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Barberry (*Berberis vulgaris L.*) is a safe approach for management of lipid parameters: A systematic review and meta-analysis of randomized controlled trials

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ABSTRACT

Objective: We performed a meta-analysis to evaluate the efficacy of barberry supplementation on plasma lipid concentration in adult population.
Methods: The search included PubMed, Scopus, ISI Web of Science, Cochrane library, and Google Scholar (up to October 2018) to identify randomized controlled trials (RCTs) investigating the effects of barberry supplementation on serum lipid parameters. Mean Difference (MD) was pooled using a random-effects model.
Results: Meta-analysis on 5 RCTs with 339 participants indicated that barberry supplementation significantly decreased the levels of total cholesterol (MD: -23.58 mg/dl, 95% CI: -31.00 to -16.16, P ≤ 0.001), triglyceride (MD: -29.16 mg/dl, 95% CI: -42.91 to -15.41, P ≤ 0.001), and low-density lipoprotein cholesterol (MD: -13.75 mg/dl, 95% CI: -19.31 to -8.20, P ≤ 0.001) whereas changes in high-density lipoprotein cholesterol (MD: 3.40 mg/dl, 95% CI: -0.06–6.87, P = 0.054) was not statistically significant.
Conclusion: This systematic review and meta-analysis suggested the efficacy of barberry supplementation on lipid parameters. However, further large-scale studies are needed to confirm these results.

1. Introduction

Cardiovascular diseases (CVDs) are currently the most common cause of death from non-communicable diseases.[1,2] According to the World Health Organization in 2015, CVDs are responsible for one third of all global deaths, about 17.7 million people, a number that is expected to grow.[3] Thus, the increase of CVDs brings major costs to the economy and health care systems, especially in developing countries.[4] Generally, a combination of various factors such as smoking, obesity, hypertension and dyslipidemia could be considered as the leading causes of CVDs.[5] Dyslipidemia is a clinical condition characterized by the increase in one or more of the lipids in the plasma including total cholesterol (TC), triglyceride (TG) and low-density lipoprotein cholesterol (LDL-C) or reduced level of high-density lipoprotein cholesterol (HDL-C).[6,7] With the decline of cigarette smoking, dyslipidemia has become the number one modifiable risk factor for CVDs.[7] At present, statins and fibrates, are widely used hypolipidemic drugs, as they efficiently reduce serum lipids; however, they also present a number of adverse side effects such as myopathy and hepatotoxicity, which have limited their usage.[8,9,10] Given these concerns, researchers continue to explore natural agents with lipid-modifying properties, especially in the field of herbal medicine, to use as adjunct therapy in people who cannot tolerate higher doses. In recent years a number of herbs or their products like ginger,[11] cumin,[12] artichoke,[13] and silymarin[14] have been proposed to be helpful in the management of dyslipidemia. In this regard, barberry has also attracted significant attention, both in the

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scientific and consumer societies.

Barberry, or *Berberis vulgaris*, belongs to the Berberidaceae family which is a red colored fruit growing in Asia and Europe.[15,16] This fruit contains ingredients such as berberine, berbamine, palmatine, oxyacanthine, malic acid, and berberubin.[17] It is used as an anti-bacterial,[18,19] anti-carcinogenic,[20] anti-histaminic,[21] anti-hyperglycaemic,[22] anti-oxidant,[23] anti-inflammatory,[24] anti-hypertensive[25] and lipid lowering agent. [26] Despite increased research on barberry in the last decade, there are inconsistencies between trials examining its effects on lipid profile. Some investigations have shown the beneficial effects of barberry supplementation on serum lipid indices,[16,27,28] while others have failed to find any considerable effects.[29,30] The variability of results in these studies may be due to the differences in study design and/or characteristics of the study subjects (age, health status, and so on).

Previously published systematic reviews or meta-analyses[31,32] have only assessed the lipid-lowering effects of berberine, an isoquinoline alkaloid which can be found in all parts of *Berberis vulgaris*, specifically the roots.[33] However, as far as we know, no study has been conducted to determine the effect of barberry fruit in this context. Therefore, a comprehensive systematic review and meta-analysis of randomized controlled trials (RCTs) was conducted to clarify the effects of barberry supplementation on lipid profile in adult populations.

2. Materials and methods

Our meta-analysis was designed and reported based on the guidelines of the preferred reporting items for systematic reviews and meta-analyses (PRISMA).[34] It was also registered in PROSPERO. The registration number is CRD42018110874.

2.1. Search strategy

An online search was carried out using the following databases: PubMed (http://www.ncbi.nlm.nih.gov/pubmed), Scopus (http://www.scopus.com), ISI Web of Science (http://www.webofscience.com), Cochrane library (http://www.cochranelibrary.com) and Google Scholar up to October 15, 2018. We used text words and medical subject headings (MeSH) to identify the potential interest articles. Search words included: (berberis OR barberry OR barberries OR *Berberis vulgaris*) AND (cholesterol OR “low density lipoprotein” OR LDL OR LDL-cholesterol OR “high-density lipoprotein” OR HDL-cholesterol OR triglyceride OR hyperlipidemia OR hyperlipidemic OR dyslipidemia OR dyslipidemic OR lipid OR lipoprotein). No language restriction was considered while searching the mentioned databases. Moreover, we hand searched the reference list of related original and review articles to identify other potentially eligible articles.

