



Biochemical components of *Berberis lycium* fruit and its effects on lipid profile in diabetic rats

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ABSTRACT

Introduction: Diabetes mellitus is characterized by chronic hyperglycemia with disturbances of carbohydrate, fat, and lipid metabolism resulting from defect in insulin secretion, insulin action, or both. It not only leads to hyperglycemia but also may cause hyperlipidemia. Herbal medicines have always been considered as a healthy source of life. Although medicinal herbs and their derivatives have long been used for hyperlipidemia, their definite effects have not yet been proven by valid research. The aim of this study was to measure minerals in *B. lycium* fruit and to evaluate the effects of its ethanolic extract on lipid profile in diabetic rats.

Methods: For this study 40 male Wistar rats were used and were divided into five equal groups. For induction of diabetes in animals, alloxan monohydrate was used. The animals were under treatment for 42 days. For healthy and diabetic control groups distilled water, for positive diabetic control metformin, for the fourth and fifth diabetic groups *Berberis lycium* extract in respectively 200 and 600 mg/kg dose were used, daily. Blood samples were collected from heart and lipid profile was measured with autoanalyzer and HPLC.

Results: The results of the study indicated that iron level in *Berberis lycium* fruit was considerably high. In diabetic rats administered with *Berberis lycium* fruit extract in 600 mg/kg dose, the lipid profile decreased significantly ($p < 0.05$).

Conclusion: The present investigation showed that the *Berberis lycium* fruit extract alleviates lipid profile level and might be used efficiently in hyperlipidemia, especially in diabetic patients. It may also be beneficial in iron deficiency.

Implication for health policy/practice/research/medical education:

Berberis lycium fruit extract alleviates lipid profile level and might be beneficial in hyperlipidemia, especially in diabetic patients. It may also be useful in iron deficiency.

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Introduction

Diabetes mellitus is characterized by chronic hyperglycemia with disturbances of carbohydrate, fat, and lipid metabolism resulting from defect in insulin secretion, insulin action, or both. The effects of diabetes mellitus include long term damage, dysfunction, and failure of various organs (1). It not only leads to hyperglycemia but also may cause hyperlipidemia, atherosclerosis, and hypertension (2). Diabetes is a chronic metabolic disorder, which is

considered as a major worldwide health problem. It is characterized by absolute or relative deficiency in insulin secretion and/or insulin action associated with chronic hyperglycemia and disturbances of carbohydrate, lipid, and protein metabolism. As a consequence of the metabolic derangements in diabetes, various complications including both macro- and micro-vascular dysfunctions develop (3).

In advanced stages of diabetes, metabolism of protein and lipid is also altered. Many factors like heredity, age,

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obesity, diet, sex, sedentary life style, socioeconomic status, hypertension, and various stresses are involved in the etiology of diabetes mellitus (4).

Diabetes mellitus is a complex, multifarious group of disorders, which has reached epidemic proportions in the present century. The number of people affected by diabetes is estimated to be 366 million by year 2030 worldwide (5). Diabetes is a substantial contributor to the global burden of disease. Excess healthcare costs of diabetes are mainly due to the complications of cardiovascular diseases (6).

Diabetes mellitus type 2 is an important cardiovascular risk factor. A significant component of the risk associated with diabetes type 2 is thought to be due to lipid profile and elevated triglycerides. Chronic elevations of free fatty acids (FFA) induce insulin resistance and contribute to the lipid triad of diabetes. Therefore, reducing their levels is likely to ameliorate insulin resistance and to improve the lipid triad of diabetes (6,7).

Hyperlipidemia is a heterogeneous group of disorders characterized by an excess of lipids in the blood stream. High lipid levels can speed up a process called atherosclerosis that leads to cardiovascular disease and diabetes (8). Many studies have previously discussed the role of oxidative stress in atherosclerosis and there is now a consensus that atherosclerosis represents a state of heightened oxidative stress characterized by lipid and protein oxidation in the vascular wall (9).

Cardiovascular diseases are the main causes of death or life-threatening morbidities throughout the world. Hyperlipidemia is a major risk factor for these disorders and is closely associated with development and progression of coronary atherosclerosis (8).

