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ORIGINAL ARTICLE

Antidiabetic Activity of Hydroalcoholic Extract of *Myrtus communis* (Myrtle) Fruits in Streptozotocin-Induced and Dexamethasone-Induced Diabetic Rats

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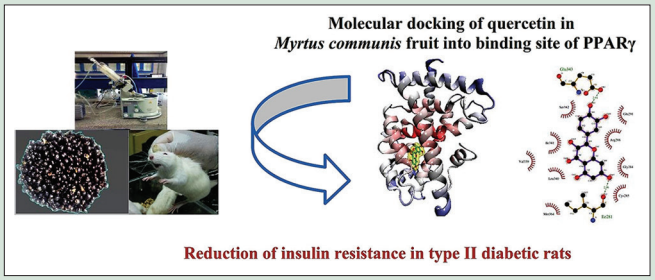
ABSTRACT

Background: Diabetes mellitus is characterized by an increase in blood glucose levels, resulting in insufficiency of insulin secretion, insulin resistance, or both. **Objective:** The effects of hydroalcoholic extract of the *Myrtus communis* (myrtle) fruits on Wistar rats were investigated in two types of diabetes mellitus. **Materials and Methods:** Intraperitoneal administration of streptozotocin (60 mg/kg) was used to induce Type I diabetes. Type II diabetes was induced by subcutaneous injection of 1 mg/kg/day dexamethasone for 10 days. Two groups of the diabetic animals received the hydroalcoholic extract of the fruit by gavage (250 mg/kg and 500 mg/kg for 45 and 10 days) and the diabetic control groups receiving distilled water. **Results:** The hydroalcoholic extract of *M. communis* fruits reduced the serum levels of the glucose, triglyceride, urine volume, urine protein, and malondialdehyde at the end of the 45 day. In Type II diabetic rats, there was a significant effect on plasma glucose levels. On this day, blood glucose-lowering effect was significantly observed after insulin administration as C2>D2M500>D2M250>D2 ($P \leq 0.05$). The plasma level of insulin was completely reversed. There were no differences in the other biochemical parameters. **Conclusions:** The hydroalcoholic extract of *M. communis* fruits has a significant effect on the improvement of diabetes mellitus complications especially Type II diabetic animals, which begins with insulin resistance.

Key words: *Myrtus communis* fruit, diabetes mellitus, hyperlipidemia, *in vivo*, insulin resistance

SUMMARY

- The hydroalcoholic extract of *Myrtus communis* fruits reduced the serum levels of the glucose, triglyceride, urine volume, urine protein, and malondialdehyde at the end of the 45th day in streptozotocin-diabetic rats. In Type II diabetic rats, there was a significant effect on plasma glucose levels
- *M. communis* fruits extract had a significant effect on the improvement of metabolic and renal complications in diabetic rats at the end of the 45th day
- *M. communis* fruits might be a good candidate for diabetes treatment, especially Type II diabetes, which begins with insulin resistance
- This finding is important due to the increased incidence of diabetes.



Abbreviations Used: *M. communis*: *Myrtus communis* (myrtle), STZ: Streptozotocin, MDA: Malondialdehyde, C1: Control 1, D1: Diabetic Type I, D1M250: Diabetic Type I + *Myrtus communis* extract (250 mg/kg/day), D1M500: Diabetic Type I + *Myrtus communis* extract (500 mg/kg/day), C2: Control 2, D2: Diabetic Type I, D2M250: Diabetic Type II + *Myrtus communis* extract (250 mg/kg/day), D2M500: Diabetic Type II + *Myrtus communis* extract (500 mg/kg/day), ROS: Reactive oxygen species, PPARs: Peroxisome proliferator-activated receptors.

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INTRODUCTION

In recent decades, the prevalence of diabetes mellitus, especially Type II diabetes, has grown in the world and is believed that the growing trend of the disease is accelerating in the next 15 years. Diabetes mellitus is an endocrine disorder of two different types that is characterized by an increase in blood glucose levels, resulting in insufficiency of insulin secretion, insulin resistance, or both. Type I disease is also known as insulin-dependent diabetes and occurs as a result of the destruction of ß cells that usually occur following an infection. Type II is also known as insulin independent. The most important pathogenesis of Type II diabetes is insulin dysfunction or insulin resistance.[1] Synthetic drugs, apart from beneficial effects, do not have the maximum efficacy and have many side effects. From this point of view, herbal drugs for treating diabetes have fewer side effects and can be added to diets.[2] Therefore, this study introduces *Myrtus communis* (myrtle) plant as an appropriate candidate for the study of antidiabetic effects. *M. communis* is from the myrtaceae family.[3] Hydroalcoholic extract of the leaves has been shown to have potent effects on blood glucose lowering in clinical and laboratory studies.[4-6] The leaves of this plant contain substances such as tannins, coumarins, galloyl glucosides, caffeic acid, gallic acid, ellagic acid, and various terpenoid compounds. Its fruits are spherical in shape, dark red

