European Journal of Integrative Medicine 32 (2019) 100998

Contents lists available at ScienceDirect

European Journal of Integrative Medicine

journal homepage: www.elsevier.com/locate/eujim

Clinical trial

Randomised clinical trial of *Berberis vulgaris* root extract on glycemic and lipid parameters in type 2 diabetes mellitus patients

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ARTICLE INFO

Keywords:
Berberis vulgaris
Type 2 diabetes mellitus
Fasting blood sugar (FBS)
Lipid profile
Randomized controlled trial

ABSTRACT

Introduction: Diabetes Mellitus is a chronic metabolic disorder and has continued to increase worldwide, from 135 million in 1995 to 300 million in the 2025. Nowadays, the use of medicinal plants is increasing worldwide. Among effective medicinal plants, *Berberis vulgaris* L. (family Berberidaceae) has shown to be capableof lowering glucose. The aim of the present study was to investigate the effect of *B. vulgaris* root extract on blood glucose and lipid profile levels in a double-blind, placebo-controlled clinical trial of patients with type 2 diabetes.

Method: The participants were divided randomly to two groups, an intervention and placebo control group. Both groups continued using their current oral hypoglycemic medication in addition to either taking the extract or placebo capsules for 6 weeks.

Results: Compared to the placebo group, the changes in fasting blood sugar (FBS), fructosamine, fasting insulin and Homeostasis Model Assessment-Insulin Resistance (HOMA-IR) were significantly improved for the intervention group ($p < 0.05$). At the end of the study, total cholesterol and low density lipoprotein in the intervention group decreased to 9.44% and 8.65%, respectively.

Conclusion: Our findings demonstrated that *B. vulgaris* may be regulating the glucose metabolism and lipid profile in patients with type 2 diabetes and has no important side effects.

1. Introduction

Diabetes Mellitus, a chronic metabolic disorder, continues to increase worldwide, from 135 million in 1995 to 300 million in 2025 [1]. Although the prevalence of type 1 and type 2 diabetes is increasing worldwide, type 2 diabetes is escalating at a faster rate [2]. This might be due to the increase of obesity and the overall ageing of societ or poor physical activity [2]. More than 8.69% of total health costs are spent trying to control diabetes in Iran. Moreover diabetes imposes intangible costs to the society by reducing quality of life [3]. The initial recommended treatment for diabetes is diet and exercise [4]. If the recommended changes of life style do not show any improvement in the overall health of the patient, the next step is the use of anti-diabetic agents [4]. These agents have different mechanisms of action such as stimulating insulin secretion, inhibiting gluconeogenesis, increasing the number of glucose transporters and decreasing absorption of glucose via intestine [4,5]. The available anti-diabetic agents have limitations in the treatment of chronic diabetes disease. Besides these drugs show a number of serious side effects. So, managing diabetes is still a challenge [6]. Nowadays, the use of medicinal plants is increasing worldwide, clinical trials and safety assessement is required. The results of these studies can be used to guide future pharmaceutical formulations. Among the effective medicinal plants, genus of *Berberis* has shown capability for lowering glucose [7,8]. Barberry (*Berberis vulgaris* L.) belongs to the family Berberidaceae which grows in Asia and Europe [9]. *B. vulgaris* is a spiny shrub, the height of about 1–3 m, with yellow wood and obovate leaves, yellow flowers and red fruits [9]. Different parts of barberry have been used in Iranian traditional medicine for various therapeutic effects [9] and the fruits of barberry have been used as food ingredient in Iranian dishes [9,10]. Some studies have reported that *B. vulgaris* was used as an anti-arrhythmic and sedative agent in Persian medicine [11].

