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The Effects of Active Ingredients of Barberry Root (Berberine) on Glycemic Control and Insulin Resistance in Type 2 Diabetic Patients

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Abstract

Background: Diabetes mellitus is one of the most common metabolic diseases in the world. Recently, willingness to use alternative treatments to control and reduce blood sugar levels has noticeably increased. The general objective of this study is to investigate the hypoglycemic effect of the active ingredient of Berberis (Berberine) in patients with type 2 diabetes.
Methods: In this double-blind randomized controlled placebo trial, 84 patients with type 2 diabetes were evaluated. The patients were divided in 2 groups (42 each). In addition to their previous drugs, new diet, and life style each group received Berberine capsules 500 mg or placebo twice daily for 4 weeks. At baseline, weight, height, blood pressure, and BMI were calculated for all patients. Fasting plasma glucose, post- meal plasma glucose, fructosamine, lipid profile, fasting blood insulin levels, BUN, creatinine, and liver enzymes were taken from all patients before the study and after 4 weeks. HOMA-IR and HOMA-β% were calculated.
Results: After administration of Berberine for a month, average blood sugar (FBS) in the Berberine group decreased from 192 $\pm$ 59.6 to 167.7 $\pm$ 51.8, which was statistically significant compared with the results of the placebo group (P = 0.036). There was a significant decrease from 266.1 $\pm$ 93.7 mg dl to 222.5 $\pm$ 76 in 2HPP in the Berberine group compared with the placebo group (P = 0.001). There was also a significant decrease from 425.7 $\pm$ 139.7 micromoles per liter to 344.9 $\pm$ 126.1 micromoles per liter in fructoseamine in the Berberine group compared with the placebo group (P = 0.014). In addition, fasting insulin, HOMA-β%, and HOMA-IR increased in the Berberine group compared with the placebo group, however, this increase was not statistically significant. There was a significant decrease in LDL, TG, VLDL in the Berberine group, however, it was not lower than that in the placebo group. Also, total cholesterol in the Berberine group decreased insignificantly compared to the placebo group. There was no significant difference between the 2 groups in terms of BMI, systolic, and diastolic blood pressure.
Conclusions: The results showed taking Berberine in patients with type 2 diabetes for 1 month significantly reduces the fasting plasma glucose, post- meal blood glucose, and fructosamine. No signification changes were found in lipid profiles, fasting insulin, HOMA-IR, and HOMA-β%.

Keywords: Type 2 Diabetes Berberine (Berberine), Barberry (Berberis. Vulgaris), Fructosamine

1. Background

Diabetes mellitus is one of the most common metabolic diseases in the world and it results from impaired insulin secretion, insulin resistance, and increased hepatic glucose output (1, 2).

Diabetes mellitus is a major cause of cardiovascular diseases, end-stage renal disease (ESRD), nontraumatic lower-limb amputations, and blindness in adults in the United States. With the increasing incidence of diabetes worldwide, it is expected that the disease remains a leading cause of morbidity and mortality (3).

Global prevalence of diabetes mellitus has increased dramatically over the past 2 decades from about 30 million in 1985 to 285 million in 2010. International diabetes federation predicts more than 438 million people will have diabetes until 2030 (3). The prevalence of diabetes in the general population is estimated to be from 2% to 3% in and in people over 30 years, it is 3.7%. At present, the prevalence of diabetes in different regions of Iran is estimated to be between 3.1% and 5.14% (4-6).

According to a survey conducted in 1999, the death rate from diabetes in 4 provinces of Iran (Eastern Azerbaijan, Bushehr, Chahar Mahal Bakhtiari and Semnan) was estimated to be 272 people for every 10000 persons. Another study in 2002 showed that approximately 100000 people

have lost their lives due to diabetes and its related complications (7).

Most of the deaths attributed to diabetes are induced by cardiovascular complications. Direct and indirect costs of diabetes and its complications are very high in comparison with other diseases (7).

The use of plants as medicine has a history of several thousand years (8). Diet and alternative therapies not only improve blood glucose control and prevent diabetes complications but also reduce the cost of treatment, in many cases type 2 diabetes as well (9).