2.2. Study selection

After conducting literature search by one investigator (A.H), all identified articles were exported into EndNote (version X7, for Windows, Thomson Reuters, Philadelphia, PA, USA) to eliminate duplications. Then, two authors (A.H and M.K) independently reviewed titles and abstracts of the remaining articles to ascertain whether these studies were eligible for our meta-analysis based on inclusion criteria. The full text of all relevant records was then reviewed. Inclusion criteria were: RCTs (either parallel or crossover design); (i) investigating the impact of barberry on plasma/serum concentrations of lipids; and (ii) with suitable controlled design, i.e., the only difference between the control and treatment groups was barberry. Studies with short duration of follow-up (< 4 weeks), trials without sufficient data and studies with duplicate data were excluded. Any different opinions between the two investigators was settled by panel discussion.

2.3. Data extraction

After reading the full text of the selected articles, following data were extracted by two independent authors (A.H and M.K), using a standardized pro forma: (i) study characteristics (first author's last name and year of publication, location of the study, sample size and study design); (ii) participants’ information (gender, mean age, mean body mass index [BMI], and health status); (iii) intervention details (duration of treatment, intervention type and dosing and control condition); and (iv) main results. We contacted the corresponding authors via e-mail in case further information was required. Disagreements between reviewers were resolved by consensus.

2.4. Quality assessment

Two reviewers (A.H and M.K) independently evaluated the methodological quality of the eligible studies through Cochrane Collaboration’s tool including seven domains as follows: 1) random sequence generation (selection bias); 2) allocation concealment (selection bias); 3) blinding of participants and personnel (performance bias); 4) blinding of outcome assessment (detection bias); 5) incomplete outcome data (attrition bias); 6) selective reporting (reporting bias); and 7) other sources of bias. Each domain was classified to three categories: low risk of bias, high risk of bias and unclear risk of bias. According to the mentioned domains, the overall quality of individual study was considered as good (low risk for more than 2 item), fair (low risk for 2 item), and weak (low risk for less than 2 item).[35] Final scores were discussed by the investigators to reach to a consensus.

2.5. Statistical analysis

Statistical analyses were carried out using the STATA software (version 11.0; Stata Corporation). All data were collected as means ± standard deviation (SD) for each variable in similar unit (mg/dl) to estimate the pooled effects. In studies in which mean change was not directly reported in intervention and control groups, it was calculated by the minus of the post-intervention data from the baseline value. When standard error (SE) was reported in place of SD, we converted it to SD for further analyses: SD=SE × sqrt (n); n = number of subjects. Based on the rejection of homogeneity hypothesis, random effect model was applied in the meta-analysis. Heterogeneity among studies was assessed by the P value and I^2 statistic (I^2 0–30%, < 30% to 60% and more than 60% indicated low, moderate and high heterogeneity, respectively).[36] To find the potential sources of between-study heterogeneity, we carried out a pre-planned subgroup analysis based on baseline BMI, intervention duration, and health status. Heterogeneity between subgroups was evaluated using fixed-effect model. To determine if any single clinical trial with extreme findings had an undue influence on the overall results, sensitivity analysis was performed. Potential of the publication bias was also explored by using Egger’s linear regression test and Begg's rank-correlation methods.[37,38] All tests were two-tailed and $P < 0.05$ indicated statistical significance.

3. Results

3.1. Identification and selection of studies

In our initial search we found 939 potential citations. After removing duplicate publications (n = 254), 689 articles remained for screening the titles or abstracts; and of them 12 studies were selected for the full-text evaluation. Of these, 7 papers were also excluded for the following reasons: reporting incomplete data (n = 2), short term follow-up (n = 1), duplicated publications (n = 4). Finally, five articles[16,27–30] appropriate for the present systematic review were selected. The details of step by step study identification and selection are illustrated in Fig. 1.

