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ORIGINAL ARTICLE

Hypoglycemic and hypolipidemic effects of two mangrove plants in a streptozotocin-induced animal model of diabetes

Isam ELDin Mohamed ELAmin Abu Zeid, Obidallah Hamdan Ali Al Jaghthmi
Department of Biological Sciences, Faculty of Sciences, King Abdulaziz University, Jeddah, Saudia Arabia

ABSTRACT

Objective: This study aims at evaluating the anti-diabetic, hypolipidemic, and pancreatic histopathological changes of *Rhizophora mucronata* and *Avicennia marina*.
Materials and Methods: The experimental rats were divided into eight groups (n = 15 each). Streptozotocin was used to induce diabetes. Daily oral administration of an aqueous extract from the leaves of *R. mucronata* and *A. marina* at 400 mg/kg BW, and a mixture of the two extracts for 6 weeks was assessed. The measurements of serum glucose, insulin, and lipid profile were carried out. Pancreatic specimens were collected from all groups and processed for pathological studies.
Results: The study revealed that the plant extracts restored the levels of diabetic markers and lipid profiles of diabetic rats, with no significant changes in non-diabetic ones. The extract of *R. mucronata* exhibited more promising anti-diabetic and hypolipidemic effects than *A. marina* singly or combined.
Conclusion: Leaf extracts from *R. mucronata*, singly or combined, and *A. marina,* induced a potent anti-diabetic and hypolipidemic potential in diabetic rats.

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Diabetic rats; *R. mucronata*; glucose; *A. marina*; insulin; lipid profile

Introduction

Diabetes mellitus (DM), a metabolic disorder that represents one of the five leading causes of death worldwide, is characterized by hyperglycemia linked with lipid metabolic abnormalities, in addition to disturbances in protein and carbohydrate metabolism [1–3]. At the present time, 171 million people are diagnosed with diabetes, and this is proposed to reach 366 million by 2030 [4]. This metabolic disorder, DM, is attributed to decreased insulin secretion or increased cellular resistance to insulin, as well as the induction of oxidative stress and disturbance in metabolism-regulating enzymes of glucose and lipid [1,5]. Recently, efficient foods and their bioactive compounds replaced the available diabetic drugs in use, which have numerous restrictions due to associated undesirable effects, such as hypoglycemia, cell injury (necrosis), and high rates of secondary failure [6].

The use of medicinal plants has been embraced worldwide since it is a critical part of public healthcare. *Rhizophora mucronata* and *Avicennia marina* are mangrove plants that grow in both humid and subtropical climates. These vulnerable plants require protection for their significance in the cure of diabetes and other disease conditions. The two plants have been proven to have antiviral and antibacterial characteristics [7]. Plant extracts of different species have also been tested to have anti-diabetic potential, including *Cordia dichotoma* fruits [8] and *Pedicularis longiflora Rudolph*, which additionally showed antioxidant properties [9].

Although the hypoglycemic potential of *R. mucronata* [10] and *A. marina* extracts was reported [11], the hypoglycemic effect of *R. mucronata* extract combined with *A. marina* extract is not investigated until now. To our knowledge, no studies have investigated the anti-diabetic and hypolipidemic effect of the combination of *R. mucronata* and *A. marina* extracts in an animal model of diabetes. Therefore, the current study was carried out to evaluate the efficacy of the aqueous extract of Saudi *R. mucronata*

Correspondence Obidallah Hamdan Ali Al Jaghthmi ✉ aljaghthmi.o.h.2030@gmail.com Department of Biological Sciences, Faculty of Sciences, King Abdulaziz University, Jeddah, Saudia Arabia.

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and *A. marina* leaves administrated to rats on improving the impact of diabetes on the glycemic state and lipid metabolism impairment.

Material and Methods

The experiment was carried out on 120 Wistar male albino rats (between 200 and 250 gm average body weight). The rats were individually kept in cages at a constant temperature (24°C ± 1°C), in alternating 12-h light/dark cycle. The animals were fed the standard chow and water. The rats were used according to the guidelines of the Animal Care and Use Committee of King Abdulaziz University [approval number 172060302].