One plant, which has played a prominent role in herbal remedies for more than 2500 years, is barberry. Barberry (family Berberidaceae) is well known in different parts of the plant, including roots, bark, leaves, and fruit have been used as folk medicine. Two decades of research have shown the effects of pharmacological treatment of barberry (Berberis. Vulgaris) and its alkaloids (especially Berberine). Studies on the chemical composition of this plant show that its main ingredients are alkaloids (Isoquinoline) such as berberine, berbamine, and palmatine. Among the alkaloids of protoberberine), berberine has attracted more scholarly attention and been used in the treatment of different diseases (10).

Berberine alkaloid is crystallized as yellow needle shaped crystals. The taste is very bitter. It is dissolved slightly in cold water but largely in hot water and alcohol. Its melting point is 145 degrees (10).

Berberine not only exists in Barberry leaves, bark, and wood, but is also found in other varieties of plants (11).

According to the traditional use of barberry plants and the limited studies on the anti-diabetic therapeutic properties of this plant in Iran, the present study was aimed to investigate the effect of Berberine on type 2 diabetic subjects.

2. Methods

This study was a double blinded, randomized control - placebo study. The participants were patients aged 30 - 65 with type 2 diabetes treated with oral hypoglycemic agents at Ahvaz Golestan hospital outpatient clinic. Written informed consent was taken from all participants. Ethical code: ETH705

Inclusion criteria:

1- Age 30 - 65 years old

2- Glycosylated hemoglobin: 7% - 8.5%

3- FBS: 126 - 200

4- Diabetes history of less than 10 years

Exclusion criteria:

1- Triglycerides $\geq$ 500

2- Diabetes diagnosed for more than 10 years

3- Pregnancy

4- Taking anticoagulants, such as Plavix, warfarin etc. (except for aspirin)

5. Chronic liver disease except for fatty liver disease

6- Advanced diabetic retinopathy

7- Nephropathy (Macroalbuminuria, kidney failure)

8- Heart failure

9- Hemorrhagic stroke

12- Hyperthyroidism and hypothyroidism

13- Insulin treatment

Diagnosis of diabetes was based on the ADA (American diabetes association) 2017 criteria.

All patients continued their previous anti-diabetic medications during the study period. In order to improve lifestyle and diet, the participants were given the necessary training. In addition, the patients were required not to take other supplemental vitamins or minerals during the study.

The subjects were allocated into 2 groups by balance block randomization.

Type II diabetic patients with poor control treated with oral glucose-lowering medicine were selected based on the exclusion and inclusion criteria and after obtaining their consent.

At baseline, weight, height, blood pressure, and BMI were calculated for all patients and their blood samples were tested for fasting blood sugar, post-meal blood glucose and fructosamine, lipid profile (HDL, LDL, Chol, TG), insulin fasting plasma, BUN, creatinine, the liver enzymes (AST, ALT, ALK), and then indexes HOMA-IR (homeostatic model assessment insulin resistance), HOMA-β% (homeostatic model assessment βcell function) based on fasting blood glucose, and fasting serum insulin were calculated.

After 2 weeks, the medication boxes were checked and any non-medical drug use was identified. At the end of the 4th week the same tests and measurements were repeated and the data were analyzed and compared.

Berberine (the active ingredient in Barberry root) was prepared from wheat flour with permitted color additives in 500 mg placebo capsules similar to Berberine powder in similar capsules and encoded by a fellow pharmacist.

To control the inclusion criteria, the initial visit was performed by the assistant of the project manager. A total of 84 type 2 diabetic patients who met the inclusion criteria were included in the study. The encoded drug prepared by a fellow pharmacist was delivered to the assistant of the project manager who was unaware of the coding approach. The drugs were administered to the patients by the assistant of the project manager through the Block method and according to the prepared list. The patients were divided into 2 groups through quadruple random-block method. A total of 42 patients were treated with 500

mg of Berberine herbal capsules twice a day i.e. every 12 hours in addition to their usual drugs, and adopting a new diet and life style. The other 42 patients were treated with 500 mg placebo capsules twice a day i.e. every 12 hours, in addition to their usual drugs, and adopting a new diet and new life style. These drugs were given to the patients for 4 weeks.

