Indian Journal of Natural Products and Resources
Vol. 13(4), Decemebr 2022, pp. 474-482
DOI: 10.56042/ijnpr.v13i4.51175

The impact of walnut leaf on the lipid and glucose profiles in diabetic patients: A systematic review and meta-analysis

Moloud Fakhri[1*], Seyde Sedighe Yousefi[1,2], Mahmood Moosazadeh[3], Mohammad Azadbakht[4] and Hafez Fakheri[5*]

[1]Traditional and Complementary Medicine Research Center, Addiction Institute;
[2]Department of Persian Medicine, Faculty of Medicine;
[3]Gastrointestinal Cancer Research Center, Non-communicable Diseases Institute; [4]Department of Pharmacognosy, Faculty of Pharmacy;
[5]Gut and Liver Research Center, Mazandaran University of Medical Sciences, Sari, Iran 48168 95475

Received 18 June 2021; revised received 12 June 2022; accepted 07 July 2022

Managing risk factors associated with cardiovascular diseases, such as blood lipids and blood sugar in people with diabetes (PWDs), is important. Besides antidiabetic medicines, herbal remedies such as walnut leaves have long been utilized to decrease blood sugar and blood lipid levels in PWDs. Hence, this study aimed to investigate the impact of walnut leaf on the lipid and glucose profiles of PWDs through a systematic review and meta-analysis. To gain access to the primary empirical studies, domestic and international databases were searched using MeSH keywords. The databases included Barakat Gostar, SID, Magiran, IranDoc, PubMed, Scopus, Web of Science, Embase, Cochrane, International Standard Randomized Controlled Trial Number (ISRCTN), International Clinical Trials Registry Platform (ICTRP), and Clinical Trial.gov (a clinical trial registration system). Data analysis was performed within Stata 14 software. The *P*-value was considered $P < 0.05$. In 4 studies with a sample size of 101 individuals, which were published between 2014 and 2018, post-test scores of the treatment and control groups pointed out that the difference between insulin and FBS levels was statistically significant. The FBS level was higher in the control group than in the treatment group. However, their insulin level was lower than those in the treatment group. The difference between the levels of HbA1C, cholesterol, triglyceride, LDL, HDL, AST, ALT, ALP, and creatinine in the control and treatment groups was not statistically significant. The pre and post-test scores of the treatment group were compared. The levels of FBS, HbA1C, and LDL decreased significantly, while the patients' insulin levels increased remarkably. No noticeable correlation was observed in other lipid profiles. Due to the thoroughly limited research resources, further studies are required to confirm the findings more confidently.

Keywords: Blood lipids, Blood sugar, Diabetic patients, Meta-analysis, Systematic review, Walnut leaf.

IPC code; Int. cl. (2021.01)-A61K 36/00, A61P 3/00

Introduction

According to the World Health Organization, 422 million people have diabetes globally, and the rate is promptly escalating[1]. Diabetes mellitus (DM) is the seventh leading cause of death and stands third for fatal complications[2]. Male reproductive system disorders and developing cataracts are notable DM complications[3]. Diabetes mellitus is one of the public health issues in the 21st century. Developed and developing nations are all undergoing an epidemic of diabetes, specifically type 2 diabetes[4]. The type 2 diabetes, which is characterized by elevated blood glucose as well as impaired insulin secretion and function, is becoming a primary global health issue[5]. Alongside blood glucose, keeping track of cardiovascular risk factors, including weight, fat levels, and blood pressure, is immensely critical in patients with type 2 diabetes[6].

The World Health Organization has advised that the impacts of herbs on the conditions such as diabetes, for which safe and modern medicines are available, be investigated[7]. Meanwhile, some potentially hazardous side effects of several oral antidiabetics have been reported. Also, no conventional medicine grants the patients utter control over blood glucose levels[8,9]. So far, the positive impact of over 1200 herbs on blood sugar or diabetes complications has been diagnosed[10]. Herbal remedies in traditional medicine include fenugreek, cinnamon, valerian, blackberry leaf, coriander seeds, garlic, onions, walnuts, and walnut leaf[11,12].

The potential success of medicinal herbs in curing diabetes and the fact that they are abundant in most regions of the world facilitate their use. One of those herbs is *Juglans regia* L. which belongs to the

*Correspondent author
Email: mmfir@yahoo.com; hafezfakheri@gmail.com
Supplementary table is available online only.

Juglandaceae family (also known as the walnut family). Members of this family are the following species: *Juglans nigra*, *Juglans cinerea*, and *Juglans regia*. However, only *J. regia* is found in Iran[13]. *J. regia* is a member of the Juglandaceae family and a species of Persian or English walnut tree. It is native to the region and extends from the Balkans to the Himalayas and southwest China. *J. regia* is a massive deciduous tree. It is 25 to 35 meters tall and has a two-meter trunk diameter[14]. This valuable tree has a long history of medicinal benefits, including treating a wide range of health issues. All parts of the plant almost have medicinal properties. Dried seeds (nuts) are very popular and viewed as a luxury in Iran. Green walnuts, endocarp, pericarp, green husk (epicarp), and leaves are used in the cosmetic, pharmaceutical, and cosmeceutical industries[15].

