Van Sag Bil Derg
2022;15(2):103-112

Orjinal Araştırma Makalesi/ Original Paper

Protective effect of *Vaccinium myrtillus* on Paraoxonase Activity, Some Biochemical Parameters and Pancreatic Functions in Diabetic Rats

Diyabetik Sıçanlarda *Vaccinium myrtillus*'un Paraoksonaz Aktivitesi, Bazı Biyokimyasal Parametreler ve Pankreas Fonksiyonları Üzerindeki Koruyucu Etkisi

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ÖZET

Amaç: Diyabet, dünyada halk sağlığı alanında en büyük sorunlardan biridir. Şifalı bitkiler arasında yer alan *Vaccinium myrtillus L.* özütü, güçlü antioksidan aktiviteye sahiptir. Bu amaçla, deneysel diyabetik sıçanlarda *Vaccinium myrtillus* ekstraktının serum paraoksonaz (PON1), pankreas enzim düzeyleri ve lipid düzeyleri üzerine olası etkileri araştırıldı.

Materyal ve Metot: Bu çalışmada toplam 32 erkek sıçan (Wistar albino) kullanıldı ve dört gruba ayrıldı. Kontrol(C), diyabetik (D), *Vaccinium myrtillus* (VM), diyabet artı *Vaccinium myrtillus* (DVM) grupları. D ve DVM gruplarında, tek doz intraperitoneal 45 mg/kg streptozotosin kullanılarak deneysel diyabet oluşturuldu. *Vaccinium myrtillus* özütü, VM ve DVM gruplarına oral gavaj yoluyla 1.2 mg/kg/21 gün olarak uygulandı. Çalışmanın sonunda; serum HbA1c, lipid parametreleri, amilaz, lipaz ve paraoksonaz (PON1) enzimleri analiz edildi.

Bulgular: VM (VM ve DVM) ile tedavi edilen diyabetik gruplarda HbA1c önemli ölçüde azaldı. Diyabetik deneklere VM uygulandıktan sonra kolesterol, LDL-C ve VLDL-C seviyeleri önemli ölçüde azalırken, diğer lipidlerin önemsiz bir şekilde azaldığı bulundu. *Vaccinium myrtillus* ekstresi DVM grubunda D grubuna göre pankreas enzimlerinde hafif bir düşüşe ve paraoksonaz enziminde istatistiksel olarak anlamlı bir artışa neden oldu.

Sonuç: Elde edilen veriler, *Vaccinium myrtillus* ekstresinin diyabetle ilişkili komplikasyonların önlenmesinde potansiyel koruyucu bir rol oynayabileceğini desteklemektedir.

Anahtar Kelimeler: *Vaccinium myrtillus*, diyabet, Paraoksonaz, Pankreas Fonksiyonu, Lipidler.

ABSTRACT

Objective: Diabetes is one of the biggest problems in the field of public health in the world. *Vaccinium myrtillus* L. extract, among the medicinal plants, has powerful antioxidant activity. For this aim, the possible effects of *Vacillus myrt*illus extract on serum paraoxonase (PON1), pancreatic enzyme levels, and lipid levels in experimental diabetic rats were investigated.

Material and Method: A total of 32 male rats (Wistar albino) were used in this study and divided into four groups. Control (C), diabetic (D), *Vaccinium myrtillus* (VM), diabetes plus *Vaccinium myrtillus* (DVM) groups. In D and DVM groups, experimental diabetes was induced using a single dose of intraperitoneal 45 mg/kg streptozotocin. *Vaccinium myrtillus* extract was administered as 1.2 mg/kg/21 days by oral gavage in VM and DVM groups. At the end of the study; serum HbA1c, lipid parameters, amylase, lipase, and paraoxonase (PON1) enzymes were analyzed.

Results: HbA1c was significantly reduced in diabetic groups treated with VM (VM and DVM). Cholesterol, LDL-C, and VLDL-C levels were significantly reduced after VM was administered to diabetic subjects, while other lipids were found to decrease insignificantly. *Vaccinium myrtillus* extract caused a slight decrease in pancreatic enzymes and a statistically significant increase in paraoxonase enzyme in the DVM group compared to group D.