Plant extraction

The aqueous extract of *R. mucronata* and *A. marina* leaves was prepared according to previous reports [12,13]. The leaf extracts of *R. mucronta* and *A. marina* were administrated orally at a dose of 400 mg/kg BW/day each, while the mixture of both plants included 200 mg/kg BW/day of each extract.

Preparation of streptozotocin (STZ) and induction of DM

Overnight-fasted adult male rats (6 weeks old) were administrated an intraperitoneal injection with a single dose (60 mg/kg) of freshly prepared STZ [14]. After three days, the levels of fasting blood glucose (FBG) were assessed in blood samples taken from the rats' tails by using the One Touch Ultra Glucometer (Lifescan, Johnson and Johnson, Milpitas, CA). The rats that had an FBG level of ≥ 250 mg/dl were assigned as diabetic rats [10].

Experimental design

Rats were randomly divided into eight groups (15 rats each). Group 1 included normal rats and group 2 included untreated diabetic rats. Groups 3–5 included diabetic rats treated with extracts of *R. mucronta*, *A. marina*, or a mixture of both plants. Group 6 included normal rats treated with the extract of *R. mucronata*, group 7 included normal rats treated with the *A. marina* extract, and group 8 included normal rats treated with a combination of both plant extracts. The daily administration of the extracts started on the fourth day after injecting STZ and lasted for 6 weeks.

Measurement of serum glucose, insulin, and lipid profile

Blood was drawn from the retroorbital venous plexus of the animals during the experiment, and serum was prepared by centrifugation for 20 min. Blood glucose and lipid profile were assessed in the sixth week post-treatment using kits (Roche Cobas Diagnostics, USA). The serum levels of the low-density lipoprotein cholesterol (LDL-C) and very low-density lipoprotein cholesterol (VLDL-C) were estimated as previously described [15]. The serum insulin level was assessed using insulin Enzyme-linked Immunosorbent Assay (ELISA) kits that comprised an enzyme immunoassay for the quantitative determination of insulin in the sera of rats (Cat. no. Ezrmi-13 Kelisa, Billerica, MA) according to the methods described previously [16,17].

Histopathological study

Pancreatic specimens were collected in the sixth week post-treatment from the sacrificed rats of all groups, kept in neutral formalin, and processed in an automated tissue processor. Paraffin sections were stained with hematoxylin and eosin for pathological studies [18].

Statistical analysis

The obtained data in this study are presented as mean ± SEM. One-way analysis of variance (Statistical Package for the Social Sciences 24) was used to determine the differences between the groups. The values were considered to be significantly different when the p-value was < 0.05.

Results

Effects of extracts on glucose, insulin, HOMA-IR, and HOMA-β levels

A significant ($p < 0.001$) rise in FBG level and a decrease in serum insulin were recorded in diabetic rats compared to that in the normal rats in the sixth week (Table 1, Fig. 1). These parameters were improved in diabetic rats that received herbal extracts (groups 3–5) compared to the STZ-induced diabetic rats. Improvement was more remarkable in *R. mucronata*-treated rats than in those treated with *A. marina*. The normal rats that received plant extracts alone or in combination showed no significant changes when compared with the control rats.

Effects of plant extract treatments on lipid profile

Rhizophora mucronata and *A. marina* extracts and the combination of both when administered to the diabetic rats for 6 weeks resulted in a significant reduction ($p < 0.05$, 0.01, and 0.001) in the serum triglycerides, cholesterol, LDL-C, and VLDL-C levels compared to the STZ-induced diabetic group. In addition, it markedly raised ($p < 0.001$) the high-density lipoprotein (HDL-C) level compared to the STZ-induced diabetic group (Fig. 1). The marked change ($p < 0.001$) in the lipid profile was seen in the group 3 rats. Therefore, the diabetic rats receiving *R. mucronata* extract showed near-normal levels of all lipogram parameters. On the contrary, those treated with *A. marina* extract singly or combined with *R. mucronata* (groups 4 and 5) showed

Table 1. Effect of *Rhizophora mucronata* and *Avicennia marina* singly or combined supplementation on FBG levels in STZ-treated diabetic rats in the zero, third, and sixth week in different groups (mean values ± SEM).

