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Review Article

The Effects of Ginger Supplementation on Lipid Profile: A Meta-Analysis of Randomized Clinical Trials

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Abstract

Background and Aim: Scientific experiments and clinical studies have revealed the lipid lowering properties of ginger and its efficacy as an adjuvant in hypercholesterolemic conditions. The aim of this meta-analysis is to evaluate the effect of ginger supplementation on human serum lipids.

Materials and Methods: A systematic search of randomized controlled trials (RCTs) written in English was conducted up to April 2016 by searching online databases including PubMed, EMBASE, Scopus, and Google Scholar**.** A total of seven RCTs met the inclusion criteria. The pooled weighted Mean Difference (MD) and its 95% Confidence Interval (CI) were calculated and pooled using a random-effects model.

Results: Compared to the controls, ginger intake significantly reduced the concentrations of total cholesterol (-13.31 mg/dL, 95% CI, -20.29 to -6.33 mg/dL, P=0.000), low-density lipoprotein (LDL) cholesterol (-11.22 mg/dL; 95% CI, -18.37 to -4.06 mg/dL, p = 0.002) and triglycerides (-14.96 mg/dL; 95% CI, -22.13 to -7.79 mg/dL, P=0.000). But the rise in high-density lipoprotein (HDL) cholesterol level was not statistically significant (WMD = 0.12 mg/dL; 95% CI, -1.01 to 1.24 mg/dL, p =0.839).

Conclusion: Ginger supplementation (tablet, capsules, powder or rhizomes) significantly reduces LDL, TG, and TC, but not HDL. This property enables ginger to manage lipid profile. However, high-quality RCTs are required to identify the effects of ginger supplementations on HDL levels.

Keywords: Ginger, zingiber, Cholesterol, Plasma lipids, Triglycerides, HDL, LDL, Serum lipids

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Introduction

Hyperlipidemia, the result of abnormality of lipid metabolism, is an important risk factor of the diseases related to lifestyle, inclusing atherosclerosis, cardiovascular disease (CVD), coronary heart disease (CHD) and stroke (1). Epidemiological studies have indicated that CVD is the major leading cause of mortality and morbidity worldwide (2). Although several epidemiological studies predicted the reduction of cardiovascular mortalities over time, over 17 million people passes away from CVD in 2008, and it is estimated that by 2030 roughly 23.6 million people will die from CVD. Hence, tremendous efforts have

been devoted to reduce the risk factors of atherosclerosis (3). It is of high significance to find natural agents beside synthetic medicine used to decrease the burden of such diseases because these medications might have adverse side effects (4). Recently, there has been a growing tendency towards the use of alternative therapies to reduce serum cholesterol because of either their safety or personal preference, particularly when conventional drug therapy is considered inappropriate or expensive (5). Plant foods play key roles in managing hyperglycemia and hyperlipidemia (6). Recently, Rhizome of ginger (Zingiber officinale Roscoe, belonging to the family Zingiberaceae), as a non-toxic spice with negligible side effects, has drawn the attention of several researchers. This plant is generally recognized to be safe by the United States Food and Drug Administration (FDA) (7, 8). The plant has currently acquired widespread nutritional utilization worldwide (9). Some articles have suggested that ginger's distinct pharmacological impacts stem from its different components, including gingerols, shogaols, zingerone and paradol. More than 40 antioxidant compounds have been detected in ginger (10). Immune-modulatory, anti-tumorigenesis, anti-inflammatory, anti-apoptosis, glucose and lipid lowering effect, and anti-emetic properties are the main pharmacological characteristics of ginger (11). Many reports are available concerning the effect of ginger on lipid metabolism but some inconsistencies still exist among these investigations. For example, a research carried out about streptozotocin-induced diabetic rats attributed hypoglycemic and lipid lowering effects to ginger (12). Another study, however, indicated opposite results on lipid profiles (13). Various human and animal studies with different designs have investigated the exact effects of ginger lipid profile to date, but there has been no systematic review in this regard. This systematic review evaluates the current and available evidence on the efficiency of ginger on lipid profile.