Conclusion: The obtained data support that *Vaccinium myrtillus* extract may play a potential protective role in preventing diabetes-associated complications.

Keywords: *Vaccinium myrtillus*, Diabetes, Paraoxonase, Pancreas Function, Lipids.

Cited: Mahmood K, Kahraman T. Protective effect of *Vaccinium myrtillus* on paraoxonase activity, some biochemical parameters and pancreatic functions in diabetic rats . *Van Sag Bil Derg*2022, *15,*(2) 103-112.
https://doi.org/10.52976/vansaglik.810482.

Arrived date: 14/10/2020
Accepted date: 30/06/2022
Published date: 31/08/2022

INTRODUCTION

Diabetes mellitus (DM) is a rapid growing metabolic disease and one of the global health the problem is expected to increase to 360 million affected people by 2030 (Ryden et al., 2013). Chronic hyperglycemia and disturbances in the metabolism of carbohydrates, proteins, and lipids, are the main

characteristic of this disease. The incidence of diabetes stems from insulin resistance and insulin insufficiency (Alberti and Zimmet, 1998).

Wide ranges of approaches have been adopted for diabetes treatment ranging from environmental properties' alteration to therapeutic drugs usage. Chemicals have various mechanisms of action, eventually resulting in the reduction of hyperglycemia (Krentz and Bailey 2005). These drugs are known to have many adverse health effects making researchers seek for alternative agents from natural sources (Kos et al., 2012; Stein et al., 2013). Potent candidates are plants and their contents; several plants have been used in the treatment of diabetes in traditional medicine (Li and Perera, 2012) since they contain many bioactive compounds that exhibit anti-diabetic activities via various pathways (Wang et al., 2013).

Vaccinium myrtillus L. (bilberry) is a medical plant that has been used for the treatment of many diseases, including DM in traditional medicine (Helmstädter and Schuster, 2010). Phytochemicals in this plant, especially anthocyanin, a phenolic compound, are responsible for ant-diabetic activity via antioxidant and anti-inflammatory actions (Chu et al., 2011).

Anthocyanins exhibit their anti-diabetic activity by improving insulin resistance, protecting pancreatic beta cells from oxidative damage and increasing insulin secretion (Sancho and Pastore, 2012). *Vaccinium myrtillus L.* and its pigments also have roles in attenuation in contributing factors to diabetes, including obesity and impaired lipid metabolism (Asgary et al., 2015).

Paraoxonase1 (PON1) is calcium-dependent glycoproteins enzyme associated with high-density lipoproteins (HDLs) and possesses detoxifying activity via organophosphate hydrolysis. Clinical importance of this enzyme is associated with anti-oxidant activity and anti-atherogenic property by protecting low-density lipoproteins LDL from oxidative modification. This enzyme protects LDL from oxidation through hydrolyzing lipid peroxides and retarding macrophage-mediated LDL oxidation (Mackness and Mackness, 2015).

The aim of this study is to examine the effect of the administration of *Vaccinium myrtillus* L. fruits' extract on both paraoxonase activities and lipoproteins levels in experimental diabetic rats.

MATERIAL and METHOD

Animal

Thirty-two (32) rats weighing 250-300 grams were supplied from the experimental Animal Unit of Van Yuzuncu Yil University. Subjects were divided equally into four groups (n=8): control (C), diabetes (D), *Vaccinium myrtillus* extract (VM), diabetes plus *Vaccinium myrtillus* extract (DVM). During three weeks of the study, rats were exposed to 12 hours light/dark system in 18-22 C°. The rats were left for 21 days for acclimatization before the experiment. This method was accepted by Experimental Animal Ethical Committee belonging to Van Yuzuncu Yil University (Order Number: 2016/04 Date: 05.05.2016).

