Research in Pharmaceutical Sciences, December 2014; 9(6): 421-429
Received: Nov 2013
Accepted: Dec 2013

School of Pharmacy & Pharmaceutical Sciences
Isfahan University of Medical Sciences

Original Article

Effect of the hydroalcoholic extract and juice of *Prunus divaricata* fruit on blood glucose and serum lipids of normal and streptozotocin-induced diabetic rats

M. Minaiyan[1], A. Ghannadi[2], A. Movahedian[3], P. Ramezanlou[4,*] and F.S. Osooli[4]

[1]Department of Pharmacology, and Isfahan Pharmaceutical Research Center, School of Pharmacy and Pharmaceutical Sciences, Isfahan University of Medical Sciences, Isfahan, I.R. Iran.
[2]Department of Pharmacognosy, and Isfahan Pharmaceutical Research Center, School of Pharmacy and Pharmaceutical Sciences, Isfahan University of Medical Sciences, Isfahan, I.R. Iran.
[3]Department of Biochemistry, and Isfahan Pharmaceutical Research Center, School of Pharmacy and Pharmaceutical Sciences, Isfahan University of Medical Sciences, Isfahan, I.R. Iran.
[4]Students' Research Committee of Pharmacy, School of Pharmacy and Pharmaceutical Sciences, Isfahan University of Medical Sciences, Isfahan, I.R. Iran.

Abstract

Prunus divaricata (*Alloocheh*) is a small tree cultivating in Iran, Middle East and central Asia. *Prunus* genus has many species with anti-oxidant, anti-hyperlipidemia and anti-hyperglycemia effects. In the present study the anti-diabetic and anti-hyperlipidemic effects of *P. divaricata* fruits were examined in normal and streptozotocin (STZ)-induced diabetic rats. Both groups, control and reference rats received normal saline and glibenclamide respectively. Test groups were treated with *Prunus* freeze dried juice (PFDJ, 200, 400, 800 mg/kg) and *Prunus* freeze dried extract (PFDE, 100, 200, 400 mg/kg) started at the 3rd day of the experiment and continued for 27 days thereafter. Weight changes of animals were checked periodically. Fasting blood glucose (FBG) level as well as serum triglyceride (TG), total cholesterol (TC), high density lipoprotein (HDL) and low density lipoprotein (LDL) cholesterol were determined. Different treatments had no significant effect on body weight increments of normal rats, while in diabetic rats, PFDJ (800 mg/kg) and PFDE (400 mg/kg) opposed with weight loss. In acute phase of experiment (0-8 h of 3rd day), none of tested fractions were effective in reducing FBG and serum lipids of normal rats. During the sub-acute phase (13th and 30th days) however, the greatest test doses of PFDJ (800 mg/kg) and PFDE (400 mg/kg) induced hypoglycema. In diabetic groups, PFDJ and PFDE, at all test doses, could diminish FBG during sub-acute phase of the experiment. In addition, PFDJ and PFDE at most examined doses could diminish TG significantly and they were also effective on cholesterol derivatives in different magnitude.

Keywords: *Prunus divaricata*; Diabetes; Hyperlipidemia; Streptozotocin; Rats

INTRODUCTION

Diabetes mellitus (DM) is a set of metabolic disturbances that is characterized by hyperglycemia with interferences in the metabolism of carbohydrates, lipids and proteins (1). Prevalence of global DM was estimated 2.8% in 2000 and 4.4% in 2030. It means diabetes shape to an epidemic disease if obesity still exists (2). Insulin deficiency or resistance and defective insulin secretion are the causes of different types of DM (1). Besides synthetic drugs, several herbal medicines are used in the treatment of diabetes, that their hypoglycemic effect in humans and animal models has been demonstrated. Some of these plants are Fenugreek (*Trigonella fornum-graecum* L.) (3), (*Carum carvi* L.) (4), green tea (*Camellia sinensis*) (5), sumac (*Rhus coriaria*) (6), and many other plants. *Prunus* tree, with the scientific name *Prunus divaricata* (*Rosaceae* family), is a shrub or small tree belonging to the Iran, Middle East and central Asia. This plant is eaten as nuts during spring and many people enjoy eating it. Two subspecies of this

*Corresponding author: P. Ramezanlou, this paper is extracted from the Pharm.D thesis No. 390637
Tel. 0098 912 5830574, Fax. 0098 3116680011
Email: pariaramezanloo@yahoo.com

plant are diagnosed in Iran: *Prunus divaricata* and *Prunus caspica* (7). In this study the unripe fruit of the first species was used. In Iranian folk medicine, following effects of prunus fruit have been reported: Lowering effect on blood pressure and hyperlipidemia, prevention of diseases such as cancer, rheumatism and atherosclerosis (8). *Prunus* genus is a rich source of vitamin C, sugar, carotene, vitamins A, B1, B2, crude fiber and etc. Rich innutrients with antioxidant capabilities leading to body's resistance against infection, fight inflammation and damaging free radicals, thus enhance the immune system (14). Vitamins B reduce stress and depression. They have a positive role in normal metabolism of carbohydrate, fat and proteins (9). In this family (*Rosaceae*), there are some plants such as *Prunus mume* which have strong hypoglycemic and plasma lipid lowering actions in rats with type 2 diabetes (10). Also Almond (*P. amygdalus*) consumption lowered LDL-C and improved insulin sensitivity markers in people with pre-diabetes condition (11).

