Iran J Psychiatry 2023; 18: 3: 362-368

Short Communication

Evaluation of the Effect of Barberry Root (Berberis Vulgaris) on the Prevention of Metabolic Syndrome Caused by Atypical Antipsychotic Drugs in Patients with Schizophrenia: A Three-Blind Placebo-Controlled Clinical Trial

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Abstract

Objective: Metabolic syndrome is a potential side effect of atypical antipsychotics which are the current standard treatment for schizophrenia. Therefore, we aimed to examine the effect of barberry root (Berberis vulgaris) on the prevention of metabolic syndrome caused by atypical antipsychotic drugs in patients with schizophrenia.
Method: Our research was a three-blind randomized clinical trial. The participants included all patients who were diagnosed with schizophrenia through the SCID-5 questionnaire and based on the DSM-5-TR criteria by two psychiatric experts. These patients were randomly divided into intervention and placebo groups. During a three-month treatment period, the intervention group received three 500 mg capsules of barberry root extract daily, whereas the placebo group received the same capsules containing 500 mg of starch powder. Metabolic syndrome variables including fasting blood glucose, serum lipids (triglyceride and cholesterol), blood pressure, weight and waist circumference were measured before and after the treatment as outcome measure. Chi-square and t-tests were used for data analysis using SPSS-22 software.
Results: At the beginning of the study, there was no significant difference between the intervention group (n = 41) and the placebo group (n = 47) in terms of demographic factors, and pre-treatment assessments including weight, waist size, fasting blood HDL, fasting blood triglycerides and systolic and diastolic blood pressure and fasting blood glucose ($P > 0.05$). Within group analysis showed that some metabolic factors significantly increased in both groups after the treatment ($P < 0.05$). Indeed, in both groups, metabolic syndrome measures worsened after the three-month treatment period. The parameters of weight and waist size were significantly higher in the intervention group than the placebo group after treatment ($P < 0.05$).
Conclusion: Barberry root extract was not able to control the Effects of antipsychotic drugs on metabolic syndrome in schizophrenia.

Key words: *Antipsychotics; Barberry Root; Metabolic Syndrome; Schizophrenia*

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Article Information:
Received Date: 2022/12/14, Revised Date: 2023/01/16, Accepted Date: 2023/01/27

Schizophrenia is a chronic and serious disorder that affects the way of thinking, feeling and behavior of the affected person. Approximately 7 or 8 out of every 1,000 people suffer from schizophrenia in their lifetime (1-4). Schizophrenia is 1.4 times more common in men than in women and typically occurs earlier in men. It is much rarer in early childhood than in middle age and old age and its prevalence is somewhat different in various races (5-8). Improvement in schizophrenia symptoms is usually gradual, but some symptoms persist for a long time in many patients (9-12). Several factors have been identified that contribute to the risk of developing schizophrenia. Recent evaluations have shown that the rate of rare genetic mutations is higher in people with schizophrenia (13-15). Indeed, schizophrenia is considered a neurodevelopmental disorder resulting from an interaction between environmental and genetic factors (16). In the treatment of this illness, typical (first generation) and atypical (second generation) antipsychotics are utilized. Today, the use of the second generation of atypical antipsychotics has increased due to fewer extrapyramidal side effects. However, metabolic symptoms such as abdominal obesity, diabetes, blood pressure and high triglycerides caused by treatment with atypical antipsychotics, lead to increased mortality and morbidity and even higher treatment costs in these patients (17-19). Therefore, prevention of metabolic syndrome caused by treatment with antipsychotics is important (20-22).

Today, the use of medicinal plants in therapeutic processes and maintaining health is highly emphasized. For many years, natural medicines, especially medicinal plants, were considered as the basic treatment and even in some cases the only means of treatment (23, 24). Barberry is a thorny plant, with the scientific name of Berberis vulgaris, and belongs to the Breberidacea family. This plant exists in different regions of the world (25). Due to its alkaloid compounds (berberine), this plant has a great effect in the treatment of different illnesses, the most important of which include leishmaniasis, preventing the growth of bacteria, reducing smooth muscle contraction, reducing inflammation, preventing the accumulation of platelets, stimulating bile secretion, lowering blood pressure, controlling metabolic syndrome, etc. (26, 27).