Experimental procedure

Diabetes was induced in D and DVM groups by injecting 45mg/kg single dose streptozotocin (Sigma-Germany) dissolved in cold citrate buffer pH:4.5 intraperitoneally (İP) (Vardi et al. 2005).

1. Control group (C): This group has been fed standard rat diets and they were given distilled water using intragastric gavage.

2. Diabetes group (D): Diabetes group was induced using 45 mg/kg STZ injection and a standard normal diet was given. After 72 hours, blood glucose of blood from the tail puncture has been measured and the rat's more than 270 mg/kg blood glucose was accepted as diabetes.

3- Group of *Vaccinium myrtillus L.* (VM): Along with the normal diet, a dose of 1.2 mg/kg of *Vaccinium myrtillus* L. extract (Bilberry, GNC, USA)

dissolved in distilled water was given to every rat using intragastric gavage (Grace et al., 2009).

4- Group of Diabetes and *Vaccinium myrtillus L*. (DVM). Diabetes was induced in this group by injecting a single dose of 45 mg/kg streptozotocin intraperitoneally given. After 72 hours, blood glucose of blood from tail puncture has been measured and the rats more than 270 mg/kg blood glucose was accepted as diabetes. a dose of 1.2 mg/kg of *Vaccinium myrtillus* L. extract (Bilberry, GNC, USA) dissolved in distilled water was given to every rat using intragastric gavage (Grace et al., 2009).

Sample collection

Blood glucose taken from tail puncture during the experimental period was determined using glucometer equipment and strips from eBsensor (Taiwan) company. All samples more than 270 mg/dl blood glucose was accepted as diabetes. After 21 days of the experimental periods, under anesthetic conditions, blood was taken from heart puncture into both jell tubes and EDTA tubes. Blood glucose analysis and HbA1c level were measured on the same day. The sera were preserved at -20 C^o until the day of analysis of paraoxonase enzyme, pancreatic functions, and lipoprotein levels.

Biochemical parameters and analyses

Serum paraoxonase (PON) activities were analyzed using the spectrophotometric kit supplied by Rel assay (Turkey) using the automated colorimetric method. The levels of glucose, HbA1c, lipoproteins and pancreatic enzymes were determined using kits and biochemical auto analyzers by (Cobas C311, Roche- Germany).

Statistical analysis

Comparisons among groups and among tissues were done using the nonparametric Kruskal-Wallis test and then the Mann-Whitney U-test as the post hoc test correction was used. Data were given as median (minimum-maximum) and P-values <0.001 and <0.049 were considered to be statistically significant, respectively. For statistical analysis, the SPSS 13.0 for Windows statistic package program was used (SPSS Inc., Illionis, USA)..

RESULTS

Biochemical parameters, pancreatic enzyme activity, and paraoxonase enzyme levels of the groups are presented in Table 1. Serum glucose level was increased significantly ($p<0.05$) in the diabetes group (D) in comparison with control group (C). No significant difference ($p<0.05$) in glucose level between the control group (C) and *Vaccinium myrtillus* group (VM) can be seen. Treatment with *Vaccinium myrtillus* was associated with significant decrease ($p<0.05$) in glucose levels in DVM group if they compared to diabetes group (D).

HbA1c level was significantly increased ($p<0.05$) in the diabetes group (D) in comparison with control group (C). HbA1c levels showed no significant difference ($p<0.05$) in *Vaccinium myrtillus* group (VM) compared to control group (C). Treatment of diabetes with *Vaccinium myrtillus* extract showed a significant decrease ($p<0.05$) in HbA1c level in DVM group compared with diabetes (D) group.

Cholesterol was significantly decreased ($p<0.05$) in *Vaccinium myrtillus* group (VM) in comparison to control group (C). Administration of *Vaccinium myrtillus* extract caused significant decrease ($p<0.05$) in DVM group in comparison with their corresponding model diabetes D group.

Diabetic rats in group D showed a non-significant increase ($p>0.05$) in triglycerides in comparison with the control (C) group. Giving *Vaccinium myrtillus* extract to *Vaccinium myrtillus* group (VM) caused significant decrease ($p<0.05$) in TG level in comparison to control group (C). Treatment with *Vaccinium myrtillus* extract showed decrease in triglycerides in DVM group (84.83±15.59 mg/dl) in comparison to Diabetes D group while the change was not statistically significant ($p>0.05$).