The green parts of the walnut plant, especially the leaves, contain antioxidant compounds, e.g., phenolic acids, flavonoids, and chlorogenic acid (CGA)[16]. Walnut leaf, is widely used in Iran as a herbal remedy to reduce blood sugar[16,17].

Studies on rats have reported antidiabetic effects of walnut leaf on diabetic rats[18-20]. They revealed that the hydroalcoholic extract of walnut mixed with antioxidants such as flavonoids increases insulin levels. It also diminishes the glucose, ALT, ALP, and AST enzyme levels in the blood of STZ-induced diabetic rats[21,22]. To see if the antidiabetic effect of walnut leaves is confirmed in the human model, studying the effect of walnut leaves on the level of blood lipids and blood sugar in diabetic patients is intended.

Studies have indicated that using walnut leaves as aqueous-alcoholic, alcoholic, cyclohexane, and powder extract reduces the blood glucose levels in STZ-induced diabetic rats[20,23,24]. In another report, dietary intake involving cyclohexane, ether, and ethanol extract of walnut leaves decreased glucose, cholesterol, triglyceride, and urea nitrogen concentrations[23]. Therefore, for the very first time, the present meta-analysis was conducted to investigate the impact of walnut leaf on the lipid and glucose profiles of people having diabetes through systematic review and meta-analysis.

Materials and Methods

Study protocol

The present study is a systematic review and meta-analysis investigating the impacts of walnut leaf on the lipid and glucose profiles of people with diabetes worldwide. This study protocol was registered on PROSPERO (ID: CRD42021260928, Date: 15.7.2021).

Statistical population

The participants of the selected studies were people with diabetes (PWD). No age group, gender, type of diabetes (type 1 diabetes or type 2 diabetes), or race ascertainment biases were inflicted through sampling.

Primary outcome

Eligible studies had at least one outcome assessment of lipid [LDL (Low-density lipoprotein)/ HDL (High-density lipoprotein)/ TG (T*riglycerides*)/ Cholesterol] and glucose (FBS/ FBG/ FPG/ Insulin/ HbA1C) profiles.

Secondary outcome

Blood creatinine, AST, ALP, and ALT levels were the secondary outcomes of the present meta-analysis.

Search strategy

Domestic, international, and electronic databases, such as PubMed, Scopus, Web of Science, Embase, Cochrane, and Google Scholar were explored with neither time nor language restrictions in this systematic review. Iranian bibliographic databases, SID, Magiran, and Barakat Gostar, were also checked out via electronic search to access the Persian resources. The study was conducted using the keywords walnut leaf, blood sugar, blood lipids, diabetic patients, *J. nigra*, *J. regia*, *J. cinerea*, meta-analysis, and systematic review, which were last updated on 30 January 2021. Their combinations were also investigated in English databases using AND and OR operators. Dissertations, research reports, and articles of research conferences and seminars were investigated in the IranDoc information system to have unofficial resources looked up as well. Clinical Trial.gov[25] as a clinical trial registration system, International Standard Randomized Controlled Trial Number (ISRCTN) owned by BioMed Central, and Clinical Trial Registration System under the World Health Organization were explored to find the protocols of the trials that were recorded but not published. Furthermore, references of all the primary studies placed at the end of the PRISMA flowchart (Supplementary Table 1) were manually searched.

Search strategy in used in PubMed was (((Blood sugar [Title/Abstract] OR (Blood lipids [Title/ Abstract]) and (Diabetes [Title/Abstract])) and (Walnut leaf [Title/Abstract]).

Inclusion and exclusion criteria

PICO components

Patient population was PWDs who consumed walnut leaves to reduce their lipid and glucose profile levels. Intervention used was various types of walnut leaves. The group that did not use the walnut leaves took the placebo instead. The primary outcome involved lipid and glucose profiles. The secondary outcome involved liver and kidney enzymes.

Inclusion criteria

In this meta-analysis, the quasi-experimental design of primary studies included randomized blinded or non-blinded clinical trials. The intervention in these trials was walnut leaves. The experimental group consumed walnut leaves, and the control group was given the placebo, i.e., no intervention. Eligible trials must have evaluated at least one lipid or glucose profile outcome. In addition, patients' blood creatinine levels and liver enzymes were considered the secondary outcomes.

Exclusion criteria

The exclusion criteria included the lack of access to the full text of some research articles, reports, and studies that had qualitatively interpreted the impacts of walnut leaf on PWDs, failure to report the required information, low quality of investigations determined by Cochrane Collaboration's quality checklist of clinical trials, studies investigating the impacts of walnut leaf on non-diabetic individuals, and studies utilizing other parts of walnut, such as nut, fruit, or shells.

