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

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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.

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...
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. mucronata 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. mucronata, 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-8 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 administrated 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
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 addition, 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 *Rhizophora mucronata* extract (group 3) (Fig. 2). Diabetic rats receiving *Avicennia marina* extract (group 4) revealed moderate degenerative and necrotic changes in both α- and β-cells of the pancreas (Fig. 2). Diabetic rats receiving 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, 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

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**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 | 398.426 ± 8.39177 a                                  |
|                         | 6th week | 285.4286 ± 39.25549 b                                |
| G3 (STZ + R. mucronata) | Week 0 | 261.5000 ± 13.14747 b                                |
|                         | 3rd week | 220.3333 ± 15.85031 d                               |
|                         | 6th week | 170.0833 ± 20.94671 e                                |
| G4 (STZ + A. marina)    | Week 0 | 279.5769 ± 13.50069 b                                |
|                         | 3rd week | 272.7000 ± 15.22377 b                               |
|                         | 6th week | 235.0000 ± 12.10054 d                               |
| G5 (STZ + R. mucronate +A. marina) | Week 0 | 262.4615 ± 10.46338 c                               |
|                         | 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 ± 4.89808 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.
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
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,
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 constituents [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

**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. mucronata* 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. mucronata* 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.
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.

References

[1] Ramesh BK, Pugalendi V. Anti-hyperglycemic effect of umbelliferone in streptozotocin-diabetic rats. J Med Food 2006; 9:562–6; https://doi.org/10.1089/jmf.2006.9.562
[2] Go HK, Rahman MM, Kim GB, Na CS, Song CH, Kim JS, et al. Anti-diabetic effects of yam ( Dioscorea batatas) and its active constituent, allantoin, in a rat model of streptozotocin-induced diabetes. Nutrients 2015; 7:8532–44; https://doi.org/10.3390/nu7105411
[3] Yang DK, Kang H. Anti-diabetic effect of cotreatment with quercetin and resveratrol in streptozotocin-induced diabetic rats. Biomol Ther 2018; 26:130–8; https://doi.org/10.4062/biomother2017.254
[4] Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. Diab Care 2004; 27:1047–53; https://doi.org/10.2337/diacare27.5.1047
[5] Gupta D, Rais J, Prakash J, Baquer NZ. Change in the lipid profile, lipogenic and related enzymes in the livers of experimental diabetic rats: effect of insulin and vanadate. Diab Res Clin Pract 1999; 46:1–7; https://doi.org/10.1016/S0168-8227(99)00067-4