In this study, diabetes caused a significant increase ($p<0.05$) in HDL levels in diabetic group (D) compared to the control group (C). There was a significant decrease ($p < 0.05$) in *Vaccinium myrtillus* group

(VM) if compared to the control group (C). Feeding *Vaccinium myrtillus* extract was related with significant decrease (p<0.05) in HDL level in DVM group in comparison with diabetic group (D).

The development of diabetes was associated with a non-statistically significant, Increase (p>0.05) in LDL levels in diabetes (D) group in comparison to the control group (C). The results showed no significant difference (p>0.05) in LDL level between *Vaccinium myrtillus* (VM) and control (C) group. Treatment with *Vaccinium myrtillus* extract caused a significant decrease (p<0.05) in LDL level in DVM group in comparison with D group.

Amylase level was decreased significantly (p<0.05) in the diabetes group (D) compared to the control group (C). No significant change (p>0.05) was obtained from the results between *Vaccinium myrtillus* (VM) and control (C) group. After treatment with *Vaccinium myrtillus* extract, there was a statistically non-significant decrease (p>0.05) in amylase in DVM group compared to the diabetes group (D).

Development of diabetes by streptozotocin was associated with a significant increase (p<0.05) in lipase activity in the diabetes (D) group compared to the control (C) group. No significant change (p>0.05) can be seen between *Vaccinium myrtillus* group (VM) and the control group (C) for lipase. The treatment by *Vaccinium myrtillus* extract showed a slight but not statistically significant (p>0.05) decrease in lipase activity in DVM group in comparison to diabetes (D) group.

Paraoxonase activity was decreased significantly (p<0.05) in diabetes (D) group compared to the control group (C). Giving *Vaccinium myrtillus* extract caused significant increase (p<0.05) in *Vaccinium myrtillus* group (VM) in comparison to control group (C). Treatment with *Vaccinium myrtillus* extract caused statistically a significant increase (p<0.05) in DVM group in comparison to the diabetes (D) group.

Table 1. Serum glucose, hemoglobin A1c, total cholesterol, total triglyceride, lipoprotein, lipase, amylase and paraoxonase levels of rats in groups.

	Control (C) X±SD	**Diabetes (D)** X±SD	***V. myrtillus* (VM)** X±SD	**Diabetes+ *V. myrtillus* (DVM)** X±SD	**p**
Glucose (mg/dL)	158±42 a	636±84 c	230±55 a	464±220b	0.001
HbA1c (%)	3,8±0,1 c	8,0±0,8 a	3,8±0,2 c	6,7±1,8 b	0.001
TC (mg/dL)	56±9 b	77±11 c	44±4 a	52±10 ab	0.001
TG (mg/dL)	94±13 b	101±32 b	54±13 a	84±16 b	0.001
HDL-C (mg/dL)	51±9 b	61±7 c	41±3 a	46±5 ab	0.001
LDL-C (mg/dL)	20±7 ab	25±4 b	14±4 a	17±10 a	0.016
VLDL-C (mg/dL)	18±3 bc	22±6 b	11±3 a	17±3 c	0.001
Amylase U/L	1073±75 b	681±238 a	1008±59 b	575±183 a	0.001
Lipase (U/L)	7,8±1.2 a	21,3±5,8 b	6,8±1,3 a	19,3±7,8 b	0.001
Paraoxonase (U/L)	34,0±29,3 ab	3,6±5,3 a	51,9±42,2 b	17,5±27,4 ab	0.049

Differences between mean values with different letters are significant (P<0.001-0,049).

HbA1c, Hemoglobin A1c; TG, triglyceride; TC, total cholesterol; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; VLDL-C, very low- density lipoprotein cholesterol.

Data were expressed as mean±SD.