It is assumed that antioxidant capacity of genus *Prunus* is responsible for most of these pharmacological functions. In this regard antioxidant effect of cafeoyl quinic acid isomers present in *P. domestica* was observed by oxygen radical absorbance capacity (ORAC) method (12).

In addition, many active phytochemicals with antioxidant effects including cinnamic acids, coumarins, diterpenes, flavonoids, lignans, monoterpenes, phenylpropanoids, tannins and triterpenes could be found in these species (13). It seems that plants particularly those with high levels and strong antioxidant compounds have an important role in improvement of disorders involving oxidative stress such as DM (14). In another study on the effects of local and traditional plants from Turkey, *P. divaricata* and *P. spinosa* were introduced as anti-diabetic plants by natives (15). In many other studies anti-diabetic and anti-lipidemic effects of *P. domestica* have been observed (9,16,17).

According to the high content of organic acids in *Prunus* genus and their significant effects on blood pressure, blood cholesterol and antioxidant effects, anti-diabetic effects of *P. divaricata* was studied. So the anti-hyperglycemic and anti-lipidemic effects of juice and hydro-alcoholic extract of *P. divaricata* were examined in normal and streptozotocin-induced diabetic rats during 30 days period.

MATERIALS AND METHODS

Chemicals

Streptozotocine (STZ) (Zanosar®) was obtained from Upjohn, Kalamazoo, MI, USA. Measuring blood glucose device glucometer provided by Bionime® (Rightest GM110, Heerbrugg, Switzerland). Diagnostic kits for determining triglycerides (TG), total cholesterol (TC) and HDL-C were purchased from Pars Azmoon® (Karaj, Iran). All solvents were of analytical grade and procured from Merck (Darmstadt, Germany).

Plant material

Fruit of *Prunus divaricata* (subsp. *Divaricata*) was purchased from a local market in Najaf-Abad, Isfahan by researcher during May 2012 and then authenticated by Mrs. Mahboobeh Khatamsaz (Forests and Rangelands Research Center, Karaj, Iran). A voucher sample numbered 2828 was deposited in Herbarium division of Pharmacognosy Department, Isfahan School of Pharmacy, Isfahan, Iran.

Prunus divaricata freeze dried juice preparation

Pieces of fruits were cut, grinded and compressed to obtain two liters juice. Then the juice was freezing dried (Christ®, UK) till 122 g powder was resulted eventually. Prunus divaricata freeze dried juice (PFDJ) powder was freshly reconstituted in distilled water to make suitable suspensions with desired concentrations.

Prunus divaricata freeze dried hydroalcoholic extract preparation

Cut pieces of fruits (1000 g) immersed in 1.7 liters ethanol/water (70/30) for 5 days, the mixture was shaken for 30 min and filtered to obtain a smooth extract (Maceration method)

(18). Finally it was freezing dried which produced 51 g of dry powder. Prunus divaricata freeze dried hydroalcoholic extract (PFDE) powder was freshly reconstituted in distilled water to make suitable suspensions with desired concentrations.

Animals

Male albino Wistar rats weighting 230-260 grams which grew in the animal house of Isfahan School of Pharmacy and Pharmaceutical Sciences were used. They were kept in polypropylene cages (3 rats per cage) at standard conditions. They were fed with pellet diet and tap water *ad libitum*. Animals were randomly assigned to two separate groups of normal and diabetic rats of six in each. The study was carried out according to the guidelines of Research Ethics Committee for animal experiments set forth by Isfahan University of Medical Sciences, Isfahan, Iran.

Induction of type 1 diabetes mellitus

Diabetes mellitus (DM) was induced by single intraperitoneal (i.p.) injection of freshly prepared STZ solution (55 mg/kg, body weight, b.w.). The rats were fasted 12 h before induction of the disease. After 72 h, fasting blood glucose (FBG) was measured and the rats showed FBG equal or greater than 200 mg/dl (maximum 500 mg/dl) were selected for the experiment (19).

Experimental design

Sixteen groups were selected for this study: In eight normal groups, control and reference groups received normal saline (5 ml/kg) and glibenclamide (1 mg/kg) respectively. Other six groups were treated with PFDJ (200, 400, 800 mg/kg) and PFDE (100, 200, 400 mg/kg). On the other set of animals, eight diabetic groups of rats were used. Control and reference groups were similarly treated with normal saline (5 ml/kg) and glibenclamide (3 mg/kg) respectively while test groups treated with PFDJ (200, 400, 800 mg/kg) and PFDE (100, 200, 400 mg/kg). All rats were fed once daily, 72 h after induction of diabetes (at the 3rd day) by a feeding tube and continued for 27 days thereafter (totally for 30 days after induction). The animals were weighted at 1st, 3rd, 13th and 30th days of the study.