Qualitative interpretation of primary research

After exploring the primary research, two authors evaluated them separately using Cochrane Collaboration's quality checklist of clinical trials. This checklist had seven items, which assesses a domain of bias in clinical trials. Also, each item in this checklist has three options: high risk of bias, low risk of bias, and unspecificity. After terminating the critical appraisal in all studies, the dissimilarities of the items were evaluated first in each study. Then all the inconsistencies became a single option through compromises between the two evaluators.

Data collection

Two researchers extracted data from studies separately to minimize the reporting bias and data collection errors. They entered the extracted data into a chart containing the researcher’s name, publication date, the number of patients, type of diabetes, type of study, type of anti-diabetic medicine used by patients, quantity and duration of walnut leaf consumption, the mean and standard deviations of lipid profile levels, glucose profiles, liver enzymes, and blood creatinine levels before and after the intervention. The third researcher analyzed the data collected by the two previous researchers to amend any inconsistencies. If the required data was not reported in one of the primary articles or research studies, the incharge author of that article was asked to send it. A maximum of three attempts was established to contact the responsible authors on three separate occasions (at least once every five days) lest they not respond to the email.

Data analysis

Since the primary outcome is quantitative, the effect size of the intervention was calculated. In addition, it was possible to calculate the intra-group mean difference (MD) in the treatment group. The standardized mean difference (SMD), which is a classic measure of effect size, shows the strength of the relationship between the intervention and the target outcome. Usually, the closer this index (SMD) is to zero, the weaker the relationship. And the closer it is to one or above, the stronger the relationship. If the confidence interval for SMD includes zero, then that relationship is not statistically significant, and vice versa. The studies were merged based on the number of samples, mean, and standard deviation. Cochran's Q test and I^2 index evaluated the heterogeneity. There are three categories for the I^2 index: low heterogeneity (less than 25%), moderate heterogeneity (between 25 to 75%), and severe heterogeneity (over 75%). The fixed-effects model is used for low heterogeneity, and the stochastic-effects model is used for high heterogeneity. Hence, the stochastic-effects model was used in the present study. Data analysis was performed within Stata14, and the significance level of the tests was considered $P < 0.05$.

Results

Data selection process

Initially, 58 articles were found on the above mentioned databases. By reviewing the titles, 23 replicate studies were eliminated. The remaining 35 articles were reviewed, and 28 of them were excluded according to the exclusion criteria. Out of the remaining 7 articles, 3 more were excluded due to inadequate information or the lack of access to the full text. Eventually, the remaining four articles, which had been of outstanding quality, entered the quality evaluation stage and then the meta-analysis process (Fig. 1).

As seen in Table 1, although the present meta-analysis is not location-specific, all the research belongs to Iran. Despite the lack of restriction for the disease type, all the studies were conducted on the patients with type 2 diabetes. No information from patients with type 1 diabetes is available. In addition, there was no significant difference between the control group and the treatment group regarding sample number, gender, and age group of patients. In the studies, the patients consumed 200 to 400 mg of walnut leaves. The consumption period of walnut leaves also varied from 60 to 90 days. However, all patients in the research studies consumed walnut leaves as capsules. The research with the smallest sample involved 19 PWDs, and the largest study sample involved 32.

