 nm. One unit of SOD inhibited the reduction of NBT by 50%, tissue SOD activities were expressed as U/g tissue.

The pancreas samples were fixed for 24 hours. After fixation, the tissues were dehydrated by passing through a graded series of ethanol, cleaned in xylene, and embedded in paraffin. Sections of 4–5 µm thickness were prepared using a rotary microtome and stained with hematoxylin-eosin (H&E). Then sections were mounted in neutral deparaffinated xylene (DPX) and visualized for histological changes under a light microscope.

Using the computer program SPSS (version 13.0), the data were analyzed using one-way analysis of variance (ANOVA), then post hoc Tukey's test. There were six rats in each group, and the results were presented as mean±SEM. p-Values <0.05 and <0.001 were defined as statistically significant.

3. Results and discussion

A cytotoxic glucose analog called STZ predominantly builds up in pancreatic beta-cells through the GLUT2. The DNA of pancreatic cells is broken up as a consequence of the alkylating activity of the STZ methylnitrosourea moiety. Poly (ADP-ribose) polymerase is overstimulated to fix DNA. As a result, cellular NAD+ will be depleted, and as ATP reserves follow, β-cell necrosis will result. Additionally, STZ's ability to release NO and ROS contributes to its ability to cause diabetes [20]. Oxidative stress, which is the primary cause of the development of diabetes complications, is brought on by persistent hyperglycemia [2].

The fasting blood glucose significantly decreased after morin administration to diabetic rats, but this effect was not dose-dependent (Table 1). The flavonoid may exert its antihyperglycemic effects by boosting either the pancreas release of insulin from preexisting β-cells, inhibiting hepatic glucose production [21], or reducing glucose absorption from the gastrointestinal tract [22]. No changes in normal animals indicate that the gastrointestinal mechanism is not effective in the morin case. Tolbutamide, a common oral hypoglycemic drug, which performs its action by stimulating insulin release from β-cells, was used as a positive control to the glucose-lowering activity.

Table 1. Effect of morin on the levels of fasting blood glucose in normal and STZ-diabetic rats

Groups	Treatment	Fasting serum glucose levels (mg/dl)			
		0^{th} day	7^{th} day	14^{th} day	21^{st} day
I	Normal control	89.66±2.49	96.66±2.65	100.33±2.77	96.16±2.84
II	Normal + morin 25 mg/kg	86.66±5.14	87.50±2.78	92.33±4.63	91.00±4.09
III	Normal + morin 50 mg/kg	105.00±2.12	107.00±1.59	101.33±2.75	103.50±2.81
IV	Diabetic control	332.33±22.72[b]	337.33±19.92[b]	364.00±22.24[b]	378.83±21.03[b]
V	Diabetic + morin 25 mg/kg	327.83±23.90[b]	223.83±31.60[bc]	194.16±23.76[ad]	162.83±21.48[d]
VI	Diabetic + morin 50 mg/kg	351.66±15.43[b]	308.00±20.39[b]	245.33±19.65[bd]	214.83±25.93[bd]
VII	Diabetic + tolbutamide (100 mg/kg)	330.16±19.31[b]	234.50±19.82[bc]	169.00±18.39[d]	126.83±9.51[d]

Values are mean ± SEM of 6 rats in each group; [a]p<0.05 vs. normal control; [b]p<0.001 vs. normal control; [c]p<0.05 vs. diabetic control; [d]p<0.001 vs. diabetic control.

Due to the excessive breakdown of fats and proteins, STZ-induced diabetes is linked with the typical decline in body weight and rise in food and fluid consumption [23]. Oral administration of morin initiates a gradual, but not significant, improvement in body weight (Fig. 2). However, improvement in food and water consumption was significant indicating the beneficial effect of morin on metabolism as well as osmotic diuresis in diabetic animals.

