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Original Article

The Effects of *Urtica dioica* (Nettle) and *Vaccinium myrtillus* (European Blueberry) on Blood Glucose Parameters and Lipid Profile in Patients With Type 2 Diabetes Mellitus: A Double-Blind Randomized Controlled Trial

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Abstract

Background: Diabetes mellitus (DM), and more specifically type 2 DM (T2DM), is a growing metabolic disease and is accompanied by changes in lipid profile and glycemic parameters which contribute to debilitating complications. Nettle and European blueberry as complementary herbal medicine could play a significant role in managing elevated levels of blood sugar and diabetic complications. The goal of this study was to determine the effects of nettle and European blueberry combination as adjunct therapy in patients with T2DM.

Methods: The randomized double-blind clinical trial included 59 T2D patients with a mean age of 57.9 years. Participants were randomly assigned to two groups to take either nettle-bilberry capsules (500/mg/dose twice a day, n=29) or a placebo (n=30) for three months. Fasting blood samples were obtained at the beginning and after the intervention to quantify 15 items, including lipid profile and glycemic factors.

Results: Sixty patients were enrolled in this study. The groups had no significant difference regarding the demographics and the study variables at the baseline. Compared with the placebo, the nettle-bilberry combination resulted in significant decreases in fasting blood sugar (FBS), triglyceride, cholesterol, and low-density lipoprotein (LDL) levels ($P<0.001$). There was no statistically significant difference in the other indices, including glycated hemoglobin (HbA1c), urea, creatinine, high-density lipoproteins, liver function tests (LFTs), C-reactive protein (CRP), insulin, and insulin resistance (HOMAIR) levels ($P>0.05$).

Conclusion: Overall, a combination of nettle and bilberry had beneficial impacts on the levels of FBS, cholesterol, and LDL. However, this combination had no significant effects on the other glycemic factors and lipid profile indicators.

Trial Registration: This study was a double-blind randomized controlled trial study that was registered in the Iranian Registry of Clinical Trials (IRCT: IRCT20140617018126N3). In addition, approval was obtained from the Ethics Committee of Tabriz University of Medical Sciences (Ethics code: IR.TBZMED.REC.1399.093).

Keywords: Diabetes mellitus, *Urtica dioica*, *Vaccinium myrtillus*, Randomized controlled trial, Traditional medical

Introduction

Diabetes mellitus (DM) is a metabolic disease in which the blood sugar of a person is higher than normal.[1] DM is categorized into two distinct groups, namely, type 1 (T1DM) and type 2 (T2DM). In T1DM, which is insulin-dependent and is called juvenile/premature diabetes, the AIN dysfunction is in the production of insulin. T2DM, which was formerly known as adulthood or insulin-independent diabetes, is a chronic disease related to a lack of balance in glucose metabolism.[1,2,3] The most recent global evaluation on the burden of different diseases on societies estimated that over half a billion people all over

the world had T2DM, and 22 million new cases will be added every year.[4,5] It is estimated that the number of people with T2DM will increase to 693 million by 2045.[5] According to estimates by the World Health Organization in 2016, the prevalence of DM in Iran stands at 10.3%, and almost 2% of mortalities are directly caused by DM.[6] Several risk factors play a role in T2DM, and the most important of them are race, family history, old age, higher body weight or obesity, unhealthy diet, lack of mobility or activity, high blood pressure, and smoking.[1,3,7]

Nettle is a medicinal plant with the scientific name *Urtica dioica*, which belongs to the *Urticaceae* family.[8] This plant is found in the rural areas of North America, northern Europe, and various locations in Asia.[7] It is widely used in Turkey and Morocco to control blood sugar.[9] This plant is rich in formic acid and flavonoids.[10] Numerous studies have shown the effect of nettle on different conditions, including rheumatoid arthritis, DM, urinary tract infections, prostate enlargement, seasonal allergies, and acne.[11,12] An eight-week, double-blind, randomized controlled clinical trial (RCT) demonstrated that the hydro-alcoholic extract of *U. dioica* is an effective additional therapy for DM.[13]