[6] Tahani AA, Piya MK, Kennedy A, Burnett AH. Glycaemic control in type 2 diabetes: targets and new therapies. Pharmacol Ther 2010; 125:328–61; https://doi.org/10.1016/j.pharmthera.2009.11.001
[7] Akagihimi OH, Heba HM, Abu Zek Z. Anti-hyperglycemic properties of mangrove plants (Rhizophora mucronata and Avicennia marina): an overview. Advan Biol Res 2017; 11:161–70.
[8] Mohamed SS, Elkhamsy AES. Anti-diabetic potential of Cordia dichotoma pulp and peel (functional fiber) in type II diabetic rats. Int J Pharmcol 2019; 15:102–9; https://doi.org/10.3923/ijp.2019.102.109
[9] Yatoo MI, Dimri U, Gopalakrishnan A, Saminathan M, Dhamma K, Mathes K, et al. Anti-diabetic and oxidative stress ameliorative potential of ethanol extract of Pedicularis longiflora Rudolph. Int J Pharmcol 2016; 12:177–87; https://doi.org/10.3923/ijp.2016.177.187
[10] Gurudeeban S, Kaliamburthi S, Thirunagarambandam R, Positive regulation of Rhizophora mucronata por extracts on blood glucose and lipid profile in diabetic rats. Herb Med 2016; 2:1–10; https://doi.org/10.21767/2472-0515.100016
[11] Kamaei L, Moghaddam HF, Mohktari M, Mard SA, Moghadamnia D. Effects of Avicennia marina fruits aqueous and hydroalcoholic extract on streptozotocin-induced diabetic male rats. Med Sci J Islam Azad Univ 2017; 27(1):9–16; https://doi.org/10.18869/acadpub.aums.6.141
[12] Sahoo G, Mulia NS, Ansari ZA, Mohandas C. Antibacterial activity of mangrove leaf extracts against human pathogens. Indian J Pharm Sci 2012; 74:348–51; https://doi.org/10.4103/0250-474X.107068
[13] Mohamadi J, Havasian MR. The study of inhibitory effect of aqueous extract leaf of Avicennia marina [Hara] on Candida albicans, In Vitro. Int J Pharm Life Sci 2017; 8:5547–51.
[14] Al-Hariri MT. Comparison the rate of diabetes mellitus induction with streptozotocin dissolved in different solvents in male rats. J Comp Clin Path Res 2012; 156–9.
[15] Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without the use of the preparative ultracentrifuge. Clin Chem 1972; 18:499–502; https://doi.org/10.1093/clinchem/18.6.499
[16] Thulesen J, Qrskov C, Holst JJ, Poulsen SS. Short term insulin treatment prevents the diabetogenic action of streptozotocin in rats. Endocrinol 1997; 138:626–8; https://doi.org/10.1210/endo.138.4.627
[17] Matthews DR, Hosker JR, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985; 28:412–9; https://doi.org/10.1007/BF00280883
[18] Suvarna SK, Layton C, Bancroft JD. Bancroft’s theory and practice of histological techniques. 7th edition, Churchill Livingstone Elsevier, London, UK, 2013.
[19] Fernández T, Suarez G, Pérez CI, Acosta T, Clapes S. Influence of diabetes and gestation in blood biochemistry variables in Wistar rats. Int J Anim Sci 2018; 2:1–4.
[20] Pournaghi P, Sadrkhanlou RA, Hasanzadeh S, Foroughi A. An investigation on body weights, blood glucose levels and pituitary gonadal axis hormones in diabetic and metformin treated diabetic female rats. Vet Res Forum 2012; 3:79–84.
[21] Mazhar FM, Moawad KM, Abdel-Gawad MH. Evidence for a reversing effect of vitamin E or curcumin on some biochemical alterations associated with diabetes in pregnant rats and their fetuses. Egypt J Zool 2005; 44:367–88.
[22] Song W, Levin DS, Varkey J, Post S, Bermudes VP, Hurwitz J, et al. A conserved physical and functional interaction between the cell cycle checkpoint clamp loader and DNA ligase I of eukaryotes. J Biol Chem 2007; 282:22721–30; https://doi.org/10.1074/jbc.M703774200
[23] Wallace MA, Liou LL, Martins J, Clement MH, Bailey S, Longo VD, et al. Superoxide inhibits 4Fe-4S cluster enzymes involved in amino acid biosynthesis. Cross-compartment protection by CuZn-superoxide dismutase. J Biol Chem 2004; 279:32055–62; https://doi.org/10.1074/jbc.M403590200