When compared to the normal control group, STZ-diabetic rats had significantly higher blood levels of TC, TG, LDL, and VLDL cholesterol and significantly lower levels of HDL cholesterol (Fig. 3). Cholesterol acyl transferase, an enzyme that is triggered in the lack of insulin, may be the cause of elevated cholesterol levels. The enzyme lipoprotein lipase is normally triggered by insulin to hydrolyze lipids. Insulin deficiency in diabetes inactivates lipoprotein lipase which leads to hypertriglyceridemia [24]. Elevated levels of serum lipids show defects in lipoproteins removal, production, or both. Some previous studies showed that flavonoids may improve lipid profiles in STZ-diabetic animals [25]. Delivery of morin greatly reduced these abnormalities in the current research, possibly by reduction of intestinal cholesterol absorption and free fatty acid synthesis, inhibition of

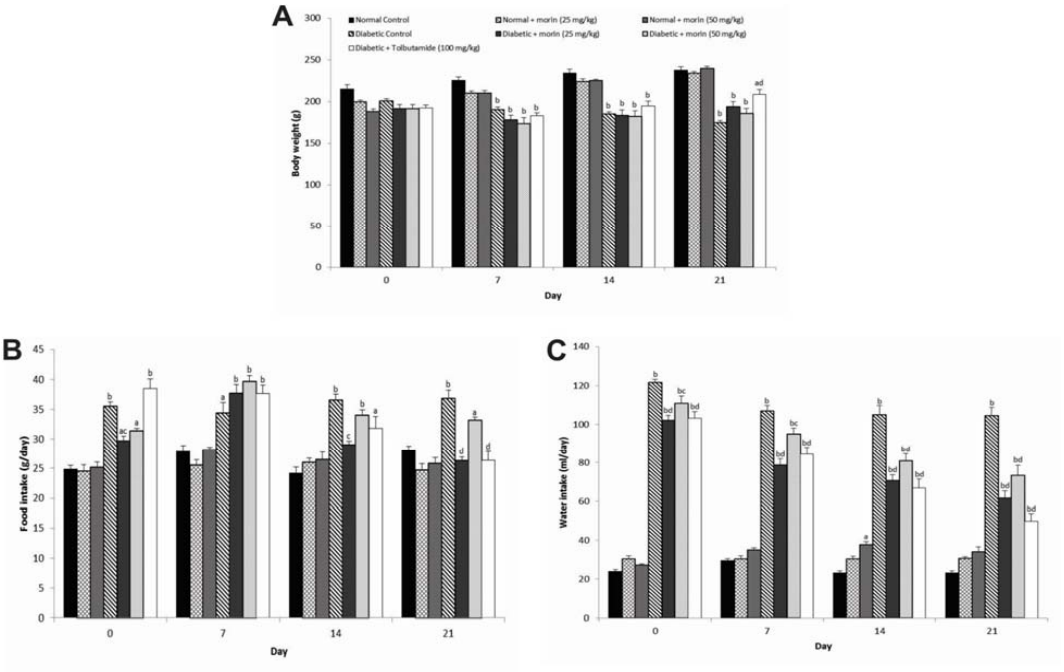

Fig. 2. Effect of morin on body weight (A), food (B) and water (C) intake in normal and STZ-diabetic rats. Values are mean ± SEM of 6 rats in each group. [a]p<0.05, [b]p<0.001 vs. normal control, [c]p<0.05, [d]p<0.001 vs. diabetic control.