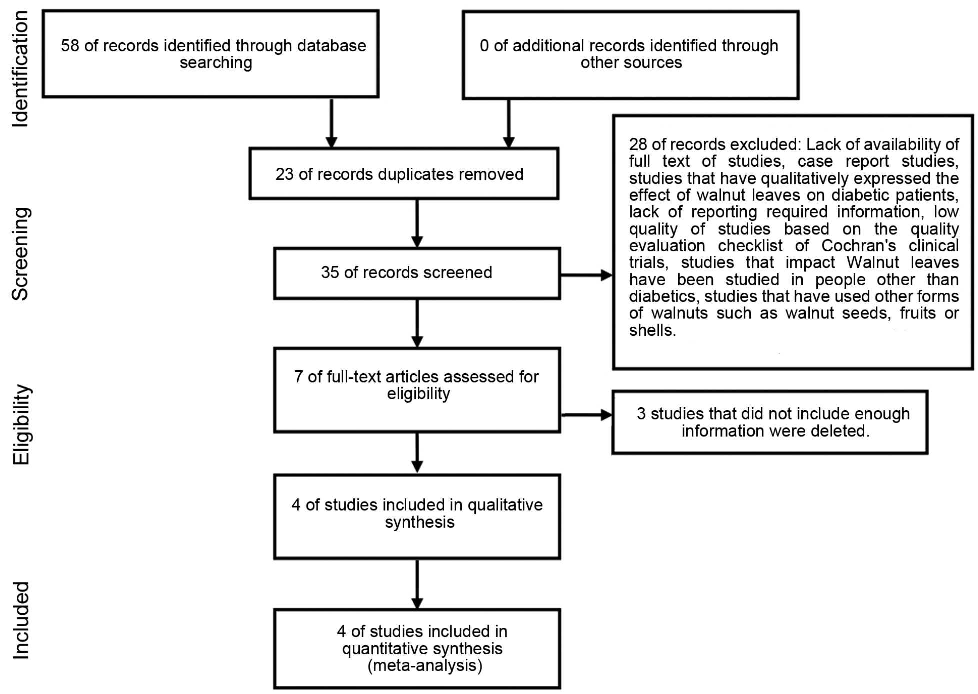

Fig. 1 — Flowchart of the research articles entering the systematic review and meta-analysis process.

Table 1 — Specifications of articles entering the systematic review and meta-analysis process

Type of study	Country	City	Sample size (Experiment)	Sample size (Placebo)	Number of female (Experiment)	Number of female (Placebo)	Number of male (Experiment)	Number of male (Placebo)	Mean age (Experiment)	Mean age (Placebo)	Type of diabetes	Duration of use (Day)	Daily consumption	Consumption instruction	Reference
Randomized double blind placebo controlled trial	Iran	Tehran	19	18	14	11	5	7	56.5	55.1	Type 2	90	250 mg	capsules	26
Randomized double blind placebo controlled trial	Iran	Ghaemshahr	20	19	19	18	1	1	50.5	49.9	Type 2	60	200 mg	capsules	27
A first human trial	Iran	Alborz	30	28	19	16	11	12	58.1	56.2	Type 2	60	400 mg	capsules	37
Randomized double-blind, placebo-controlled clinical trial	Iran	Alborz	32	29	17	16	15	13	54.8	55.4	Type 2	90	200 mg	capsules	38

Sugar profiles

The FBS level decreased remarkably in the treatment group. However, the FBS level did not change in the control group. HbA1C levels significantly decreased and increased in the treatment and control groups, respectively. Insulin levels increased in both control and treatment groups, although this relationship was statistically significant in the treatment group and insignificant in the control group (Table 2).

Lipid profiles

Patients showed lower blood cholesterol levels in both control and treatment groups, but these relationships were not statistically significant. However, cholesterol reduction was greater in the treatment group than in the control group. While the patients' triglyceride levels decreased in the treatment group, it was increased in the control group, but the changes were not statistically significant. LDL levels decreased in both groups, yet the decrease was not statistically significant in the control group. HDL levels increased in both control and treatment groups, but these relationships were not statistically significant. Note that the HDL levels increased nearly in the control group compared to the treatment group (Table 2).

Liver enzymes

AST levels decreased in the treatment group, but this relationship was not statistically significant. On the contrary, the AST level of patients increased significantly in the control group. While the ALT levels did not increase significantly in the treatment group, they increased remarkably in the control group. In the treatment group, the ALP level decreased but was not statistically significant. However, the ALP level increased significantly in the control group (Table 2). Moreover, blood creatinine levels increased notably in both control and treatment groups (Table 2).

After comparing the post-test scores of both groups, it was found that the difference between insulin and FBS levels in the placebo and treatment groups was statistically significant. Though the FBS level of the placebo patients was higher than those of the treatment group, their insulin level was lower. The difference between HbA1C, cholesterol, triglyceride, LDL, HDL, AST, ALT, ALP, and creatinine levels in the both control and treatment groups was not statistically significant (Table 3).

Discussion

In the present meta-analysis (articles published between 2014 and 2018) with a sample size of 101 PWDs, the difference in post-test scores explicated that the FBS level in the control group was higher than in the treatment group although their insulin level was lower. Comparing the pre- and post-intervention scores of the experimental group showed that the levels of FBS, HbA1C, and LDL decreased significantly, while the insulin level of the patients increased.

The findings of Abdoli *et al.*[26], whose study included 19 patients in the treatment group and 18 patients in the control group, aimed to investigate the impacts of walnut leaf aqueous extract on blood glucose in patients with type 2 diabetes. It was revealed that walnut leaf aqueous extract has a diminishing effect on FPG, PPG, and HbA1c. All three studies confirm the positive impact of walnut leaf consumption on the lipid and glucose profiles of patients with type 2 diabetes.