Since ancient times, people have used plants to treat their illnesses. Every day, the popularity of medicinal plants is increasing in the world. As it is increasingly believed now that traditional medicines have become more popular worldwide, there is growing evidence suggesting medicinal plants are unlimited resources of drugs (10). Therefore, it is rationale to search for new, safer medicinal drugs (5). Herbal medicines have always been considered as a healthy source of life and different experimental and clinical researches have shown promising effects for various conditions such as atherosclerosis, diabetes, cancer, infection, gastrointestinal and central nervous system disorders (11). Although medicinal herbs and their derivatives have long been used as a remedy for hyperlipidemia, their definite effects have not yet been proven by valid research (12).

Nutraceuticals and functional foods have attracted considerable interest as potential alternative therapies for treatment of different cardiovascular disorders and insulin resistance. Efficacy of a combination of two types of Barberry extract in a sample of overweight, dyslipidemic patients at low cardiovascular risk was evaluated and it was found to be safe and effective in improving lipid profile (13).

The Berberidaceae family (order Ranunculales), a member of the basal eudicots in the flowering plants, comprises 15–17 genera of the flowering plants commonly called the barberry family and is apparently monophyletic. This family is distributed in the temperate regions of the northern hemisphere (14). Barberry is the largest genus in the family and contains about 450–500 species of deciduous or evergreen shrubs from 1 to 5 m tall with thorny shoots, native to the temperate and subtropical regions of Europe, Asia, Africa, and North and South America (15).

The genus has two important centers of diversity, Eurasia with about 300 species and South America with about 200 species.

Twenty two alkaloids have been reported so far from root, stem leaves, and fruit of this plant, which are of medicinal importance. As a herbal remedy it has been peerless in serving human race since ancient times (16).

The genus includes several species in Iran, such as *B. integerrima* Bunge, *B. crataegina* DC, *B. vulgaris* L., *B. orthobotrys* Bienert ex, and *B. lycium*. The plant *B. vulgaris* belongs to the Euro-Siberian floristic region and three other species are Irano-Turanian elements. The distribution range of *B. orthobotrys* is restricted to the Alborz Mountains and Kopetdagh-Khorasan (17,18). Various parts of this plant including its root, bark, leaf, and fruit have long been used in folk medicine in Iran. In Iranian traditional medicine several properties, such as antibacterial, antipyretic, antipruritic, and antiarrhythmic activities for different parts of *B. vulgaris* have been reported with unknown mechanisms of actions (19,20). There are phenolic compounds in different parts of berberis including barberry fruit (20).

The aim of this study was to measure minerals in *B. lycium* fruits and to evaluate the effects of its ethanolic extract on levels of cholesterol, TG, high density lipoprotein (HDL), low density lipoprotein (LDL), very low density lipoprotein (VLDL), and malondialdehyde (MDA) in diabetic rats.

Materials and Methods

Animals

For this study, healthy adult male Wistar rats (8 weeks old), weighing 250–275 g, were purchased from Central Animal House, Shahid Beheshti University of Medical Sciences. The animals were kept in individual plastic cages with stainless steel covers (4 animals per cage) and were kept at temperature of 25 ± 2 °C, humidity of $60 \pm 5\%$, and 12-h dark/light cycle. All rats had free access to water and food and fasted overnight before blood and tissue taking (21). The experiments were conducted in accordance with the Guidelines for the Care and Use of Laboratory Animals and the study was approved by Shahrekord University of Medical Sciences Ethics Committee.

Induction of diabetes

Prior to diabetes induction, a group of eight rats was isolated and kept as control in two cages of four each. For

other animals, alloxan monohydrate was used to induce diabetes mellitus. Alloxan (Sigma Co., USA), dissolved in cool saline, was injected through back of the neck, with a dose of 125 mg/kg body weight (BW). The three injections of alloxan were done for each animal in three consecutive days. The alloxan-induced diabetes was confirmed by determining the serum glucose levels in the blood taken from the animals' tails using glucosometer (22). Animals with blood glucose above 300 mg/dl were considered diabetic and included in the study. For the animals in control group distilled water was injected subcutaneously.

