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Soy milk: A functional beverage with hypocholesterolemic effects? A systematic review of randomized controlled trials

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ABSTRACT

Objective: Current guidelines have highlighted the role of diet in conjunction with drug therapy in the management of dyslipidemia. Over the last two decades, the effect of soy milk, a derivative of soybean, on blood lipids has been the focus of nutritional researches. The present study aimed to provide a comprehensive review of clinical trials investigating the effect of soy milk on blood lipids.

Methods: An electronic database searching including PubMed, EMBASE, Scopus, and CENTRAL was performed to extract all the records that were published up to May 2018 using MeSH terms and relevant keywords. Randomized clinical trials that had evaluated the effect of soy milk consumption on serum lipids including total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C) were eligible for inclusion to this systematic review.

Results: Eight eligible trials comprising a total of 263 subjects were included in this review. Three studies reported no significant improvement in any of the serum lipid parameters following soy milk consumption. A significant decrease in serum TG, TC, and LDL-C was reported by 1, 1 and 3 trials. Also, 1 trial found that soy milk consumption was accompanied by a significant increase in HDL-C.

Conclusion: Evidence from clinical trials regarding the hypolipidemic effect of soy milk is limited and controversial. More well-designed clinical trials with large sample size and longer duration are warranted.

1. Introduction

Dyslipidemia is a broad term refers to an imbalance of blood lipids, including high levels of low-density lipoprotein cholesterol (LDL-C) and/or triglycerides (TG), and/or low levels of high-density lipoprotein cholesterol (HDL-C).[1] It is known as the main risk factor for progression of atherosclerosis, coronary heart disease (CHD) and myocardial infarction (MI). Pharmacological agents have long been used for controlling of the blood lipids levels.[2] In addition, the Adult Treatment Panel III (ATP III) guideline has highlighted the magnitude of lifestyle modification, particularly dietary changes in conjunction with drug therapy for primary and secondary prevention of CVD.[3] During the last decades, a great attention has been devoted to the natural food sources that could aid in lowering blood lipids and thus serve as an alternative to the lipid-modifying agents.

Soy milk is a natural product derived from soybean, which its history of use back to more than 2000 years ago among Chinese people. It is one of the most popular milk-substitutes for individuals with lactose-intolerance or those with the allergy to cow's milk proteins.[4] Like to the other soy products, in the recent years, a growing interest has been paid to the hypolipidemic effect of soy milk. This is mainly due to the fact that they comprise a variety of nutrients, which have been shown to exert a potential role in lipid metabolism including high quality protein, polyunsaturated fatty acids, saponins as well as phytostrols, soy lecithins and isoflavones.[5] Of these, soy protein and isoflavones have gained a lot of attention from researchers in regards to the health effects of soy. As a matter of fact, studies on the health effects of soy foods put a spotlight on the role of soy protein, mainly due to the health claim that intake of at least 25 g/day soy protein can reduce blood cholesterol.[6] It is presumed that soy protein may reduce the blood cholesterol through up-regulating LDL receptors [7,8] and increasing fecal excretion of bile acids.[9,10] In addition to the soy protein, studies in the experimental models have suggested that soy isoflavones can exert hypolipidemic effects. They found that genistein and daidzein, the two major soy isoflavones, could stimulate the mRNA expression of genes and/or increase the activity of enzymes involved in fatty acid β-oxidation such as peroxisome-proliferator activated receptors-α (PPARα), very long-chain acyl CoA dehydrogenase, 5′-AMP-activated protein kinase, carnitine parmitoyltransferase and enoyl-CoA hydratase. Furthermore, isoflavones could decrease the expression of genes and/or activity of

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enzymes involved in the lipogenesis such as liver X receptor-α, sterol-regulatory element-binding protein-1c, PPARγ, retinoid X receptor-α, acetyl CoA carboxylase 2, fatty acid synthase and pyruvate kinase.[11–14]