Groups	Time	Fasting blood glucose levels (mg/dl)
G1 (Control)	Week 0	87.3333 ± 5.32338 f
	3rd week	92.0833 ± 3.83457 f
	6th week	89.9167 ± 2.93995 f
G2 (STZ-induced diabetes)	Week 0	285.9000 ± 39.94741 b
	3rd week	398.4286 ± 8.39177 a
	6th week	285.4286 ± 39.25549 b
G3 (STZ + *R. mucronata*)	Week 0	261.5000 ± 13.14747 bcd
	3rd week	220.3333 ± 15.85031 de
	6th week	170.0833 ± 20.94671 e
G4 (*STZ + A. marina*)	Week 0	279.5769 ± 13.50069 b
	3rd week	272.7000 ± 15.22377 bc
	6th week	235.0000 ± 12.10054 de
G5 (*STZ + R. mucronate +A. marina*)	Week 0	262.4615 ± 10.46338 cd
	3rd week	235.7000 ± 26.59652 de
	6th week	189.4000 ± 16.94163 e
G6 (*R. mucronata*)	Week 0	93.7364 ± 1.94526 f
	3rd week	92.0909 ± 4.98808 f
	6th week	87.8545 ± 3.68477 f
G7 (*A. marina*)	Week 0	89.0000 ± 2.96273 f
	3rd week	84.7000 ± 4.36412 f
	6th week	85.9900 ± 5.32792 f
G8 (*R. mucronata + A. marina*)	Week 0	72.8600 ± 4.95913 f
	3rd week	91.3000 ± 4.50937 f
	6th week	96.4000 ± 2.74955 f
p-value		0.000

Mean values having different letters are significantly different.

enhancements in serum cholesterol, LDL-C, and VLDL-C levels.

Histopathological examinations of pancreatic tissue

Examination of the pancreas from control rats (group 1) revealed intact histo-morphological structures (Fig. 2). The pancreas of diabetic rats (group 2) showed characteristic changes consistent with decreased densities of the islet cells and degenerative changes in the *β*-cells of the islets, mainly cloudy swelling and hydropic degenerations. In addtition, necrotic changes in moderate numbers of *β*-cells were a pathognomonic lesion, as the cells entirely or partially lost their nuclei and/or the cytoplasmic components (Fig. 2). The exocrine pancreas showed minor changes, mainly cystic dilatation and fibrosis of the affected ductal walls. Regarding the treatment of diabetic rats, pancreatic sections from groups 3–5 were healthy in most parts; however, a few histopathological lesions were encountered in diabetic groups receiving *R. mucronata* extract (group 3) (Fig. 2). Diabetic rats receiving *A. marina* extract (group 4) revealed moderate degenerative and necrotic changes in both α- and *β*-cells of the pancreas (Fig. 2). Diabetic rats receiviing a mixture of the two extracts (group 5) showed normal pancreatic islet *β*-cells; however, a few degenerated α- and *β*-cells were encountered (Fig. 3). Normal rats that were administered the plants extract, as single or in combination (groups 6–8), showed no significant histo-morphologic changes compared with the normal rats (Fig. 3).

Discussion

In the current study, hyperglycemia and hypoinsulinemia were the characteristic findings in diabetic rats. The gradual rise in serum glucose levels appeared to be due to