Blood glucose level was measured by Bionime® glucometer at 0, 1, 3, 5 and 8 h at day 3 of experiment and repeated for two more times at the 13th and 30th days (20). Serum lipid profile including triglyceride (TG), total cholesterol (TC), and HDL-cholesterol (HDL-C) were also determined at the end (30th day) of experiment by respective diagnostic kits. LDL-cholesterol (LDL-C) was measured by using following formula

LDL-C = TC - (HDL-C + TG/5) (21).

Blood samples were taken by heparinized microcapillary from orbital sinus plexus under light ether anesthesia (22). At the end of study the animals were euthanized by ether overdose inhalation.

Statistical analyses

Data was analyzed with one way ANOVA with Tukey Post Hoc test (SPSS software version 17) to compare the means with the level of significance set at $P<0.05$. Results are presented as mean ± SD.

RESULTS

Figs 1 and 2 show the changes of body weight at time zero and at 3, 13, and 30 days of experiment in two separate sets of normal and diabetic rats respectively.

As it is shown in Fig. (1a and 1b), different treatments had no significant effect on body weight increments of normal rats found during experiment. Fig. (2a and 2b) demonstrates the data of body weight changes in diabetic rats. As it is shown, body weight reduction is obvious in different groups especially in control groups. Glibenclamide (3 mg/kg) as well as PFDJ (800 mg/kg) and PFDE (400 mg/kg) were effective to reverse this trend and re-establish the rats' body weight loss indicating a metabolic improvement.

Fig. (3a and 3b) shows the effect of different treatments on FBG of normal rats. In acute phase of the experiment (0-8 h of the 3rd day) none of test extracts were effective to reduce FBG with the exception of glibenclamide. During the sub-acute phase on the other hand, the greatest test doses of PFDJ

(800 mg/kg) and PFDE (400 mg/kg) were hypoglycemic at the the end of experiment (30th day) in comparison with control groups (P<0.05).

In diabetic groups a different pattern of action could be observed. As it is shown in Fig. (4a and b), all doses of PFDJ (200,400,800 mg/kg) and PFDE (100,200,400 mg/kg) were effective to diminish FBG during sub-acute phase of experiment compared to control groups. Glibenclamide was similarly effective in this respect while it had hypoglycemic effect in both phases of the treatment.

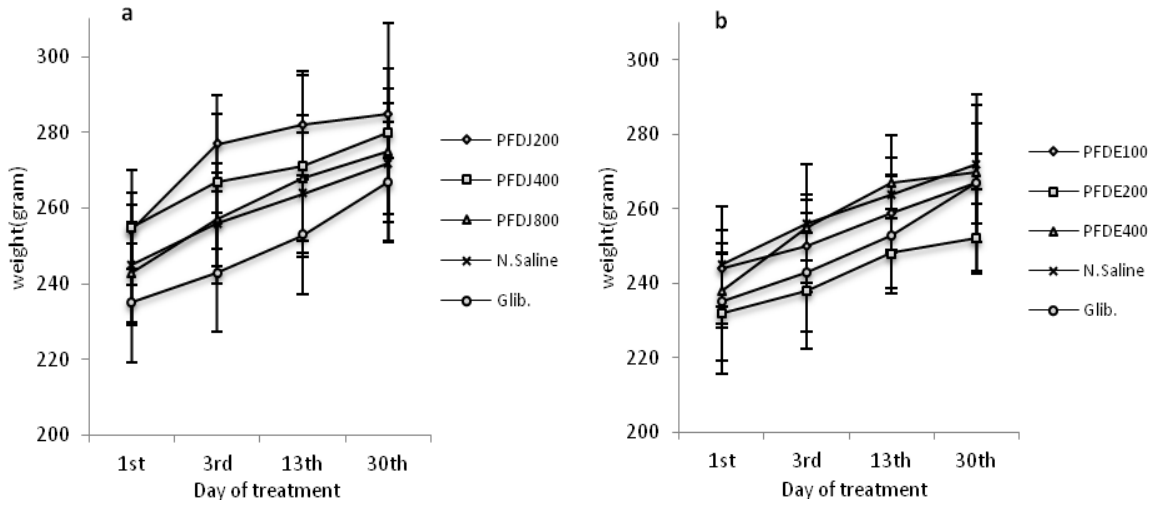

Fig. 1. Changes in body weight of normal rats after treatment with *Prunus divaricata* freeze dried juice preparation and *Prunus divaricata* freeze dried hydroalcoholic extract preparation fractions. Data are presented as mean ± SD. PFDJ: *Prunus divaricata* freeze dried juice (200, 400, 800 mg/kg), PFDE; *Prunus divaricata* freeze dried hydroalcoholic extract (100, 200, 400 mg/kg), N. Saline; normal saline (5 ml/kg), Glib.;glibenclamide (1 mg/kg).