Several studies in the experimental models have shown the favorable effects of soy milk consumption on reducing TG, total cholesterol (TC), and/or LDL-C, as well as increasing HDL-C.[15–18] However, current evidence from randomized clinical trials (RCTs) is inconsistent. While a number of clinical trials showed a significant reduction in serum cholesterol following soy milk intake,[19–21] the others did not confirm such a beneficial effect.[22,23]

To the best of our knowledge, there is a lack of comprehensive literature review regarding the effect of soy milk on blood lipids. Notably, Findings of a recent meta-analysis of 35 RCTs by Tokede et al. showed that consumption of soy products was associated with a significant decrease in TG, TC, and LDL-C, and also, a significant increase in serum HDL-C.[24] Although, it should be noted that of the trials included in this meta-analysis, only one eligible trial had evaluated the effect of soy milk on blood lipids, while most of them had used other types of soy foods such as soy nuts and the processed forms such as soy protein isolate or isoflavones supplements. With this regard, the present study attempted to provide a systematic review of RCTs investigating the effect of soy milk consumption on blood lipids.

2. Methods

2.1. Search strategy

This report was designed in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) guideline.[25] PubMed, EMBASE, Scopus, and Cochrane Central Register of Controlled Trials (CENTRAL) were searched to extract all the electronic records that were published up to May 2018. The MeSH terms and keywords for database searching were as follows: ('soy milk' OR 'soy drink' OR 'soy beverage' OR 'soya milk') AND ('high density lipoprotein cholesterol' OR 'HDL cholesterol' OR 'low density lipoprotein cholesterol' OR 'LDL cholesterol' OR 'lipoproteins' OR 'cholesterol' OR 'triglycerides' OR 'hypercholesterolemia' OR 'hyperlipidemia' OR 'dyslipidemia' OR 'hypertriglyceridemia' OR 'hyperlipidemic' OR 'hypercholesterolemic' OR 'dyslipidemic' OR 'hypertriglyceridemic' OR 'lipid profile' OR 'blood lipids'). The search was restricted to the RCTs, with no restriction on the age of participants and the date of publication. In addition, a manual search of the reference lists of the relevant articles was performed to ensure no eligible article had been missed.

2.2. Study selection and data extraction

Following the database searching by one author (O.E.), each author (O.E. and F.Sh.) screened independently the titles and abstracts of all records and identified the duplicate and non-relevant documents. Thereafter, the full-texts of the remaining articles were evaluated to extract the eligible ones. In case of any disagreement between the two authors, it was settled by consulting with a third academic expert who provided technical assistance to determine whether a trial met the inclusion criteria for this systematic review. Clinical trials that had evaluated the effect of soy milk consumption on serum lipids including TC, TG, LDL-C, and HDL-C were eligible for inclusion to this systematic review. Studies were excluded if they: 1) had used soy milk in conjunction with other soy foods, 2) had used fermented- or fortified soy beverages, 3) had used other liquid types of soy foods such as soy protein shakes or beverages, or mixture of soy milk with other foodstuffs, 4) were conducted in individuals with inherited disorders of cholesterol metabolism, 5) had not used a control group, 6) had non-English language, and 7) were published as the conference/meeting abstracts or review articles. Information regarding the participants' characteristics such as age, sex, as well as study design, sample size, duration of follow-up, type of intervention, and the study outcomes was collected from the eligible studies.

2.3. Evaluation of risk of bias

The risk of bias for studies was evaluated by each author independently using the Cochrane Collaboration's tool.[26] This tool assesses several sources of bias including random sequence generation (selection bias), allocation sequence concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective outcome reporting (reporting bias) and other potential sources of bias (such as no consideration for confounding factors). For all eligible trials, the risk of bias for each source was categorized as "Low", "High", and "Unclear".