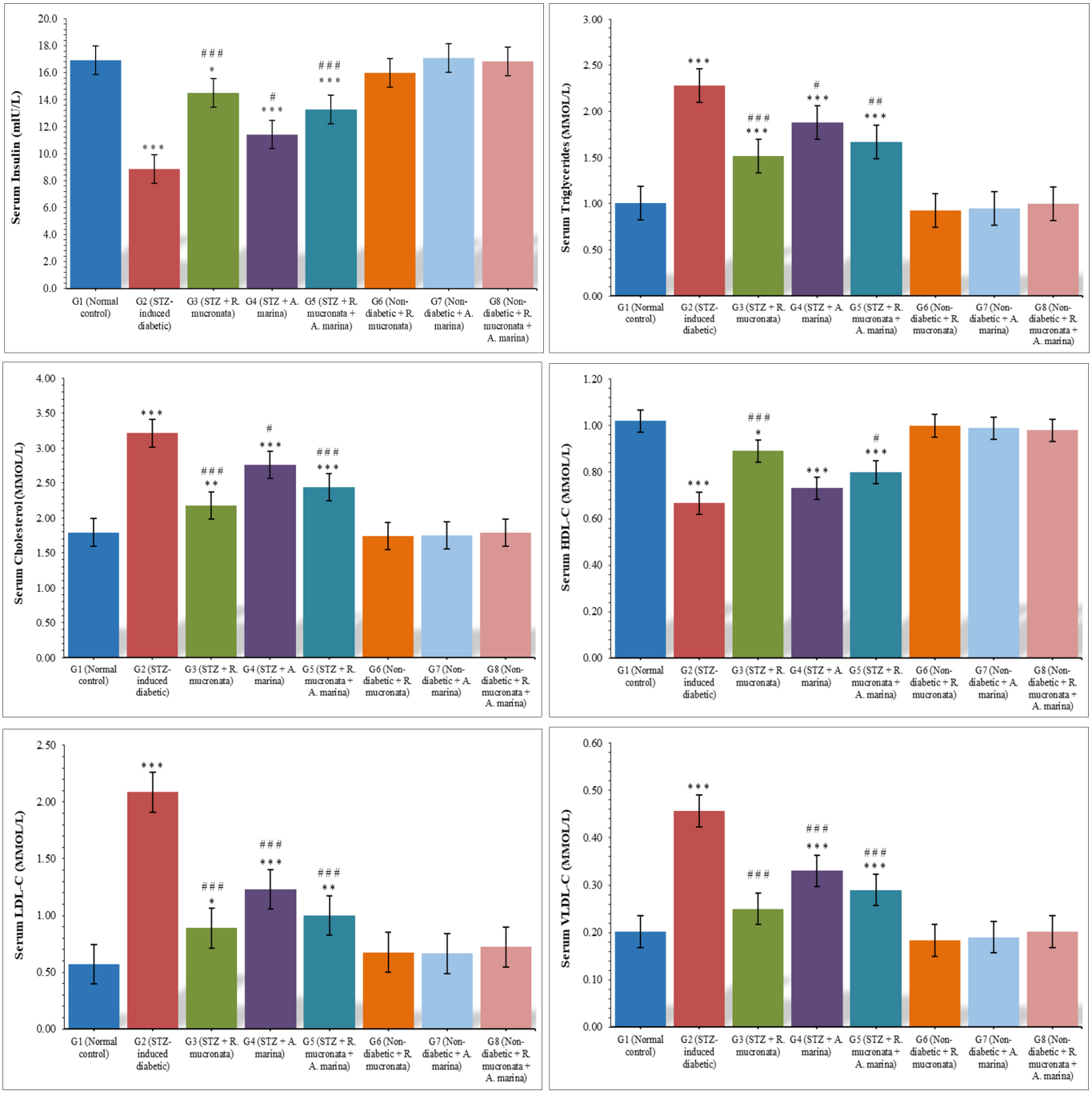

Figure 1. Serum insulin, triglycerides, cholesterol, HDL-C, LDL-C, and VLDL in the studied groups. Results are expressed as mean ± SEM (n = 15). Mean values are significantly different at $p \leq 0.001^{***}$; $p \leq 0.01^{**}$ compared to the normal control group. Mean values are significantly different at $p \leq 0.001^{\#\#\#}$; $p \leq 0.01^{\#\#}$ compared to STZ-induced diabetic group. GI (Normal control), GII (STZ-induced diabetic), GIII (STZ + *R. mucronata*), GIV (STZ + *A. marina*), GV (STZ + *R. mucronata* + *A. marina*), GVI (Non-diabetic + *R. mucronata*), GVII (Non-diabetic + *A. marina*), GVIII (Non-diabetic + *R. mucronata* + *A. marina*).

limited insulin, as a result of β-cell damage induced by STZ [19,20]. Therefore, it is known that when β-cell dysfunction is responsible for the occurrence of diabetes, insulin resistance and deficiency are also required for hyperglycemia to occur [21]. The HOMA model is a commonly utilized method to assess insulin resistance and β-cell function [22,23].