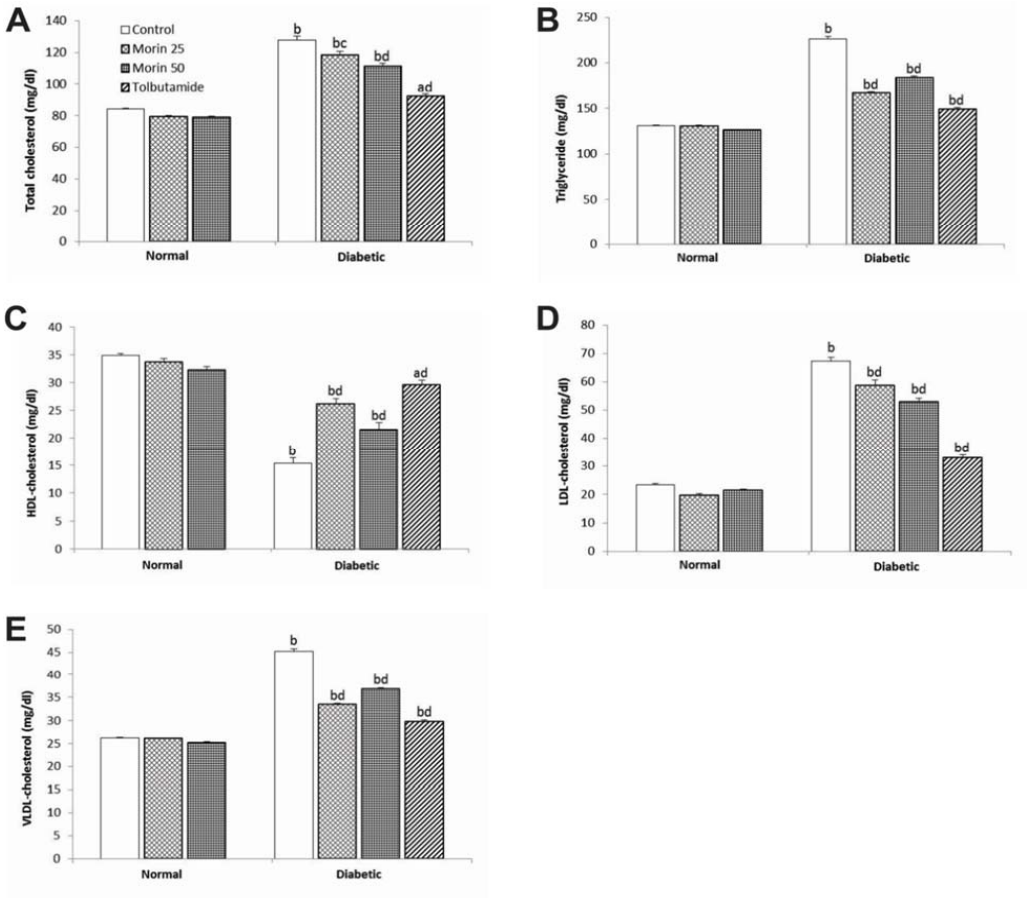

Fig. 3. Effect of morin on the levels of serum lipid profile (A-E) in normal and STZ-diabetic rats. Values are mean ± SEM of 6 rats in each group. [a]$p<0.05$, [b]$p<0.001$ vs. normal control, [c]$p<0.05$, [d]$p<0.001$ vs. diabetic control.

HMG-CoA reductase, acetyl CoA carboxylase activities, increase LDL receptor levels, or activation of lipase and LCAT (lecithin-cholesterol acyltransferase) [26]. Atherosclerosis may be prevented by lowering these factors.

The effects of morin on serum AST and ALT levels of normal and diabetic rats are summarized in Fig. 4. Serum transaminases (AST and ALT) are considered important indicators for hepatic injury. The necrotic effect of STZ leads to leakage of these enzymes from liver cytosol into the bloodstream, which leads to a significant increase in serum activity levels of AST and ALT. Oral administration of morin to diabetic rats significantly decreased elevated transaminases activity, indicating the hepatoprotective nature of morin which can be due to the antioxidant activity of this flavonoid [27].