The main components of barberry are isoquinoline alkaloids such as berberine, berbamine and palmatine [9]. In some studies berberine

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https://doi.org/10.1016/j.eujim.2019.100998
Received 24 January 2018; Received in revised form 14 October 2018; Accepted 23 October 2019

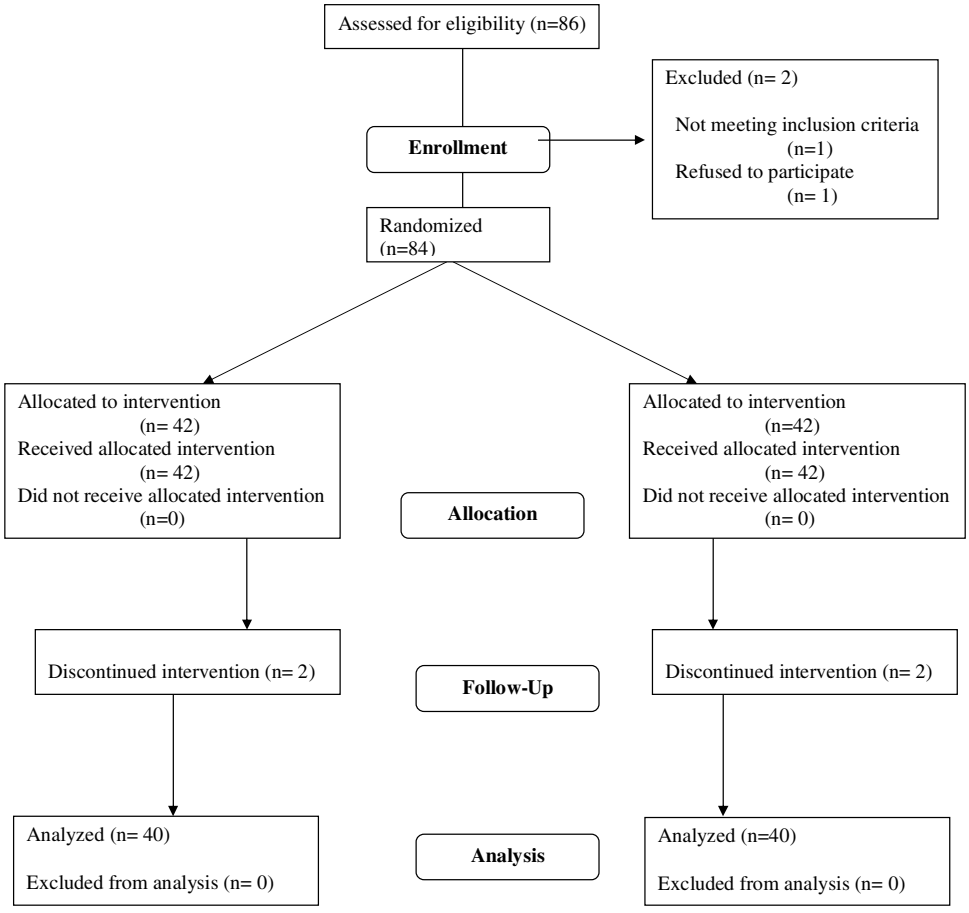

Fig. 1. The flow chart of participants through each stage of the randomized trial.

showed different pharmacological effects [9,12,13]. Berberine is quaternary ammonium salt that is highly concentrated in the roots and stem bark of *B. vulgaris* [10,14]. Berberine affects glucose metabolism by inhibiting carbohydrate hydrolyzing enzyme and decreasing intestinal glucose absorption [15]. Berberine increases glucagon like peptide-1 (GLP-1) level, therefore decreases pancreatic B cell apoptosis [16]. Some research has indicated that berberine reduces insulin resistance [12].

Previous studies pointed out the lipid lowering effect of berberine [8,12]. Berberine has been shown to be safe in the majority of clinical trials [17]. In a few patients, berberine has been reported to cause nausea, vomiting, constipation, hypertension, respiratory failure and paresthesia. However, clinical evidence of such adverse effects is not prominent [16].

The aim of present study was to investigate the effect of hydro alcoholic extract from *B. vulgaris* root on blood glucose and lipid profile levels of type 2 diabetes patients. This was a randomized, double-blind, placebo-controlled clinical trial.

2. Materials and methods

2.1. Plant material

The *B. vulgaris* roots were collected from South Khorasan, Iran. The voucher specimen of plant (JPS018117) was deposited in the herbarium of the Faculty of Pharmacy, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran.

2.2. Preparation of extract and placebo capsules

B. vulgaris hydro alcoholic root extract was prepared by the maceration method, using ethanol 80% for 72 h at room temperature. Then the extract concentrated by rotary evaporator, and dried with freeze-drying technique. The extract stored at 4 °C until required.