DISCUSSION

In this study, the effect of *Vaccinium myrtillus* L. extract on paraoxonase enzyme activity, lipoproteins and pancreatic enzyme levels were studied. Despite anti-diabetic activity of *Vaccinium myrtillus* L. extract, the possible protective activity of this plant against diabetic cardiovascular complications via enhancing paraoxonase activity was also examined.

The extract of this plant contains many bioactive compounds that exhibit this anti-diabetic activity including anthocyanins and flavonoids such as quercetin and catechin (Chu et al., 2011). The role of anthocyanins emphasizes many mechanisms including improvement of insulin resistance and increasing insulin level, reduction in carbohydrates catabolism and, protection of pancreatic beta cells from oxidative damage (Sancho and Pastore, 2012). The overall consequence of these actions is a reduction in blood glucose as concluded in this study and agreed to the previous studies (Asgary et al., 2015).

Antioxidant activity of both anthocyanins and phenolic compounds in *Vaccinium myrtillus* is one protective mechanism against oxidative damage of pancreatic beta cells by caused by oxidative stress. It is known that hyperglycemia in diabetes leads to the generation of reactive oxygen species (ROS), and this causes beta cellular apoptosis and eventually leads to damage of the beta cells (Ahren, 2005).

The significance of the determination of HbA1c is the clarification of the anti-diabetic activity of *Vaccinium myrtillus* extract in chronic terms since; this parameter is applicable for the detection of chronic rather than acute hyperglycemia. Moreover, most of the other previous works have focused on glucose only (Asgary et al., 2015).

The results of the present study showed about 28% and 17% decrease in the levels of glucose and HbA1c respectively by using 300 mg/kg of anthocyanins. Because of the importance of the dose used in alternative medicine, and because it was approved that greater hypoglycemic activity was obtained from the greater dose of anthocyanins, it's important to study further different doses of anthocyanins (Grace, 2009).

The results obtained from the current study indicate that inducing diabetes with streptozotocin was associated with a significant increase in total cholesterol, triglycerides, LDL, and VLDL. These findings are in agreement with the results obtained from previous studies (Adiels et al., 2006; Yadav, 2013).

Diabetic dyslipidemia is implicated with increased risks of cardiovascular complications. A key point of the pathophysiology in dyslipidemia is an elevation in triglycerides-rich VLDL levels by the liver (Farbstein and, Levy, 2012). It was known that the overproduction of large particles of VLDL is one of the most important mechanisms of triglycerides elevation in type 2 diabetes (Adiels et al., 2006).

Insulin hormone has its roles since it inhibits the secretion of chylomicrons which are molecules of lipoproteins that transfer triglycerides and cholesterols from enterocytes to the circulation through the lymphatic system. Thus, insulin level decreases in diabetes, causing excessive secretion of chylomicrons, thereby inducing hyperlipidemia (Xiao and Lewis, 2012).

Elevation in LDL levels in diabetes is induced mainly by the increased the levels of triglycerides and insulin resistance (Nakajima et al., 2011). The mechanism of production of LDL includes the transfer of triglycerides from VLDL via the action of cholesterol ester transfer (CETP). Thus, the presence of VLDL which contains a large amount of triglyceride is required for the production of LDL and this may explain hypertriglyceridemia- related increase in LDL level in diabetes (Taskinen and Borén, 2015).

In general, cholesterol elevation in diabetes may result from increased glycation of cholesterol- rich

lipoproteins, insulin deficiency and, insulin resistance. It was known that the synthesis of cholesterol is up-regulated in insulin resistance and type 2 diabetes. Moreover, this increase was related to insulin resistance independently to obesity (Gylling et al., 2010).

Results from the present study showed that giving *Vaccinium myrtillus* extract to diabetic rats caused a reduction in cholesterol, triglycerides, LDL, and VLDL. The same results were obtained from other previous studies (Asgary et al., 2015, Kruger et al., 2014). These findings indicate that the extract of *Vaccinium myrtillus* is positively associated with the improvement of diabetic dyslipidemia and may alleviate most of the abnormalities in diabetes (Asgary et al., 2015). Anthocyanins and other bioactive compounds may account for the improvement of diabetic dyslipidemia via the regulation of enzymes involved in lipoprotein metabolism (Tsuda et al., 2003).