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to violet in color, and contain citric acid, malic acid, caffeic acid, tannin, resins, anthocyanin arabinosides, anthocyanin glucosides, kaempferol, quercetin, myricetin 3-O-glucoside, myricetin 3, 3-di-o-galactoside, myricetin 3 rutinoside, aesculin, scopoletin, hesperidin, hesperidin methyl chalcone, esculin, and myricitrin.[3,7-9] However, polyphenolic constituents of *M. communis* fruits were characterized by high concentrations of flavanols, especially flavonols and flavonol glycosides.[8,9] Based on several animal models and some human studies, flavonoids appear to play a role in many of the metabolic processes involved in Type II diabetes mellitus.[10]

Continuous administration of the hydroalcoholic extract of the leaves reduces hyperglycemia induced by streptozotocin (STZ).[4] The leaves of the plant have been used to lower the blood glucose levels in Type II diabetes in traditional Turkish medicine.[3] Furthermore, the hypoglycemic effects of the essential oil obtained from the leaves of myrtle have been proven.[3] Experiments have shown that the essential oil of this plant reduces intestinal absorption of glucose and acts as a α-glucosidase inhibitor.[6] It seems that there is a large difference in the type of composition between leaf and fruit of myrtle.[3] Diabetes-related studies have mostly been carried out on leaf extract of *M. communis* and so far limited studies have been done on the fruit of this plant. Recently, Tas *et al*.[8] showed that the hydroalcoholic extract of *M. communis* fruits increased the insulin secretion and decreased the blood glucose and lipid levels in the diabetic rats. They suggested that different doses and accordingly different administration times of *M. communis* fruit hydroalcoholic extract have to be examined.[8] Therefore, the purpose of this study was to evaluate the antidiabetes effect of the hydroalcoholic extract from the fruit of this plant at the two different doses on two types of diabetes mellitus – Type I and II. In this study, STZ was used to induce Type I diabetes mellitus and dexamethasone to induce Type II diabetes mellitus.[11,12]

MATERIALS AND METHODS

STZ and Rat Insulin ELISA Kit were purchased from Sigma and DRG international, respectively. Triglycerides, cholesterol, creatinine, and blood urea nitrogen (BUN) were measured by commercial kits from Pars Azmun, Iran. Urine protein was measured according to Bradford method.

Experimental animals and storage conditions

In this study, eighty adult male Wistar rats were used. The study was approved at the Ethics Committee of Yasuj University of Medical Sciences. To study the effects of *M. communis* fruit hydroalcoholic extract on diabetes, adult male Wistar rats were used. Male Wistar rats (250–300 g) were obtained from Animal Breeding Center, Yasuj University of Medical Sciences, Yasuj, Iran. The rats were kept at a temperature of 23°C–25°C and a 12-h light–dark cycle for 3 days. Experiments were conducted in two series; the first series was Type I diabetes and the second series was Type II diabetes. The animals were selected in such a way that each group of rats was 10.

Experimental protocols

Preparation of hydroalcoholic extract

The fruit was dried and powdered, and then, the resulting powder was soaked in 70% ethanol. The solution was concentrated by rotary device under vacuum, and alcohol was removed from the plant extract. The solution was then dried in an incubator at 50°C, and the final extract was obtained. The extract was stored in small vials in the refrigerator until it was used. The extract was dissolved in distilled water with concentration (e.g., 5 g of extract per 100 cc of water) and was gavaged to the rats at the desired dose.