Considering the effect of barberry root (Berberis vulgaris) in regulating triglyceride, cholesterol and glucose metabolism through increasing relevant protein expression, we decided to examine the impact of berberine on the prevention of metabolic symptoms caused by atypical antipsychotics in patients with schizophrenia.

Materials and Methods

Design and participants

Our research was a three-blind randomized clinical trial (RCT) that was performed in Golestan Hospital, Ahvaz Psychiatric Clinic in 2021-2022. Participants included all patients who referred to the psychiatric clinic and were diagnosed with schizophrenia through the SCID-5 questionnaire and based on the DSM-5-TR criteria by two psychiatric experts. Adult patients (≥ 20 years) who were treated with atypical antipsychotics, whose guardians signed the informed consent form to participate in the RCT were included in the study, in case of the absence of any major comorbid psychiatric and neurological illnesses and not receiving electroconvulsive therapy in the current hospitalization. Exclusion criteria for this RCT included unwillingness to continue the RCT, non-adherence to the assigned treatment during the study, and occurrence of any side effects during treatment.

A total of 140 patients with schizophrenia were assessed, and among them, 106 patients who met the inclusion criteria were randomly divided into intervention (n = 53) and placebo (n = 53) groups. Patients were treated with medication packages predetermined by the study supervisor. These packages were completely similar in shape. The patient and the project manager were not aware of the contents of these packages. Furthermore, data collection, assessment of patients and completion of forms were done by the project manager and his assistant, who were unaware of the content of the package. In the data analysis stage, the analysis was done by the project advisor and manager, who were unaware of the contents of the drug packages. Therefore, this study was a three-blind RCT, and the contents of the two drug packages were not known from the stage of patient admission to the end of the study, including data collection and data analysis.

Trial procedure

At the beginning of the study, a demographic questionnaire including questions about age, sex, duration of illness and the use of any type of medicine was completed by the patients. Then, we measured metabolic syndrome variables. After allocating the patients to one of the intervention or placebo groups, 500 mg capsules of barberry root were prescribed and delivered to the intervention group at a dose of 1500 mg per day (i.e., three 500 mg capsules) for three months. Barberry root, as the medicine used in this study, was purchased from barberry farms in Khorasan and loaded into 500 mg capsules by a pharmacognosy expert at Ahvaz Medicinal Plants Research Center. The control group was given the same amount of placebo capsules (i.e., three 500 mg capsules per day), which were made of starch powder with the same color as the medicinal powder. They were loaded in the same capsules and were prescribed for three months.

Outcome measures

The effect of the drug on metabolic symptoms was evaluated before and after three months of treatment through measuring metabolic syndrome variables including fasting blood glucose, serum lipids (triglyceride and cholesterol), blood pressure (systolic and diastolic), weight and waist circumference.

Statistical analysis

Statistical analysis was administered with SPSS-22. For quantitative variables, mean and standard deviation were utilized to describe the data, whereas frequency and percentage were utilized to describe qualitative variables. The normality of the data was assessed by Kolmogorov-Smirnov test and Q-Q diagram. To measure the significance of the differences and compare the quantitative variables between the two placebo and intervention groups, the statistical t-test (non-parametric Mann-Whitney test) was used. The chi-square test (Fisher's exact test) was also applied to compare demographic variables between the two groups. The significance level in the tests was set at 0.05.

Ethical considerations

A pre-designed consent form was filled out by all enrolled subjects, and patients could easily withdraw from the study at any time. This research was done after obtaining the code of ethics from the Ethics Committee of Ahvaz Jundishapur University of Medical Sciences (IR.AJUMS.HGOLESTAN.REC.1400.001). It is also registered in the National Clinical Trial System (IRCT20210425051074N1).