3. Results

3.1. Study selection

A total of 381 records were extracted through database searching. Of these, 216 were duplicates and also, 119 were irrelevant articles. The full-text of the remaining 46 articles were carefully evaluated to determine the eligible ones. In addition, 2 articles were extracted by searching the references lists of the remaining articles. Of 48 articles, 40 did not meet the inclusion criteria for the following reasons: 1) had used soy milk in combination with the other soy products (n = 7), 2) had used the probiotics-fermented or stanol- fortified types of soy milk (n = 7), 3) had used other liquids types of soy or soy formula (n = 13), 4) had not reported the *P*-values for post-intervention comparison of serum lipids between soy milk and control group (n = 1), 5) were conducted in the experimental models (n = 6), 6) were conducted in subjects with familial hypercholesterolemia (n = 2), 7) were designed without a control group (n = 1), 8) were published as the review article (n = 1) and conference abstract (n = 1), and 9) the full-text was not available (n = 1). Finally, implementing the search strategy yielded to the 8 articles that fulfilled the eligibility criteria (Fig. 1).

3.2. Study characteristics

The main characteristics and results of the eligible studies have been summarized in Table 1. Three studies [22,27,28] were conducted in the apparently healthy individuals, three in hyperlipidemic subjects, [19,20,23] one in type 2 diabetic patients with nephropathy [29] and one in overweight/obese women.[21] Three studies were performed in the females [21,22,28] and the others were conducted in both sexes.[19,20,23,29,30] The sample size of studies was varied between 10 to 60 subjects. Five trials had a cross-over design,[19–21,23,29] while three had a parallel design.[22,27,28] The amount of soy milk consumption was varied between studies ranging from 240 ml to 1 L/day. Also, four studies had not reported the total isoflavones content of the soy milk.[21,22,27,29] The effect of soy milk on blood lipids was compared with dairy milk, dairy milk plus rice milk, and usual diet in 6, [19–23,29] 1 [27] and 1 [28] studies, respectively. The duration of follow-up was ranged between 4 to 8 weeks. Six studies [19,21,22,27–29] had measured all blood lipid parameters including TG, TC, LDL-C and, HDL-C. While, Gardner et al. [20] had evaluated the effect of soy milk intake on serum levels of TG, LDL-C, and HDL-C, and also Sirtori et al. [23] had just compared the serum TC and LDL-C concentrations between the soy milk/dairy milk phases.

3.3. Risk of bias

Table 2 shows the assessment of risk of bias for included studies based on the Cochrane Collaboration's criteria. Of the eligible trials, only one study [20] had reported the method used for random sequence generation and allocation concealment in sufficient details, while the others had not provided any information to judge about the risk of

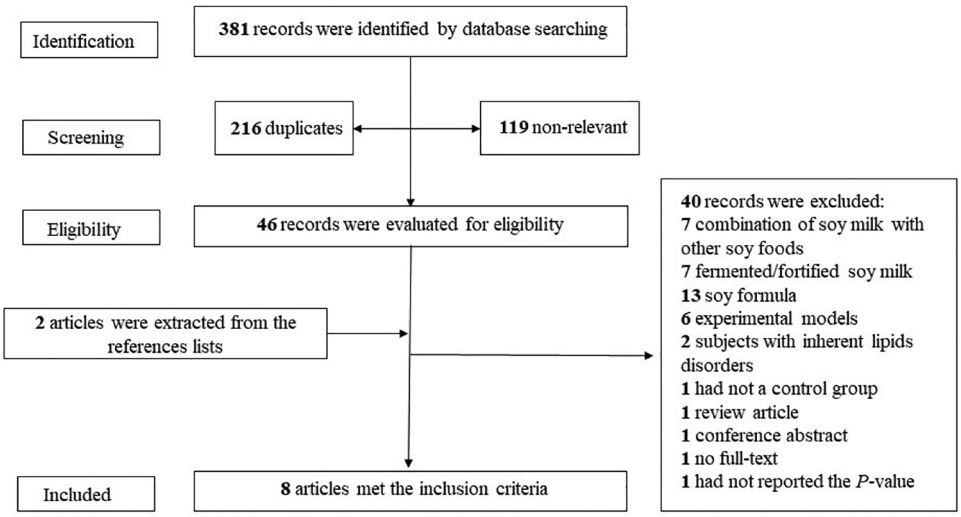

Fig. 1. The process of articles selection.

selection of bias. In 6 trials, [20–22,27–29] participants and/or investigators were aware of the type of intervention, and thus, they were likely to have a high risk of performance bias. Also, 2 out of 6 trials [20,21] had explicitly reported that the outcome assessors were blinded to the treatment groups. The details about the attrition rate of participants were fully described in 6 trials. [20–23,28,29] The risk of selective reporting bias was determined as "Low" for all included trials. Except for one trial,[27] which had not considered some confounding factors such as dietary intakes and physical activity, others had adequately addressed the effect of major potential confounders.