Table 2 — Post-intervention and pre-intervention scores in control and treatment groups

Outcomes		Expriment group						Placebo group				
		Number of study	SMD	SMD lower limit	SMD upper limit	P-Value	I^2 (%)	SMD	SMD lower limit	SMD upper limit	P-Value	I^2 (%)
Sugar profile	FBS	4	-0.39	-0.67	-0.12	0.878	0	0	-0.28	0.29	0.934	0
	HbA1C	4	-0.62	-1.02	-0.23	0.133	46.4	1.10	0.79	1.41	0.939	0
	Insulin	2	0.81	0.40	1.21	0.611	0	0.56	-0.01	1.12	0.177	45.1
Lipid profile	Cholesterol	3	-0.26	-0.59	0.07	0.977	0	-0.03	-0.37	0.31	0.738	0
	TG	3	-0.15	-0.48	0.18	0.975	0	0.11	-0.23	0.45	0.573	0
	LDL	3	-0.36	-0.70	-0.03	0.892	0	-0.11	-0.45	0.23	0.397	0
	HDL	3	0.15	-0.18	0.48	0.600	0	0.35	-0.26	0.97	0.047	67.3
Liver enzymes	AST	3	-0.01	-0.31	0.30	0.528	0	0.75	0.42	1.08	0.787	0
	ALT	3	0.13	-0.18	0.44	0.656	0	0.61	0.28	0.94	0.577	0
	ALP	3	-0.03	-0.33	0.28	0.787	0	0.85	0.52	1.19	0.945	0
Creatinine		2	0.95	0.54	1.35	0.916	0	1.01	0.58	1.43	0.740	0

Table 3 — Subgroup analysis

Outcomes		Number of study	WMD	WMD lower limit	WMD upper limit	P-Value	I^2 (%)
Sugar profile	FBS	4	0.29	0.01	0.58	0.594	0
	HbA1C	4	0.12	-0.16	0.40	0.549	0
	Insulin	2	-0.50	-0.98	-0.03	0.247	25.4
Lipid profile	Cholestrol	3	0.06	-0.27	0.40	0.777	0
	TG	3	0.01	-0.39	0.41	0.249	28.1
	LDL	3	0.17	-0.20	0.55	0.295	18.2
	HDL	3	-0.02	-0.50	0.47	0.130	50.9
Liver enzymes	AST	3	-0.05	-0.37	0.26	0.954	0
	ALT	3	-0.25	-0.56	0.06	0.653	0
	ALP	3	-0.20	-0.52	0.11	0.847	0
Creatinine		2	0.08	-0.31	0.47	0.752	0

However, the study carried out by Rabiei *et al.*, which aimed to explore the impacts of hydroalcoholic extract of walnut leaf on blood glucose levels and cardiovascular risk factors in patients with type 2 diabetes showed that walnut leaf extracts have no significant impact on blood sugar and insulin resistance. None the less, body weight, body mass index (BMI), and systolic blood pressure decreased significantly as opposed to the initial measurements. Lipid profiles did not change considerably compared to the initial measurements[27]. This study claimed that walnut leaf is not beneficial in improving the lipid and glucose profiles of type 2 diabetes patients. Due to the conflicting reports of the analyzed studies, it seemed essential that a meta-analysis study be conducted.

No meta-analysis has been conducted on the impacts of walnut leaf on the lipid and glucose profiles of PWDs, but information on other herbal remedies is already available. For instance, in the following two meta-analyses, the positive impacts of cinnamon and green tea on patients' glucose profiles are obvious. Deyno *et al.*[28], conducted a meta-analysis consisting of 16 samples to investigate the effect of cinnamon on patients with type 2 diabetes. It was established that cinnamon increased fasting blood glucose (FBG), and HOMA-IR (Homeostatic Model Assessment for Insulin Resistance) decreases significantly as opposed to the control group with the weighted mean difference of -0.545 (95% CI: -0.910, -0.18) mmol/L, but no significant change was observed in the mean differences of HbA1c and lipid profile. Findings of the study administered by Liu *et al.*[29], on 17 patients, aiming to quantitatively evaluate the impact of green tea on glucose control and insulin sensitivity, showed that green tea consumption significantly reduced the concentrations of fasting glucose (MD: -0.09 mmol/L; 95% CI -0.15 to -0.0) and haemoglobin A1c (MD: -0.30 mmol/L; 95% CI - 0.37 to -0.22).