Results

Figure 1 shows the consort flow diagram of the steps involved in our trial. As indicated, 12 patients from the intervention group and six patients from the placebo group were unable to complete the trial procedure due to non-compliance or side-effect issues and were excluded from the final analysis. At the beginning of the study, there was no significant difference between the two groups in terms of demographic factors such as gender, marriage, duration of illness, hospitalization or non-hospitalization, mean age, and type of medication (Table 1). Also, there was no significant difference between the two groups in pre-treatment assessments of weight, waist size, fasting blood HDL, fasting blood triglycerides and systolic and diastolic blood pressure and fasting blood glucose ($P > 0.05$).

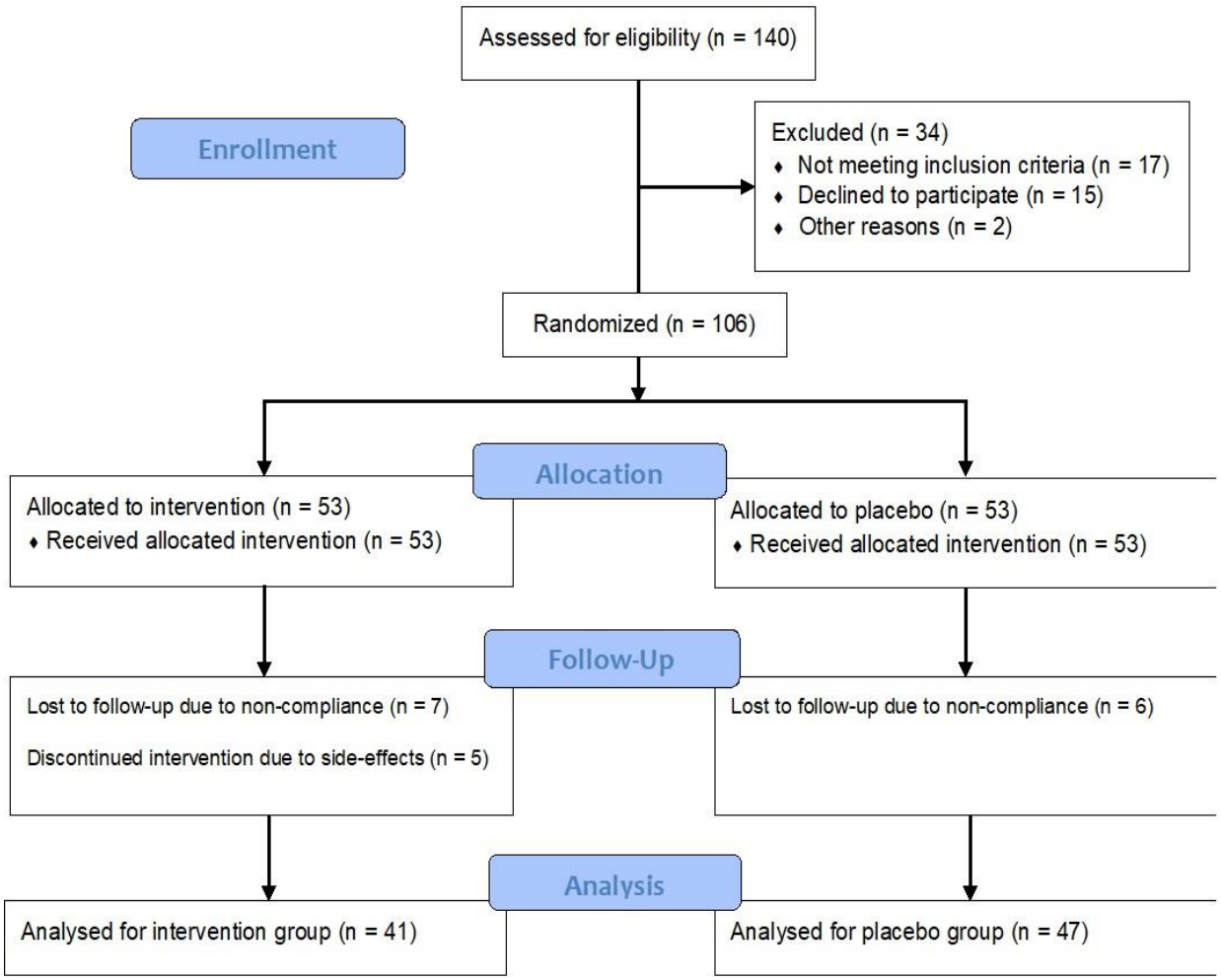

Figure 1. Consort Flow Diagram of the Steps Involved in the Randomized Controlled Trial to Assess the Effect of Barberry Root on the Prevention of Metabolic Syndrome Caused by Atypical Antipsychotic Drugs in Patients with Schizophrenia