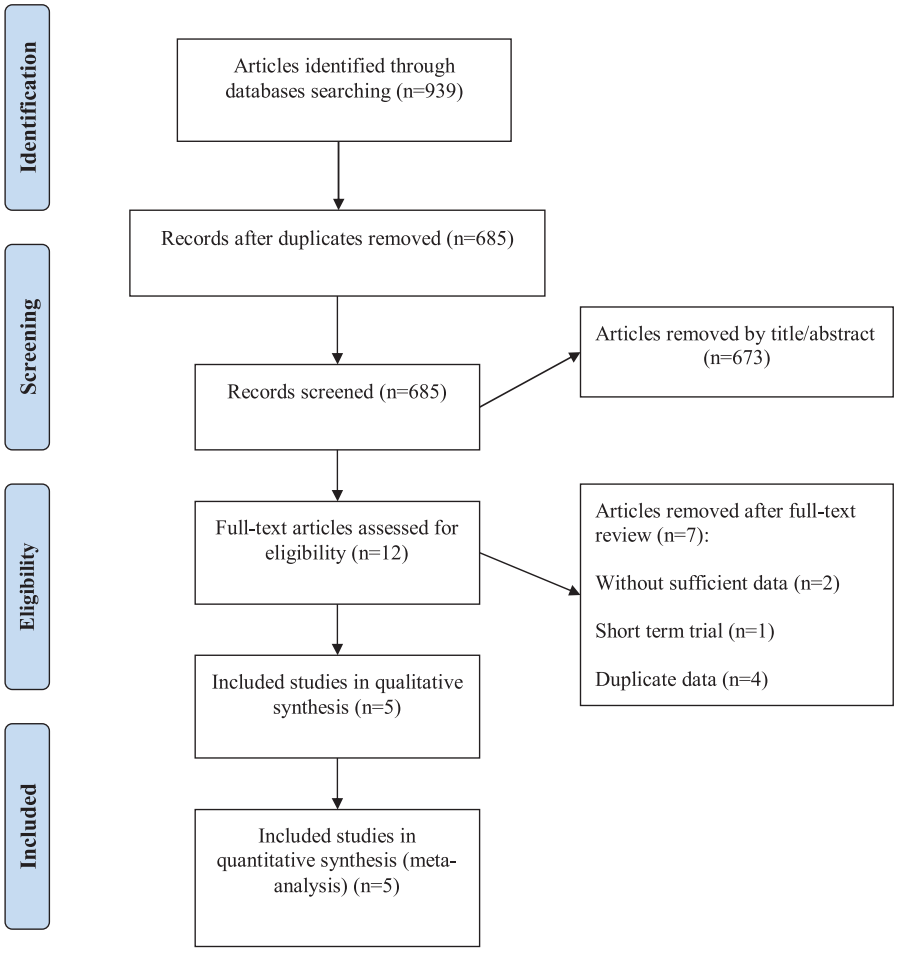

Fig. 1. PRISMA flow diagram of study selection process.

3.2. Characteristics of studies

The general characteristics of the included studies are shown in Table 1. Data were pooled from 5 RCTs [16,27–30] with sample size ranging from 42 to 106 subjects. In overall, 339 participants (154 in the barberry arm and 185 in the control group) were included in these trials. Selected studies were published between 2009 and 2018 and all of them were carried out in Iran. All trials adopted a parallel study

Table 1
Characteristics of included studies.

First author (publication year)	Country	Sample size (M/F)	Mean age (year)	Mean BMI (kg/m^2)	RCT design (blinding)	Duration (week)	Target population	Intervention (name and daily dose)	Control	Results
Ebrahimi-Mamaghani (2009)	Iran	25 M/40F	56	30	Parallel (No)	8	T2DM	5 g/day barberry fruit plus 770 cc/day apple vinegar	770 cc/day apple vinegar	TC ↔ TG ↔ LDL ↓ HDL↑
Shidfar (2012)	Iran	42NR	53	27	Parallel (Yes)	12	T2DM	3 g/day barberry fruit	Placebo	TC ↓ TG ↓ LDL ↓ HDL↔
Zilaee (2014)	Iran	27 M/79F	39	31	Parallel (Yes)	6	Metabolic syndrome	600 mg/day barberry fruit extract	Placebo	TC ↓ TG ↔ LDL ↔ HDL↔
Iloon (2015)	Iran	32 M/48F	43	32	Parallel (Yes)	12	NAFLD	750 mg/day barberry fruit extract	Placebo	TC ↓ TG ↓ LDL ↔ HDL↔
Lazavi (2018)	Iran	19 M/27F	55	28	Parallel (No)	8	T2DM	200 ml/day barberry juice plus usual diet	Usual diet	TC ↓ TG ↔ LDL ↔ HDL↔

RCT, randomized controlled trial; M, male; F, female; BMI, body mass index; NR, not reported; T2DM, type 2 diabetes mellitus; NAFLD, nonalcoholic fatty liver disease; TC, total cholesterol; TG, triglyceride; LDL, low-density lipoprotein; HDL, low-density lipoprotein.

Table 2
Quality assessment of included studies based on Cochrane guidelines.

Study	Random Sequence Generation	Allocation concealment	Blinding of participants, personnel and outcome assessors	Incomplete outcome data	Selective outcome reporting	Other sources of bias	Score	Overall quality
Ebrahimi-Mamaghani (2009)	+	+	–	+	?	+	4	Good
Shidfar (2012)	+	+	+	+	?	+	5	Good
Zilaee (2014)	+	+	+	+	?	+	5	Good
Iloon (2015)	+	+	+	+	?	+	5	Good
Lazavi (2018)	+	+	–	+	?	+	4	Good