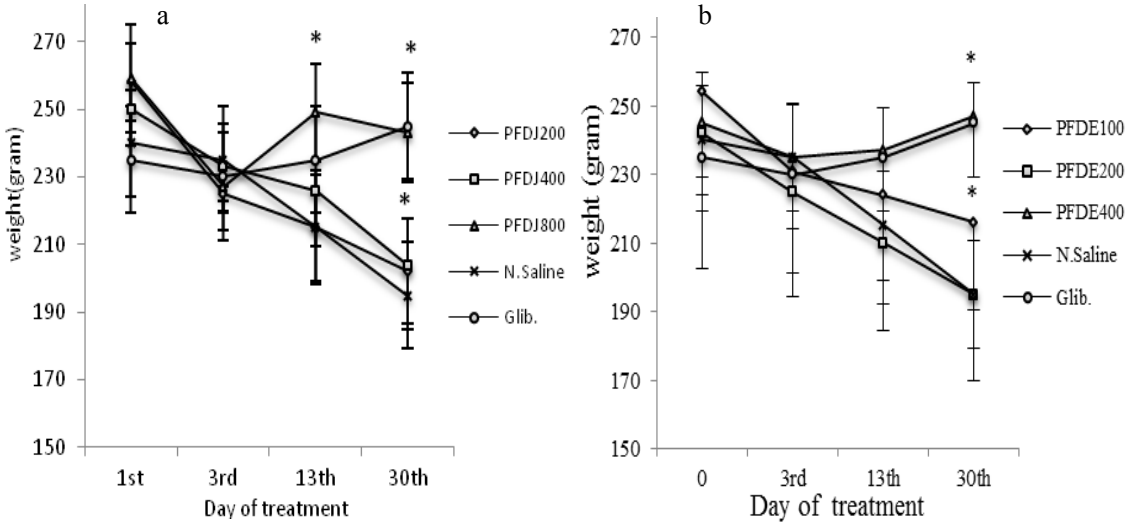

Fig. 2. Changes in body weight of streptozocin-induced diabetic rats after treatment with *Prunus divaricata* freeze dried juice preparation and *Prunus divaricata* freeze dried hydroalcoholic extract preparation fractions. Data are presented as mean ± SD, PFDJ; *Prunus divaricata* freeze dried juice (200, 400, 800 mg/kg), PFDE; *Prunus divaricata* freeze dried hydroalcoholic extract (100, 200, 400 mg/kg), N. Saline; normal saline (5 ml/kg), Glib.; glibenclamide (3 mg/kg)**,** *P<0.05 compared to normal saline group (ANOVA).

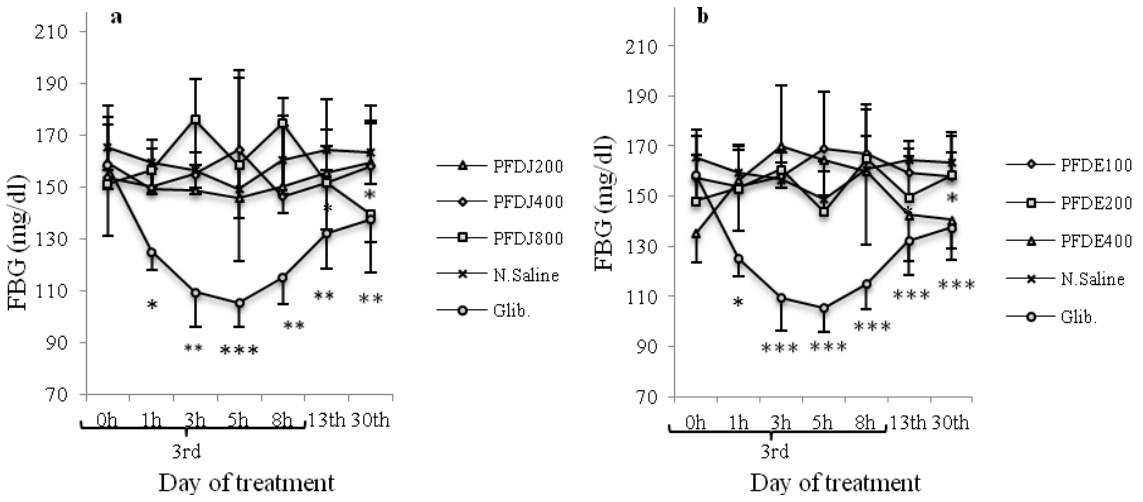

Fig. 3. Changes in fasting blood glucose levels of normal rats after treatment with *Prunus divaricata* freeze dried juice preparation and *Prunus divaricata* freeze dried hydroalcoholic extract preparation fractions fractions. Data are presented as mean ± SD, PFDJ; *Prunus divaricata* freeze dried juice (200, 400, 800 mg/kg), PFDE; *Prunus divaricata* freeze dried hydroalcoholic extract (100, 200, 400 mg/kg), Glib.; glibenclamide (1 mg/kg), N. Saline; normal saline (5 ml/kg), FBG; fasting blood glucose,**P*<0.05, ***P*<0.01, ****P*<0.001 compared tonormal saline group (ANOVA).