2.1. Statistical Methods

The statistical method used in this study was Intention-to-treat. The t-test was used to compare the studied factors of both groups. However, paired t-test was used to compare pre and post intervention indices.

3. Results

A total of 84 type 2 diabetic patients participated in this study in 2 groups of 42 members. During the study, 2 cases of Berberine group and 1 case of placebo group were excluded from the study since they had failed to cooperate appropriately with the research team. The average age of the case group was 50.18 $\pm$ 4.22 while that of the control group was 45.12 $\pm$ 9.55. Also, 35%of the case group was male and 65% was female, while in the control group (placebo group), the proportion was 45.5% versus 58.5%, respectively. There was no significant difference between Berberine and placebo groups. No important side effect was seen in both groups. Two cases of Berberine group became feeble, however, they felt better after taking sugar substances.

As seen in Table 1, the following indices showed significant differences in the Berberine group: HOMA.β%, 2hpp, FBS, LDL, HDL, ALK, Fructosamine, and BUN while the following indices showed no significant difference in the placebo group: Fructosamine, HDL, CHO, Cr, HOMA.β%, and BMI. As can be seen, FBS decreased significantly in the case group (P = 0.001) while the decrease was not significant in the control group (placebo cases) (P = 0.3). The comparison of Δ FBS (mean changes of FBS) in both groups reveals that the decrease of FBS in the Berberine cases was significant compared with the placebo cases (P = 0.036).

In the Berberine cases, receiving Berberine decreased FBS by 24 units while in the placebo cases, receiving placebo decreased FBS by only 6%. This difference was significant (P = 0.036). However, in the case group, 2hpp decreased by 44 units while in the placebo group it decreased by only 6%. Again, this difference was statistically significant (P = 0.001) (Table 2).

In the Berberine group (case group), Fructsamine decreased by 80 units while in the placebo cases it decreased by 35 units. This implies that Fructsamine decreased in the Berberine cases twice as much as that in placebo cases and this difference was significant (P = 0.014).

As far as Fasting Insulin Level, Homa-β% and Homa-IR were concerned, there was no significant difference in both groups.

The comparison of lipid profiles between the 2 studied groups showed that there was a 2 time decrease in LDL and a 3 time reduction in TG among the Berberine cases compared with the placebo cases, however, the differences were not significant. Other factors, showed no significant difference (Table 3).

In the Berberine cases, taking Berberine decreased ALK by 18 units while the decrease in the placebo cases was only 6 units; this difference was significant. However, the changes of ALT and AST levels were significant in both groups (P = 0.007) (Table 4).

In the Berberine cases, receiving Berberine decreased BUN by 3.5 mg.dL, while the decrease in the placebo cases was 0.05 mg.dL, and the difference was significant (P = 0.007). However, Cr change was not significant in both groups (P = 0.35) (Table 5).

4. Discussion

Berberine has recently been shown to have glucose-lowering effects. In patients with poor beta-cell function, berberine may improve insulin secretion through restoring beta islets (11). It has also been reported to mimic insulin function (12). Berberinee may also act as an alpha-glucosidase inhibitor. It may have additional beneficial effects on cardiovascular complications of diabetes by reducing the cholesterol levels (11).

In the present study, the role of berberine in reducing blood glucose and lipid levels was investigated in 81 diabetic patients who were divided into 2 groups of berberine (n = 40) and placebo (n = 41) with the mean age of 50.18 $\pm$ 9.9 and 45.15 $\pm$ 9.5, respectively.

After a month of berberine consumption, the mean fasting blood sugar decreased significantly, while in the placebo group, mean fasting blood glucose decreased, however, the difference was not significant. Comparing the variations in blood glucose levels in both groups showed that the difference was significant, and in the berberine group, the reduction in blood sugar was approximately 4 times the placebo group.