Designing experiments and protocol for Type I diabetes

Grouping of animals was as follows: healthy control group (C1) and Type I diabetes group. Type I diabetes was induced by intraperitoneal injection of STZ (60 mg/kg intraperitoneal). Animals with blood glucose levels above 250 mg/dl on day 5 were used as diabetic animals and used for the next studies. The C1 group received equal volume of STZ carrier (phosphate buffer at PH: 4.5). From day 6, diabetic animals were divided into two groups, which received the hydroalcoholic extract of the *M. communis* fruit by gavage at a daily dose of 250 and 500 mg/kg/day for 45 days. On day 5 and 45, animals were transferred to a metabolic cage, and their 24-h urine was collected to measure protein. Blood samples were taken from the heart at 5 and 45 days, and glucose, cholesterol, creatinine, and triglyceride levels were determined.

Designing experiments and protocol for Type II diabetes

In the second series, the grouping of animals was like above. Type II diabetes was induced by subcutaneous administration of dexamethasone (1 mg/kg/day) for 10 days. Control group received the same volume of carrier (normal saline + ethanol 4%). For Type II diabetes, treatment was given for 10 days. Measurement of the above-mentioned parameters was done on day 10 and compared with zero days. To evaluate insulin resistance, plasma glucose concentration was measured after 30 min of intraperitoneal injection of fast-acting (regular) insulin (3 U/kg). Furthermore, plasma insulin levels were determined on day 0 and 10 using ELISA insulin kit of rat. Insulin measurement was performed according to the instructions of the manufacturer of the kit. The effects of insulin-induced hypoglycemia and increased insulin level were considered as insulin resistance.

Measurement of biochemical parameters

The blood glucose level was determined by glucometer (Accu-Chek). Furthermore, blood collection was also performed at the end of the diabetes period, and blood glucose was measured. To separate serum, blood samples were centrifuged at 3000 rpm for 15 min. The serum was stored for further measurements in a freezer at a temperature of −20°C.

Malondialdehyde measurement

The basis for measuring malondialdehyde (MDA) was the reaction between the product of lipid peroxidation (MDA) and thiobarbituric acid. Absorption of the pink complex from this reaction at high temperature was read by spectrophotometer at 532 nm and measured using a standard curve to determine the concentration of MDA. The MDA concentration for plasma was reported in μM (μmol/L).[13]

Histopathologic examination

The right kidney was cut out after sacrifice, halved, and fixed by immersion in 10% formaldehyde solution for several days. Next, the fixed tissues were embedded in paraffin and cut into 4–5 mm slices. The slices were on the glass slides and marked with hematoxylin and eosin (H and E) for light microscopy analysis. The assessment was performed by a pathologist in a blinded way.

Statistical tests

In this study, all data were expressed as mean ± standard error of mean. Appropriate statistical tests including the one-way ANOVA with Tukey's *post hoc* test was performed for multiple comparisons and Paired samples *t*-test for weight mean between groups before and after the end of the experiment. $P < 0.05$ was considered as statistically significant.

RESULTS

Blood biochemical and weight changes in D1M rats

There was no significant difference in mean weight between groups at baseline. Comparison of the mean weight of the studied groups in the process of weight changes during the experiment showed an increase of 19.2% in the control group, and a decrease of 9.7%, 6.1%, and 5.2% in diabetic and treated groups with doses of 250 and 500 mg/kg of extract, respectively. At the end of the study, the mean weight loss in the diabetic group was significantly higher than the control group. Administration of the extract to some extent prevents weight loss but is not significant in comparison to the diabetic group [Table 1].

Animals considered as diabetic had a significant increase in blood glucose levels on day 5 compared to the control group. Furthermore, BUN, urinary volume, and 24-h urine protein were significantly increased in D1M animals [Table 2]. On day 45, plasma levels of glucose, cholesterol, triglyceride, urine volume, and 24-h urine protein were significantly higher in groups D1 and D1M than in the C1 group. There was also a significant difference between the D1 and D1M groups so that the fruit extract of *M. communis* in both doses could significantly reduce these factors. Plasma levels of creatinine did not differ significantly between the four groups [Table 2]. On this day, even though plasma levels of BUN were significantly increased in the D1 and D1M (250 and 500) groups compared to the C1 group, this value in the D1M250 and D1M500 groups showed a significant reduction compared to the D1 group.

Blood biochemical and weight changes in D2M rats

There were no significant differences in weight among the groups at baseline. At the end of the study, the control group showed significant weight gain. Ten days after dexamethasone administration, weight loss was significant in the diabetic group. Fruit extract of *M. communis* with a dose of 250 mg/kg could not prevent weight loss, but high-dose extract could significantly increase weight [Table 3].