Experimental design

In this experiment research, 40 male Wistar rats were used. Animals were divided into five equal groups, with 8 rats in each group, as follows:

Group I, healthy control rats; group II, diabetic control rats; group III, positive control rats under metformin treatment (150 mg/kg); group IV, diabetic rats under treatment with *Berberis lycium* fruit extract (200 mg/kg); and group V, diabetic rats with *Berberis lycium* fruit extract (600 mg/kg). Extract fruits and drug were given orally by gavage for 42 days.

Preparation of the plant

Berberis lycium fruits was purchased from reputable stores in Shahrekord. The genus and species of the *Berberis lycium* was confirmed by the botanists Agriculture Research Center of Shaherkord. The purchased samples were prepared and kept in Medical Plants Research Center Herbarium of Shahrekord University of Medical Sciences, Shahrekord, Iran.

Extraction

For extraction, 250 g dried *Berberis lycium* fruit at one balloon was macerated with 700 ml distilled water for 72 hours. The resulting solution was filtered and

then the alcohol existing in the one solutions was evaporated by rotary machine (23). Then, it was dried in incubator at 37 °C.

Animals' treatment

The animals were under treatment for 42 days. For healthy and diabetic control groups distilled water, for positive diabetic control metformin, for the fourth and fifth diabetic groups *Berberis lycium* extract in respectively 200 and 600 mg/kg dose was used daily.

Collection and storage of samples

After 42 days of the study, the animals were anesthetized by chloroform blood samples were collected heart. Serum (plasma) was isolated by centrifugation of blood samples at 3000 rpm for 10 minutes. All samples were stored at 4 °C until analysis.

Biochemical analysis

Lipid profile was measured using a diagnostic commercial kits (Pars Azmoon, Iran), and total cholesterol, triglyceride, LDL, HDL, VLDL using autoanalyzer and MDA using HPLC (24).

Statistical analysis

The data were analyzed by ANOVA and Tukey tests using SPSS software version 16.0 to determine the statistical significance of data obtained from study groups. $P < 0.05$ was considered significant.

Results

The results of the study indicated that Iron (Fe) level in *Berberis lycium* fruit was considerably high (Table 1) and *Berberis lycium* fruit extract reduced the plasma lipid levels and reversed to normal levels in rats (Table 2).

Total cholesterol, triglyceride, LDL, MDA, and VLDL values increased significantly ($p < 0.05$) in diabetic rats and

Table 1. Minerals in *Berberis lycium* fruit.

Mineral	Mn mg.kg ⁻¹	Cu mg.kg ⁻¹	Zn mg.kg ⁻¹	Fe mg.kg ⁻¹	Cd mg.kg ⁻¹	Mg %	Ca %	K %	P %	N %
<i>Berberis lycium</i>	58.67	33.50	27.50	2649.99	1.67	0.541	0.155	1.056	0.280	1.326

Table 2. Lipid profile and malondialdehyde in groups following 42 days usage of *Berberis lycium* fruit extract or metformin.

Groups	Total chol.(mg/dl)	TG (mg/dl)	LDL (mg/dl)	HDL (mg/dl)	VLDL (mg/dl)	MDA (μM)
Group 1	82.00±3.02	93.25±3.08	17.87±0.29	76.37±3.28	18.65±0.61	5.28±0.30
Group 2	118.50±5.15	135±2.90	27.50±0.53	40.62±2.03	27.05±0.58	19.08±2.39
Group 3	104.25±4.33	84.00±2.84	22.75±0.79	58.87±3.56	16.80±0.56	18.99±1.16
Group 4	101.25±5.08	116.75±1.30	22.37±1.13	37.62±2.24	23.35±0.26	19.15±0.90
Group 5	84.00±5.09	100.00±4.66	21.12±0.93	48.00±0.56	20.00±0.93	10.73±0.42

Group I, control rats; group II, Alloxan-induced diabetic control rats; group III, diabetic rats given solution of *metformin* in water (150 mg/kg); group IV, diabetic rats with *Berberis lycium* fruit extract (200 mg/kg); group V, diabetic rats with *Berberis lycium* fruit extract (600 mg/kg).

HDL value decreased significantly compared with control rats ($p < 0.05$) (Table 2).