Fructosamine also decreased in both berberine and placebo groups. Results showed that the decrease in fructosamine in the berberine group was more than twice the placebo group, and the difference was significant (80.8 vs. 35.9 μmol.L).

Table 1. Comparison of Measured Indices in Case and Control Groups Before and After Medical Intervention

Variables	Berberine			Placebo		
	Before	After	P Value	Before	After	P Value
FBS, mg/dL	192 ± 59.6	167.7 ± 51.8	0.001	178.7 ± 50.2	172.2 ± 61.7	0.30
2HPP, mg/dL	266.1 ± 93.7	222.5 ± 76	0.001	237.4 ± 76.4	243.5 ± 94.8	0.49
Fructosamine, μmol/L	425.7 ± 139.7	344.9 ± 126.1	0.0001	414.8 ± 155.7	378.9 ± 126.4	0.014
Fasting Insulin, mg/dL	9 ± 3.2	10.7 ± 5.1	0.08	8.4 ± 5.5	10.1 ± 3.4	0.10
HOMA.IR	4.25 ± 1.9	4.3 ± 1.9	0.8	3.6 ± 2.7	4.3 ± 2.19	0.13
HOMA.ß%	31.2 ± 16.9	45.7 ± 30.1	0.001	35.4 ± 24.1	44.6 ± 35.2	0.017
TG, mg/dL	180.6 ± 137.6	158.2 ± 86	0.12	184.2 ± 86.9	171.5 ± 70.7	0.31
LDL, mg/dL	109.5 ± 38.3	95.07 ± 34.8	0.003	104.5 ± 36.2	97.2 ± 31.6	0.06
Cholesterol, mg/dL	183.2 ± 41.6	172.6 ± 41.2	0.056	183.6 ± 46.9	171.8 ± 45.7	0.027
VLDL, mg/dL	33.6 ± 20	30.6 ± 15.4	0.16	35 ± 12.1	38.6 ± 33.5	0.50
HDL, mg/dL	43.3 ± 8.2	46.6 ± 8.1	0.002	43.5 ± 8	45.6 ± 9.4	0.024
ALT, U/L	17 ± 7.3	16.7 ± 8.2	0.76	16.1 ± 7.9	16.5 ± 6.2	0.65
AST, U/L	22.8 ± 8.4	22.5 ± 7.1	0.73	21.8 ± 6.7	21.7 ± 5.2	0.89
ALKp, mg/dL	233.2 ± 72.7	214.9 ± 66.2	0.0001	199 ± 47.5	192.8 ± 54.2	0.07
Creatinine, mg/dL	0.87 ± 0.18	0.89 ± 0.17	0.33	0.88 ± 0.15	0.91 ± 0.16	0.04
BUN, mg/dL	29.7 ± 9.6	26.18 ± 8.25	0.0001	27.7 ± 7	27.6 ± 7.6	0.95
BP: Systolic, mmHg	136.5 ± 21.7	133.7 ± 18.9	0.23	135.1 ± 17.6	130.7 ± 20.8	0.11
BP: Diastolic, mmHg	81.1 ± 10.6	78 ± 12.4	0.16	83.4 ± 10.4	79.4 ± 10.7	0.08
BMI, kg/m^2	29.83 ± 4.1	29.7 ± 4	0.31	29.07 ± 5.07	28.8 ± 4.9	0.011

Table 2. Comparison of Glycemic Indexes in 2 Groups Before and After Intervention[a]

Δ	Berberine	Placebo	P Value
ΔFBS, mg/dL	-24.35 ± 41.65	-5.878 ± 35.95	0.036
Δ2hpp, mg/dL	-43.67 ± 74.01	6.14 ± 56.44	0.001
ΔFructosamine, μmol/L	-80.82 ± 69.4	-35.92 ± 89.91	0.014
ΔFasting- Insulin, mg/dL	1.72 ± 6.24	1.61 ± 6.17	0.93
ΔHOMA-IR	0.09 ± 2.44	0.7256 ± 3.05	0.30
ΔHOMA- β%	14.52 ± 26.76	9.19 ± 23.67	0.34

[a]Values are expressed as mean ± SD.