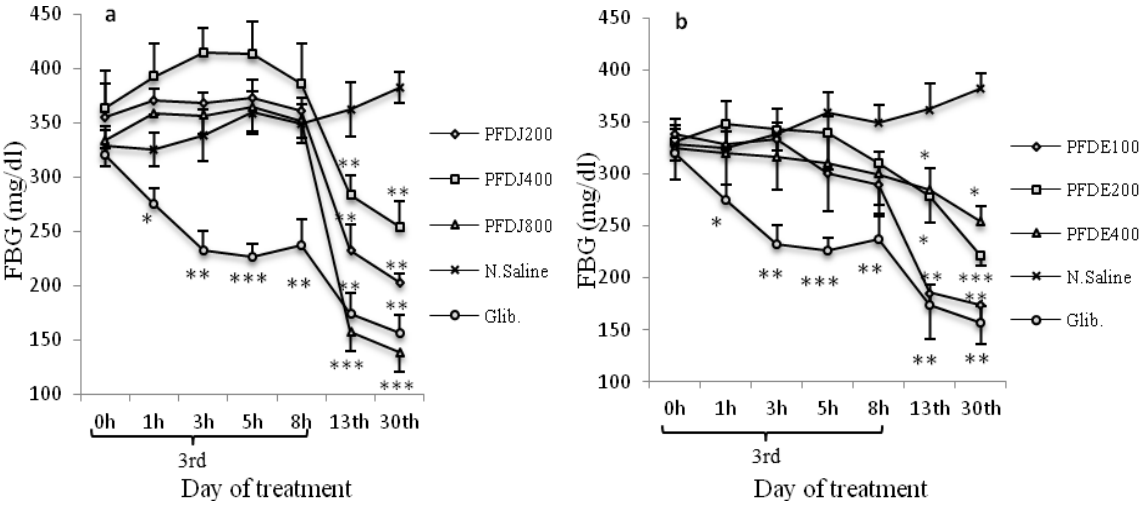

Fig. 4. Changes in fasting blood glucose levels of streptozocin-induced diabetic rats after treatment with *Prunus divaricata* freeze dried juice preparation and *Prunus divaricata* freeze dried hydroalcoholic extract preparation fractions . Data are presented as mean ± SD, PFDJ; *Prunus divaricata* freeze dried juice (200, 400, 800 mg/kg), PFDE; *Prunus divaricata* freeze dried hydroalcoholic extract (100, 200, 400 mg/kg), Glib; glibenclamide (3 mg/kg), N. Saline; normal saline (5 ml/kg), FBG; fasting blood glucose,**P*<0.05, ***P*<0.01, ****P*<0.001 compared tonormal saline group (ANOVA).

In the case of lipid profile in normal rats, both plant fractions (PFDJ and PFDE) were not effective to diminish serum lipids including TG, TC, LDL-C (Table 1).

The same results were obtained with glibenclamide. In diabetic rats however, all test doses of PFDJ and two greater doses of PFDE (200, 400 mg/kg) could diminish TG significantly while PFDJ was the only fraction effective on TC as well as LDL-C levels in subacute phase of the treatment (30^{th} day) (at least $P<0.01$). PFDJ was also effective to increase HDL-C levels in diabetic group (at least $P<0.01$)+ (Table 2). Glibenclamide was also effective in TC and LDL-C reduction of diabetic rats ($P<0.01$).

Table 1. Effect of *Prunus divaricata* freeze dried juice preparation and *Prunus divaricata* freeze dried hydroalcoholic extract preparation fractions on serum triglycerides, total cholesterol, low density lipoprotein cholesterol and high density lipoprotein cholesterol of normal rats at 30th day of experiment.

Groups	TG (mg/dl)	TC (mg/dl)	LDL-C (mg/dl)	HDL-C (mg/dl)
N.Saline	70.9 ± 9.4	117.3 ± 5.7	36.5 ± 8.6	66.3 ± 10.2
PFDE100	68.5 ± 8.2	117.8 ± 8.1	34.1 ± 12.6	70 ± 7.1
PFDE200	67 ± 9.1	122 ± 15.2	38.3 ± 16.8	70.3 ± 3.5
PFDE400	74.6 ± 9.5	118.4 ± 3.9	35 ± 5.0	69.4 ± 3.8
PFDJ 200	72.8 ± 5.6	120.4 ± 3.6	37.6 ± 5.7	68.2 ± 5.9
PFDJ 400	75.8 ± 5.2	119.4 ± 9.1	37.9 ± 10.7	66.4 ± 6.5
PFDJ 800	77.4 ± 16.1	125.7 ± 12.8	37.2 ± 19.2	73 ± 15.2
Glib.	70.5 ± 5.9	120.4 ± 10.2	39.1 ± 11.7	67.2 ± 1.2

Data are presented as mean ± SD, PFDJ; *Prunus divaricata* freeze dried juice (200, 400, 800 mg/kg), PFDE; *Prunus divaricata* freeze dried hydroalcoholic extract (100, 200, 400 mg/kg), Glib.; glibenclamide (1 mg/kg), N.Saline: normal saline (5 ml/kg). TG; serum triglycerides, TC; total cholesterol, LDL-C; low density lipoprotein cholesterol and HDL-C; high density lipoprotein cholesterol.

Table 2. Effect of *Prunus divaricata* freeze dried juice preparation and *Prunus divaricata* freeze dried hydroalcoholic extract preparation fractions on serum triglycerides , total cholesterol , low density lipoprotein cholesterol and high density lipoprotein cholesterol of streptozocin-induced diabetic rats at 30th day of experiment .