STZ-diabetic rats showed a significant increase in MDA levels in all studied tissues ($p<0.001$) (Table 2). Chronic hyperglycemia leads to the formation of free radicals, followed by a shortage in antioxidant defense systems, which cause oxidative stress [28]. Free radicals like ROS and polyunsaturated fatty acids interact to create lipid peroxidation (LP), resulting in

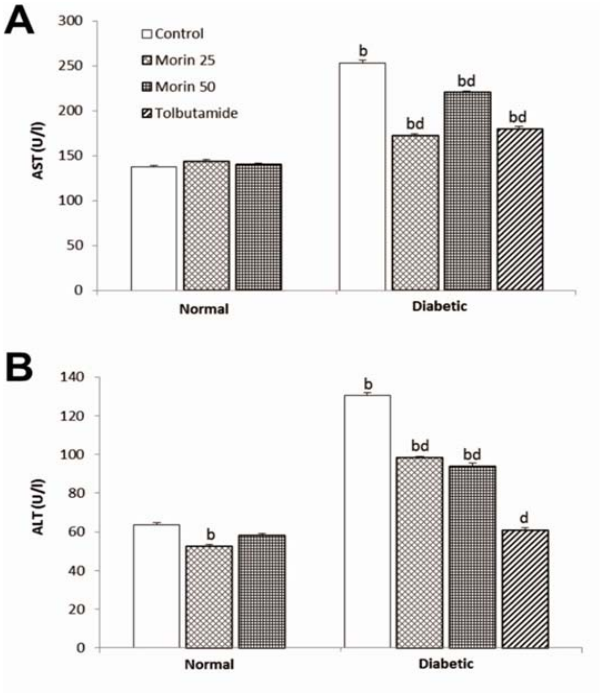

Fig. 4. Effect of morin on the levels of serum AST (A) and ALT (B) in normal and STZ-diabetic rats. Values are mean ± SEM of 6 rats in each group. [a]$p<0.05$, [b]$p<0.001$ vs. normal control, [c]$p<0.05$, [d]$p<0.001$ vs. diabetic control.

lipid products like MDA. LP is one of the main mechanisms of cell damage leading to necrosis or apoptosis [29]. The present study showed a significant elevation in liver, kidney, and pancreas MDA levels in diabetic rats. These results are in agreement with the results of El Ghoul and colleagues [30]. The elevated MDA levels in diabetic rats suggest that peroxidative damage may be involved in the development of complications in diabetes. In our research, MDA levels in the hepatic, renal, and pancreatic tissues of diabetic rats were substantially decreased by both morin and tolbutamide. This may be because antioxidants have the ability to scavenge free radicals produced by ROS and counteract their harmful effects.

There was a significant reduction ($p<0.001$) in NO and GSH levels in diabetic control rats (Table 2). In diabetes, an increase in the activity of the polyol pathway occurs as a consequence of hyperglycemia. In this case, there will be an increase in consumption of NADPH for activation of aldose reductase. Depletion of cellular NADPH is an indicator of disturbances in cellular homeostasis. NADPH is needed for nitric oxide (NO) synthesis; therefore, a lack of NADPH causes a decrease in NO synthesis, which means an elevation in vascular complications of diabetes. High glucose levels inhibit endothelial nitric oxide synthase, which causes a decrease in the secretion of NO, and our results show behavior similar to the diabetic control group. Flavonoids, such as quercetin have increased NO levels in STZ-induced diabetic rats [31]. Morin administration ameliorated NO levels in renal and pancreatic tissues of diabetic animals. Thus, morin could be effective in preventing angiopathy which is one of the serious complications of diabetes. Enzymatic and non-enzymatic antioxidant mechanisms are used to defend against oxidative stress. An essential intracellular free radical scavenger, GSH works by neutralizing free radicals, preserving redox equilibrium, and participating in detoxification processes. In diabetes, NADPH depletion via the polyol pathway results in a GSH deficit, which then reduces GPx function [32]. Morin showed a significant improvement in GSH levels of hepatic and pancreatic tissues of STZ-induced diabetic rats. This activity reflects the strong antioxidant nature of this flavonoid. Furthermore, morin treatment did not show significant changes in GSH levels of renal tissue of diabetic rats. This result is in agreement with previous studies [33].