3.4. Main findings

Of the eight studies, 3 [22,23,27] did not show any significant improvement in serum lipids following soy milk consumption. While 5 trials [19–21,28,29] reported significant changes in serum levels of TG, TC, LDL-C, and/or HDL-C. Bricarello et al. [19] reported that in comparison to the dairy milk, intake of 1-liter soy milk per day for 6 weeks resulted to a significant increase in serum HDL-C and conversely, a significant decrease in LDL-C in patients with primary hypercholesterolemia. Although, such a favorable effect was not found for serum TC and TG. Also, Takatsuka et al. [28] found that healthy premenopausal women that consumed 400 ml soy milk per day during the two menstrual cycles had significantly lower serum TC compared to the control group at the end of trial (165.7 ± 23.3 mg/dl for soy milk group vs. 177.7 ± 24.9 mg/dl for control group; $P = 0.02$). While, the post-intervention levels of TG, LDL-C, and HDL-C were not significantly different between the study groups. Another trial by Miraghajani et al [29] found that consumption of 240 ml soy milk daily for 4 weeks had significantly reduced serum TG compared to the dairy milk in type 2 diabetic patients with nephropathy (mean changes: -15.22 ± 5.14 mg/dl in soy milk phase vs. 2.37 ± 6.57 mg/dl in dairy milk phase; P = 0.02). Although it had no significant effect on other components of lipid profile including TC, LDL-C and HDL-C.

Two studies [20,21] found a significant reduction in serum LDL-C following soy milk consumption, without any significant improvement in serum TC, TG, and HDL-C. In a three-way cross-over trial by Gardner et al. [20], it was reported that consumption of two types of soy milk, each for 4 weeks including whole bean soy milk (950 ml/day) and soy protein isolate milk (830 ml/day), which had provided 25 g/day protein from each soy, reduced significantly serum LDL-C levels compared to the dairy milk (end of trial: 161 ± 20 mg/dl for whole bean soy milk, 161 ± 26 for soy protein isolate milk, vs. 170 ± 24 mg/dl for dairy milk; $P = 0.02$ for each soy milk vs. dairy milk). In addition, Nourieh et al [21] showed that intake of 240 ml soy milk per day for 4 weeks was accompanied by a greater reduction in serum LDL-C concentrations compared to the dairy milk, which was statistically significant (mean changes: -11.22 ± 3.85 mg/dl in soy milk phase vs. −1.18 ± 2.82 mg/dl in dairy milk phase; $P = 0.01$).

4. Discussion

The present systematic review, to our knowledge, was the first study to provide a comprehensive review on the effect of soy milk consumption on circulating lipids. There was a remarkable heterogeneity between the studies particularly in terms of the baseline health status of study participants and amount of soy milk consumed per day.

In a recent meta-analysis performed by Tokede et al. [24], it was found that intake of whole soy foods (e.g. roasted soy beans, soy nuts, soy milk and soy flour) were almost three times more effective on LDL-C reduction compared to the processed soy products (e.g. soy extract or soy protein supplements). In addition to the bioactive peptides and isoflvones, whole soy foods such as soy milk contain other constituents including linoleic acid, saponins, lecithins and phytosterols, which these components may regulate cholesterol levels synergically in conjunction with bioactive peptides and isoflvones or through independent mechanisms.[5] Therefore, it is more likely that whole soy products such as soy milk have more favorable effects on serum cholesterol rather than the processed soy products. However, even among the whole soy products, it is suggested that the bioavailability of nutrients may be differed according to the food matrix. Several reports have found that absorption of isoflavones were more effective form liquid matrix of soy foods such as soy milk rather than the solid forms.[31–34] Therefore, it is expected that soy milk had a greater effect compared to the solid forms of soy foods, while the results of clinical trials in favor of such hypothesis is still controversial.[22,23,35] Moreover, unlike the solid matrix of soy products, soy milk is lack of fiber. This is may be a possible reason for the limited effect of soy milk on serum cholesterol, since there is almost convincing evidence that the dietary fibers [36,37] as well as soy fibers [38,39] have positive effect on lowering serum cholesterol.