Materials and Methods

Search Strategy

The current meta-analysis was designed following the guidelines published in 2009 on the preferred reporting items for systematic reviews and meta-analysis (PRISMA) (14). International databases, including PubMed, EMBASE, Scopus and Google Scholar, were searched from inception up to 2016. The keywords that were searched in the titles and abstracts included ginger OR zingiber OR ‘‘Zingiber officinale” and Cholesterol OR ‘‘plasma lipids” OR triglycerides OR HDL OR LDL OR ‘‘serum lipids”.

Eligibility Criteria

Articles were included provided that they met the following criteria: (1) to be clinical trials; (2) to use ginger or ginger-containing products as the intervention; and (3) to report mean changes and their standard deviations (SD) of lipid profile (HDL cholesterol, LDL cholesterol, total cholesterol and triglyceride) (or data for calculating the indicators). Moreover, the dosage of ginger supplementation and intervention duration should be clearly reported. On the other hand, articles were excluded if (1) they were not written in English or Persian languages; (2) they did not report the data required for meta-analysis; (3) their full texts or their relevant data were not accessible; (4) they were not original papers (such as reviews, comments, or letters); (5) they were duplicated papers.

Data Extraction and Quality Assessment

Extracted data included author’s full name, the year of publication, the country in which the research was conducted, study design, the number of participants in the ginger and control groups, the intervention assigned to the control group, the administered dose on both ginger and placebo, treatment duration, age, gender, body mass index (BMI), baseline and final values for TC, LDL, HDL, TG in the form of Mean±SD and total Jadad Score. Before performing the meta-analysis, the lipid levels in millimoles per liter (mmol/L) were converted into milligrams per deciliter (mg/dL**)** prior to calculations. We used Jadad scoring system to assess the quality of the selected studies (15). The Jadad scale contains questions that address randomization, randomization scheme and withdrawal in intervention and placebo groups (16). Each study gets a score from zero to five points in this scoring system. Low quality studies receive ≤ 2 and high quality studies ≥ 3 (16).

Statistical Analysis

Data analysis was carried out using STATA software (version 12.0, StataCorp, College Station, Texas, USA). The pooled Mean Difference (MD) and its 95% Confidence Interval (CI) were calculated to measure the impacts of ginger supplementation on lipid profile.

Before conducting the analysis, the lipid levels in mmol/L were converted to mg/dL and mean net changes (mean±SD) in the TC, HDL, LDL and TG for each study were calculated. The heterogeneity of studies was assessed using the I^2 statistics, and random-effects model (the Der Simonian-Laird estimator) was utilized if heterogeneity >50% and P-value of heterogeneity <0.1.

In case of meta-analyses with more than 10 studies (not in the present case) to examine the publication bias, the Egger's test is utilized. In case of bias, the funnel plot indicates an asymmetric shape. A P-value <0.05 was considered to be statistically significant. (17).

Results and Discussion

A Summary of Selected Studies

Figure 1 shows a flow diagram of article selection for this meta-analysis. Of 361 articles retrieved in initial electronic searches, a total of 54 duplicated articles were removed and 295 studies were excluded by screening the titles or abstracts (48 *in vitro* experiments, 169 animal experiments, 19 other effects of ginger, 37 other herbal plants, 22 reviews). Finally, seven RCTs met the inclusion criteria (18-24). The study performed by Atashak S *et al*. (21) included two intervention groups, and each pair-wise comparison was included into the meta-analysis as a separate trial. Subsequently, eight trial arms were included in the meta-analysis. General information on the included RCTs is summarized in Table 1. The data of differences about pre and post-intervention phases in serum lipids including TC, LDL-C, HDL-C and TGs, was described in seven articles. In a study conducted by Andallu B *et al.*, the researchers provided the data for post-intervention serum lipids. In this meta-analysis, six studies had a 2-arm parallel design (ginger powder and placebo groups), one RTC (19) had a 4-arm parallel design (ginger powder, two other herbs and placebo group) and another (24) had a 5-arm parallel design including ginger powder, three other herbs and the placebo group.