The anti-diabetic and hypolipidemic effects of the currently used plant extracts may be attributed to the increased expression of the nuclear receptor, peroxisome

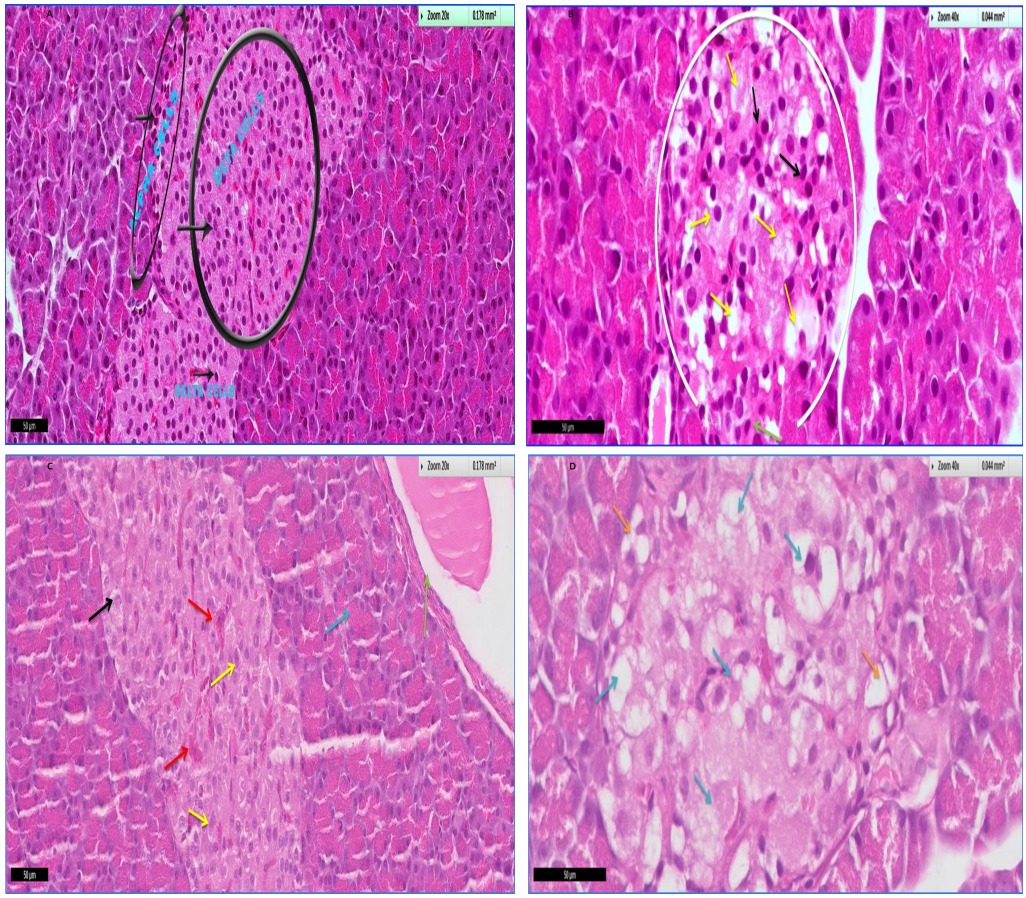

Figure 2. Photomicrograph of the rat pancreatic tissues. Group 1(A) shows the normal features of both exocrine and endocrine glands with preserved exocrine acinar structures and normal endocrine Langerhans cells, including α-cells (small circle and arrow), *β*-cells (large circle and arrow), and delta cells (arrow). Group 2(B) shows the necrotic changes in *β*-cells (yellow arrows) and the normal α-cells (black arrows) and δ-cells (green arrow). Group 3(C) shows the normal pancreas with healthy active islets *β*-cells (yellow arrows), capillary network (red arrows), a few degenerated *β*-cells (black arrow), normal pancreatic acini (blue arrow), and cystic pancreatic duct (green arrow). Group 4(D) shows moderate degenerative and necrotic changes in both α-cells (golden yellow arrows) and *β*-cells (blue arrows). H&E. Scale bar = 50 um.

proliferator-activated receptor-gamma, commonly recognized to enhance insulin sensitivity, and is thus being utilized in targeting the treatment of type 2 DM [24,25].