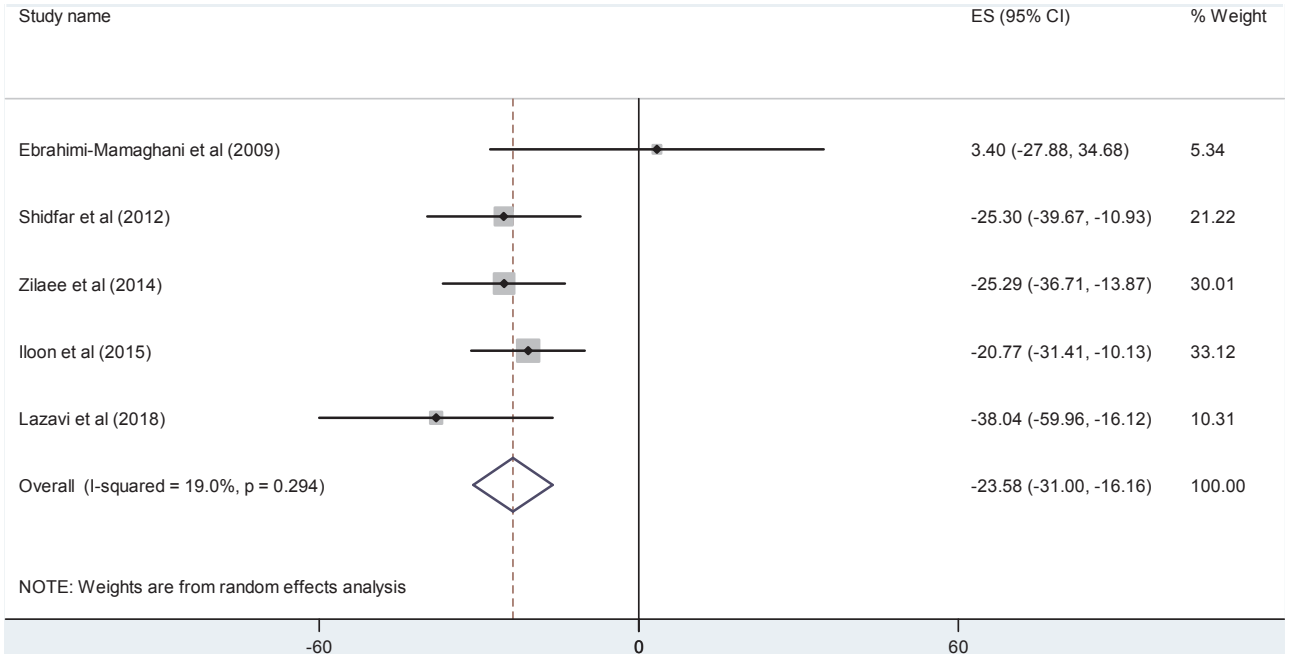

Fig. 2. Forest plot of the effect of barberry supplementation on total cholesterol.

design. Mean age of the participants ranged between 39 and 56 years. Four studies were conducted in both gender,[16,28–30] and one study[27] did not report the gender. Included trials was conducted in participants with metabolic syndrome, [30] nonalcoholic fatty liver disease (NAFLD),[16] and type 2 diabetes mellitus (T2DM).[27–29] Different barberry forms were used for the intervention: two studies[27,28] used barberry fruit, one study [29] used barberry fruit juice, and the remaining two studies[16,30] used barberry fruit extract in the form of capsules. Intervention periods ranged from 6 to 12 weeks. Control groups differed as well: placebo capsules were used for the control group in three studies, [16,27,30] one study[28] used apple cider vinegar, and another study[29] recommended the participants of the control group to keep their regular diet. The baseline BMI of the participants indicated that all trials examined overweight and obese subjects (BMI $>$ 25 kg/m^2).

Table 2 describes risk of bias assessment based on different quality domains using Cochrane collaboration tool. After evaluating the quality of included studies all of them were classified as good quality. All trials present enough information of sequence generation and allocation concealment. Three studies[16,27,30] had blinding design and all of them described methodology of blinding.in addition, all studies showed low/unclear risk of bias based on incomplete outcome data and selective outcome reporting.

3.3. The effects of barberry supplementation on TC

The pooled estimate from the random-effect model performed on 5 studies,[16,27–30] showed that barberry supplementation significantly reduced TC concentrations (MD: -23.58 mg/dl, 95% CI: -31.00 to -16.16, P ≤ 0.001). There was low heterogeneity between the effect sizes of the included studies (I^2 = 19.0%, P = 0.294) (Fig. 2). When the meta-analysis was sub grouped by participants' baseline BMI, intervention duration and participant's health status, the results remained significant among all subgroups. Furthermore, among these subgroups higher significant reduction in serum TC concentration was perceived at participants with baseline BMI of 30 kg/m^2 (MD: -29.13 mg/dl, 95% CI: -41.14 to -17.11, I^2 = 0.0%), intervention less than 12 weeks (MD: -23.28 mg/dl, 95% CI: -41.00 to -15.56, I^2 = 55.8%), and T2DM patients (MD: -23.05 mg/dl, 95% CI: -41.81 to -4.28, I^2 = 55.8%) (Table 3).

3.4. The effects of barberry supplementation on TG

Pooling 5 studies[16,27–30] together revealed a significant reduction in TG concentrations following barberry supplementation (MD: -29.16 mg/dl, 95% CI: -42.91 to -15.41, P ≤ 0.001) with moderate inter-studies heterogeneity (I^2 = 43.9%, P = 0.129) (Fig. 3). When the studies were stratified based on participants' baseline BMI, intervention

Table 3
Result of subgroup analysis of included studies in meta-analysis.