Table 1: Comparison of mean weight in different groups

Time of study	Groups			
	C1	D1	D1M250	D1M500
Day 5	281±6	268±10	292±9	287±7.5
Day 45	335±8	242±4	274±10	272±9
Changes percentage	19.2	−9.7	−6.1	−5.2

C1: Control 1; D1: Diabetic Type I, D1M250: Diabetic Type I + *Myrtus communis* extract (250 mg/kg/day); D1M500: Diabetic Type I + *Myrtus communis* extract (500 mg/kg/day). Day 5: 5 days after STZ injection; Day 45: 45 days after STZ injection; STZ: Streptozotocin

There was no significant difference in the mean glucose level in accordance with Table 4 between the different groups on the 1st day, while there was a significant difference between the diabetic group and the control group and extract treated group for 10 days after administration of dexamethasone. There was no significant difference in the mean glucose level in the treated group with the extract and the control group, and therefore, it can be concluded that the extract of *M. communis* significantly reduced glucose levels in the diabetic group. The order of insulin-induced hypoglycemia was C2>D2M500>D2M250>D2. While the order of blood levels of insulin was exactly reversed (D2>D2M250>D2M500>C2). On day 10, the plasma level of triglyceride, cholesterol, creatinine, and BUN did not show any significant differences among groups.

Histopathology

Kidney of normal rats did not show abnormal pathological changes in H and E staining [Figure 1]. In kidney specimens of STZ-diabetic rats, increased glomerular space, decreased red cell count, endothelial cell swelling, and increased number of mesenchymal cells were observed. Treatment with hydroalcoholic extract of *M. communis* fruits at all dose levels (250 and 500 mg/kg/day) reduced the changes made by STZ.

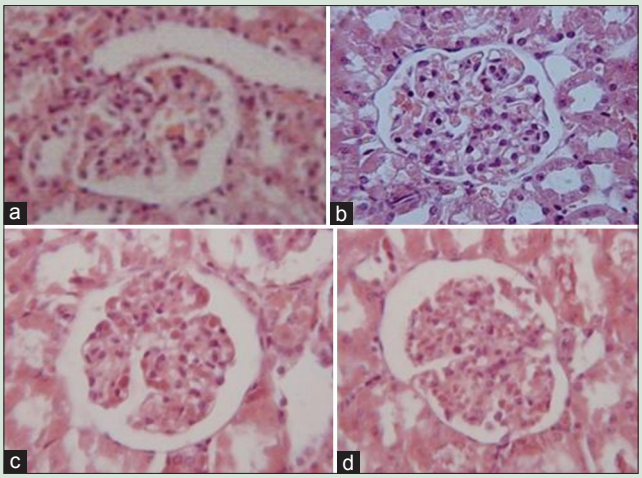

Figure 1: (a) Control (glomerolari are normal), (b) STZ-diabetic group (increased glomerular space, decreased red cell count, endothelial cell swelling, and increased number of mesenchyma), (c) simultaneous treatment with STZ and *Myrtus communis* (250 mg/kg/day), and (d) 500 mg/kg/day. STZ: Streptozotocin

Table 2: Comparison of mean±standard error of mean values of biochemical parameters in the studied groups

Biochemical parameters	Groups							
	C1 (day 5)	D1 (day 5)	D1M250 (day 5)	D1M500 (day 5)	C1 (day 45)	D1 (day 45)	D1M250 (day 45)	D1M500 (day 45)
Glucose (mg/dl)	124±10	403±18*	428±26*	423±23*	118±7	555±24¥	324±32¥,#	230±15¥,#
T-cholesterol (mg/dl)	35±3	40±3	40±4	39±3	38±3	68±4¥	46±4#	42±2#
Triglyceride (mg/dl)	65±7	54±12	84±12	54±6	56±6	212±30¥	151±16¥,#	126±12¥,#
Creatinine (mg/dl)	1.10±0.09	1.30±0.01	1.20±0.09	1.20±0.04	1.08±0.11	1.10±0.008	1.10±0.11	1.05±0.06
BUN (mg/dl)	38±2.5	48±3	42±2	40±3	35±2.3	68±6¥	46±4#	49±4#
Urine volume (ml)	8±0.8	34±2.5*	43±4*	43±2.5*	7.5±0.5	56±4¥	35±4¥,#	28.5±2¥,#
Pr 24 h (mg)	9±0.7	24±3*	8±1	10±1.5	8.5±0.9	20±2¥	25±1¥	13.5±1.2#
MDA (µm/l)	-	-	-	-	1.20±0.05	4.10±0.19¥	1.90±0.14¥,#	2.08±0.13¥,#