In the next three meta-analyses, the positive impacts of garlic, aloe Vera, and cinnamon consumption in improving the lipid profile of PWDs are clear. In a meta-analysis performed by Shabani *et al.*[30], to investigate the effect of garlic on lipid profiles and glucose parameters in PWDs, it was indicated that garlic reduced the level of fat profiles including triglycerides (WMD: 16.87 mg/dL (95% CI: -21.01, - 12.73)), total cholesterol (WMD: 9.65 mg/dL (95% CI: -15.07, -4.23)), HDL (WMD: 12.44 mg/dL (95% CI: -18.19, -6.69)), LDL (WMD: 3.19 mg/dL (95% CI: -1.85, -4.53)), fasting blood sugar (FBS) (WMD: 10.90 mg/dL (95% CI: - 16.40, -5.40), and HbA1C (WMD: 0.60 mg/dL (95% CI: -0.98, -0.22)) more effectively than placebo. Zhang *et al.*[31], conducted a meta-analysis including 5 RCT studies aiming to evaluate the evidence regarding the impact of aloe vera on adjusting prediabetes and untreated diabetes. The results showed that compared to the control group, aloe vera supplements significantly decreased the concentrations of fasting blood glucose (FBG) ($P = 0.02$; WMD: -30.05 mg/dL; 95% CI: -54.87 to -5.23 mg/dL), HbA1c ($P < 0.00001$; WMD: -0.41%; 95% CI: -0.55% to -0.27%), triglycerides (P=0.0001), total cholesterol (TC) ($P < 0.00001$), and LDL-C ($P < 0.00001$). Also, aloe vera was more effective than placebo in increasing serum concentration of HDL-C (P =0.04). Jamali *et al.*[32], conducted a meta-analysis consisting of 16 studies on the effect of cinnamon supplementation on lipid profiles in patients with type 2 diabetes. It showed that cinnamon supplements significantly reduced triglycerides (TG) (WMD: - 26.27 mg/dL, 95% CI: [-38.93, -13.61], $P < 0.001$), total cholesterol (TC) (WMD: -13.93 mg/dL, 95% CI: [-25.64, -2.22], P = 0.020), and LDL-C (WMD: -6.13

mg/dL, 95% CI: [-10.72, -1.53], P = 0.009), while no change in HDL concentration (WMD: 0.64 mg/dL, 95% CI: [-0.18, 1.46], P = 0.128) was observed in patients with type 2 diabetes.

The following two meta-analyses investigating the impact of *Nigella sativa* (black caraway or black seed) and fenugreek supplementation report that the lipid and glucose profiles were improved in some patients but remained intact in the rest. Daryabeygi-Khotbehsara *et al.*[33], conducted a meta-analysis of 7 studies which indicated that consuming *N. sativa* significantly increased fasting blood sugar (FBS) (−17.84 mg/dL, 95% CI: −21.19 to −14.49, *P* <0.001), HbA1c (−0.71%, 95% CI: −1.04 to −0.39, *P* <0.001), total cholesterol (TC) (WMD: −22.99 mg/dL, 95% CI: −32.16 to −13.83, *P* <0.001), and LDL-c (−22.38 mg/dL, 95% CI: −33.60 to −11.15, *P* <0.001). It was also found that *N. sativa* did not have any notable impact on triglycerides (TG) (−6.80 mg/dL, 95% CI: −33.59 to 19.99, P = 0.61) and HDL-c (0.37 mg/dL, 95% CI: −1.59 to 2.33, P = 0.71. Furthermore, a meta-analysis conducted by Gong *et al.*[34], consisting of 12 studies, reported that fenugreek considerably decreased levels of FBG (MD: -0.84 mmol/L; 95% CI -1.38 to -0.31), HbA1c (MD: -1.16; 95% CI -1.23 to -1.09), and total cholesterol (MD: -0.30 mmol/L; 95% CI -0.56 to -0.03). However, despite the decreasing levels of TG or LDL-c and the increasing level of HDL-c, these findings were not statistically significant.

Moreover, we discovered that using tea and walnut had little influence on improving the patients' health by analyzing the results of two meta-analyses that examined the impact of the consumption of herbal remedies on the glucose and lipid profiles of PWDs. Li *et al.*[35], conducted a meta-analysis of 10 clinical trials which investigated the effects of tea or tea extract on metabolic profiles in patients with type 2 diabetes. The results implied that tea can decrease fasting blood insulin and waist circumference only after 8 weeks of intervention, while there was not a statistically significant difference in insulin resistance determined by Homeostasis Model Assessment (HOMA) (MD: 0.38 (-0.18, 0.95).), fasting blood sugar (FBS) (MD: -0.05 mmol/L (-0.51, 0.40)), LDL (MD: 0.07 mmol/L (-0.15, 0.29)), HDL (MD: 0.01 mmol/L (-0.08, 0.09), triglycerides (MD: -0.11 mmol/L (-0.28, 0.05)), and fasting cholesterol (MD: -0.05 mmol/L (-0.20, 0.11)) in patients with type 2 diabetes. Neale *et al.*[36], performed a meta-analysis of 16 studies aiming to investigate the impact of walnuts on glycemic control. The findings registered that walnut consumption led to no significant difference in fasting blood sugar levels (WMD: 0·331 mg/dL; 95 % CI −0·817, 1·479) or other variables. The findings of the mentioned study with the results of the present meta-analysis were compared. Conclusively, consuming walnut leaves results in more desirable outcomes for patients with type 2 diabetes than consuming walnuts. Nevertheless, further clinical trials are required to confirm this statement.

Limitations

a) The number of articles published in this field was so limited that analysis based on subgroups such as walnut leaf dose, period of walnut leaf consumption, age groups and gender was not possible.

b) No study had investigated the impact of walnut leaves on patients with type 1 diabetes. Therefore, its impacts on type 1 DM patients with type 2 DM patients were not comparable.

c) Since all the published articles regarded Iran, it was impossible to compare the findings of various countries and interpret the impacts of diverse species of walnut leaves.