Vaccinium myrtillus or European blueberry or bilberry is native to Europe and is one of the richest natural sources of anthocyanins. Bilberry is a source of dietary anthocyanin, which is a crucial dietary factor associated with DM.[14] Several studies reported reducing blood glucose, anti-inflammatory, and lipid reduction properties for berries.[15] It also strengthens antioxidant defense and lowers oxidative stress.[16]

Due to the reported efficacy of these herbal components and the lack of reliable evidence, this study aimed to investigate the effects of the combination of *U. dioica* and *V. myrtillus* on blood glucose parameters, lipid profile, kidney and liver function, and inflammation in patients with T2DM.

Methods

This was a double-blind RCT study. An eligible sample was selected after registering the study in the Iranian Registry of Clinical Trials (identifier: IRCT20140617018126N3) and obtaining approval from the Ethics Committee of Tabriz University of Medical Sciences (Ethics code: IR.TBZMED.REC.1399.093).

Inclusion Criteria

1. T2DM
2. Regular oral use of hypoglycemic agents (people who only take glucose-lowering drugs to control DM)
3. Age 40-70
4. Body mass index (BMI) of 18.5-30 kg/m^2
5. Fasting blood sugar (FBS) level higher than 126 mg/dL
6. Willingness to take part in the present study.

Exclusion Criteria

1. T1DM or the other types of diabetes
2. Episodes of insulin therapy in the past three months
3. Serious gastrointestinal (GI) diseases, including peptic ulcer and GI bleeding
4. History of diabetic ketoacidosis, non-ketotic hyperosmolar diabetic coma, severe infection, or surgery in the previous month
5. Uncontrolled hypertension (blood pressures equal to or above 160/100 mm Hg)
6. History of mental illnesses
7. History of alcohol, drug, or psychedelic abuse
8. Pregnancy, lactation, or planning to become pregnant
9. Cardiovascular diseases, kidney failure, liver dysfunction, thyroid or parathyroid dysfunctions, and cancers
10. High physical activities
11. Chronic complications related to DM (e.g., neuropathy or retinopathy according to the patient's records), diabetic nephropathy, hypothyroidism, and hyperthyroidism
12. Allergy to Nettle and *V. myrtillus* or their derivatives.

Patient's Selection

The researcher in charge of selecting the population received a list of T2DM patients from the East Azerbaijan Diabetes Association and randomly selected participants for the present study using a table of random numbers. Then, this researcher contacted the selected participants and briefed them about the study and its aims while matching selected peoples' conditions with the inclusion and exclusion criteria. In case the selected participants met the eligibility criteria and were willing to participate in the study, they could participate in this study.

Randomization and Random Allocation

The samples were randomly assigned to four blocks using Random Allocation Software. Blocking and allocation sequences for concealment were performed by the non-involved researcher. The sample allocation ratio was Allocation 1:1 and was divided into two groups of receiving *U. dioica* and *V. myrtillus* (nettle-bilberry/active intervention group), and placebo. Then, based on blocks and allocation sequences, each patient was given white pockets that were prepared in equal sizes and on which numbers 1 to 60 were written in order of the allocation sequence. The pockets included white boxes containing nettle-bilberry or placebo capsules. Only the person in charge of packing the capsules knew the numbers of the relevant pockets, and none of the researchers or patients were aware of the type of medicine that each person receives.

Plant Preparation

Nettle-bilberry and placebo capsules were similar in shape, size, color, and smell. Both identical nettle-bilberry and placebo capsules placed inside the white boxes were to be taken along with food by the participants every 12 hours (BID) for three months. Each 500 mg nettle-bilberry

capsule contained 300 mg of nettle and 150 mg of bilberry along with filler material. Each placebo capsule consisted of 500 mg of a placebo. The participants were advised to continue taking their regularly prescribed medicines. The raw materials of herbs were collected from the rural areas of East Azerbaijan.