Groups	TG (mg/dl)	TC (mg/dl)	LDL-C (mg/dl)	HDL-C (mg/dl)
N.Saline	132.1 ± 4.5	189.5 ± 4.6	130.5 ± 4.0	32.5 ± 3.6
PFDE100	130 ± 8.5	181.8 ± 5.5	117.5 ± 9.1	38.5 ± 6.4
PFDE200	126.4 ± 9.1*	183.6 ± 10.2	120.6 ± 16.2	37.7 ± 8.5
PFDE400	125.8 ± 4.7**	182.5 ± 9	115.6 ± 6.6	41.7 ± 8.6
PFDJ200	122.2 ± 4.6**	178.6 ± 6.1*	118.8 ± 7.1	35.3 ± 3.9
PFDJ400	79.2 ± 6.9***	159.1 ± 2.5***	97 ± 5.8***	46.3 ± 6.6**
PFDJ800	69.6 ± 5.4***	148.6 ± 4.2***	85.3 ± 7.3***	49.3 ± 6.1***
Glib.	114.4 ± 5.0	165.9 ± 7.0*	99.3 ± 3.2*	43.7 ± 8.0

Data are presented as mean ± SD, PFDJ; *Prunus divaricata* freeze dried juice (200, 400, 800 mg/kg), PFDE; *Prunus divaricata* freeze dried hydroalcoholic extract (100, 200, 400 mg/kg), Glib.:glibenclamide (3 mg/kg), N.Saline: normal saline (5 ml/kg), TG; serum triglycerides, TC; total cholesterol, LDL-C; low density lipoprotein cholesterol and HDL-C; high density lipoprotein cholesterol. *$P<0.05$, **$P<0.01$, ***$P<0.001$ compared to normal saline group (ANOVA with Tukey post hoc test).

DISCUSSION

This study presented for the first time the anti-hyperglycemic and anti-lipidemic effects of *P. divaricata* two fractions (juice and extract) on normal and STZ-induced diabetic rats. Other species of this genus like *P. domestica* (Allou), *P. amygdalus* (Baadam), *P. davidiana* and *P. mume* showed significant anti-hyperglycemic and/or anti-lipidemic activities in the past studies (10,11,15,23-24,28,29). A literature survey revealed no report on the effects of *P.divaricata*, while this delicious fruit is commonly eaten during spring a lot.

STZ is one of the most powerful diabetogenic agents which results in body weight loss promptly through increasing muscle wasting and decreasing tissue proteins (26). According to our results, rats' body weight changes were not altered in normal groups due to therapeutic interventions. However, in diabetic rats; maximum doses of two PFDJ and PFDE fractions opposed to body weight loss of animals during the experimen period. This suggests that test *Prunus* fractions were able to improve metabolic and physiologic activities in diabetic rats (30). By reviewing the results obtained after blood glucose analysis, it is found that PFDJ and PFDE reduced FBG only in sub-acute phase. In the *Prunus* genus, there are many species with anti-diabetic activities which act via different mechanisms including α-glucosidase inhibitor due to the existence of Prunusides A-C (25), adiponectin-related mechanism (27), activation of PPAR-γ (10) and insulin like hypoglycemic effects due to

Prunin, a flavanone glycoside (28). *Prunus* genus is a rich source of organic acids like chlorogenic and neochlorogenic acids as well as fibers, sorbitol, and phenolic constituents that may interfere with carbohydrate absorption in gastrointestinal tract or at least make a significant delay in it (9). This may explain why two different examined fractions had various effects on FBG of diabetic rats. By reviewing the results related to antihyperlipidemic effects of *P. divaricata,* it could be found that both fractions were not effective in normal animals as it is expected. On the other hand, PFDE reduced TG levels while greater doses of juice fraction PFDJ were able to cause a significant decline in TG, TC, LDL-C as well as an increase in HDL-C levels during subacute phase of treatment.

The HDL level inversely correlates with the risk of atherosclerotic cardiovascular disease. HDL protects against or reverse atherosclerosis by their ability to serve as acceptor particles for macrophage cholesterol efflux, prevention of endothelial dysfunction and maintenance of endothelial integrity (31). A diet enriched with almond (*P. amygdalus*) reduced total cholesterol, LDL-C and LDL-C to HDL-C ratio significantly, but did not affect TG and HDL-C, in type 2 DM patient (11). In another study, opposite results obtained when an almond-enriched diet decreased HDL-C with no effect on LDL-C to HDL-C ratio, suggesting that almond has a similar effect to high-monounsaturated fat oils (32). Lipid profile results obtained in the present study were similar to a study carried out by Tinker and cworkers (33) in which total cholesterol and LDL-C levels following administration of *P. domestica* was reduced. Many herbs and plant products have been shown to have hypolipidemic properties (34-36). Covas and colleaues (37) reported that consumption of polyphenol-rich olive oil increases HDL-C levels and lowers levels of oxidative stress markers and oxidized LDL-C.