In this systematic review, all clinical trials that had reported significant improvement in blood lipids, [19,20,28] except for studies by Nourieh et al. [21] and Miraghajani et al. [29] (which had not provided the information on total isoflavone content of soy milk) the dosages of soy milk intake, and also, the intake of soy protein and total isoflavones from soy milk, were relatively high. Therefore, the hypolipidemic effect of soy milk found in these trials might be due to the high dosage of soy milk supplementation and subsequently higher soy protein/isoflavones

Table 1
Characteristics and main outcomes of clinical trials investigating the effect of soy milk consumption on blood lipids.

First author / year	Participants	Sample size	Age (years)	Design	Treatment groups/ Phases	Soy milk Protein; total isoflavones content	Duration	Outcomes	Effects
Beavers KM [22], 2010	Healthy postmenopausal women	32	40 to 60	Parallel	Intervention group: 3-servings/ day (740 ml) Soy milk (n = 16) Control group: 3-servings/ day dairy milk (n = 16)	18 g; NR	4-wks	TG TC LDL-C HDL-C	↔ ↔ ↔ ↔
Bricarello LP,[19] 2004	Subjects with primary hypercholesterolemia (serum TC: 200 to 350 mg/dL; and TG < 400 mg/dL)	60	20 to 70	Cross-over	Phase A: 1-liter/day soy milk Phase B: 1-liter/day non-fat dairy milk	25 g; 88 mg	Each phase: 6-wks, Washout period: NR	TG TC LDL-C HDL-C	↔ ↔ ↓ ↑
Gardner CD,[20] 2007	Subjects with serum LDL-C 160 to 220 mg/ dL,	28	30 to 65	Cross-over	Phase A: 950 ml/day whole bean soy milk Phase B: 830 ml/day soy protein isolate milk Phase C: 550 ml/day dairy milk	Whole bean soy milk: 25 g; 125 ± 17 mg, Soy protein isolate milk: 25 g/ 39 ± 1 mg	Each phase: 4-wks, Washout period: 4-wks	TG LDL-C HDL-C	↔ ↓ ↔
Miraghajani MS,[29] 2013	Type 2 diabetic patients with nephropathy	29	Mean ± SD 51 ± 10	Cross-over	Phase A: 240 ml/day soymilk Phase B: 240 ml/day dairy milk	2.5 g; NR	Each phase: 4-wks, Washout period: 2-wks	TG TC LDL-C HDL-C	↓ ↔ ↔ ↔
Mitchell JH. [27] 1999	Apparently healthy men	10	20-50	Parallel	Group 1: 1-liter/day soy milk (n = 4) Group 2: 1-liter/day rice milk (n = 3) Group 3: 1-liter/day dairy milk (n = 3)	NR	4-wks	TG TC HDL-C/ LDL-C ratio	↔ ↔ ↔
Nourieh Z, [21], 2012	Non-menopausal overweight/obese (BMI ≥ 25 kg/m^2) women	24	20 to 50	Cross-over	Phase A: 240 ml/day soymilk + low calorie diet Phase B: 240 ml/day dairy milk + low calorie diet	6 g; NR	Each phase: 4-wks, Washout period: 2-wks	TG TC LDL-C HDL-C	↔ ↔ ↓ ↔
Sirtori CR, [23] 2002	Subjects with type II hypercholesterolemia (serum TC > 7 mmol/l and LDL-C < 5.5 mmol/l.)	20	38 to 76	Cross-over	Phase A: 500 ml/day soy milk Phase B: 500 ml/day dairy milk	25 g; 77 mg	Each phase: 4-wks, Washout period: NR	TC LDL-C	↔ ↔
Takatsuka N, [28] 2000	Premenopausal females	60	NR	Parallel	Intervention group :400 ml/day soy milk (n = 27) Control group: usual diet (n = 25)	17 g; 109 mg	From day 11 menstrual cycle 1 until day 11 menstrual cycle 3; Mean ± SD : 60.6 ± 8.7 days	TG TC LDL-C HDL-C	↔ ↓ ↔ ↔