Data Collection

This study was conducted between March and September of 2021, and patients had been taking medications for three months. To collect personal information of the participant, a questionnaire was handed out, which contained demographic information, including age, gender, level of education, a brief history of medicines and supplements presently used and their doses and the duration, history of special diets (if any), current illnesses and disorders, and history of diabetes. Fasting blood samples of the participant were taken, and their weight, height, BMI, waist size, wrist size along with urine samples and blood pressure were recorded after having breakfast. The medication intake questionnaire was used to obtain data about medications taken by the participants.

Sample Size

The sample size for the present study was calculated based on previous studies and by considering the results obtained from G*Power software (Power: 0.095, significance level (α): 0.05, and SD: 28.5 to be 27 people for each group). By taking into account a 15% dropout, the final sample size was taken to be 30 people in each group and a total of sixty people.

Statistics

All statistical analyses were conducted using the 23rd version of SPSS software with 95% confidence intervals (CIs) and a 0.05 level of significance for the *P* value. The quantitative variables were reported as means ± standard deviations (SDs), and the qualitative data were presented in numbers and percentages. Finally, independent sample *t* test, chi-square test, and Mann-Whitney U test were employed for comparing the variables between the groups.

Results

Sixty patients (30 per group) were enrolled in this study. During the trial, one of the intervention group participants left the study because of personal reasons, and the final count of the participants in the intervention group was 29 (Figure 1). The obtained results demonstrated that the two understudy groups had no significant difference in terms of demographics and the study variables at the baseline (Table 1).