Table 2. Effects of morin treatment on oxidative stress and antioxidant defense system in the tissues of normal and STZ-diabetic rats

Groups	Normal control	Normal + morin 25 mg/kg	Normal + morin 50 mg/kg	Diabetic control	Diabetic + morin 25 mg/kg	Diabetic + morin 50 mg/kg	Diabetic+ tolbutamide 100 mg/kg
MDA (nmol/g tissue)							
Liver	270.55±10.91	262.78±8.28	248.13±5.55	365.04±14.2^{b}	310.49±5.98^{a}	340.01±5.23^{b}	287.36±5.51^{d}
Kidney	446.98±8.11	429.99±5.29	418.24±3.97	503.92±13.3^{b}	480.60±6.57^{a}	452.10±4.26^{d}	462.43±4.71^{c}
Pancreas	128.92±3.43	134.36±2.28	126.38±3.30	226.77±4.70^{b}	159.16±5.42^{bd}	181.63±4.77^{bd}	172.74±5.84^{bd}
NO (µmol/g tissue)							
Liver	1.87±0.11	1.70±0.11	1.70±0.09	0.61±0.06^{b}	0.93±0.03^{b}	0.77±0.02^{b}	0.81±0.03^{b}
Kidney	0.41±0.01	0.46±0.04	0.45±0.03	0.16±0.01^{b}	0.39±0.03^{d}	0.37±0.01^{d}	0.45±0.03^{d}
Pancreas	0.82±0.02	0.80±0.01	0.75±0.03	0.28±0.03^{b}	0.60±0.02^{bd}	0.48±0.02^{bd}	0.80±0.03^{d}
GSH (µmol/g tissue)							
Liver	10.82±0.27	10.47±0.27	10.20±0.11	5.30±0.35^{b}	11.35±0.21^{d}	7.75±0.30^{bd}	9.58±0.39^{d}
Kidney	7.42±0.21	7.60±0.28	6.97±0.24	7.80±0.29	7.94±0.12	7.79±0.13	8.20±0.18
Pancreas	9.65±0.38	9.41±0.38	9.07±0.25	2.50±0.30^{b}	3.54±0.13^{b}	4.70±0.25^{bd}	6.57±0.35^{bd}
SOD (U/g tissue)							
Liver	298.51±1.95	297.72±4.71	294.39±6.80	348.35±3.89^{b}	329.92±1.38^{bc}	320.75±1.18^{ad}	303.36±2.78^{d}
Kidney	303.64±2.40	307.55±1.22	311.72±1.74	319.88±1.09^{b}	313.68±2.00^{a}	304.99±2.42^{d}	311.30±2.34
Pancreas	310.40±4.53	312.40±0.84	314.71±1.01	347.27±1.39^{b}	324.94±2.12^{ad}	326.91±2.19^{bd}	333.72±2.31^{bc}

Values are mean ± SEM of 6 rats in each group; $^{a}p<0.05$ vs. normal control; $^{b}p<0.001$ vs. normal control; $^{c}p<0.05$ vs. diabetic control; $^{d}p<0.001$ vs. diabetic control