*P<0.05 compared with C1 on 5th day, ¥P<0.05 compared with C1 on 45th day. #P<0.05 compared with D1 on 45th day. C1: Control 1; D1: Diabetic Type I; D1M250: Diabetic Type I + *Myrtus communis* extract (250 mg/kg/day); D1M500: Diabetic Type I + *Myrtus communis* extract (500 mg/kg/day). Day 5: 5 days after STZ injection; Day 45: 45 days after STZ injection (60 mg/kg intraperitoneal); STZ: Streptozotocin; BUN: Blood urea nitrogen; MDA: Malondialdehyde

DISCUSSION

In this study, the effect of STZ on diabetic rats caused a reduction in body weight. Other studies have shown that induction of diabetes by STZ in rats causes weight loss of the body.[14] STZ is associated with a rapid deterioration of β cells, resulting in a significant decrease in plasma insulin levels and hyperglycemia. Insufficient insulin in the diabetic group causes weight loss by reducing lipid synthesis. Furthermore, insulin deficiency decreases the body's ability to use glucose and causes weight loss.[15] In this study, administration of hydroalcoholic extract of *M. communis* fruit caused a significant increase in weight in diabetic rats [Table 1]. It is probable that quercetin in *M. communis* fruit will increase serum insulin levels and insulin increases the weight in the diabetic group by enhancing the activity of lipoprotein lipase and inhibiting the function of the hormone-sensitive lipase enzyme.[10,16,17] In addition, myristin can has therapeutic potential in diabetic nephropathy, since it significantly reduces glomerulosclerosis and reduces BUN, body weight, urine output and protein excretion, and decreases hypoclastolemia and hyperglycleridemia, which has been strongly increased in diabetic rats.[10,17-19]

In the present study, STZ caused severe hyperglycemia, elevated triglyceride, cholesterol, plasma BUN levels, urine volume, and increased 24-h urine protein [Table 2]. Increased plasma BUN may be due to dehydration and nephropathy. Regarding the high level of glucose in the nephrons and their lack of reabsorption, the osmotic pressure of the urine is increased, and more water will be discharged; therefore, the volume of urine will increase and drinking in diabetic animals is quite obvious. For this reason, it is recommended that adequate water be available to the animals and given the high volume of urine, the cages of these animals are cleaned every day. Observing these points will reduce the mortality rate in diabetic animals.[20] The presence of protein in the urine and increased creatinine indicate nephropathy.[20] Researchers agree that STZ-induced renal damage is a glomerular injury. The main cause of nephropathy is hyperglycemia.[20] These metabolic changes are in line with the results of other studies.[21,22] In Type I diabetes, fruit extract lowers level of urine protein compared to diabetic control groups. It also significantly reduced plasma BUN levels [Table 2]. The pathogenesis of diabetic nephropathy is not fully understood, but it can be associated with chronic hyperglycemia.[20] The mechanisms by which hyperglycemia leads to nephropathy include the effects of growth factors, angiotensin II and endothelin, changes in small renal circulation (glomerular hyperperfusion), and structural changes in glomeruli.[1] Following STZ administration, increased glomerular size, decreased red cell count, endothelial cell swelling, and increased number of mesenchyma cells have been seen compared to healthy control group [Figure 1]. The pathologic results observed by Mestry *et al.* following STZ administration are approximately similar in type and severity of renal complications with our pathological changes.[22] The histological changes of the kidneys in the group treated with hydroalcoholic extract of *M. communis* showed that the extract could improve the renal damage caused by STZ. Pathological changes due to the administration of *M. communis* fruit extract confirm the mentioned biochemical changes. Some herbal extracts improve diabetes nephropathy by reducing hyperglycemia, and some of them have direct effects on the kidney.[18,23] Generally, effect of hydroalcoholic extract of *M. communis* on proteinuria and plasma level of BUN can also be attributed to hemodynamic improvement of the kidney and the effect of the extract on insulin-induced hyperglycemia [Table 2]. Furthermore, STZ caused hypercholesterolemia and hypertriglyceridemia [Table 2]. Hypertriglyceridemia seen in this model is due to an increase in the liver flow of free fatty acids from adipose tissue, which is similar to that seen in Type I diabetic patients who do not have proper glucose control.[24] Increasing free fatty acids can increase the oxidative stress and lipid peroxidation.[25] In the present study, similar changes were observed in diabetic control group. In diabetic control group, after administration of STZ, increased triglyceride and total cholesterol were observed. Furthermore, MDA, a lipid peroxidation product, increased [Table 2]. In a study, Alam Khan and his colleagues has been shown that the hydroalcoholic extract of the *M. communis* fruits can have beneficial effects on lipid profile.[26] In the present study, hydroalcoholic extract of *M. communis* fruits reduced significantly the level of triglyceride and cholesterol [Table 2]. The antihyperlipidemic effect of the plant can be attributed to the presence of polyphenols and anthocyanins in the plant. In various studies, it has been proven that these compounds can have a beneficial effect on blood lipids.[5,27,28] Another aspect of this study is the antihyperlipidemic and antihyperglycemic effects of the plant caused by its antioxidant properties, and the decrease in MDA in this study, along