Study Characteristics

Table 1 displays the characteristics of the included trials. Seven trials (18-24) were published from 2003 to 2015, six of them were Iranian cases (19) and one was Indian. Of these eight RCTs, seven used a double-blind design and one (24) utilized a single-blind design with a placebo. Of eight RCTs, two had (18, 19) hypercholesterolemic patients, three (20, 23, 24) recruited patients with type 2 diabetes mellitus, two (21) were applied on obese men and one (22) had patients with peritoneal dialysis (PD). Three of them (19, 21) included only men and the rest reported their results for both men and women. The sample size ranged from 8 to 45, with a total number of 366 participants. Follow-up duration lasted from 4.28 to 12 weeks with a median of 8.58 weeks. The daily dose of ginger consumption varied from 1000 to 3000 mg with a median of 1950 mg. Average age ranged from 23.6 to 58 years and the mean BMI ranged from 26.8 to 34.5 kg/m^2. In one RCT (19), the mean BMI was not reported. In one study (Tabibi H *et al.*), different units (mmol/L) were applied for TG, TC, HDL-C, and LDL-C. Hence, before meta-analysis these indexes were transformed to the unified unit (mg/dL). The qualitative assessment for each study in our meta-analysis was conducted via applying Jadad scale. Except one case (19), randomization and blinding were described in all studies. In two cases (20, 22) the randomization scheme and in four cases (20-23) the method of blinding were explained. There was a description of dropouts and withdrawals in two trials (20, 23). Three studies (18, 19, 24) scored 0-2 on the Jadad scale and obtained low quality, and five studies (20-23) scored 3-5 on the Jadad scale and obtained high quality.

Outcome

The meta-analysis of all RCTs did not show any significant effect of ginger supplementation on LDL, HDL, TC and TG. The study by Azimi *et al*. (24) was excluded due to its outlier results. Findings from the sensitivity analysis indicated a significant decrease in LDL, TC and TG concentration. Random effects model was applied to evaluate this effect. Figure 2 shows the effect of ginger supplementation on LDL-c