There are many evidences indicating that diabetes induced by STZ will result finally in lipid profile disturbances in experimental animals (38). In the presence of insulin secretion paucity or shortage, the increase in the total serum cholesterol, triglyceride and LDL-C levels in the diabetic rats will happen which is mainly due to increased mobilization of free fatty acids from peripheral deposits to central blood circulation. The increase in the serum LDL-C level may also result from glycosylation of the lysyl residues of apoprotein B, which leads to a decrease in LDL metabolism due to a decrease in the affinity of LDL for its receptors (39).On the other hand, disturbed lipid profile is usually observed in diabetic patients and most of diabetics usually receive lipid lowering agents mostly statins together with antidiabetic drugs (40). For defining the active constituents with antihyperglycemic and antihyperlipidemic properties of *P. divaricata*, detailed phytochemical analysis is necessary. Additionally, to clarify exact mechanism of its action, measuring serum insulin, HbA1C, liver enzymes activities and glycogen contents in liver are highly recommended.

CONCLUSION

Our findings demonstrate that juice and hydroalcoholic fractions of *P. divaricata* reduce FBG and improve lipid profile after continuous use especially in long term schedule. Measuring other biochemical parameters and histological studies will help to determine active involved mechanisms.

ACKNOWLEDGMENTS

This study was financially supported by Isfahan University of Medical Sciences under project number of 390637. The authors also thank Mrs. Khatamsaz for valuable assistance.

REFERENCES

1. Kuzuya T, Nakagawa S, Satoh J, Kanazawa Y, Iwamoto Y, Kobayashi M, *et al*. Report of the committee on the classification and diagnostic criteria of diabetes mellitus. Diabetes Res Clin Pract. 2002;55:65-85.
2. Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes estimates for the year 2000 and projections for 2030. Diabetes Care.2004;27:1047-1053.
3. Hasanzadeh E, Rezazadeh SA, Shamsa S, Doulatabadi R, Zarin Ghlammoghadam J. Review on phytochemistry and therapeutic properties of

Fenugreek (*Trigonella foenum-graceum*). J Med Plants. 2010;9:1-17.
4. Eydi A, Eydi M, Haeri Rouhani SA, Basati F. Hypoglycemic effect of ethanolic extract of *Carum carvi* L. seeds in normal and streptozotocin-induced diabetic rats. J Med Plants. 2010;9;106-113.
5. Ebrahiminia F, Elahi A, Sadeghzade M, Ghahfarrokhi SF, Masoudi H. Effect of green tea (*Camellia sineisis* L.) extract on blood glucose and body weight in male induced diabetic rats. J Gorgan Uni Med Sci. 2009;11:8-12.
6. Kouhsari S, Feshani A. Antidiabetic properties of the ethanolic extract of *Rhus coriariafruits* in rats. DARU J Pharm Sci. 2010;18:270-275.
7. Khatamsaz M. *Rosaceae*. In: Flora of Iran. Tehran, Iran:Research Institute of Forests &Rangelands Publications; 1992.
8. Del Caro A, Piga A. Prunes: Are theyFunctional Foods? In: Dried Fruits: Phytochemicals and health effects. Oxford, UK: Blackwell Publishing Ltd; 2013.p.357-71.
9. Stacewicz-sapuntzakis M, Bowen PE, Hussain EA, Damayanti-wood BI, Farnsworth NR. Chemical composition and potential health effects of prunes: a functional food? Crit Rev Food Sci Nutr. 2001;41:251-286.
10. Hwang J, Yang H, Hur H, Park J. Anti-diabetic effect and mechanism of action of MaEsil (*Prunusmume*) extract. Planta Med. 2012;78:PF25.
11. Wien M, Bleich D, Raghuwanshi M, Gould-Forgerite S, Gomes J, Monahan-Couch L, *et al*. Almond consumption and cardiovascular risk factors in adults with prediabetes. J Am Coll Nutr. 2010;29:189-197.
12. Kayano SI, Kikuzaki H, Fukutsuka N, Mitani T, Nakatani N. Antioxidant activity of prune (*Prunus domestica* L.) constituents and a new synergist. J Agric Food Chem. 2002;50:3708-3712.
13. Larkins N, Wynn S. Pharmacognosy: Phytomedicines and their mechanisms. VetClin North Am Small AnimPract. 2004;34:291–327.
14. Rahimi R, Nikfar S, Larijani B, Abdollahi M. A review on the role of antioxidants in the management of diabetes and its complications. Biomed Pharmacother. 2005;59:365–373.
15. Kültür Ş. Medicinal plants used in Kırklareli province (Turkey). J Ethnopharmacol. 2007;111:341-364.
16. Jabeen Q, Aslam N. The pharmacological activities of prunes: The dried plums. J Med Plants Res. 2011;5:1508-1511.
17. Tinker L, Schneeman B, Davis P, Gallaher D, Waggoner C. Consumption of prunes as a source of dietary fiber in men with mild hypercholesterolemia. Am J Clin Nutr. 1991;53:1259-1265.
18. Ottah AA, Augustine O, Obiora IO, Maxwell E. Antihyperglycemic effects of the methanol leaf extract of *Diaphananthe bidens* in normoglycemic and streptozotocin-induced hyperglycemic rats. Asian Pac J Trop Med. 2012;5:192-196.
19. Balamurugan R, Ignacimuthu S. Antidiabetic and hypolipidemic effect of methanol extract of *Lippianodiflora* L. in streptozotocin induced diabetic rats. Asian Pac J Trop Biomed. 2011;1:30-36.
20. Agrawal NK, Gupta U. Evaluation of hypoglycemic and antihyperglycemiceffectsof *Acacia tortilis* seed extract in normal and diabetic rats. Evaluation. 2013;5:330-336.
21. Movahedian A, Zolfaghari B, Sajjadi SE, Moknatjou R. Antihyperlipidemic effect of *Peucedanum pastinaci folium* extract in streptozotocin-induced diabetic rats. Clinics. 2010;65:629-633.
22. Zolfaghari B, Shokoohinia Y, Ramezanlou P, Sadeghi A, Mahmoudzadeh M, Minaiyan M. Effects of extract and total saponins of *Allium elburzense* Wendelbo bulbs on blood glucose level of normal and STZ-induced diabetic rats. Res Pharm Sci. 2012;7:201-207.
23. Kayano SI, Kikuzaki H, Yamada NF, Aoki A, Kasamatsu K, Yamasaki Y, *et al*. Antioxidant properties of prunes (*Prunus domestica* L.) and their constituents. Biofactors. 2004;21:309-313.
24. Shin EJ, Hur HJ, Sung MJ, Park JH, Yang HJ, Kim MS, *et al*. Ethanol extract of the *Prunusmume* fruits stimulates glucose uptake by regulating PPAR-γ in C2C12 myotubes and ameliorates glucose intolerance and fat accumulation in mice fed a high-fat diet. Food Chem. 2013;141:4115-4121.
25. Kosar S, Fatima I, Mahmood A, Ahmed R, Malik A, Talib S, *et al*. Purunusides AC, α-glucosidase inhibitory homoisoflavone glucosides from *Prunus domestica*. Arch Pharm Res. 2009;32:1705-1710.
26. Knoll KE, Pietrusz JL, Liang M. Tissue-specific transcriptome responses in rats with early streptozotocin-induced diabetes. Physiol Genomics. 2005;21:222-229.
27. Utsunomiya H, Yamakawa T, Kamei J, Kadonosono K, Tanaka S-I. Anti-hyperglycemic effects of plum in a rat model of obesity and type 2 diabetes, Wistar fatty rat. Biomed Res. 2005;26:193-200.
28. Choi JS, Yokozawa T, Oura H. Improvement of hyperglycemia and hyperlipemia in streptozotocin-diabetic rats by a methanolic extract of *Prunus davidiana* stems and its main component, Prunin. Planta Med. 1991;57:208-211.
29. Choi JS, Suh SS, Young HS, Park HJ. Hypolipemic and hypoglycemic activities of *Prunus davidiana* in high fat-fed rats. Arch Pharm Res. 1991;14:44-47.
30. Negahdari-zadeh M, Mokhtari M, Malek-zadeh JM, Mohammadi J. The effects of *Capparis Spinosa* hydroalcoholic extract on blood glucose and lipids serum in diabetic and normal male rats. Armaghane-danesh J Yasuj Uni Med Sci. 2011;16:181-190.
31. Linsel-nitschke P, Tall AR. HDL as a target in the treatment of atherosclerotic cardiovascular disease. Nat Rev Drug Discov. 2005;4:193-205.
32. Lovejoy JC, Most MM, Lefevre M, Greenway FL, Rood JC. Effect of diets enriched in almonds on insulin action and serum lipids in adults with normal glucose tolerance or type 2 diabetes. Am J Clin Nutr. 2002;76:1000-1006.