Wheat flour was used as placebo. It was colored with food colors in order to look the same as the herbal extract. The herbal extract and the placebo powder were put in 500 mg capsules by capsule filling instrument. Each container was packed with 50 capsules.

2.3. Patients

84 newly diagnosed type 2 diabetes mellitus (T2DM) patients in the range of 20–65 years old were enrolled in the study. This study was conducted in the Golestan hospital, Ahvaz, Khouzestan province, Iran between October 2014 and May 2015

Inclusion criteria: Age 20–65, newly diagnosed type 2 diabetes according to the American Diabetes Association criteria (2011), hemoglobin A1c (HbA1c) < 8.5%, fasting blood sugar (FBS) < 200, less than 1 year of diabetes diagnosis, and the patients only used oral hypoglycemic medicine for treatment.

Exclusion criteria: Triglyceride (TG) > 500, pregnancy, use of any antiplatelet drugs such as plavix or warfarin except aspirin, any chronic liver disease except fatty liver disease, heart failure, hemorrhagic stroke, renal insufficiency Creatinine Cr >1.5 in men and Cr>1.4 in women, hypothyroidism and hyperthyroidism.

At the beginning, the patients underwent initial tests include: blood pressure and waist to hip ratio. Besides the blood sample was taken in order to be used for following laboratory tests:

Table 1
Baseline data of study population.

Variable	Treatment group n = 40	Placebo group n = 40	P-value
Gender	Male:17 Female:23	Male:15 Female:25	0.34
Age (years) [a]	54.05 ± 8.00	53.07 ± 7.741	0.23
Fasting blood sugar (FBS)[a]	147.35 ± 29.70	134.05 ± 45.15	0.12
Fructosamine [a]	347.38 ± 112.50	344.78 ± 135.60	0.93
2hpp [a]	237.85 ± 84.83	232.95 ± 78.21	0.79
Systolic blood pressure (SBP) [a]	12.13 ± 1.06	12.33 ± 1.79	0.54
Diastolic blood pressure (DBP)[a]	7.68 ± 0.76	8 ± 1.06	0.12

[a] Data are presented as mean ± SD.

FBS, Glucose, 2 h post prandial plasma glucose (2hpp), fructosamine, triglyceride (TG), Total cholesterol (TC), low density lipoprotein (LDL), high density lipoprotein (HDL), very low density lipoprotein (VLDL), blood urea nitrogen/serum creatinine (BUN/CR), aspartate aminotransferase (AST), alanine aminotransferase (ALT), fasting insulin (FI), Homeostasis Model Assessment-Insulin Resistance (HOMA-IR), HOMA-B%.

After 6 weeks that patients received placebo or *B. vulgaris* root extract capsules the all the above tests were repeated.

2.4. Study design

This study was a double-blind, randomized, controlled clinical trial that was conducted for six weeks. The clinical trial was approved by Ahvaz Jundishapur University of Medical Sciences Ethics Committee (ajums.REC.1392.285). In addition, the trial was registered in the Iranian Registry of Clinical Trials under the number IRCT201504264610N3. The patients diagnosed with T2DM in according to the American Diabetes Association criteria were enrolled. All patients were blinded to the treatment they received. Patients received a full explanation of the study and provided their written informed consent to participate in this study. A physician prescribed capsules (extract or placebo) to the patients according to the label numbers. The pharmacist was the only one who was aware of the numbers assigned to the *B. vulgaris* extract or placebo.

The participants were divided randomly to two groups. Random group assignments were done using a simple random allocation strategy, using a block randomization method. Fig. 1 shows the flow of participants through each stage of recent randomized trial.

Both groups continued using their oral hypoglycemic medications as prescribed by their physician. In addition to take extract (intervention) or placebo capsules for 6 weeks as a complementary preventive treatment. The patients used the extract or placebo twice daily after meal that patients received 1000 mg dry extract and 157.3 mg berberine per day.

All participants of both groups were instructed to record the onset of any side effects in a personal daily diary, with the specific description of their symptoms (including diarrhea, nausea, vomiting, abdominal pain, dizziness, depression, back pain, pruritus, erythematous rash, increased sweating, paraesthesia, anorexia, insomnia, nervousness, dry mouth, gastroenteritis and menstrual disorder).