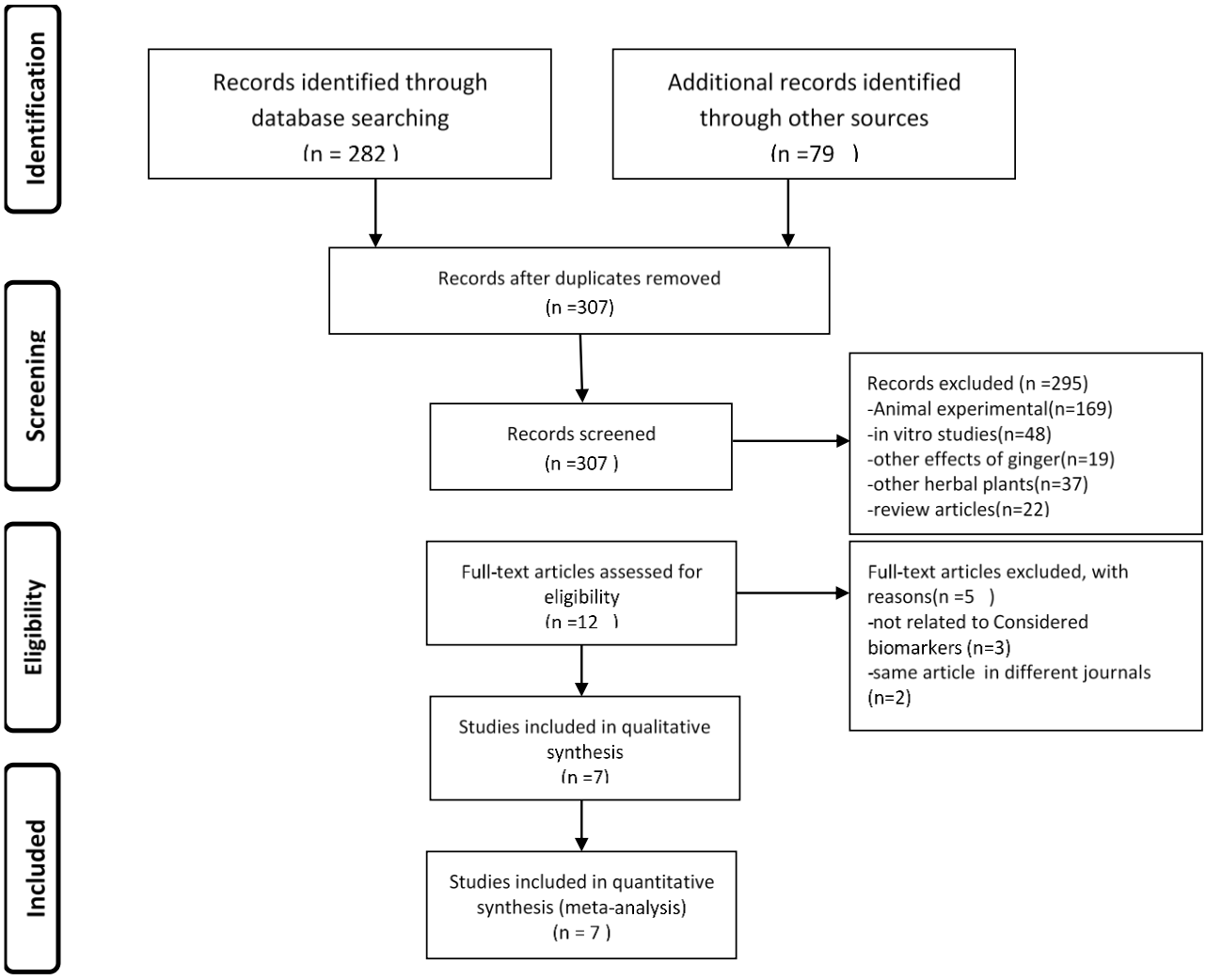

Figure 1. Flow diagram of the literature search for the effect of Ginger on serum lipids (TC, TG, LDL, HDL).

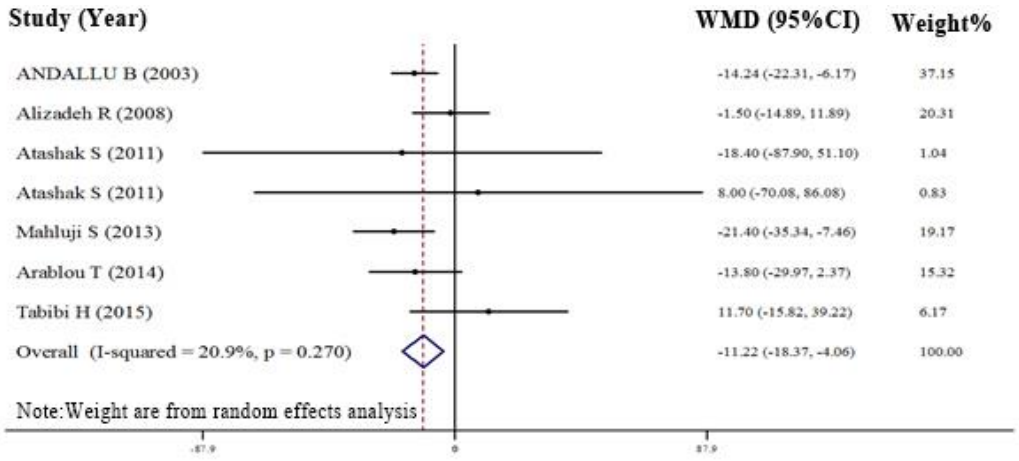

Figure 2. Forest plots depicting the effect of Ginger supplement on LDL-c.

(MD = -11.22 mg/dL; 95% CI, -18.37 to -4.06 mg/dL, p = 0.002). Corresponding changes for TC and TG were -13.31 mg/dL (-20.29 to -6.33 mg/dL, P=0.000) (Figure 3), and -14.96 mg/dL (-22.13 to -