In diabetic rats administered with *Berberis lycium* fruit extract in 600 mg/kg dose, the total cholesterol, triglyceride, LDL, MDA and VLDL values decreased significantly ($p < 0.05$) and HDL value decreased significantly compared with diabetic control rats ($p < 0.05$) (Table 2).

Discussion

In the present study it was observed that extract of *Berberis lycium* fruit had antihyperlipidemic effect in diabetic rats, consistent with the results reported for alloxan-induced diabetic rabbits (19).

In this study, iron in *Berberis lycium* was high. In patients with thalassemia, it is recommended that more attention be paid in consuming *Berberis lycium*.

Berberine is the alkaloid of barberry. Oral administration of berberine in 32 hypercholesterolemic patients for three months reduced serum cholesterol by 29%, triglycerides by 35%, and LDL-cholesterol by 25%. Treatment of hyperlipidemic hamsters with berberine, reduced serum cholesterol by 40% and LDL-cholesterol by 42%, with a 3.5-fold increase in hepatic low-density lipoprotein receptor (LDLR) mRNA and a 2.6-fold increase in hepatic LDLR protein (25). The results of this study showed that barberry's extract reduced lipid profile, consistent with those of Fattahi *et al.* study (20).

Oral administration of *Berberis* extract and berberine to normal and experimental diabetic rats produced a significant reduction in blood glucose levels within 3–7 days of treatment. Significant effects were also observed on the glucose tolerance, glycosylated hemoglobin, serum lipid profiles, and body weight of experimental animals (26). Some studies indicated that berberine exerted protective effects on cardiac dysfunction induced by hyperglycemia and hypercholesterolemia through alleviating cardiac lipid accumulation and promoting glucose transport (27).

A study demonstrated that *Berberis lycium* root bark had anti hyperlipidemic effect on alloxanized rabbits and decreased total cholesterol, triglycerides, and LDL while it increased the HDL level in alloxan-induced diabetic rabbits, partially consistent with our findings. Another study also showed that *Berberis lycium* could have antihyperlipidemic effect (19).

Aqueous extract of *Berberis vulgaris* fruit at amount of 3.5 and 7.5% of drinking water did not exhibit the hypoglycemic and hypolipidemic effects in streptozotocin-diabetic rats during a 6-week treatment. However, the usage of barberry fruit in traditional medicine for the treatment of diabetes should be further studied (28).

In this study the extract has been poured into water and it is not obvious how much extract has been received by animals and how much it has been affected by light and environment.

A study showed the beneficial use of this extract in

traditional medicine, although the total extract had no clear superiority over well-known sulfonylurea drugs. *Berberis integerrima* aqueous extract showed antiglycemic, antilipidemic, and antioxidant effects in alloxan-induced diabetic rats (29), in agreement with the results of our study.

Various pharmacological studies reported support *Berberis lycium* traditional use and may be useful in the development of some commercial drugs. Moreover, the nutritional properties such as high content of vitamins, minerals, and anthocyanin of *Berberis lycium* have added to its value. The fruits of the plant are also very nutritious and rich in vitamins, minerals, antioxidants, anthocyanin, etc. (30), which is somehow consistent with our study. The aim of the present study was to evaluate the effects of extract fruit *Berberis lycium* on various lipid profiles in alloxan-induced diabetic rats. Oral administration of 200 mg/kg and 600mg/kg extract fruit of *Berberis lycium* for six weeks resulted in significant reduction in total cholesterol, triglyceride, and LDLs levels. *Berberis lycium* treatment increased the levels of HDLs. Thus, our investigation clearly shows that extract fruit of *Berberis lycium* has antihyperlipidemic effect.

Conclusion

The present investigation showed that the *Berberis lycium* fruit extract reduced the plasma lipid levels and reversed to normal levels in rats. Thus, our investigation clearly shows that extract fruit of *Berberis lycium* has antihyperlipidemic effect in hyperlipidemic patients and might be useful in these patients. It may also be useful in iron deficiency.

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Authors' contributions

All the authors wrote the manuscript equally.

Conflict of interests

The authors declared no competing interests.

Ethical considerations

Ethical issues (including plagiarism, misconduct, data fabrication, falsification, double publication or submission, redundancy) have been completely observed by the authors.

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