Table 1. Comparison of the Distribution of Demographic Factors between the Intervention and Placebo Groups

Parameters		Intervention (n = 41)	Placebo (n = 47)	P-value
Gender (Frequency%)	Male	63.4%	72.3%	0.37
	Female	36.6%	27.7%	
Marital Status (Frequency%)	Single	63.4%	63.8%	0.217
	Married	31.7%	21.3%	
	Divorced	4.9%	14.9%	
Hospitalization or non-hospitalization (Frequency%)	Hospitalized	85.4%	70.2%	0.13
	Non-Hospitalized	16.6%	29.8%	
Type of Medicine (Frequency%)	Resperidone	53.7%	66.0%	0.25
	Olanzapine	14.6%	19.1%	
	Quetiapine	22.0%	12.8%	
	Clozapine	9.8%	2.1%	
Age (years, m ± SD)		36.73 ± 9.33	37.26 ± 8.78	0.78
Duration of disease (months, m ± SD)		35.61 ± 31.61	49.02 ± 36.65	0.12

Note: m = mean; SD = standard deviation.

Within group analysis showed that some metabolic factors including weight, waist size, fasting blood triglyceride and fasting blood glucose significantly increased in the intervention group after the treatment ($P < 0.05$). However, there was no significant difference in other variables of metabolic syndrome such as fasting blood HDL, and systolic and diastolic blood pressures in the intervention group after the treatment ($P > 0.05$). Furthermore, waist size, fasting blood triglyceride and glucose significantly increased in the placebo group after the treatment ($P < 0.05$). However, other variables such as fasting blood HDL, weight, and systolic and diastolic blood pressures did not significantly change in the placebo group after the treatment ($P > 0.05$).

Table 2 indicates the pre- and post-treatment measures for the two groups and compares them between the groups. As shown, in both groups, metabolic syndrome measures worsened after the three-month treatment period. The parameters of weight and waist size were significantly higher in the intervention group than the placebo group after the treatment ($P < 0.05$).

Table 2. Comparison of Outcome Measures between Intervention and Placebo Groups to Assess the Effect of Barberry Root on Metabolic Symptoms of Patients with Schizophrenia Treated with Atypical Antipsychotics

Parameters	Assessment time	Intervention group (n = 41) m ± SD	Placebo group (n = 47) m ± SD	t-value	P-value
Weight (Kg)	Pre	70.00 ± 8.13	67.28 ± 10.92	2.844	0.005*
	Post	74.59 ± 9.42	68.26 ± 11.21		
Waist Size (cm)	Pre	73.52 ± 9.06	68.33 ± 17.40	2.366	0.020*
	Post	79.54 ± 13.38	71.11 ± 19.08		
Blood Fasting HDL (mg/dL)	Pre	47.27 ± 8.13	46.47 ± 9.74	0.554	0.581
	Post	45.90 ± 6.97	44.96 ± 8.70		
Blood Fasting Triglycerides (mg/dL)	Pre	177.29 ± 65.83	189.11 ± 56.22	0.372	0.710
	Post	205.59 ± 55.64	209.72 ± 48.50		
Systolic Blood Pressure (mmHg)	Pre	112.07 ± 13.60	115.64 ± 12.45	0.905	0.368
	Post	116.13 ± 13.75	118.72 ± 13.08		
Diastolic Blood Pressure (mmHg)	Pre	75.56 ± 7.32	77.21 ± 5.64	0.814	0.418
	Post	77.50 ± 7.92	78.72 ± 6.12		
Blood Fasting Glucose (mg/dL)	Pre	90.15 ± 15.11	85.98 ± 15.48	0.224	0.823
	Post	101.83 ± 25.02	102.91 ± 20.23		

Note: m = mean; SD = standard deviation.