Sub-grouped by	No. of trials	Effect size[a]	95% CI	I^2 (%)	P for heterogeneity	P for between subgroup heterogeneity
TC						
Baseline BMI						**0.282**
≥ 30 kg/m^2	3	− 20.56	− 30.38, -10.75	30.4	0.238	
< 30 kg/m^2	2	− 29.13	− 41.14, -17.11	0.0	0.341	
Intervention duration						**0.686**
≥ 12 weeks	2	− 22.37	− 30.92, -13.83	0.0	0.619	
< 12 weeks	3	− 23.28	− 41.00, -5.56	55.8	0.104	
Health status						**0.766**
T2DM	3	− 23.05	− 41.81, -4.28	55.8	0.104	
Other	2	− 22.87	− 30.65, -15.09	0.0	0.570	
TG						**0.825**
Baseline BMI						
≥ 30 kg/m^2	3	− 14.75	− 52.11, 22.6	71.5	0.030	
< 30 kg/m^2	2	− 31.35	− 37.93, -24.77	0.0	0.781	
Intervention duration						**0.219**
≥ 12 weeks	2	− 32.11	− 38.36, -25.87	0.0	0.438	
< 12 weeks	3	− 9.41	− 51.52, 32.70	60.2	0.081	
Health status						**0.757**
T2DM	3	− 18.24	− 55.35, 18.87	64.9	0.058	
Other	2	− 32.08	− 51.14, -13.03	25.5	0.247	
LDL						
Baseline BMI						**0.678**
≥ 30 kg/m^2	3	− 13.03	− 21.42, -4.56	36.6	0.206	
< 30 kg/m^2	2	− 16.01	− 28.04, -3.98	0.0	0.467	
Intervention duration						**0.433**
≥ 12 weeks	2	− 12.22	− 21.07, -3.36	22.4	0.256	
< 12 weeks	3	− 16.23	− 24.54, -7.91	0.0	0.381	
Health status						**0.936**
T2DM	3	− 13.40	− 23.65, -3.15	0.0	0.558	
Other	2	− 14.32	− 25.17, -3.46	62.4	0.103	
HDL						
Baseline BMI						**0.011**
≥ 30 kg/m^2	3	6.22	− 1.13, 13.57	91.7	< 0.001	
< 30 kg/m^2	2	0.49	− 0.65, 1.63	0.0	0.996	
Intervention duration						**0.163**
≥ 12 weeks	2	0.07	− 1.88, 2.03	0.0	0.825	
< 12 weeks	3	6.34	− 0.80, 13.48	93.1	< 0.001	
Health status						**0.074**
T2DM	3	2.81	− 1.79, 7.40	75.7	0.016	
Other	2	4.27	− 0.06, 6.87	94.8	< 0.001	

BMI, body mass index; T2DM, type 2 diabetes mellitus; TC, total cholesterol; TG, triglyceride; LDL, low density lipoprotein; HDL, low-density lipoprotein.
[a] Calculated by Random-effects model.

duration and participant's health status heterogeneity was disappeared in the studies with the baseline BMI of30 kg/m^2 (I^2 = 0.0%, P = 0.781) and intervention duration equal or higher than 12 weeks (I^2 = 0.0%, P = 0.438). However, the effect of barberry supplementation on TG was not further significant in studies that enrolled T2DM participants (MD: -18.24 mg/dl, 95% CI: -55.35 to 18.87, I^2 = 64.9%), those with the baseline BMI ≥ 30 kg/m^2 (MD: -14.75 mg/dl, 95% CI: -52.11–22.06, I^2 = 71.5%), and studies with intervention duration < 12 weeks (MD: -9.41 mg/dl, 95% CI: -51.52 to 32.70, I^2 = 60.2%) (Table 3).

3.5. The effects of barberry supplementation on LDL-C

Combining effect sizes from 5 studies,[16,27–30] we showed that barberry supplementation significantly reduced LDL-C concentrations (MD: -13.75 mg/dl, 95% CI: -19.31 to -8.20, P ≤ 0.001) as compared to the controls, with no heterogeneity (I^2 = 0.0%, P = 0.429) (Fig. 4). When the meta-analysis was sub-grouped by participants' baseline BMI, intervention duration and participant's health status, the results remained significant among all subgroups. Furthermore, among these subgroups, higher significant reduction in serum LDL-C concentration was perceived in participants with baseline BMI of30 kg/m^2 (MD: -16.01 mg/dl, 95% CI: -28.04 to -3.98, I^2 = 0.0%), intervention less than 12 weeks (MD: -16.23 mg/dl, 95% CI: -24.54 to -7.91, I^2 = 0.0%), and participants with other conditions (MD: -14.32 mg/dl, 95% CI: -25.17 to -3.46, I^2 = 62.4%) (Table 3).