Abbreviations: RCT Randomized controlled trial; NR Not reported; TG Triglycerides; ; TC Total cholesterol; ; HDL-C High-density lipoprotein cholesterol; LDL-C Low-density lipoprotein cholesterol; SD Standard deviation; BMI Body mass index.
↔No significant effect; ↓significant decrease; ↑significant increase.

Table 2
Summary of the risk of bias in randomized trials using the Cochrane Collaboration's tool.

Study	Source of bias						
	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective outcome reporting	Other bias
Beavers KM,2010	Unclear risk	Unclear risk	High risk	Unclear risk	Low risk	Low risk	Low risk
Bricarello LP, 2004	Unclear risk	Unclear risk	Low risk	Unclear risk	Unclear risk	Low risk	Low risk
Gardner CD, 2007	Low risk	Low risk	High risk	Low risk	Low risk	Low risk	Low risk
Miraghajani MS, 2013	Unclear risk	Unclear risk	High risk	Unclear risk	Low risk	Low risk	Low risk
Mitchell JH, 1999	Unclear risk	Unclear risk	High risk	Unclear risk	Unclear risk	Low risk	High risk
Nourieh Z, 2012	Unclear risk	Unclear risk	High risk	Low risk	Low risk	Low risk	Low risk
Sirtori CR 2002	Unclear risk	Unclear risk	Low risk	Unclear risk	Low risk	Low risk	Low risk
Takatsuka N, 2000	Unclear risk	Unclear risk	High risk	Unclear risk	Low risk	Low risk	Low risk

intake. Nevertheless, in Sirtori et al. study [23] among patients with hypercholesterolemia, intake of 500 ml soy milk, which had provided 25 g protein and 77 mg total isoflavones, was not accompanied by significant changes in TC and LDL-C. It should be noted that the amount of that the amount of soy protein and total isoflavones achieved by intake of 500 soy milk in this study was comparable to the amounts of soy milk that consumed by patients with hyperlipidemia in Bricarello et al. [19] (25 g protein and 88 mg isoflavones) and Gardner et al. [20] (25 g protein and 88 mg isoflavones 125 mg).

It seems that the differences in the isoflavone subtypes in terms of their amount in soy milk might affect the efficacy of soy milk on serum cholesterol levels. In sirtori et al study,[23] the amount of glycitein was almost equal to genistein and daidzein in the soy milk (24 mg, 25 mg, and 28 mg respectively). While in Bricarello et al. [19] and Gardner et al. [20] studies, gensitein and diadzein were much higher rather than glycitein in the soy milks (almost 7 to 20 times more than glycitein). Glycitein comprises 5 to 10% of total isoflavones and has a weaker estrogenic activity rather than genistein and daidzein.[40] Because of the structural similarity of isoflavones with 17-β-estradiol, they are known to have weak estrogenic effects, i.e. they can bind to the estrogen receptors and mimic the activity of estrogen in several tissues. Since estrogen has a favorable effect on lowering LDL cholesterol and increasing HDL cholesterol, isoflavones are presumed to have the similar effect.[6,41] Therefore, it is hypothesized that higher amount of genistein and daidzein rather than glycitein found in soy milk might have a greater effect on reducing LDL-cholesterol. Although, data on the isoflavone subtypes from other eligible studies are lacking and even some had not reported the total isoflavone content, which made it difficult to test this hypothesis.