After three months of intervention, the average decrease

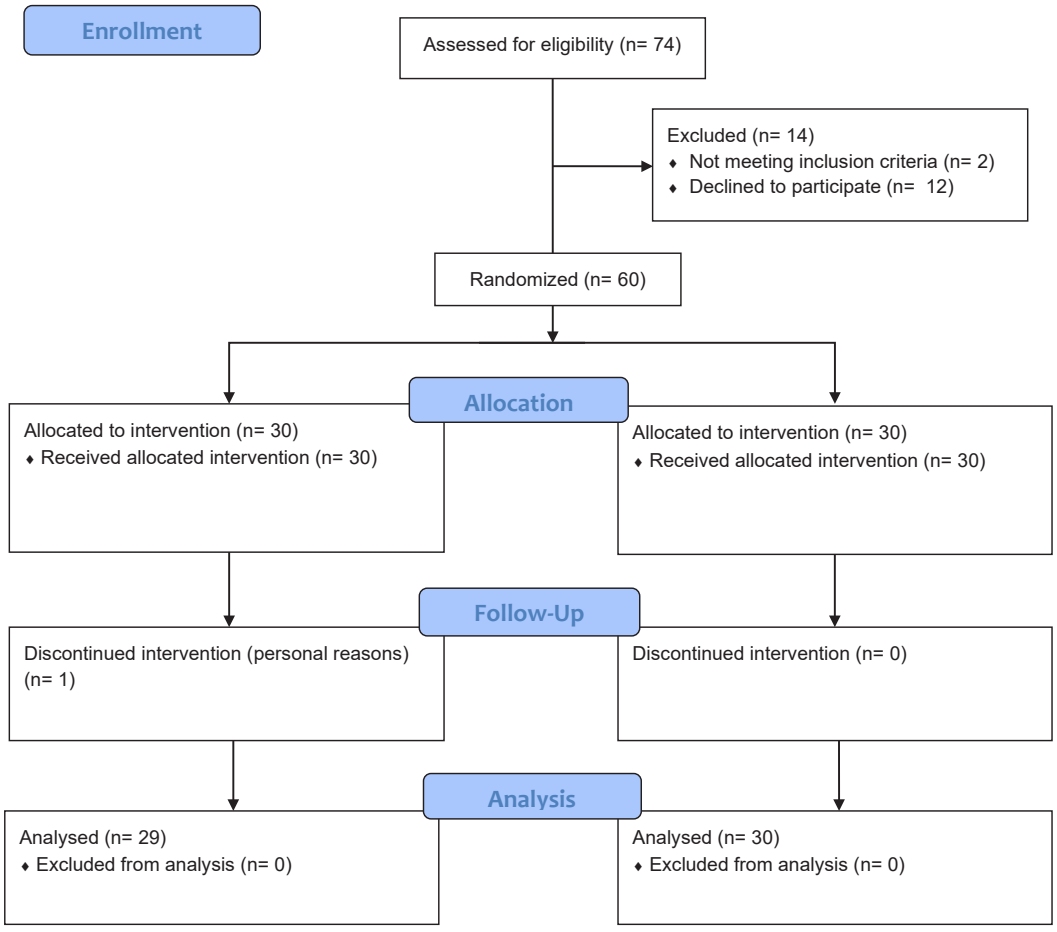

Figure 1. CONSORT Flow Diagram.

Table 1. Baseline Characteristics of Participants in the Study Groups

Variable		Intervention (n = 29)	Placebo (n = 30)	*P* Value
Age (year)		57.17 ± 4.10	58.70 ± 4.17	0.161*
Gender	Male	17 (56.67%)	14 (48.28%)	0.519**
	Female	13 (43.33%)	15 (51.72%)	
Used medication	Metformin	18 (60.00%)	10 (34.48%)	0.927***
	Glibenclamide	0 (0.00%)	0 (0.00%)	
	Metformin and Glibenclamide	10 (33.33%)	10 (34.48%)	
	None	2 (6.67%)	3 (10.34%)	
Other underlying diseases	Positive	5 (16.67%)	6 (20.69%)	0.692
	Negative	25 (83.33%)	23 (79.31%)	
BMI		27.44 ± 3.67	28.09 ± 1.93	0.392*
FBS		129.41 ± 37.58	142.50 ± 39.31	0.197*
HbA1C		7.6 ± 0.62	7.14 ± 39.31	0.327*
Urea		31.55 ± 4.13	32.1031.55 ± 4.134.78	0.640*
BUN		14.79 ± 2.01	14.73 ± 2.26	0.915*
Creatinine		0.72 ± 0.11	0.76 ± 0.13	0.236*
Triglyceride		114.63 ± 46.24	117.33 ± 29.68	0.789*
Cholesterol		154.90 ± 37.73	160.27 ± 37.93	0.588*
HDL		44.00 ± 4.93	42.33 ± 4.44	0.177*
LDL		94.93 ± 29.41	103.27 ± 22.14	0.223*
AST		20.86 ± 6.46	18.0 ± 6.74	0.102*
ALT		19.31 ± 7.19	21.37 ± 6.93	0.268*
ALP		147.21 ± 18.79	154.97 ± 19.97	0.130*
CRP		2.82 ± 1.08	2.37 ± 0.95	0.095*
Insulin		13.72 ± 5.47	14.52 ± 7.32	0.640*
Insulin resistance (HOMAIR)		2.73 ± 0.27	2.82 ± 0.22	0.149*

Note. BMI: Body mass index; FBS: Fasting blood sugar; HbA1C: Hemoglobin A1C; BUN: Blood urea nitrogen; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; ALP: Alkaline phosphatase; CRP: C-reactive protein.
* Independent T-test, ** Chi-square test; *** Accuracy test.

in the FBS levels of the group taking nettle and bilberry was significantly higher than this value in the placebo-taking group ($P < 0.001$). Further, the reduction in the triglyceride level in the nettle-bilberry-taking group was 4.72 ± 4.48 units, representing a significant difference from the placebo-taking group (0.53 ± 3.49, $P < 0.001$). The combination of nettle and bilberry had the potential to lower the average cholesterol level by 8.90 ± 33.55 units in comparison to the reduction of the same parameter by 4.96 ± 3.81 units in the placebo-taking group ($P < 0.001$). The difference in high-density lipoprotein was not statistically different ($P = 0.175$), while the decrease in low-density lipoprotein (LDL) was considerably higher in the active intervention group ($P < 0.001$). Regarding the other parameters of the blood samples of the two understudy groups, including hemoglobin A1c (HbA1c), urea, blood urea nitrogen (BUN), Creatinine, aspartate transaminase (AST), alanine transaminase (ALT), alkaline phosphatase (ALP), C-reactive protein (CRP), insulin, and Homeostatic Model Assessment for Insulin Resistance (HOMA-IR), no difference was detectable ($P > 0.05$, Table 2).