3.6. The effects of barberry supplementation on HDL-C

Pooled results revealed that barberry supplementation has no significant effect on HDL-C concentrations (MD: 3.40 mg/dl, 95% CI: -0.06–6.87, P = 0.054). There was a significant heterogeneity between the effect sizes of the included studies (I^2 = 86.9%, P ≤ 0.001) (Fig. 5). When the studies were stratified based on participants' baseline BMI, intervention duration and participant's health status, heterogeneity disappeared in the studies with the baseline BMI of 30 kg/m^2 (I^2 = 0.0%, P = 0.996) and intervention duration equal or higher than 12 weeks (I^2 = 0.0%, P = 0.825). However, after subgroup analysis, the results remained non-significant among all subgroups (Table 3).

3.7. Sensitivity analysis

The sensitivity analysis showed that removing any of the studies could not substantially change the effect of barberry supplementation on TC and LDL-C concentrations. Although, sensitivity analysis for TG concentrations showed that omitting one of the studies by Shidfar et al. [27] changed the overall effect into significant (MD: -22.68 mg/dl, 95% CI: -49.69 to 4.32). In addition, removing the abovementioned study

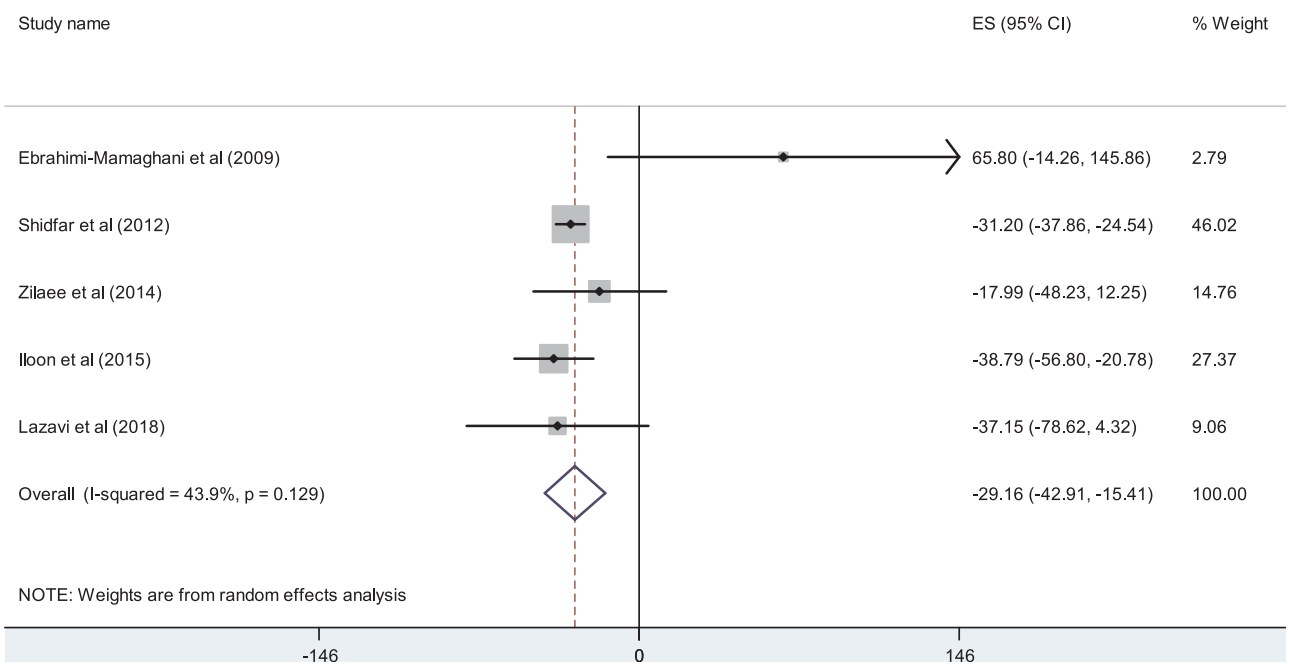

Fig. 3. Forest plot of the effect barberry supplementation on triglyceride.