Table 3: The effect of administration of different doses of hydroalcoholic extract of *Myrtus communis* extract on the weight of the groups studied during the course of treatment

Time of study	Groups			
	C2	D2	D2M250	D2M500
Day 0	270±14	280±12	244±8	248±7
Day 10	306±12	243±5	241±11	274±11
Changes percentage	21*	-13.2¥	-1.2	10.5#

*P<0.05 compared with control group before and after the end of the experiment, ¥P<0.05 compared with Type II diabetic group, #P<0.05 compared with D2M500 group before and after the end of the experiment. C2: Control 2; D2: Diabetic Type II; D2M250: Diabetic Type II + *Myrtus communis* extract (250 mg/kg/day); D2M500: Diabetic Type II + *Myrtus communis* extract (500 mg/kg/day). Day 0: Before dexamethasone injection; Day 10: 10 days after daily injection of dexamethasone (1 mg/kg/day)

Table 4: Comparison of mean±standard error of mean values of biochemical parameters in the studied groups

Biochemical parameters	Groups							
	C2 (day 0)	D2 (day 0)	D2M250 (day 0)	D2M500 (day 0)	C2 (day 10)	D2 (day 10)	D2M250 (day 10)	D2M500 (day 10)
Glucose (mg/dl)	135±9	117±8	106±5	116±6	124±6	233±12*	157±11¥	137±7¥
Δ% glucose (mg/dl)	54±6	54±8	48±4	44±2	62±4	33±3*	52±2¥	54±2¥
T-cholesterol (mg/dl)	35±4	46±5	39±3	46±3	54±6	55±4	58±4	50±5
Triglyceride (mg/dl)	61±8	74±6	54±5	70±5	63±8	89±9	100±9	79±7
Creatinine (mg/dl)	1.20±0.90	1.10±0.10	1.10±0.07	1.05±0.07	0.98±0.12	1.20±0.05	1.06±0.10	1.07±0.06
BUN (mg/dl)	40±2	35±3	44±4	48±2	44±2	46±2	49±3	52±3
Insulin (μg/L)	1.24±0.05	1.21±0.07	1.70±0.14	1.41±0.08	1.30±0.08	4.40±0.25*	3.23±0.20*,¥	3.14±0.30*,¥

*P<0.05 compared with C2 on 10th day, ¥P<0.05 compared with D2 on 10th day. C2: Control 2; D2: Diabetic Type II; D2M250: Diabetic type II + *Myrtus communis* extract (250 mg/kg/day); D2M500: Diabetic Type II + *Myrtus communis* extract (500 mg/kg/day). Day 0: Before dexamethasone injection; Day 10: 10 days after daily injection of dexamethasone (1 mg/kg/day); Δ% glucose: The percentage of serum glucose lowered after regular insulin injection at a dose of 3 U/kg. BUN: Blood urea nitrogen

with the reduction of glucose and lipid levels, is in agreement with other studies.[11,29]