Discussion

In the present study, the effects of a combination of nettle and bilberry were investigated in patients with T2DM. Based on our findings, after three months of intervention, evaluation of changes in FBS levels in the two understudy groups represented a significant difference, while this difference in the reduction of HbA1c was not statistically significant between the placebo and active intervention groups. It should be pointed out that this difference in kidney function tests (BUN, urea, and creatinine) was not statistically meaningful in our sample. In addition, regarding the liver function tests (LFTs), the average reduction in AST, ALT, and ALP, as well as the inflammation biomarkers (CRP), the difference was not statistically significant as well.

The currently utilized strategy to treat T2DM depends on a combination of insulin-stimulating and insulin-sensitizing drugs. Despite good glycemic control drugs at the beginning of treatment, their efficacy decreases over time. Furthermore, side effects such as severe hypoglycemia, lactic acidosis, idiosyncratic liver cell damage, GI discomfort, dizziness, and even death have

Table 2. Changes in Lipid Profile and Glycemic Parameters in the Understudy Groups Before and After Intervention

Variable	Stage	Grouping		*P* Value for Changes*
		Intervention (n = 29)	Placebo (n = 30)	
FBS	Before	129.41 ± 37.58 123.00 (71 to 238)	142.50 ± 39.31 137.50 (88 to 292)	< 0.001
	After	119.55 ± 37.40 113.00 (63 to 227)	137.60 ± 39.75 133.50 (85 to 284)	
	Changes	9.86 ± 5.01 10 (-5 to 18)	4.90 ± 3.48 5 (-5 to 11)	
HbA1C	Before	7.06 ± 0.62 7.04 (5.70 to 9.00)	7.14 ± 0.75 7.16 (6.00 to 9.30)	0.100
	After	5.90 ± 0.82 5.92 (3.10 to 7.90)	5.82 ± 1.02 5.86 (4.00 to 8.60)	
	Changes	1.12 ± 0.55 1.10 (0.21 to 3.10)	1.33 ± 0.36 1.33 (0.20 to 2.10)	
Urea	Before	31.55 ± 4.13 31 (25 to 40)	32.1 ± 4.78 32 (20 to 43)	0.076
	After	29.14 ± 3.30 29 (23 to 37)	32.37 ± 4.89 32 (19 to 43)	
	Changes	2.41 ± 4.90 4 (-10 to 9)	-0.27 ± 4.64 0 (-11 to 11)	
BUN	Before	14.79 ± 2.01 15 (11 to 19)	14.73 ± 2.26 15 (9 to 20)	0.333
	After	16.31 ± 1.63 16 (13 to 20)	15.73 ± 2.18 16 (9 to 20)	
	Changes	-1.52 ± 2.89 -2 (-7 to 4)	-1.00 ± 2.41 -1 (-6 to 5)	
Creatinine	Before	0.72 ± 0.11 0.70 (0.54 to 1.00)	0.76 ± 0.13 0.75 (0.53 to 1.10)	0.826
	After	0.69 ± 0.10 0.70 (0.42 to 0.87)	0.73 ± 0.08 0.71 (0.60 to 1.00)	
	Changes	0.04 ± 0.10 0 (-0.11 to 0.27)	0.04 ± 0.08 0.04 (-0.12 to 0.19)	
Triglyceride	Before	114.62 ± 46.24 114 (58 to 267)	117.33 ± 29.68 114 (82 to 185)	< 0.001
	After	109.90 ± 44.86 106 (49 to 257)	116.80 ± 29.51 109.5 (78 to 189)	
	Changes	4.72 ± 4.48 6 (-3 to 10)	0.53 ± 3.49 -0.5 (-4 to 7)	
Cholesterol	Before	154.90 ± 37.73 155 (101 to 210)	160.27 ± 37.93 162.5 (101 to 255)	< 0.001
	After	146.00 ± 38.73 145 (88 to 201)	155.63 ± 37.42 155 (94 to 250)	
	Changes	8.90 ± 3.55 10 (-1 to 13)	4.63 ± 3.81 5 (-2 to 10)	
HDL	Before	44.00 ± 4.93 44 (36 to 55)	42.33 ± 4.44 43 (32 to 48)	0.175
	After	47.52 ± 9.32 47 (34 to 70)	43.80 ± 6.05 45 (31 to 52)	
	Changes	-3.52 ± 4.97 -3 (-15 to 5)	-1.47 ± 2.27 -2 (-6 to 4)	
LDL	Before	94.93 ± 29.41 97 (49 to 140)	103.27 ± 22.14 101 (80 to 183)	< 0.001
	After	67.93 ± 31.29 74 (15 to 111)	96.33 ± 21.45 93.5 (71 to 171)	
	Changes	27.00 ± 7.95 28 (5 to 40)	6.93 ± 2.69 7 (1 to 12)	
AST	Before	20.86 ± 6.46 19 (13 to 32)	18.00 ± 6.74 16 (10 to 35)	0.205
	After	19.24 ± 6.13 20 (8 to 30)	17.33 ± 5.84 16 (10 to 35)	
	Changes	1.62 ± 2.80 2 (-5 to 6)	0.67 ± 3.44 1 (-6 to 8)	