33. Tinker LF, Davis PA, Schneeman BO. Prune fiber or pectin compared with cellulose lowers plasma and liver lipids in rats with diet-induced hyperlipidemia. J Nutr. 1994;124:31-40.
34. Movahedian A, Ghannadi A, Vashirnia M. Hypocholesterolemic effects of Purslane extract on serum lipids in rabbits fed with high cholesterol levels. Int J Pharmacol. 2007;3:285-289.
35. Pari L, Latha M. Antihyperlipidemic effect of *Scopariadulcis* (sweet broomweed) in streptozotocin diabetic rats. J Med Food. 2006;9:102-107.
36. Thompson-coon JS, Ernest E. Herbs for serum cholesterol reduction: a systematic view. J Fam Pract. 2003;52:468-478.
37. Covas MI, Nyyssonen K, Poulsen HE, Kaikkonen J, Zunft HJ, Kiesewetter H, *et al*. The effect of polyphenols in olive oil on heart disease risk factors: a randomized trial. Ann Intern Med. 2006;145:333–341.
38. Movahedian A, Sadeghi H, Ghannadi A, Gharavi M, Azarpajooh S. Hypolipidemic activity of *Allium Porrum*L. in cholesterol-fed rabbits. J Med Food. 2006;9:98-101.
39. Pepato MT, Mori DM, Baviera AM, Harami JB, Vendramini RC, Brunetti IL. Fruit of the jambolantree (*Eugenia jambolana*Lam.) and experimental diabetes. J Ethnopharmacol. 2005;96:43-48.
40. Hadjibabaie M, Vosough-ghanbari S, Radfar M, Gholami K, Khoei SH, Nakhjavani M, *et al*. Comparative efficacy of dailyversus alternate-day dosing of atorvastatin in type 2 diabetic patients. Therapy. 2007;4:541–45.