For induction of Type II diabetes and insulin resistance, daily dexamethasone injection at a dose of 1 mg/kg was used for 10 days.[12] In our study, this dose caused insulin resistance and increased blood glucose levels and no change in triglycerides and cholesterol levels [Table 4]. One of the indicators of this model is the occurrence of insulin resistance that was observed in almost all studies.[12,30,31] Various studies have shown that the possible mechanism of insulin resistance in this model is endothelial dysfunction due to the reduction of nitric oxide synthase endothelial activity. Therefore, endothelial dysfunction leads to increased insulin resistance and as a result causes hyperinsulinemia. Other factors, such as oxidative stress, which can arise due to dyslipidemia, can also contribute to reduce NO and insulin resistance,[32] although some studies have shown that insulin levels decrease after dexamethasone administration.[33-35] In this study, after long-term administration of dexamethasone, the level of insulin was increased [Table 4], and this effect is in accordance with other studies.[30,36] In some studies, dyslipidemia occurred before the onset of hyperglycemia in Type II diabetes, and our study in this regard contradicts these studies.[8,37,38] Furthermore, in this study, there was no change in the level of urinary protein excretion, which indicates that the body has been able to prevent dehydration, nephropathy, and changes in protein lyse and BUN levels. In general, metabolic effects and blood level of insulin are likely to be depending on the dose and duration of dexamethasone administration.[39] After prolonged use of dexamethasone, reactive oxygen species (ROS) production occurs and ROS reacts with pancreatic ß cells and damages them.[40] Considering the key role of ROS in the incidence of diabetes complications, it seems that at least part of the important and desirable effect of the *M. communis* extract on these complications is related to its high antioxidant effect. This property is due to many bioactive molecules including flavonoids, polyphenols, phenolic acids, proanthocyanidins, anthocyanins, and polyunsaturated fatty acids.[27,41] Montoro *et al*.[42,43] have studied the stability and antioxidant activity of polyphenols in alcoholic extracts of *M. communis* berries. They showed the presence of six flavonoids and eight anthocyanins.[42,43] Major peaks identified in flavonoid profile were myricetin-3-O-galactoside, myricetin-3-O-rhamnoside, and quercetin-3-O-glucoside as the most abundant flavonoids in the extract.[43] In addition to, quercetin and kaempferol identified in the berry extracts from *Myrtus* that aren't present in other berry extracts.[9] These flavonol compounds are existent in most fruits and plants and are also the most studied.[9] Myricetin and its glycosides derivatives (myricetin-3-O-arabinoside) from the flavonol family were the main constituents from myrtle berries, and phenolic acids were at low concentrations.[9] The major compounds were formerly identified in the literature.[42-44] On the other hand, the antidiabetic properties of the *M. communis L* can be associated with the flavonoids as major phytochemicals in *M. communis* berries.[2,8,10,17] In addition, *M. communis* extract could improve insulin resistance and reduce hyperinsulinemia in dexamethasone-induced Type II diabetes in this study. In addition, *M. communis* extract could improve insulin resistance and reduce hyperinsulinemia in dexamethasone-induced Type II diabetes in this study, since flavonoids act on various molecular targets such as the peroxisome proliferator-activated receptors (PPARs).[2,8,17] PPARs act by regulation of lipid and glucose metabolism.[45] Activation of PPARγ as a member of the nuclear receptor superfamily improves insulin resistance. PPARγ is an established molecular target for the treatment of Type II diabetes.[45] The molecular detail of action mechanism of the major flavonoids on PPARγ was further confirmed by several studies.[17,19] According to the results of these studies, various known antioxidants including flavonoids (kaempferol, quercetin, myricetin, and its flavonol glycosides) which are isolated from myrtle may increase insulin secretion from the pancreas, insulin release from insulin bands, or sensitivity to insulin-receptors, and therefore lower blood glucose and insulin resistance in rats affected Type II diabetes.[2,10,17,19]

CONCLUSIONS

In summary, in these two different types of diabetes induction model, which was studied in our study, the complications of diabetes were similar to those observed in studies and humans. *M. communis* fruits extract with antioxidant properties had a significant effect on the improvement of metabolic and renal complications in diabetic rats at the two different doses. These findings can introduce the hydroalcoholic extract of *M. communis* fruit as a good candidate for diabetes treatment, especially Type II diabetes, which begins with insulin resistance. Because ROS play a significant role in the development of insulin resistance and ultimately diabetes complications, it seems that desirable effect of the *M. communis* extract on these complications is related to its high antioxidant effect. This finding is important due to the increased incidence of diabetes.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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