Discussion

We aimed to examine the impact of barberry root on the prevention of metabolic syndrome caused by atypical antipsychotics in patients with schizophrenia using a placebo-controlled, three-blind clinical trial. Based on our findings, there was no significant difference in fasting blood glucose, triglyceride and HDL in terms of metabolic changes between the two groups after barberry root intervention. Surprisingly, the average weight change in the intervention group was significantly higher than the placebo group, and we observed negative results in this work. Consistently, some previous studies found that Berberis vulgaris had no significant effect on some metabolic parameters such as fasting blood sugar (28-30). However, other studies reported the significant positive effects of berberine on metabolic syndrome and lipid profile in different populations (31-34). They attributed these effects to the reduction of β-glycosidase and disaccharide activity, the hypoglycemic effect of berberine caused by inducing the glycolysis and activating the adenosine monophosphate-activated protein kinase pathway, and regulation of glucose metabolism mechanisms through glucose tolerance improvement (34). First, it should be noted that none of these researches were conducted on patients with schizophrenia, and secondly, none of them examined the effect of barberry root in combination with antipsychotics. Therefore, one possible interpretation of our finding is that the use of barberry root concurrently with antipsychotics may lead to an initial weight gain associated with the initiation of antipsychotics and the first episode of psychosis. However, further research is required in this regard. Additionally, most previous studies have been conducted on people with metabolic syndrome and overweight (35-37), so berberine may be more effective in people with poorer primary metabolic health. Furthermore, the observed differences between the findings of our trial and other studies can be due to the extraction method and the difference in the studied plant organs.

Previous studies have been mostly aimed at treating metabolic syndrome caused by various conditions such as diabetes. However, the current study was conducted with the aim of preventing metabolic syndrome caused by treatment with antipsychotics. Therefore, it is suggested to investigate the effects of barberry root on the treatment of metabolic syndrome caused by antipsychotics in the future. In addition, the examination of the effect of different organs of this plant on the prevention or treatment of metabolic syndrome in schizophrenia is suggested for the future.

Limitation

Lack of control over dietary intake and physical activity of the patients is the main limitation of this study.

Conclusion

According to the findings of this study, it can be concluded that barberry or berberine root extract did not have a preventive effect on metabolic syndrome factors (lipid profile, sugar, blood pressure, etc.) caused by taking atypical antipsychotics in schizophrenia. It also had no effect on preventing weight gain, at least in the three-month period of the treatment. All told, there is a strong possibility that antipsychotic drugs outweigh the possible effects of berberine.

Conflict of Interest

None.

References

1. Anghelescu I. Successful smoking cessation and improvement of negative symptoms with varenicline in a stable schizophrenia patient. J Neuropsychiatry Clin Neurosci. 2009;21(1):102-3.
2. Goff DC, Bottiglieri T, Arning E, Shih V, Freudenreich O, Evins AE, et al. Folate, homocysteine, and negative symptoms in schizophrenia. Am J Psychiatry. 2004;161(9):1705-8.
3. Smith RC, Lindenmayer JP, Davis JM, Cornwell J, Noth K, Gupta S, et al. Cognitive and antismoking effects of varenicline in patients with schizophrenia or schizoaffective disorder. Schizophr Res. 2009;110(1-3):149-55.
4. Alavi SS, Mohammadi MR, Hooshyari Z, Mohammadi Kalhori S, Salehi M, Salmanian M, et al. Epidemiology of Psychotic Disorders Based on Demographic Variables in Iranian Children and Adolescents. Iran J Psychiatry. 2021;16(1):1-12.
5. Caroff SN, Leong SH, Roberts CB, Berkowitz RM, Campbell EC. Correlates of the Abnormal Involuntary Movement Scale in Veterans With Tardive Dyskinesia. J Clin Psychopharmacol. 2020;40(4):373-80.
6. Foulds J, Russ C, Yu CR, Zou KH, Galaznik A, Franzon M, et al. Effect of varenicline on individual nicotine withdrawal symptoms: a combined analysis of eight randomized, placebo-controlled trials. Nicotine Tob Res. 2013;15(11):1849-57.
7. Hawley C, Fineberg N, Roberts A, Baldwin D, Sahadevan A, Sharman V. The use of the Simpson Angus Scale for the assessment of movement disorder: A training guide. Int J Psychiatry Clin Pract. 2003;7(4):349-2257.
8. Mohammadi MR, Ahmadi N, Khaleghi A, Mostafavi SA, Kamali K, Rahgozar M, et al. Prevalence and Correlates of Psychiatric Disorders in a National Survey of Iranian Children and Adolescents. Iran J Psychiatry. 2019;14(1):1-15.
9. Al Rihani SB, Deodhar M, Darakjian LI, Dow P, Smith MK, Bikmetov R, et al. Quantifying