[24] Mahmood S, Khan MA, Sarvar M, Nisa M. Chemical treatments to reduce antinutritional factors in salseed (Shorea robusta) meal: effect on nutrient digestibility in colostomized hens and intact broilers. Poult Sci 2006; 85:2207–15; https://doi.org/10.1093/ps/85.12.2207

[25] Aminuddin F, Ali F, Ismail A, Pei CP, Hamid M. Cocoa polyphenol-rich extract enhances the expression levels of PPAR-γ in the skeletal muscle and adipose tissue of obese-diabetic rats fed a high-fat diet. Int J Pharmacoal 2015; 11:309–17; https://doi.org/10.3923/ijp.2015.309.317

[26] Akbarzadeh A, Norouzian D, Mehrabi MR, Jamshidi SH, Farhangi A. Induction of diabetes by streptozotocin in rats. Indian J Clin Biochem 2007; 22:60–4; https://doi.org/10.1016/0149-0402(96)00025-0

[27] Farid MM, Marzouk MM, Hussein SR, Elkhateeb A, Abdel-Hameed ES. Comparative study of Posidonia oceanica L.: LC/ESI/MS analysis, cytotoxic activity and chemosystematic significance. J Mater Environ Sci 2018; 9:1676–82.

[28] Matsunami T, Sato Y, Hasegawa Y, Ariga S, Kashimura H, Sato T, et al. Enhancement of reactive oxygen species and induction of apoptosis in streptozotocin-induced diabetic rats under hyperbaric oxygen exposure. Int J Clin Exp Pathol 2011; 4:255–66.

[29] Hardoko H, Yuniwaty H, Stevellaverena W. In vitro anti-diabetic activity of “green tea” Soursop leaves brew through α-glucosidase inhibition. Int J Pharmatech Res 2015; 8:30–7.

[30] Nebula M, Harinckar HS, Chandramohanakumar N. Metabolites and bioactivities of Rhizophoraceae mangroves. Nat Prod Bioprospect 2013; 3:207–32; https://doi.org/10.1097/BNF.0b013e31825576f7

[31] Gaffar MU, Morshed MA, Uddin A, Roy S, Hannan JMA. Study the efficacy of Rhizophora mucronata poir leaves for diabetes therapy in long evans rats. Int J Biomol Biomed 2011; 1:20–6.

[32] Babaselemv MS, Abideen T, Gunasekaran BJ, Margarej, Dhinakarraj M. Biotivity of Avicennia marina and Rhizophora mucronata for the management of diabetes mellitus. World J Pharma Res 2014; 3:311–8.

[33] Sout RW. Diabetes and atherosclerosis. Biomed Pharmacother 2005; 47:1–2.

[34] Chehade JM, Gladysz M, Mooradian AD. Dyslipidemia in type 2 diabetes: prevalence, pathophysiology, and management. Drugs 2013; 73:327–39; https://doi.org/10.1007/s40265-013-0023-5

[35] Cullen FEckardsteinA, SoursIS, SchulteH, AssmannS. Dyslipidaemia and cardiovascular risk in diabetes. Diabet Obes Metab 1999; 1:189–98; https://doi.org/10.1046/j.1463-1326.1999.00030.x

[36] Reynisdottir S, Angelin B, Langin D, Lithell D, Eriksson M, Holm C, et al. Adipose tissue lipoprotein lipase and hormone sensitive lipase. Contrasting findings in familial combined hyperlipidemia and insulin resistance syndrome. Aterioscler Thromb Vasc Biol 1997; 17:2287–92; https://doi.org/10.1161/01.ATV.17.10.2287

[37] Aminuddin F, Ali F, Ismail A, Pei CP, Hamid M. Cocoa polyphenol-rich extract enhances the expression levels of PPAR-γ in the skeletal muscle and adipose tissue of obese-diabetic rats fed a high-fat diet. Int J Pharmacoal 2015; 11:309–17; https://doi.org/10.3923/ijp.2015.309.317

[38] Al-Naqeep G, Ismail M, Allaudin Z. Regulation of low-density lipoprotein receptor and 3-hydroxy-3-methylglutaryl coenzyme a reductase gene expression by thymoquine-rich fraction and thymoquine in HepG2 cells. J Nutrigenet Nutrigenomics 2009; 2:163–72; https://doi.org/10.1159/000227264

[39] Amer MM, Ramadan MF, Abd El-Gleel W. Impact of Pulicaria incisa, Diplotaxis harra and Avicennia marina as hypocholesterolemic agent. Deut Lebensm Rundsch 2007; 103:320–7.

[40] Shaheen M, Khan RA, Ahmed M, Mustag N, Khan N. Anti-diabetic efficacy of methanolic crude extract of Quercus dilatata fruit: a randomized control trial. Int J Pharmacoal 2017; 13:501–6; https://doi.org/10.3923/ijp.2017.501.506

[41] Abdel-Daim MA, Abd Elrasoul AS, Abd Elaziz SA. An aqueous extract from Moringa oleifera leaves ameliorates hepatotoxicity in alloxan-induced diabetic rats. Biochem Cell Biol 2017; 95:524–30; https://doi.org/10.1139/bcb-2016-0256

[42] Al-Jaghthmi OHA, Zeid IEMEA. Hypoglycemic and hepatoprotective effect of Rhizophora mucronata and Avicennia marina against streptozotocin-induced diabetes in male rats. J Adv Vet Anim Res 2020; 26;7(1):177–85; https://doi.org/10.5455/javar.2020.g408