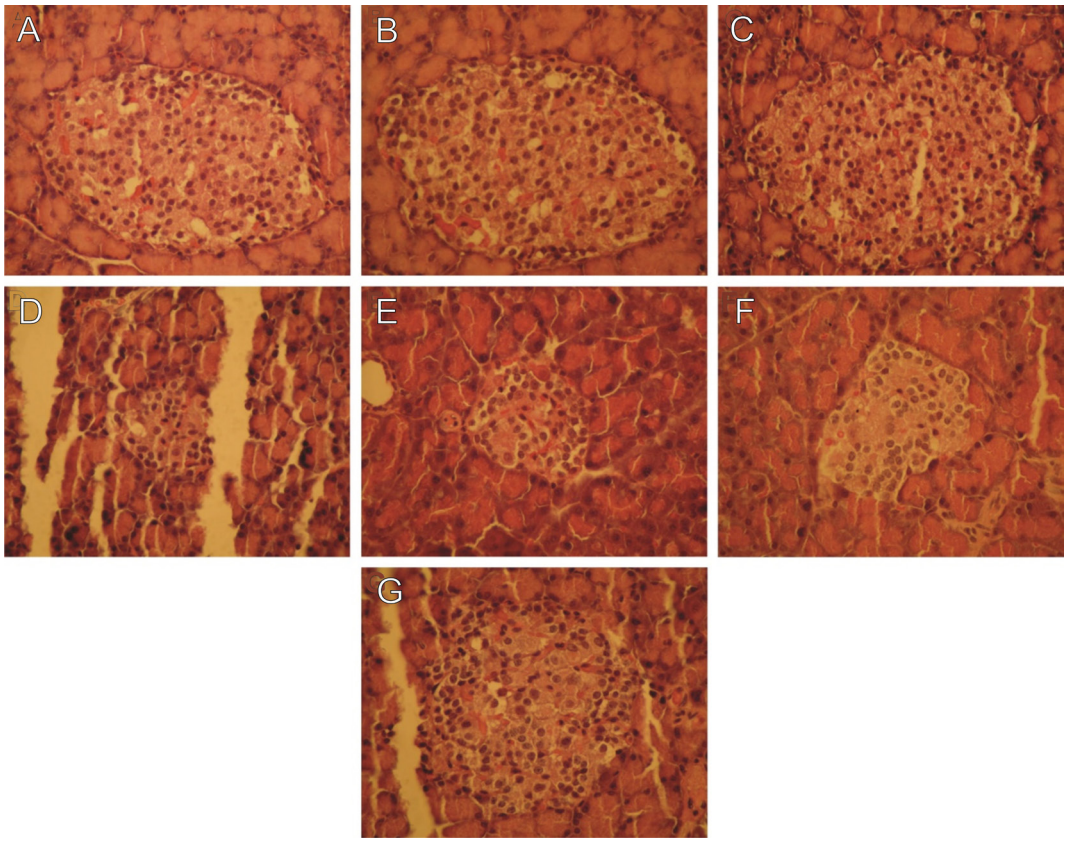

Fig. 5. Histopathological alterations in pancreas islet tissue of normal and STZ-diabetic rats. (H&E, 400×). (A) Normal control, (B) Normal + morin 25 mg/kg, (C) Normal + morin 50 mg/kg showing normal architecture of islets of Langerhans. (D) Diabetic control showing necrotic changes with atrophy (shrinkage) of islets. (E) Diabetic + morin 25 mg/kg, (F) Diabetic + morin 50 mg/kg showing preservation of islet cells architecture. (G) Diabetic + tolbutamide 100 mg/kg showing normal architecture of islets comparable to normal control rats.

Liver, kidney, and pancreas SOD activity was significantly increased in STZ-diabetic rats compared to the normal control group (Table 2). SOD is one of the important enzymes that plays a crucial role against the toxic effects of free radicals. Different studies showed that SOD activity in diabetes could be increased, decreased, or unchanged [34]. In our study, an increase has been detected in SOD activity of diabetic control rats which can be a response to elevated LP during diabetes. Oral delivery of morin to diabetic rats showed a marked improvement in the activity of SOD due to its antioxidant potential.

STZ selective degeneration of pancreatic β cells in experimentally-induced diabetes, and impairment in cellular organelles leads to inhibition of synthesis and secretion of insulin [35]. Our histopathological studies revealed that morin treatment for 21 days showed obvious improvement in the architecture of the damaged Langerhans islets (Fig. 5). This effect can be attributed to morin antioxidant activity since oxidative stress plays a crucial role in the destruction of pancreatic β cells in diabetes. Also, an improvement has been noticed in Langerhans islets of diabetic rats treated with tolbutamide, which was in agreement with others [36]. Flavonoids' nuclear structural configuration, total quantity of hydroxyl groups, and functional group substitution all affect their bioavailability, metabolism, and biological activity [37].