The findings of this study are supported by several other previous reports [26,27]. The administration of STZ induced a higher degree of apoptosis in the islets of Langerhans [28].

Treating the diabetic groups with the plant extracts showed potent anti-diabetic activity, especially in *R. mucronata*-treated rats. The effect of *R. mucronata* as an anti-diabetic compound could either be due to the improvement of insulin secretion by *β*-cells of the pancreatic islets [29] or due to the existence of a similar insulin protein in the plant extracts [30]. The extracts of *R. mucronata* cause strong hypoglycemic and antihyperglycemic reactions; these findings have been further confirmed by other researchers [31,32].

An analysis of the lipid levels in the animals revealed a significant increase in the concentrations of cholesterol, triglycerides, LDL, and VLDL, and a reduction in blood serum HDL in the diabetic group when compared to the control rats. These findings point out significant dyslipidemia in diabetic animals. Such diabetic dyslipidemia and hyperglycemia are thought to be a prognosticator of cardiovascular complications [33,34]. Increased triglycerides and cholesterols in rats with diabetes may be attributed to activating hormone-sensitive lipase, which enhances fatty acids mobilization from triacylglycerols stored in adipocytes [35,36]. Thus, the large number of fatty acids recurring to the liver are reunited to triacylglycerols and excreted as VLDL. Insulin deficiency and/or insulin resistance may be responsible for hyperlipidemia [15].

Controlling hyperlipidemia is a requirement to prevent diabetic microvascular changes, such as retinopathy,