Table 2. Continued.

Variable	Stage	Grouping		*P* Value for Changes*
		Intervention (n = 29)	Placebo (n = 30)	
ALT	Before	19.31 ± 7.19 18 (11 to 38)	21.37 ± 6.93 23 (12 to 37)	0.825
	After	17.97 ± 10.05 18 (3 to 43)	20.30 ± 9.82 23 (5 to 38)	
	Changes	1.34 ± 4.17 2 (-5 to 9)	1.07 ± 4.18 1.5 (-8 to 10)	
ALP	Before	147.21 ± 18.79 152 (108 to 174)	154.97 ± 19.97 156 (125 to 185)	0.584
	After	142.97 ± 18.61 146.00 (110 to 171)	150.43 ± 19.69 152.50 (120 to 180)	
	Changes	4.24 ± 2.76 4 (-2 to 9)	4.53 ± 3.08 4 (-8 to 10)	
CRP	Before	2.82 ± 1.08 2.82 (1.20 to 4.53)	2.37 ± 0.95 2.21 (1.14 to 4.71)	0.110
	After	2.32 ± 1.31 2.02 (1.00 to 5.10)	2.49 ± 1.53 2.17 (1.00 to 6.44)	
	Changes	0.50 ± 0.99 0.42 (-2.02 to 2.55)	-0.12 ± 1.42 0.23 (-2.15 to 2.82)	
Insulin	Before	13.72 ± 5.47 14.11 (5.20 to 21.47)	14.52 ± 7.32 13.3 (2.32 to 33.62)	0.564
	After	18.57 ± 11.56 20.42 (1.45 to 36.89	19.08 ± 14.25 15.44 (1.02 to 57.38)	
	Changes	-4.84 ± 6.16 -4.57 (-15.56 to 4.28)	-4.57 ± 7.23 -4.10 (-23.76 to 4.70)	
Insulin resistance (HOMAIR)	Before	2.73 ± 0.27 2.81 (2.23 to 3.25)	2.83 ± 0.22 2.88 (2.26 to 3.16)	0.328
	After	2.90 ± 0.79 3.00 (1.58 to 5.33)	3.24 ± 0.99 3.12 (1.07 to 6.30)	
	Changes	-0.17 ± 0.81 -0.22 (-2.52 to 1.19)	-0.41 ± 0.99 -0.25 (-3.32 to 1.40)	

Note. FBS: Fasting blood sugar; HbA1C: Hemoglobin A1C; BUN: Blood urea nitrogen; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; ALP: Alkaline phosphatase; CRP: C-reactive protein.
*Mann-Whitney test.