4. Conclusion

Based on the results of this study, it can be concluded that morin has the potential to be an effective alternative treatment for diabetes. The delivery of morin to STZ-diabetic rats resulted in significant improvements in blood glucose levels, lipid profile, and antioxidant status, indicating its antihyperglycemic, antihyperlipidemic, and antioxidant properties. Furthermore, the study suggests that morin may also promote the regeneration of pancreatic β cells, which are responsible for producing insulin. Although the effect of morin was not found to be dose-dependent in this study, further investigations are needed to determine the optimal dose and duration of morin treatment. Additionally, clinical trials involving human subjects are necessary to confirm the efficacy and safety of morin as an alternative treatment for diabetes.

Overall, the findings of this study provide promising evidence for the potential use of morin in the treatment of diabetes, and further research in this area could have significant implications for improving the lives of individuals with this condition.

References

[1]. American Diabetes Association, Diabetes Care. 31 (1, Suppl. 1) (2008) S12–S54. DOI: 10.2337/dc08-S012

[2]. D. Bonnefont-Rousselot, *Curr. Opin. Clin. Nutr. Metab. Care* 5 (2002) 561–568. DOI: 10.1097/00075197-200209000-00016

[3]. B. Halliwell, J.M. Gutteridge, Free Radicals in Biology and Medicine. Oxford University Press, USA, 2015. DOI: 10.1093/acprof:oso/9780198717478.001.0001

[4]. The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Diabetes Care. 20 (1997) 1183–1197. DOI: 10.2337/diacare.20.7.1183

[5]. A.F. Fidan, I. Kucukkurt, H. Yuksel, A. Ozdemir, et al., *Journal of Animal and Veterinary Advances* 8 (2009) 920–927.

[6]. S. Srinivasan, L. Pari, *Chem. Biol. Interact.* 195 (2012) 43–51. DOI: 10.1016/j.cbi.2011.10.003

[7]. A. Caselli, P. Cirri, A. Santi, P. Paoli., *Curr. Med. Chem.* 23 (2016) 774–791. DOI: 10.2174/0929867323666160106150821

[8]. K. Sinha, J. Ghosh, P.C. Sil. Morin and its role in chronic diseases. In: Anti-inflammatory Nutraceuticals and Chronic Diseases. Springer, 2016, p. 453–471. DOI: 10.1007/978-3-319-41334-1_19

[9]. A. Beyatli, E.G.G. Peker, N. Gül, Ş.C. Cevher, *J. Anatol. Environ. Anim. Sci.* 7 (2022) 257–262. DOI: 10.35229/jaes.1103000

[10]. S.H. Fang, Y.C. Hou, W.C. Chang, S.L. Hsiu, et al., *Life Sci.* 74 (2003) 743–756. DOI: 10.1016/j.lfs.2003.07.017

[11]. S. Mottaghi, H. Abbaszadeh, *Phytother. Res*. 35 (2021) 6843–6861. DOI: 10.1002/ptr.7270

[12]. K.S. Shali, N.P.P. Soumya, S. Mondal, S. Mini, *Bioact. Compd. Health Dis*. 5 (2022) 53–66. DOI: 10.31989/bchd.v5i3.893

[13]. Q. Meng, L. Pu, Q. Lu, B. Wang, et al., *Int. Immunopharmacol.* 100 (2021) 108096. DOI: 10.1016/j.intimp.2021.108096

[14]. N. Wang, J. Zhang, M. Qin, W. Yi, et al., *Int. J. Mol. Med.* 41 (2018) 1409–1418. DOI: 10.3892/ijmm.2017.3357

[15]. T. Yugarani, B.K.H. Tan, M. Teh, N.P. Das, *Lipids* 27 (1992) 181–186. DOI: 10.1007/bf02536175

[16]. J.A. Buege, S.D. Aust, *Methods Enzymol.* 52 (1978) 302–310. DOI: 10.1016/S0076-6879(78)52032-6