Conclusion

The strongest impact of walnut leaves in the treatment group was on HbA1C, FBS, and LDL levels respectively. In other cases, it had no statistically significant effect. In other words, the FBS level of patients in the control group was higher than in the treatment group after the intervention. But the insulin level of patients in the placebo group was lower than those in the treatment group.

Due to the study limitations, it is recommended that other clinical trials be conducted to evaluate the impact of walnut leaf consumption on improving the lipid and glucose profiles of PWD (types 1 and 2). The inadequate number of studies in this field may be due to the side effects of walnut leaf, including liver complications, although this study did not display a significant impact on liver enzymes.

Acknowledgement

Mazandaran University of Medical Sciences sponsored the research project of this article (Grant #9083).

Conflict of interest

The authors declare that they have no conflict of interest.

References

1 Mathers C and Loncar D, Projections of global mortality and burden of disease from 2002 to 2030, *PLoS Med*, 2006, **3**(11), e442.

2 Shaw J, Sicree R and Zimmet P, Global estimates of the prevalence of diabetes for 2010 and 2030, *Diabetes Res Clin Pract*, 2010, **87**(1), 4-14.

3 Paschou S, Papadopoulou-Marketou N, Chrousos G and Kanaka-Gantenbein C, On type 1 diabetes mellitus pathogenesis, *Endocr connect*, 2018, **7**(1), R38-46.

4 Zimmet P, Globalization, coca-colonization and the chronic disease epidemic: Can the Doomsday scenario be averted?, *J Intern Med*, 2001, **249**(S741), 17-26.

5 Norris S, Engelgau M and Narayan K, Effectiveness of self-management training in type 2 diabetes: A systematic review of randomized controlled trials, *Diabetes Care*, 2001, **24**(3), 561-87.

6 Kurukulasuriya L and Sowers J, Therapies for type 2 diabetes: Lowering HbA1c and associated cardiovascular risk factors, *Cardiovasc Diabetol*, 2010, **9**, 45.

7 Kim J, Kang S, Park M, Jung T, Choi H, *et al.*, Ameliorative anti-diabetic activity of dangnyosoko, a Chinese herbal medicine, in diabetic rats, *Biosci Biotechnol Biochem*, 2007, **71**(6), 1527-1534.

8 Philippe J and Raccah D, Treating type 2 diabetes: how safe are current therapeutic agents?, *Int J Clin Pract*, 2009, **63**(2), 321-332.

9 Gilbert M and Pratley R, Efficacy and safety of incretin-based therapies in patients with type 2 diabetes mellitus, *Eur J Intern Med*, 2009, **20**, S309-18.

10 Jelodar G and Nazifi S, Effect of coriander, pomegranate and walnut leaf on serum biochemical parameters of diabetic rats, *J Shahid Sadoughi Univ Med Sci*, 1999, **7**(1), 77-85.

11 Jelodar G and Nazifi-Habibabadi S, Effect of walnut leaf extracts on serum biochemical parameters of diabetic rats, *J Shaheed Beheshti Univ Med Sci*, 1998, **22**(2), 18-25.

12 Mirheidar H, Plants information and plants apply in disease protection and treatment, *Tehran Nashr-e-Farhang e-Eslami Press*, 2001.

13 Mozafarian V, Walnut tree. Identification of medicinal and aromatic plants of Iran. Tehran, Iran, *Farhang Moaser Press*, 2012, 473–5.

14 Zargari A, Walnut tree and black mulberry in medicine, *Tehran University Press, Tehran, Iran*, 2012, **4**, 439–62.

15 Chopra R, Varma B and Chopra I, Supplement to glossary of Indian medicinal plants, Publications and Information Directorate-CSIR, 1986.

16 Panth N, Paudel K and Karki R, Phytochemical profile and biological activity of *Juglans regia*, *J Integra Med*, 2016, **14**(5), 359-73.

17 Zarshenas M, Khademian S and Moein M, Diabetes and related remedies in medieval Persian medicine, *Indian J Endocrinol Metab*, 2014, **18**(2), 142–9.

18 Jelodar G, Mohsen M and Shahram S, Effect of walnut leaf, coriander and pomegranate on blood glucose and histopathology of pancreas of alloxan induced diabetic rats, *Afr J Tradit Complement Altern Med*, 2007, **4**(3), 299-305.

19 Gholamreza K and Hossein B, Effects of walnut leaf aqueous extract on blood sugar and lipids in male diabetic rats, *Saudi Med J*, 2008, **29**(9), 1350-2.

20 Asgary S, Parkhideh S, Solhpour A, Madani H, Mahzouni P, *et al.*, Effect of ethanolic extract of *Juglans regia* L. on blood sugar in diabetes-induced rats, *J Med Food*, 2008, **11**(3), 533-538.