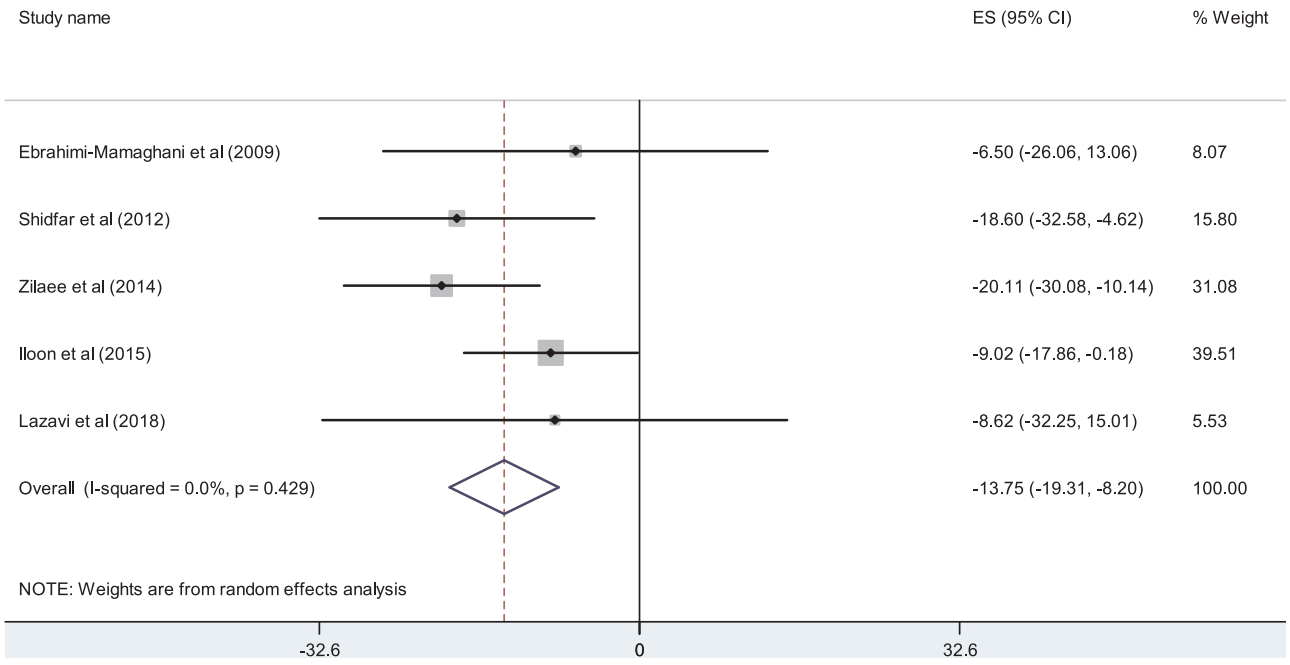

Fig. 4. Forest plot of the effect of barberry supplementation on LDL- cholesterol.

changed the results to significant for the meta-analysis of the effect on HDL-C concentrations (MD: 4.18 mg/dl, 95% CI: 0.03–8.33).

3.8. Publication bias

Begg's rank correlation and Egger's weighted regression tests were performed to explore the publication bias. The results of Begg's test indicated no publication bias for TC (P = 0.987), TG (P = 0.327), LDL-C (P = 0.993) and HDL-C (P = 0.142). Moreover, the results of Egger's test showed no publication bias for TC (P = 0.728), TG (P = 0.371), LDL-C (P = 0.767) and HDL-C (P = 0.229).

4. Discussion

The present study, to the best of our knowledge, is the first meta-analysis examining the effects of barberry supplementation on lipid profiles in RCTs. Our results showed that supplementation with barberry was associated with a decrease in TC, TG, and LDL-C, but had no significant effect on HDL-C compared with controls.

Lipid abnormalities, including elevated levels of TG, increased number of LDL-C particles and low levels of HDL-C are positively associated with atherosclerosis. So, it has been documented in a vast number of studies that dyslipidemia treatment leads to cardiovascular disease reduction.[39,40,41] Berberis vulgaris is a bush with yellow to brown colored bark. The plant has obovate leaves, bearing pendulous