Anticholinergic Burden and Sedative Load in Older Adults with Polypharmacy: A Systematic Review of Risk Scales and Models. Drugs Aging. 2021;38(11):977-94.
10. Bourque F, van der Ven E, Malla A. A meta-analysis of the risk for psychotic disorders among first- and second-generation immigrants. Psychol Med. 2011;41(5):897-910.
11. Kirkbride J, Coid JW, Morgan C, Fearon P, Dazzan P, Yang M, et al. Translating the epidemiology of psychosis into public mental health: evidence, challenges and future prospects. J Public Ment Health. 2010;9(2):4-14.
12. Biological insights from 108 schizophrenia-associated genetic loci. Nature. 2014;511(7510):421-7.
13. Brown AS, Begg MD, Gravenstein S, Schaefer CA, Wyatt RJ, Bresnahan M, et al. Serologic evidence of prenatal influenza in the etiology of schizophrenia. Arch Gen Psychiatry. 2004;61(8):774-80.
14. Brown AS, Derkits EJ. Prenatal infection and schizophrenia: a review of epidemiologic and translational studies. Am J Psychiatry. 2010;167(3):261-80.
15. Sullivan PF, Kendler KS, Neale MC. Schizophrenia as a complex trait: evidence from a meta-analysis of twin studies. Arch Gen Psychiatry. 2003;60(12):1187-92.
16. Khaleghi A, Mohammadi MR, Shahi K, Nasrabadi AM. Computational Neuroscience Approach to Psychiatry: A Review on Theory-driven Approaches. Clin Psychopharmacol Neurosci. 2022;20(1):26-36.
17. Clarke MC, Tanskanen A, Huttunen M, Whittaker JC, Cannon M. Evidence for an interaction between familial liability and prenatal exposure to infection in the causation of schizophrenia. Am J Psychiatry. 2009;166(9):1025-30.
18. Handunnetthi L, Saatci D, Hamley JC, Knight JC. Maternal immune activation downregulates schizophrenia genes in the foetal mouse brain. Brain Commun. 2021;3(4):fcab275.
19. Kuo CJ, Yang SY, Liao YT, Chen WJ, Lee WC, Shau WY, et al. Second-generation antipsychotic medications and risk of pneumonia in schizophrenia. Schizophr Bull. 2013;39(3):648-57.
20. Lund BC, Perry PJ, Brooks JM, Arndt S. Clozapine use in patients with schizophrenia and the risk of diabetes, hyperlipidemia, and hypertension: a claims-based approach. Arch Gen Psychiatry. 2001;58(12):1172-6.
21. Suttajit S, Pilakanta S. Prevalence of metabolic syndrome and its association with depression in patients with schizophrenia. Neuropsychiatr Dis Treat. 2013;9:941-6.
22. Vancampfort D, Sweers K, Probst M, Maurissen K, Knapen J, Minguet P, et al. Association of the metabolic syndrome with physical activity performance in patients with schizophrenia. Diabetes Metab. 2011;37(4):318-23.
23. Kwon CY, Lee B, Ha DJ. Herbal medicine for behavioral and psychological symptoms of dementia: A protocol for systematic review. Medicine (Baltimore). 2021;100(8):e24577.
24. May BH, Lit M, Xue CC, Yang AW, Zhang AL, Owens MD, et al. Herbal medicine for dementia: a systematic review. Phytother Res. 2009;23(4):447-59.