General mechanisms by which anthocyanins ameliorate abnormalities in lipid metabolism include antioxidant activity, anti-inflammatory activity and, anti-ischemic effect and cardioprotective effects of this substance (Kruger et al., 2014). By these actions, anthocyanins are able to reduce insulin resistance and incidence of diabetes and these are confirmed by some studies (Tsuda et al., 2003).

A decrease in cholesterol level after *Vaccinium myrtillus* feeding in this study may result from the effect of anthocyanins content via increasing fecal cholesterol content. A study showed that anthocyanin from certain plants caused a decrease in plasma levels of cholesterol via increasing acidic and neutral sterols in the faces (Liang et al., 2013).

Results of HDL levels from this study disagreed with the previous studies and also contraindicated with our hypothesis. It was known that HDL level has decreased in diabetes, and this reduction is associated with the pathophysiology of diabetes and the development of a diabetic complication, especially cardiovascular complication. However, the conflicts of our result in HDL level may arise from technical issues either in the experimental animal management, preparation of plant extract solution method and/or HDL level assay procedure (Farbstein and Levy, 2012; Kostapanos, 2014).

According to the results obtained from the current, study, inducing diabetes by streptozotocin caused a significant decrease in amylase levels in rats. And also giving *Vaccinium myrtillus* extract in diabetic rats led to a further decrease in amylase activity. Diabetic reduction of amylase was also found in previous studies (Nakajima et al., 2011; Yadav et al., 2013; Mahmood and Kahraman, 2019;).

Many mechanisms have been suggested to interpret exocrine pancreatic deficiency in diabetes. As long as diabetes disease affects the pancreas organ, this effect comprises also the modification in the exocrine portion. The first important explanatory mechanism is related to the insulin hormone. Insulin is known to have trophic activity on amylase hormone via acting on acinar cells. So in diabetes, one consequence of insulin deficiency is a decrease in amylase. In contrast to insulin, glucagon prossesses an inhibitory effect on amylase activity. Thus, elevation of the glucagon level may the associate with amylase reduction (Singh et al., 1998). Histological modifications due to diabetes as pancreatic fibrosis, atrophy and fatty infiltration result in loss of acinar cells (Matsuda et al., 2014).

Results of amylase sometimes show conflict results. In some studies increase the activity of this enzyme has been observed in type 1 diabetes and diabetic ketoacidosis. The difference in pathological picture and mechanism of development of this type of diabetes may stand behind amylase elevation (Yadav et al., 2013).

The study supported that administration of *Vaccinium myrtillus* extract to the diabetic rats was associated with a 15.5% reduction in amylase activity. Inhibitory effects on amylase level can be regarded as one mechanism of hypoglycemic activity of this plant since many other plants extracts have targeted amylase in their anti-diabetic activities. By reducing amylase, these plants have restricted carbohydrate

sources because the function of amylase is catabolism of intestinal carbohydrate (Cheng et al., 2013).

The sudden increase in blood glucose level in type 2 diabetes is mediated by hydrolysis of starch by the action of amylase. Therefore, the finding of amylase inhibition by *Vaccinium myrtillus* extract is significant for illustrating of one mechanism of hypoglycemic activity exhibited by this plant (Gray, 1995).

In the present study, the development of diabetes caused a significant increase in lipase activity. And the treatment of diabetic rats with *Vaccinium myrtillus* extracts was associated with a slight decrease in lipase. The degree of this reduction was not statistically significant; however, it was about 10%. The diabetic increase in lipase has also been observed in other studies (Steinberg et al., 2014; Mahmood and Kahraman 2019).

A slight reduction in lipase activity (10 %) after treatment with *Vaccinium myrtillus* has been observed in this study. Anti-lipase activities of bioactive compounds from many plants other than *Vaccinium myrtillus* were approved in previous studies (Jeong et al., 2014; Dechakhamphu and Wongchum, 2015).