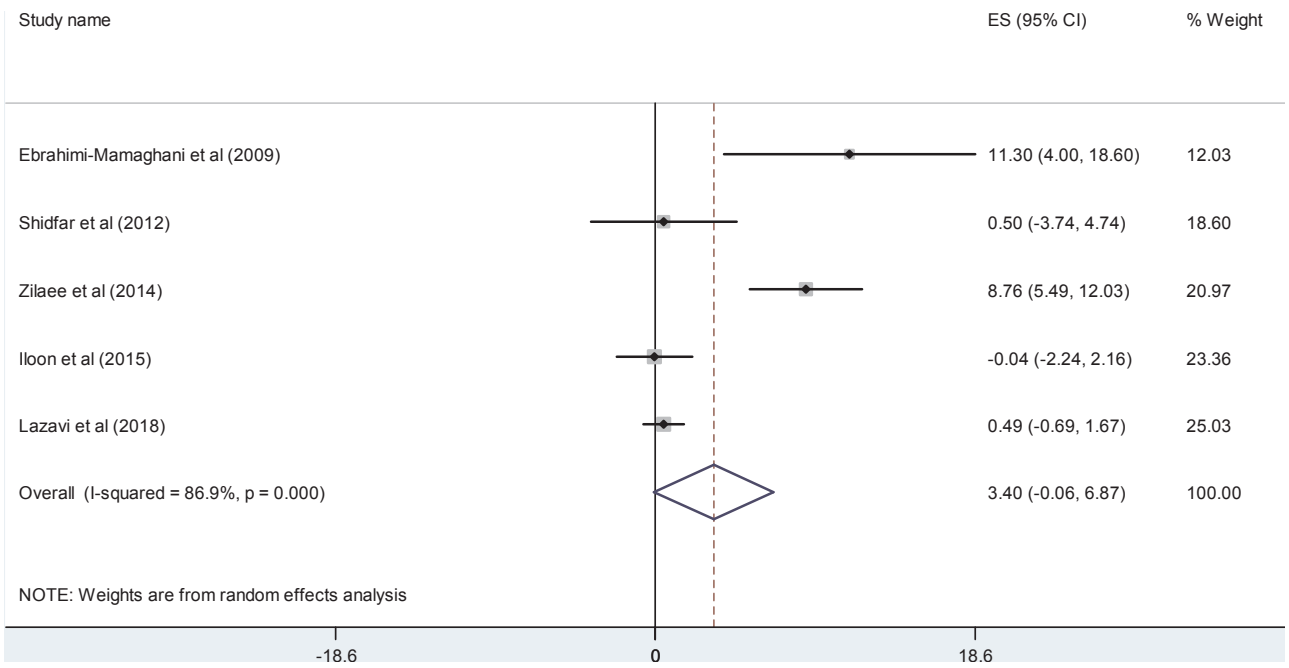

Fig. 5. Forest plot of the effect of barberry supplementation on HDL- cholesterol.

yellow flowers in spring succeeded by oblong red-colored fruits (barberry).[15] Furthermore, it is safe for human consumption and is approved by the United States Food and Drug Administration.[42]

Significant reduction of serum TG was consistent with prior human studies.[16,27] Based on previous reports, berberine, an isoquinoline alkaloid which can be found in all parts of *Berberis vulgaris* effect on TG is similar to fibrate.[43] Barberry, like fibrate, is able to activate gene transcription factors because they are synthetic ligands for peroxisome proliferation activated receptor-α (PPAR-α), which is known as a ligand-activated transcription factor and a member of the nuclear hormone receptor superfamily.[43] It is predominantly expressed in tissues that metabolize fatty acids (FAs), such as liver, heart, kidney and muscle. Activation of PPAR-α could reduce serum TG and also raise HDL-C level.[27] Another mechanism of hypo- triglyceridemic activity of barberry is related to berberine which reduces the deposition of lipid drops in pre-adipocytes and inhibits the terminal differentiation of adipocyte.[27] This mechanism is related to down-regulation of PPAR-γ2 mRNA, which result in lower TG and lipid stores.[27]

In our study, we found that barberry consumption decreased TC level which is consistent with previous reports.[16,29,30] It could down-regulate the expression of lipogenesis genes and up-regulate the expression of those involved in energy expenditure in muscle and adipose tissues.[43] Barberry could increase AMP-activated protein kinase (AMPK) activity in adipocytes and myotubes, which is accompanied with reduction of lipid accumulation in adipocytes.[44,45] AMPK is an enzyme involved in cellular energy homeostasis by activating glucose and fatty acid uptake and oxidation in the absence of enough cellular energy.[46] Activation of extracellular signal-regulated kinase, improving liver function and bile acid secretion, inhibiting intestinal cholesterol absorption and inactivation of hydroxyl methyl glutaryl coenzyme A (HMG-CoA) reductase are among other related mechanisms of barberry actions in reduction of blood cholesterol.[21,43,47,48,49]

Our analysis illustrated a significant reduction in LDL-C after barberry consumption, which is in line with previous reports.[27,30] Increase in the LDL receptor expression through a post transcriptional mechanism which enhances the stability and half-life of LDL receptor mRNA is the probable mechanism of barberry, which is different from statin drugs.[29]

We could not find any HDL-C elevating effects for barberry consumption, which were consistent with previous studies[16,27,29] but were not confirmed by other studies.[28,30] An important note which should be taken into account is the effects of barberry consumption on paraoxonase 1 (PON1). PON1 is an anti-atherosclerotic component of HDL-C, which was increased by barberry consumption. In another word, although barberry did not increase serum HDL-C levels, it might enhance anti-atherosclerotic function of remaining HDL-C.[29,43,50]

Two factors should be considered when interpreting the current findings. The preparation process of barberry in the included studies was somehow different, which could alter the components of it.[51,52] Also, many barberry varieties are found in different geographical regions that possess genetic diversity and distinct polyphenolic component load.[53]

Like all reviews, there are some potential limitations in our study. First, pathological status of participants was different, including patients with T2DM, metabolic syndrome and NAFLD fatty liver disease. Second, different forms of barberry including fruit, juice and extract with distinct polyphenol contents were used. Third, duration of preferred studies was different and most of them were short in period with small sample size and absence of blinding. Forth, all of the included studies have been done in Iran, which makes it difficult to generalize the results to the rest of the world. Fifth, none of the included studies measured serum polyphenol content so it is difficult to examine the compliance of the participants.

There is no previous systematic review and meta-analysis assessing the beneficial effects of barberry consumption on lipid profile in different populations which this point is our study strength.

5. Conclusion

According to what have been discussed, the current findings suggest the beneficial effects of barberry consumption on reduction of plasma levels of LDL-C, TG and TC. Finally, in order to draw a firm link between barberry consumption and lipid profile, more clinical trials with adequate sample size and better methodology are warranted.

Author contribution

A.H and M.K carried out the concept, design, and drafting of this

study. A.H searched databases, screened articles and extracted data. A.H performed the acquisition, analysis, and interpretation of data. A.H, A.A, N.R and M.M critically revised the manuscript. All authors approved the final version of the manuscript. M.K and A.H are the guarantors of this study.

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Conflict of interest

The authors declare no conflict of interest.

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