As such, 2hpp was significantly reduced in the berberine group (about 43.6 mg.dL), while it increased about 6.1 mg.dL in the placebo group.

Our results are consistent with those obtained by Gu et al., in China, in 2010, who studied 60 patients with type 2 diabetes for 3 months and reported a significant improvement in FBS, HBA1C, and 2hpp following berberine consumption (13).

Our findings are also consistent with those reported by Zhang et al., in 2009 (14).

In another study conducted by Yin et al., it was reported that compared with metformin, berberine leads to a significant reduction in postprandial HbA1C, FBS, and blood sugar, which is consistent with our results (15).

Zhang et al., reported a significant reduction in fasting blood sugar, postprandial blood sugar, and HbA1C in the berberine group compared to the placebo group, which is also consistent with our results (16).

Hui Dong et al. (17), Di Pierro et al. (18), and Meliani (19) reported significant hypoglycemic properties of berber-

Table 3. The Comparison of Changes of Lipid Profiles Between 2 Studied Groups[a]

Δ	Berberine	Placebo	P Value
ΔVLDL, mg/dL	-3.02 ± 13.49	3.63 ± 34.59	0.25
ΔLDL, mg/dL	-14.47 ± 28.45	-7.24 ± 24.79	0.22
ΔHDL, mg/dL	3.22 ± 5.99	2.07 ± 5.67	0.37
ΔChol, mg/dL	-9.65 ± 30.97	-11.78 ± 32.89	0.76
ΔTG, mg/dL	-22.7 ± 64.42	-7.43 ± 58	0.26

[a]Values are expressed as mean ± SD.

Table 4. Comparison of Changes of Liver Enzymes Between 2 Studied Groups[a]

Δ	Berberine	Placebo	P Value
ΔALT, U/L	-0.3 ± 6.4	0.39 ± 5.55	0.6
ΔALKp, U/L	-18.27 ± 17.3	-6.2 ± 21.7	0.007
ΔAST, U/L	-.35 ± 6.58	-0.097 ± 0.72	0.82

[a]Values are expressed as mean ± SD.

Table 5. Comparison of Kidney Function Changes Between Two Studied Groups[a]

Δ	Berberine	Placebo	P Value
ΔBUN, mg/dL	-3.5 ± 5.8	-0.05 ± 5.5	0.007
ΔCreatinie, mg/dL	0.145 ± 0.09	0.035 ± 0.10	0.35

[a]Values are expressed as mean ± SD.

ine, which is consistent with our results.

In a study conducted by Yin et al., in Shanghai diabetes center, China, fasting blood glucose did not significantly decrease compared to the placebo group; however, postprandial blood glucose and Hb A1C significantly reduced (15).

In another study conducted in 2009 by Ebrahimi-Mamaghani et al. (20), on 57 patients, results showed that, in contrast to our study, glucose did not change in the barberry group.

In our study, there was an insignificant increase in HOMA-IR in the berberine group. The same occurred in the placebo group and again, the difference was not significant. The mean increase in the berberine group was 0.05, while it was 0.72 in the placebo group. The difference between the 2 groups was not statistically significant.

Also, in our study, the fasting insulin increased in both berberine and placebo groups. The mean increase was 1.72 and 1.61 in the berberine and placebo groups, respectively, and the difference between the 2 groups was not statistically significant. In a study conducted by Zhang et al., on 97 patients, the results showed a significant decrease in insulin levels in the berberine group, which is inconsistent with our study (14). As mentioned earlier, one of the mechanisms of berberine in reducing blood sugar is increasing insulin secretion. In our study, increased insulin secretion may also be due to a mechanism of blood glucose reduction.

In another study conducted by Yin et al., fasting plasma insulin and HOMA-IR significantly reduced (15), which is again inconsistent with our results.

Di Pierro et al., (18) suggested effect of berberine on HOMA-IR and insulin levels after 90 days of treatment was significantly improved. This is inconsistent with our results.