Lipase enzyme exhibits main role in lipid absorption in the small intestine via hydrolysis of triglycerides from dietary fats to fatty acids. So, by inhibiting lipase, *Vaccinium myrtillus* extract is able to decrease fatty acid absorption and thus participate in the alleviation of dyslipidemia and obesity (Hegele et al., 2001). Anti-lipase activities of bioactive compounds in *Vaccinium myrtillus* plant may account for lipase reduction. It was concluded that extracted phenolic compounds especially quercetin showed strong inhibitory effects against lipase enzyme (You et al., 2012). Similarly, some types of anthocyanins have decreased lipase activity (Guo et al., 2012).

In the present study, paraoxonase (PON) activities have declined in diabetes, and treatment of diabetic rats with *Vaccinium myrtillus* extract caused an increase in the activity of this enzyme. Reduction in PON in diabetic subjects has been observed in many previous works (Abbott et al., 1995, Ying, 2010).

PON is associated with HDL and its' clinical role is the prevention of LDL from peroxidation. However, the decrease in this enzyme in diabetes may result from the disruption in association of the enzyme molecule to HDL. Normally, PON is associated to HDLs that contain Apo A-1 proteins and clusterin. It was known that there is a loss or weakness in the correlation between the enzyme protein, Apo A-1, and HDL molecules. In addition, a larger portion of the enzyme protein may be inactive in diabetes due to the existence of endogenous circulating inhibitors and/or due to increased glycosylation of paraoxonase (Abbott et al., 1995).

The current study showed that *Vaccinium myrtillus* extract caused an increase in PON in diabetic subjects. Increase in PON level by effects of various plants fond by other researchers (Takaeidi et al., 2014; Mahmood and Kahraman 2019).

Bioactive compounds in our plant possibly drive the elevation of PON activity, and this can be regarded as one mechanism of antioxidant activity of this plant. Anthocyanins were known to have a critical role in improving PON activity, and this caused enhancement in cholesterol efflux capacity in hypercholesterolemic rats. This finding has the linked lipid-lowering ability of anthocyanin to PON increasing the ability of this substance (Zhou et al., 2014). Increase in PON activity contributes to the improvement of HDL function and aortic cholesterol reduction (Farrell et al., 2015).

The significance of stimulatory effects of *Vaccinium myrtillus* on PON activity which is concluded in the present study can be clarified by important positive roles in health and those multiple physiological roles that exhibited by this enzyme. PON is able to prevent LDL from oxidation and inhibits cell membrane oxidation, thus, this enzyme is regarded as an atheroprotective enzyme since LDL concentration is directly related to the incidence of atherosclerosis. PON1 participates in the antioxidant activities of HDL. Deficiency in PON activity is common in

many diseases related to inflammatory basics and this is deficiency is believed to result in dysfunction of HDL and consequently promote inflammation and atherosclerosis. Because of all of these positive roles of PON in health especially related to coronary heart disease (CHD), *Vaccinium myrtillus* extract may exhibit preventive roles in the progression of these diseases via increasing PON activity and improving dyslipidemia. However, despite these conclusions, further confirmatory studies may be required.

Conclusions

Vaccinium myrtillus L. extract presented antidiabetic activity against experimental diabetes. Our studies have shown that *Vaccinium myrtillus* L. extract can be helpful in improving hypoglycemia and alleviating dyslipidemia in diabetes. Feeding *Vaccinium myrtillus* L. extract to diabetic rats caused a significant decrease in blood glucose level and glycated hemoglobin (HbA1c) and reduced the levels of total cholesterol, triglycerides, LDL, and VLDL. *Vaccinium myrtillus* L. extract administration to diabetic rats was associated with a slight decrease in the pancreatic exocrine function via decreasing both amylase and lipase enzymes. This study suggests that *Vaccinium myrtillus* L. may play an important role in the prevention of diabetes and its complications.

Conflict of interest

The authors declare that there is no conflict of interest.

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