Another factor that might influence the potential hypocholesterolemic effect of soy milk is the ability of human gut flora to produce equol from daidzein. This metabolite has been shown to have a higher estrogenic activity, as well as higher bioavailability rather than soy isoflavones including genistein and daidzein and glycitein.[42,43] Thus, it is supposed that equol may have a greater effect on reducing cholesterol rather compared to the isoflavones. Notably, almost less than 50% of individuals who consumed soy have the ability to metabolize daidzein to equal (i.e. they are considered as the equol producers).[43] Findings of several clinical trials have demonstrated a significant improvement in blood lipids in equol producers compared to the non-equol producer ones.[44–46] Taken together, the effect of soy milk on lipid profile might be differed according to the equol—production phenotype. However, in this systematic review, only one study had examined the effect of soy milk on blood lipids both in equol and non-equol producers and found no significant differences between the two groups regarding changes in serum lipid parameters.[20] It should be noted that the number of equol producers in this trial was small and only 9 of 28 participants were equol-producers, which this might have resulted in the non-significant finding in serum lipids. In addition, several factors are proposed that may determine the eqoul production including host genetic, background diet, race, and gut function, and these may even contribute to the complexity of the relationship. [47]

The ratio of aglycone-to-glycoside isoflavones in the soy foods may be also a potential predictor of health effect of soy products. Fermentation of soy foods using probiotic species made the conversion of glucosides to the aglycones.[48] There is some evidence that soy isoflavone aglycones absorbed in a greater extent compared to the isoflavone glucoside,[49,50] and thus, it is hypothesized that fermented soy milk may provide more beneficial effect on cardiovascular risk factors especially lipid profile compared to the unfermented ones.[51–53] In line with this hypothesis, Feizollahzadeh et al. [54] showed that consumption of probiotic-fermented soy milk at a dose of 200 ml/day for 8 weeks significantly increase HDL-C and conversely, reduced LDL-C rather than the pure soy milk in patients with type 2 diabetes mellitus. Nevertheless, evidence regarding the bioavalibitly of isoflavones glucoside/aglycone forms remains controversial yet, since other studies reported no significance differences between the both isoflavone forms in terms of their bioavailability [55], and even some had shown a greater bioavalibility of isoflavone glucosides rather than isoflavone aglycones.[56] Taken together, the bioavalibility of isoflavones and subsequently the health effect of soy foods are a complex issue as it should be noted that in addition to ratio of aglycone-to-glycoside isoflavones, several other factors may influenced the pharmacokinetics of isoflavones including food matrix, background diet, gut microflora, gastrointestinal transit time, ethnic background, and the processing and storage conditions of soy products.[57]

Studies included in this review had some limitations that should be considered when interpreting the findings of this review. First, except for two studies,[19,23] others had not used blinding for soy milk consumption and participants were aware of the type of intervention, which they had received. This might cause some biases in the follow-up and outcomes of the studies since blinding is an important aspect of the methodology of a clinical trial, which can reduce the risk of co-intervention bias and also, enhance the validity of the study outcomes.[58] Second, the clinical trials included had a low sample size with relatively short duration, which make the generalizability of the findings to the general population or to the longer duration difficult. Third, the assessment of the methodological quality of trials revealed a poor to fair quality, which this may raise concerns regarding the validity of the findings of some trials.

5. Conclusion

In conclusion, the present systematic review revealed that the evidence in support of the positive effect of soy milk on components of lipid profile is limited and remains controversial yet. More well-designed clinical trials with large sample size and longer duration are needed to elucidate the effect of soy milk on blood lipids.

Authors' contribution

O.E. developed the search strategy, performed the literature search, selected the eligible articles, checked the quality of eligible articles and drafted the manuscript. F.Sh. as the chief supervisor initiated the development of the search strategy, confirmed the eligibility of the articles, reviewed the quality of the eligible articles, revised the manuscript and critically reviewed the manuscript. Both authors have read and approved the final version of the manuscript.

Declarations of interest

None.

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