25. Meliani N, Dib Mel A, Allali H, Tabti B. Hypoglycaemic effect of Berberis vulgaris L. in normal and streptozotocin-induced diabetic rats. Asian Pac J Trop Biomed. 2011;1(6):468-71.
26. Doroodgar A, Arbabi M, Razavi MR, Mohebali M, Sadr F. Treatment of cutaneous leishmaniasis in murine model by hydro alcoholic Essence of Artemisia sieberi. 2008;2(2):42-7.
27. El-On J, Jacobs GP, Witztum E, Greenblatt CL. Development of topical treatment for cutaneous leishmaniasis caused by Leishmania major in experimental animals. Antimicrob Agents Chemother. 1984;26(5):745-51.
28. Asemani S, Montazeri V, Baradaran B, Tabatabiefar MA, Pirouzpanah S. The Effects of Berberis Vulgaris Juice on Insulin Indices in Women with Benign Breast Disease: A Randomized Controlled Clinical Trial. Iran J Pharm Res. 2018;17(Suppl):110-21.
29. Shidfar F, Ebrahimi SS, Hosseini S, Heydari I, Shidfar S, Hajhassani G. The Effects of Berberis vulgaris Fruit Extract on Serum Lipoproteins, apoB, apoA-I, Homocysteine, Glycemic Control and Total Antioxidant Capacity in Type 2 Diabetic Patients. Iran J Pharm Res. 2012;11(2):643-52.
30. Safari Z, Farrokhzad A, Ghavami A, Fadel A, Hadi A, Rafiee S, et al. The effect of barberry (Berberis vulgaris L.) on glycemic indices: A systematic review and meta-analysis of randomized controlled trials. Complement Ther Med. 2020;51:102414.
31. Hadi A, Arab A, Ghaedi E, Rafie N, Miraghajani M, Kafeshani M. Barberry (Berberis vulgaris L.) is a safe approach for management of lipid parameters: A systematic review and meta-analysis of randomized controlled trials. Complement Ther Med. 2019;43:117-24.
32. Iloon Kashkooli R, Najafi SS, Sharif F, Hamedi A, Hoseini Asl MK, Najafi Kalyani M, et al. The effect of berberis vulgaris extract on transaminase activities in non-alcoholic Fatty liver disease. Hepat Mon. 2015;15(2):e25067.
33. Tabeshpour J, Imenshahidi M, Hosseinzadeh H. A review of the effects of Berberis vulgaris and its major component, berberine, in metabolic syndrome. Iran J Basic Med Sci. 2017;20(5):557-68.
34. Firouzi S, Malekahmadi M, Ghayour-Mobarhan M, Ferns G, Rahimi HR. Barberry in the treatment of obesity and metabolic syndrome: possible mechanisms of action. Diabetes Metab Syndr Obes. 2018;11:699-705.
35. Zilaee M, Safarian M, Kermany T, Emamian M, Mobarhan M, Ferns GAA. Effect of barberry treatment on blood pressure in patients with metabolic syndrome. J Natural Products. 2015;8:59-63.
36. Pérez-Rubio KG, González-Ortiz M, Martínez-Abundis E, Robles-Cervantes JA, Espinel-

Bermúdez MC. Effect of berberine administration on metabolic syndrome, insulin sensitivity, and insulin secretion. Metab Syndr Relat Disord. 2013;11(5):366-9.

37. Lazavi F, Mirmiran P, Sohrab G, Nikpayam O, Angoorani P, Hedayati M. The barberry juice effects on metabolic factors and oxidative stress in patients with type 2 diabetes: A randomized clinical trial. Complement Ther Clin Pract. 2018;31:170-4.