been experienced by long-term use of these drugs and are considered the other drawbacks.[5] Due to the high prevalence of DM in different societies and its complications, physicians and druggists have been looking for alternative treatment options, especially medicinal/herbal plants.[17] The use of medicinal/herbal plants has been popular among people for a long time. Some of them have been proven to be effective and are considered complementary treatment options,[18-20] while some others were found to be ineffective.[21]

Nettle leaves comprise flavonoids, peptides, and amines with anti-diabetic effects.[7] These components take part in some mechanisms such as stimulating glycogenesis, closing potassium channels in pancreatic cells, and interfering with glucose absorption from the intestinal wall. Several studies have documented the positive effects of using nettle leaf extract or its other parts in the form of injection or oral use in treating DM.[13]

Vaccinium is a genus of shrubs with wide usage in herbal medicine. Cranberry is an effective and important medicinal plant in preventing inflammation, lowering blood lipids and glucose, decreasing oxidative stresses, preventing cardiovascular diseases, and treating dementia and other age-related diseases. There is also evidence of the antimicrobial properties of cranberry.[22] Cranberry is well known for its anti-diabetes properties and through ages, different kinds of this fruit along with leaves have been used to improve diabetic symptoms.[23] In a study on Italian herbal medicine, cranberry has been ranked fourth in the list of plants for controlling blood glucose.[22] This study could not detect a significant anti-inflammatory effect for a nettle-bilberry product based on serum CRP levels.

In two studies conducted by Ghalavand et al[23] and Ziaei et al,[24] it was reported that consuming nettle supplements is an effective way to control blood sugar and high blood pressure in T2DM people. In our sample of T2DM patients, the average reduction in the level of insulin, as well as HOMA-IR, was not significantly different between the groups, while changes in FBS levels were different between the groups. The onset of T2DM disease is when the cells of the body are unable to produce and secrete enough insulin or to respond to insulin, which is known as resistance to insulin.[1-3] In healthy people, insulin acts as a means to transport glucose into cells and signals them to take it up. Nonetheless, when insulin resistance is developed, cells become desensitized to this signaling.

When resistance is developed in a noticeable number of cells, blood sugar and thus T2DM increase, which is usually called hyperglycemia.[1,3]

DM is associated with long-term damage and dysfunctions of various organs such as the retina (retinopathy), nerves (neuropathy), heart and blood vessels, and amputation.[2] Moreover, poorly controlled T2DM can lead to multiple complications such as kidney failure and liver dysfunction.[2,3] In our sample, this difference in kidney function tests (BUN, urea, and creatinine), as well as the LFT, including AST, ALT, and ALP, the difference was not statistically significant between the nettle-bilberry and placebo groups.

Bilberry and nettle are among the most commonly used medicinal plants in anti-diabetic formulas.[25,26] A decoction of the combination of *V. myrtillus* and *U. dioica* leaves is widely employed in Russia as a blood glucose-lowering component. This binary combination has been found to reduce glycemia, enhance the utilization of glucose, protect pancreatic β-cells, inhibit intestinal glucose absorption, and show total cholesterol-lowering activity.[27-30] The current study assessed the efficacy of this combination in T2DM patients, and the results revealed that it was effective in controlling FBS levels and cholesterol.

The present study was designed by considering the serious side effects of using hypoglycemic drugs, on the one hand, and the lack of significant side effects of the therapeutic doses of medicinal/herbal plants, including nettle and bilberry, on the other hand. The willingness and encouragement of physicians to use medicinal plants due to their wider and easy availability and the strong belief of people in the effectiveness of herbal medicine were also taken into account. The limited sample size as a single-center study was the main limitation of this study.

Conclusion

Overall, a combination of nettle and bilberry was effective in controlling FBS levels in patients with T2DM, while this production did not affect HbA1C levels in these patients. Nettle-bilberry intervention is similar to a placebo regarding kidney function, LFTs, and inflammation biomarkers, but this herbal product is effective in controlling cholesterol. There is a need for future studies on this topic to obtain more conclusive evidence.

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Conflict of interests declaration

The authors declare that they have no known competing financial interests or personal relationships that could have influenced the work reported in this paper.

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