[17]. L.C. Green, D.A. Wagner, J. Glogowski, P.L. Skipper, et al., *Anal. Biochem.* 126 (1982) 131–138. DOI: 10.1016/0003-2697(82)90118-x

[18]. G.L. Ellman, *Arch. Biochem. Biophys.* 82 (1959) 70–77. DOI: 10.1016/0003-9861(59)90090-6

[19]. Y.I. Sun, L.W. Oberley, Y. Li, *Clin. Chem.* 34 (1988) 497–500. DOI: 10.1093/clinchem/34.3.497

[20]. S. Lenzen, *Diabetologia* 51 (2008) 216–226. DOI: 10.1007/s00125-007-0886-7

[21]. Y.X. Lu, Q. Zhang, J. Li, Y.X. Sun, et al., *Am. J. Chinese Med.* 38 (2010) 713–725. DOI: 10.1142/S0192415X10008184

[22]. O. Kwon, P. Eck, S. Chen, C.P. Corpe, et al., *FASEB J.* 21 (2007) 366–377. DOI: 10.1096/fj.06-6620com

[23]. R.K. Murray, D.K. Granner, P.A. Mayes, V.W. Rodwell. Harper's Biochemistry. Appleton and Lange, Stamford, CT., 2000.

[24]. A.D. Mooradian, *Nat. Rev. Endocrinol.* 5 (2009) 150–159. DOI: 10.1038/ncpendmet1066

[25]. A.A.H. Fernandes, E.L.B. Novelli, K. Okoshi, M.P. Okoshi, et al., *Biomed. Pharmacother.* 64 (2010) 214–219. DOI: 10.1016/j.biopha.2009.08.007

[26]. A. Lemhadri, L. Hajji, J.B. Michel, M. Eddouks, *J. Ethnopharmacol.* 106 (2006) 321–326. DOI: 10.1016/j.jep.2006.01.033

[27]. G.K. Oloyede, P.A. Onocha, O.A. Adaramoye, S.E. Thonda, *Res. J. Phytochem*. 5 (2011) 190–200. DOI: 10.3923/rjphyto.2011.190.200

[28]. Ç. Karasu, *Free Radic. Biol. Med.* 27 (1999) 16–27. DOI: 10.1016/s0891-5849(99)00028-3

[29]. G.J. Stark, *J. Membr. Biol.* 205 (2005) 1–16. DOI: 10.1007/s00232-005-0753-8

[30]. J. El Ghoul, M. Smiri, S. Ghrab, NA Boughattas, et al., *Pathophysiol.* 19 (2012) 35–42. DOI: 10.1016/j.pathophys.2011.12.001

[31]. W. Zhang, Y. Wang, Z. Yang, J. Qiu, et al., *J. Biosci. Bioeng.* 112 (2011) 215–218. DOI: 10.1016/j.jbiosc.2011.05.013

[32]. M. Lorenzi, *J. Diabetes Res.* 2007 (2007). DOI: 10.1155/2007/61038

[33]. A.C. Maritim, B.H. Moore, R.A. Sanders, J.B. Watkins, *Int. J. Toxicol.* 18 (1999) 161–166. DOI: 10.1080/109158199225440

[34]. M.Y. Qi, K. Chen, H.R. Liu, Y. Su, S.Q. Yu, *J. Ethnopharmacol.* 138 (2011) 731–736. DOI: 10.1016/j.jep.2011.10.015

[35]. P. Arulselvan, S.P. Subramanian, *Chem. Biol. Interact.* 165 (2007) 155–164. DOI: 10.1016/j.cbi.2006.10.014

[36]. M. Gayathri, K. Kannabiran, *Indian J. Clin. Biochem.* 23 (2008) 394–400. DOI: 10.1007%2Fs12291-008-0087-2

[37]. S. Kumar, A.K. Pandey, *Sci. World J.* 2013 (2013) 162750. DOI: 10.1155/2013/162750