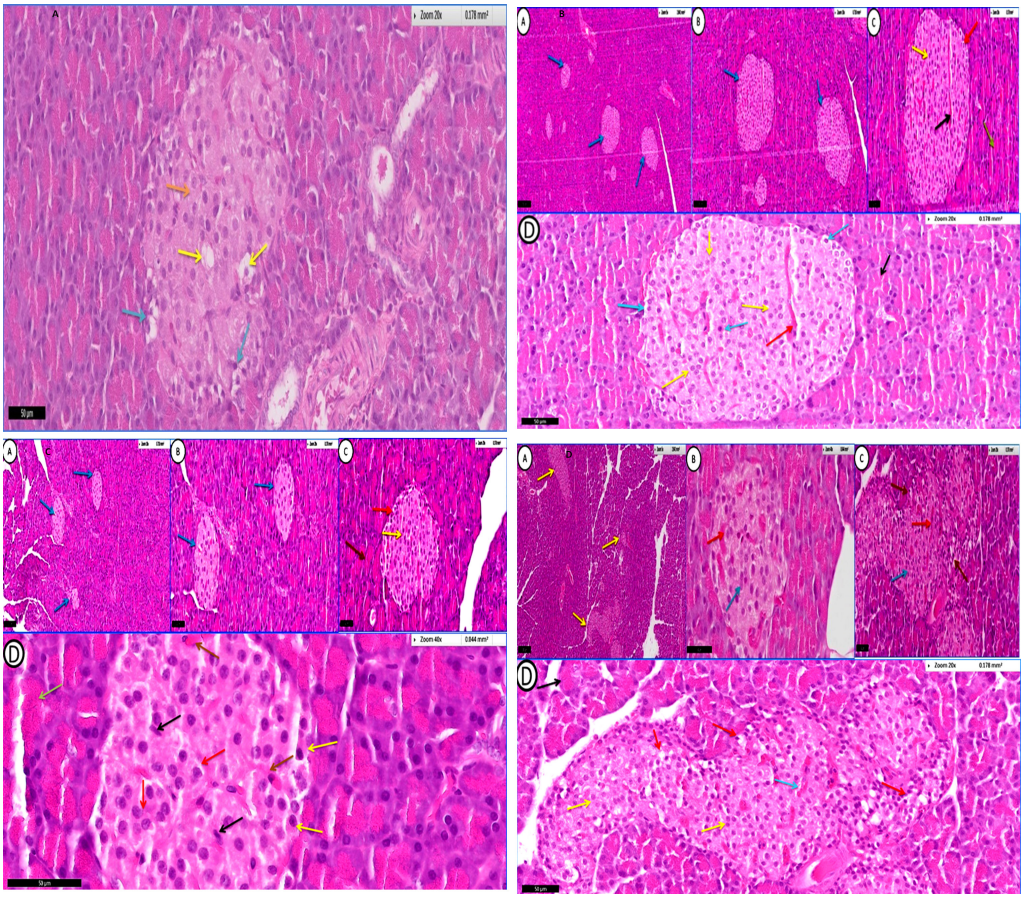

Figure 3. Photomicrograph of rat pancreatic tissues. Group 5(A) shows the normal pancreatic islets *β*-cells (golden yellow arrow) and a few degenerated α-cells (blue arrow) and *β*-cells (yellow arrows). Group 6(B) is the group treated with *R. mucronta* showing normal islets of Langerhans, regarding populations, distributions, and sizes (blue arrows). The α- (red arrow) and *β*-cells (yellow arrow) are normal, and the capillary network (black arrow) is seen among islet cells. H&E. Scale bars, 50 um. Group 7(C) is the group treated with *A. marina* showing normal populations, distributions, sizes, and structures of islets of Langerhans (blue arrows) and normal pancreatic acini with active secretory granules (brown arrow). The α- (red arrow) and β-cells (yellow arrow) of the pancreatic islets are normal and in a good active condition with a dispersed capillary network among them. H&E. Scale bars, 50 um. Group 8(D) is the group treated with a mixture of *R. mucronta* showing normal pancreatic islets, regarding populations, sizes, and distributions (yellow arrows) with normal *β*-cells (blue arrows), vacuolated cytoplasm of some α-cells (brown arrows) and normal capillary network among islets cells (red arrows). H&E. Scale bars, 50 um.

neuropathy and nephropathy, and macrovascular changes like cerebral vascular disease, ischemic heart disease, and arteriosclerosis [34]. Interestingly, the current study further demonstrates that lipid and lipoprotein irregularities were opposed by the plant extracts in diabetic rats. The hypolipidemic effects of *R. mucronata* might be due to the impact of its diverse bioactive components, and other consitituents [37] or the downregulation of LDL epitopes and prevention of 3-hydroxy 3-methylglutaryl coenzyme A reductase [38]. Indeed, low doses of *A. marina* had been used as anti-cholesterolemic agents due to its contents in bioactive constituents that might have an antioxidants-like effect, scavenger free radical, and enhance lipid profile and organ function [39]. Similar findings regarding the anti-diabetic and hypolipidemic efficiency of an extract of *Quercus dilatata* fruit had been reported by Shaheen et al. [40].

The flavonoids constituents of *R. mucronata* could have a vital role in preventing *β*-cell apoptosis, promotion of *β*-cell proliferation, increase in secreting insulin, and enhancement of insulin bioactivity [7]. Similar findings were obtained by Abdel-Daim et al. [41]. They reported that *Moringa oleifera* leaf extracts prevented the histo-architecture changes of the pancreatic tissues of diabetic rats and reduced the percentage of pancreatic apoptotic cells. The extracted form of *R. mucronata* alone or combined with *A. marina* induced a powerful anti-diabetic and

hepatoprotective activities against liver disorders. It addition, they observed to alleviate the histopathological and immunohistochemical changes induced by diabetes on the liver in the animal model of diabetic rats [42]. In this study, the mechanism behind the hypoglycemic and hypolipidemic and the potential of *R. mucronata* and *A. marina* was not explored in depth, and this is one of the limitations of this study.

Conclusion

The leaf extracts from *R. mucronata*, alone or combined, with *A. marina*, induced an effective anti-diabetic and hypolipidemic activity in the used animal model of diabetic rats.

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Conflict of interest

The authors of this study did not have any conflicts of interest.

Authors' contribution

Both the authors had an equal contribution to the supervision of the experiment, data collection and analysis, manuscript writing, and approval of the manuscript.

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