2.5. Determination of the amount of active ingredient

The standard solutions of berberine in methanol were prepared by a serial dilution method (15.62, 7.8, 3.9, 1.9, 0.97 g/ml). The absorbance was detected by spectrophotometer in 346 nm, and the calibration curve was plotted. A standard solution of root extract powder in methanol was prepared and its absorption was detected at 346 nm. The berberine content of root extract was calculated. Each test was repeated three times [18].

2.6. Data analysis

Sample size calculations were based on the previous studies [17]. The data are expressed as mean ± standard deviation. Comparison between each group at baseline and after 6 weeks treatment analyzed by paired-sample t- test. Comparison between the placebo and the drug group analyzed by ANCOVA method, using SPSS version 22.

3. Results

In this randomized, double-blind, placebo-controlled study, the effect of hydro alcoholic extract from *B. vulgaris* root was examined in 80 type 2 diabetes patients. The evaluated items were glycemic, lipid and renal biochemical parameters, hepatic enzymes, waistline, systolic blood pressure (BP) and diastolic blood pressure.

The yield of *Berberis vulgaris* root extract was determined as 12%. Berberine content of *B. vulgaris* root in reference to the calibration curve ($y = 40.909x + 0.0165$, $R^2 = 0.9997$) was 157.3 mg / 1 g dry extract. Barberry root extract capsules are standardized based on berberine content. Each capsule contains 500 mg dry residue and 78.65 mg berberine.

Table 1 shows the characteristics of the study population. There were 23 female and 17 male patients in the intervention group and 25 female and 15 male in the control group. The average age of patients in the group receiving extract was 54.05 ± 8.006 and the average age of patients receiving placebo was 53.07 ± 7.741. There were no significant differences between patients in terms of age or gender in the intervention and placebo groups ($p > 0.05$). 84 patients enrolled in this study. Two patients failed to complete the study in the intervention group, two patients also did the same in the placebo group. The reasons for discontinuing included failure to follow up or noncompliance.

The remaining 80 patients successfully completed the 6-weeks treatment with *B. vulgaris* or placebo and were included in this analysis. The baseline parameters did not show any statistically significant difference between the intervention and control groups ($p > 0.05$) (Table 1).

Participants did not report any important side effects. However two patients complained of heartburn. The level of FBS before and after treatment with *B. vulgaris* was 147.35 ± 29.70 vs. 129.95 ± 33.39 ($p = 0.011$). The level of fructosamine before and after treatment with herbal extract was 347.38 ± 112.50 vs. 321.43 ± 117.60 ($p = 0.004$), showing a significant reduction. Compared to the placebo group, the changes in FBS, fructosamine, fasting insulin and HOMA-IR after intervention in the intervention group was also significant ($p < 0.05$) (Table 2). In the placebo group, after intervention, the changes of glycemic parameters were not significant ($p > 0.05$).

In the intervention group, at baseline, serum TG, TC, HDL and LDL were 141.5 ± 55.92, 177.13 ± 34.44, 45.5 ± 10.18 and 94.78 ± 30.12, respectively. Regarding the lipid profile, *B. vulgaris*

Table 2
The changes in FBS, 2HPP, fructosamine, fasting insulin, HOMA-IR and HOMA.B% after intervention in the placebo and treatment groups.

Variable	Placebo group	Treatment group	p-value
FBS[a]	140.48 ± 45.651	129.95 ± 33.390	0.013*
2HPP[a]	205.45 ± 78.110	223.65 ± 77.848	0.221
Fructosamine[a]	345.68 ± 144.796	321.43 ± 117.596	0.047*
Insulin[a]	14.6658 ± 7.9858	9.4913 ± 3.8440	0.009*
HOMA-IR[a]	4.6143 ± 2.9167	3.2143 ± 1.5938	0.011*
HOMA.B%[a]	80.0469 ± 51.024	63.1102 ± 42.674	0.17

[a] Data are presented as mean ± SD.
* $P < 0.05$.

Table 3
The changes in different parameters after intervention in the placebo and treatment groups.