In another study conducted in 2009 by Ebrahimi-Mamaghani et al., the results showed a significant increase in insulin concentrations and insulin resistance. In our study, both factors increased, however, the increase was not significant (20) and the longer study period may have significantly increased the insulin concentration.

The effect of berberine on lipid factors was also examined here. While the lipid factors decreased in both berberine and placebo groups, no significant differences

were observed in any group. A comparison of the TG variations in the 2 groups showed that although the reduction in berberine group was almost 3 times as much as the other group, the difference was not statistically significant, which is inconsistent with the results obtained by Yan Gu (13) and Huo Zhang (14). There may be other reasons. The mechanisms that reduce triglyceride may need more than 1 month to show their effect. The patients' race and diet are also the factors that may have a bearing on our results.

Berberine significantly reduced LDL in the placebo group. However, the difference between the berberine and placebo groups in terms of LDL reduction was not significant, and this was not consistent with the results reported by Gu (13) and Zhang in China (16) as well as Ebrahimi-Mamaghani in 2009 (20). This can also be due to our study period and the Iranian diet.

The reductions in the total cholesterol levels were almost the same in both groups (9.65 vs. 11.78). Therefore, berberine was not effective in controlling cholesterol. This is inconsistent with the findings of Farhadi et al., who reported a significant decrease in blood cholesterol level (from 259.64 mg.dL to 224.57 md.dL) in the placebo group. Our results are consistent with those of Ebrahimi-Mamaghani in 2009 who showed that the mean total cholesterol did not change in the barberry group. Our results are inconsistent with those obtained by Zhang who suggested a significant reduction in TG, cholesterol, and LDL compared to the placebo group (16).

The effect of berberine on hepatic factors was also investigated in the present study. The ALK indices decreased in both groups. The reduction in ALK in the berberine group was 3 times as much as that in the control group, and the difference was statistically significant.

ALT and AST are other hepatic factors, which decreased in the berberine group and increased in the placebo group. The variations, however, were negligible.

In a study conducted by Zhang et al., (14) on patients with hepatitis B and C, the patients' blood glucose and liver function improved following consumption of berberine, which was consistent with our study.

Yin (15) and Di Pierro (18) reported no liver damage prior to receiving berberine, which is consistent with our study.

In our study, systolic and diastolic blood pressure did not change in the berberine group compared to the placebo group, which is consistent with the study conducted by Golzarand and Ebrahimi-Mamaghani in 2008 (21).

BMI in the berberine group did not change compared to the placebo group, which is consistent with the study conducted by Ebrahimi-Mamaghani in 2009 (20) and Yin in 2012 in China (15).

The effect of berberine on renal function was also examined in this study. No significant difference was observed in Cr in the berberine group compared to the placebo group, while BUN significantly reduced in the berberine group compared to the placebo group, which suggests that berberine is not a nephrotoxic medication. Yin found that berberine did not have any renal complications, which is consistent with our results (15).

4.1. Conclusion

The results of this study indicate that taking Berberine with a dose of 1 gram for 1 month on a daily basis resulted in a significant decrease of FBS, 2hpp FBS, and Fructsamine in type 2 diabetic cases, however, it did not lead to a significant decrease of fat profile as well as fasting insulin level, HOMA-β%, and HOMA-IR. However, it didn't have any effect on blood pressure nor any side effect on kidney and liver.

Regarding the ever-increasing trend of diabetic patients across the world, it is necessary to conduct more and large-scaled studies in order to better recognize the benefits and effects of different medications. Therefore, the following suggestions are in order.

- Long-term studied should be carried out
- Studies should be carried out with different doses of Berberine
- Studies should be done on pre-diabetic cases
- Studies should be done on type 2 diabetic patients, who receive insulin, in order to decrease insulin dose

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Footnotes

Authors' Contribution: Homeira Rashidi, Foroogh Namjoyan, and Seyed Bahman|Ghaderian proposed the idea. Foroogh Namjoyan provided the placebo and capsules. Zahra Mehraban wrote the search proposal. Mehrnoosh Zakerkish visited patients. Seyed Mahmoud|Latifi analyzed the data. All authors read and edited the final manuscript.

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