21 Hosseini S and Karimzadeh K, Anti-diabetic effects of hydroalcohlic *Juglans regia* male flower extract on blood glucose level and on liver enzymes activity in intact and diabetogenized adult male rat [persian], *J Birjand Univ Med Sci*, 2012, **19**(2), 165-72.

22 Hosseini S, Karimzadeh K and Vessal M, Effects of a hydroalcoholic extract of walnut male flowers on diabetic rats [persian], *Zahedan J Res Med Sci*, 2013, **15**(11), 55-8.

23 Jelodar G and Nazifi S, Effect of walnut leaf extracts on serum biochemical parameters of diabetic rats, *J Faculty Vet Univ Tehran*, 2001, **56**, 37-40.

24 Divband K, Komeili G and Saeidi-Neek F, Effects of walnut leaves aqueous extract on blood sugar and serum lipids in diabetic rats, *J Birjand Univ Med Sci*, 2010, **17**, 11-8.

25 Abdoli M, Dabaghian F, Goushegir A, Shirazi M, Nakhjavani M, *et al.*, Anti-hyperglycemic effect of aqueous extract of *Juglans regia* L. leaf (walnut leaf) on type 2 diabetic patients: A randomized controlled trial, *Adv Integr Med*, 2017, **4**(3), 98-102.

26 Rabiei K, Ebrahimzadeh M, Saeedi M, Bahar A, Akha O, *et al.*, Effects of a hydroalcoholic extract of *Juglans regia* (walnut) leaves on blood glucose and major cardiovascular risk factors in type 2 diabetic patients: A double-blind, placebo-controlled clinical trial, *BMC Complement Altern Med*, 2018, **18**(1), 1-7.

27 Deyno S, Eneyew K, Seyfe S, Tuyiringire N, Peter E, *et al.*, Efficacy and safety of cinnamon in type 2 diabetes mellitus and pre-diabetes patients: A meta-analysis and meta-regression, *Diabetes Res Clin Pract*, 2019, **156**, 107815.

28 Liu K, Zhou R, Wang B, Chen K, Shi L, *et al.*, Effect of green tea on glucose control and insulin sensitivity: A meta-analysis of 17 randomized controlled trials, *Am J Clin Nutr*, 2013, **98**(2), 340-8.

29 Shabani E, Sayemiri K and Mohammadpour M, The effect of garlic on lipid profile and glucose parameters in diabetic patients: A systematic review and meta-analysis, *Prim Care diabetes*, 2019, **13**(1), 28-42.

30 Zhang Y, Liu W, Liu D, Zhao T and Tian H, Efficacy of *Aloe vera* supplementation on prediabetes and early non-treated diabetic patients: A systematic review and meta-analysis of randomized controlled trials, *Nutr*, 2016, **8**(7), 388.

31 Jamali N, Kazemi A, Saffari-Chaleshtori J, Samare-Najaf M, Mohammadi V, *et al.*, The effect of cinnamon supplementation on lipid profiles in patients with type 2 diabetes: A systematic review and meta-analysis of clinical trials, *Complement Ther Med*, 2020, **29**, 102571.

32 Daryabeygi-Khotbehsara R, Golzarand M, Ghaffari M, Djafarian K, Nigella sativa improves glucose homeostasis and serum lipids in type 2 diabetes: A systematic review and meta-analysis, *Complement Ther Med*, 2017, **35**, 6-13.

33 Gong J, Fang K, Dong H, Wang D, Hu M, *et al.*, Effect of fenugreek on hyperglycaemia and hyperlipidemia in diabetes and prediabetes: A meta-analysis, *J Ethnopharmacol*, 2016, **194**, 260-8.

34 Li Y, Wang C, Huai Q, Guo F, Liu L, *et al.*, Effects of tea or tea extract on metabolic profiles in patients with type 2 diabetes mellitus: A meta analysis of ten randomized controlled trials, *Diabetes Metab Res Rev*, 2016, **32**(1), 2–10.

35 Neale E, Guan V, Tapsell L and Probst Y, Effect of walnut consumption on markers of blood glucose control: A systematic review and meta-analysis, *Br J Nutr*, 2020, **124**(7), 641-53.

36 Hosseini S, Huseini H, Larijani B, Mohammad K, Najmizadeh A, *et al.*, The hypoglycemic effect of *Juglans regia* leaves aqueous extract in diabetic patients: A first human trial, *DARU J Pharm Sci*, 2014, **22**(1), 1-5.

37 Hosseini S, Jamshidi L, Mehrzadi S, Mohammad K, Najmizadeh A, *et al.*, Effects of *Juglans regia* L. leaf extract on hyperglycemia and lipid profiles in type two diabetic patients: A randomized double-blind, placebo-controlled clinical trial, *Ethnopharmacol*, 2014, **152**(3), 451-6.