Variable	Placebo group	Intervention group	p-value
TG[a]	145.4 ± 85.361	140.05 ± 72.10	0.58
TC[a]	170.8 ± 35.35	160.4 ± 33.89	0.003*
HDL[a]	47.03 ± 9.678	47.88 ± 7.881	0.02*
LDL[a]	94.68 ± 29.849	86.58 ± 25.409	0.003*
VLDL[a]	29.08 ± 17.05	28.31 ± 11.17	0.59
GOT[a]	25.75 ± 15.11	22.85 ± 8.03	0.36
GPT[a]	23.03 ± 9.020	22.45 ± 8.031	0.93
ALP[a]	227.21 ± 92.34	226.77 ± 73.17	0.94
sys BP[a]	12.28 ± 1.48	11.95 ± 1.24	0.37
Dia BP[a]	7.99 ± 1.12	7.55 ± 0.99	0.30
Waistline[a]	0.97 ± 0.05	0.9503 ± 0.05	0.31
Cr[a]	0.85 ± 0.23	0.86 ± 0.18	0.84
BUN[a]	14.50 ± 4.03	14.13 ± 3.57	0.91

[a] Data are presented as mean ± SD.
* $P < 0.05$.

extract significantly reduced TC and LDL to 160.4 ± 33.89 and 86.58 ± 25.40, respectively. Moreover it significantly increased HDL to 47.88 ± 7.89. While, in the placebo group, at the baseline and at the end of the study, TC was 159.6 ± 34.40 vs. 170.8 ± 35.35 ($p = 0.002$). It clearly showed a significant increase. The intervention group in comparison to the control group, showed significant changes in TC, LDL and HDL ($p = 0.003$, $p = 0.003$ and $p = 0.019$ respectively). In the intervention group TG reduced to 140.05 ± 72.99 but it was not statistically significant. While in the placebo group, TG increased to 145.4 ± 85.36. In the interevntion and control group, the level of hepatic enzymes included glutamic oxaloacetic transaminase (GOT), glutamic-pyruvate transaminase (GPT) and alkaline phosphatase (ALP) and did not change statistically after treatment. There were no significant changes in GOT, GPT and ALP in intervention group as compared to the control group. The renal biochemical parameters, Cr and BUN, did not show any statistically significant difference between the interventionand control groups after the intervention. Also, there were no significant changes in Cr and BUN in the intervention group as compared to the baseline.

Treatment with *B. vulgaris* did not modify waistline, systolic blood pressure (BP) and diastolic blood pressure (Table 3).

4. Discussion

In the present clinical trial, all patients were previously treated with oral hypoglycemic medications. By enrolling in this study, they also received barberry extract as an adjunct to their treatment. During 6 weeks treatment FBS and fructosamine in the intervention group reduced by 11.81% and 7.47% respectively, representing a reduction of more than 10% in FBS. At the end of the study, TC and LDL in the case group decreased by 9.44% and 8.65% respectively, indicating that *B. vulgaris* reduced TC by approximately 10% during the trial period. After treatment with *B. vulgaris* extract, HDL increased to 5.23% while in placebo group it was increased to 3.86%. Compared to the placebo group, the increase in HDL in the intervention group was significant ($p = 0.019$). After intervention, TG reduced by 1.02% in the group receiving *B. vulgaris* but it was not statically significant. While in placebo group, TG increased to 6.73%. The reduction in glycemic and lipid parameters over 6 weeks attests to the clinical effect of *B. vulgaris*.

Berberine shows its effect in diabetes treatment through different mechanisms acting as: an AMP-activated protein kinase (AMPK) activator, an inhibitor of mitochondrial function, or in stimulating glycolysis and insulin secretion, and improving insulin function [10,15]. Also, the hypoglycemic effect of berberine may be related to the inhibition of α-glucosidase enzyme and reduce glucose absorption from the intestine [15]. There are several clinical trials that showed hypoglycemic effect of berberine [8,13,15,17]. These studies confirmed berberine's ability to decrease fasting blood glucose (FBG) and Hemoglobin A1c (HbA1c) level in patients with type 2 diabetes [13,15,17]. Furthermore, berberine reduced the plasma triglycerides, total cholesterol and low-density lipoprotein (LDL) [12,13,17].

In a previous clinical trial, 36 patients with type 2 diabetes randomly received berberine or metformin (1.5 g/day) for 3 months. The

Table 4
The comparison of results from present and previous studies of berberine effect on glycemic, lipid and biochemical parameters.

Authors	Derosa G. et al.[21]	Di Pierro F. et al.[7]	Shidfar F. et al.[8]	Moazezi Z. et al.[10]	Yin J. et al.[13]	Zhang Y. et al.[17]	Present study
Plant or compound	*Berberis aristata* and *Silybum marianum*	*B. aristata* and *S. marianum*	*B. vulgaris*	*B. vulgaris*	Berberine	Berberine	*B. vulgaris*
Year	2013	2013	2011	2014	2008	2008	2014
Country	Italy	Italy	Iran	Iran	China	China	Iran
Number of patients	105	69	31	30	36	116	84
Daily dose	1176 mg *B. aristata* and 210 mg *S. marianum*	1176 mg *B. aristata* and 210 mg *S. marianum*	3000 mg fruit extract	1000 mg fruit extract	1500 mg berberine	1000 mg berberine	1000 mg root extract
Treatment time	3 months	4 months	3 months	8 weeks	3 months	3 months	6 weeks
FBS	SR[1]	SR	SR	SR	SR	SR	SR
2HPP	ND[2]	ND	ND	ND	SR	SR	No SR
Fructosamine	ND	SR	No Ch[4]	SR	SR	SR	SR
Insulin	SR	ND	SR	ND	SR	No SR	SR
HOMA-IR	SR	ND	SR	ND	SR	No SR	SR
HOMA.B%	ND	ND	ND	ND	ND	ND	No SR
TG	SR	SR	SR	ND	ND	SR	No SR
TC	SR	SR	SR	ND	SR	SR	SR
HDL	SI[3]	ND	No Ch	ND	ND	ND	SI
LDL	SR	SR	SR	ND	SR	SR	SR
GOT	ND	SR	ND	ND	ND	ND	No SR
GPT	ND	SR	ND	ND	ND	ND	No SR
ALP	ND	ND	ND	ND	ND	ND	No SI
Cr	ND	ND	ND	ND	ND	ND	No SR
BUN	ND	ND	ND	ND	ND	ND	No SI

[1] Significant reduction.
[2] Not determined.
[3] Significant increasing.
[4] No change.

results are shown in Table 4 [13].

It has been reported that berberine has poor bioavailability and low intestinal absorption. P-glycoprotein in normal intestinal epithelia could limit the intestinal absorption of berberine which suggests that berberine absorption is improved by using the P-glycoprotein inhibitors [19].

According to the previous studies, silymarin, derived from *Silybum marianum*, could be considered as a P-glycoprotein inhibitor [7,20]. In some studies the effect of combination of *Berberis aristata* and *S. marianum* extracts on blood glucose and lipid profile levels were investigated. The results of these studies are shown in Table 4 and were compared with present study [7,21].

In another clinical trial, the efficacy of combination of *B. aristata* (1176 mg/day) and *S. marianum* (210 mg/day) on glycemic and lipid profile in 137 patients with previous adverse effect to statins at high doses was studied. The reduction of FBS, insulin and HOMA-index levels were significant during 6 months treatment with *B. aristata/S. marianum*. After treatment since the reduction of statin dosage, *B. aristata/S. marianum* did not reduce TC, LDL and TG significantly while lipid profile increased in placebo group. Also, in our study, *B. vulgaris* reduced TG but not statistically significant [22].

In other studies, the effect of *Berberis* fruit extract in patients with type II diabetes was investigated. The results showed significant reduction in FBS and HbA1c level after intervention (Table 4) [8,10].

5. Conclusion

In conclusion, our findings demonstrated that *B. vulgaris* may be regulating glucose metabolism and lipid profile in patients with type 2 diabetes with no important side effects. Extract of *B. vulgaris* root showed significant promise for its efficacy in the reducing glycemic and lipid parameters in type 2 diabetes. *B. vulgaris* and berberine are safe that could be introduced as new drugs for the treatment of type 2 diabetes. Since this is a small study, these findings need to be confirmed in a much larger population of diabetic patients.

Declaration of Competing Interest

The authors declare that there is no conflict of interest.

Acknowledgement

This research was supported by Ahvaz Jundishapur University of Medical Sciences (Grant number MPRC-40).

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