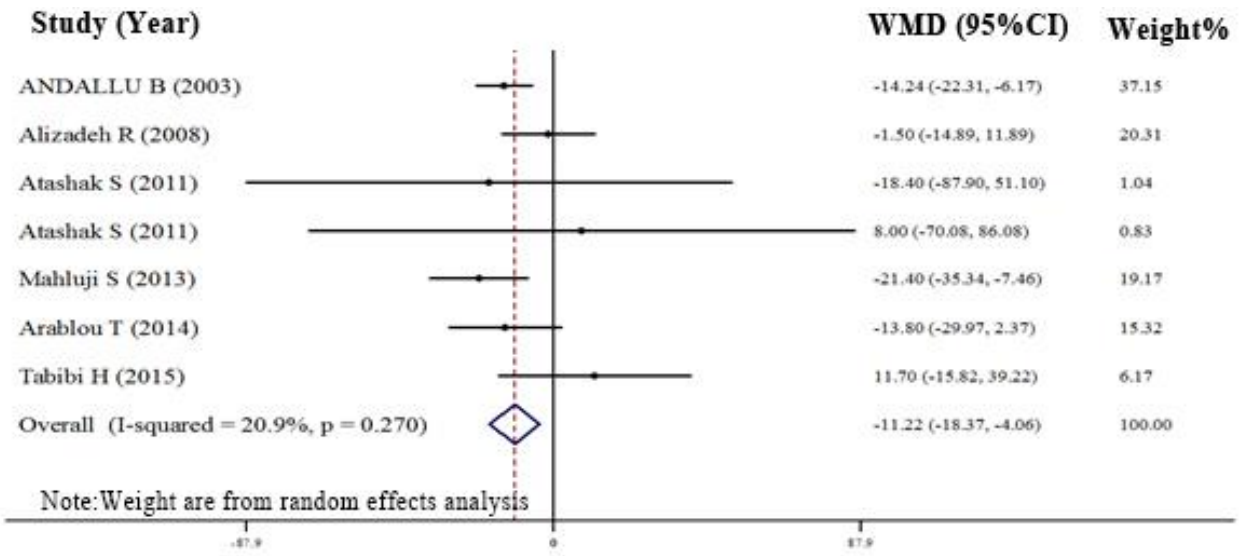

Figure 3. Forest plots depicting the effect of Ginger supplement on HDL-c.

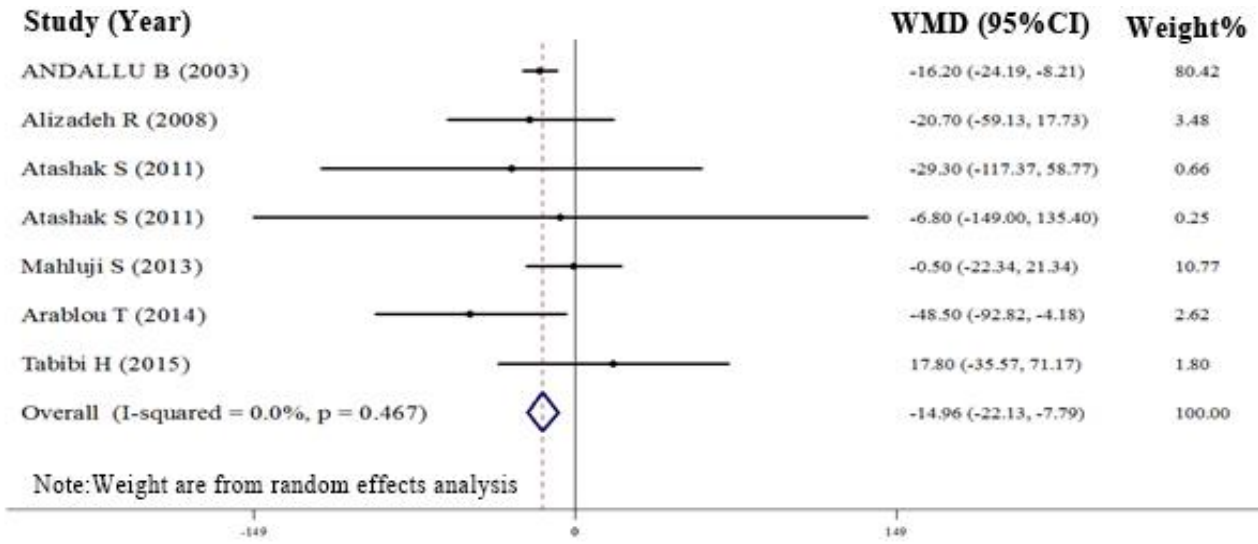

Figure 4. Forest plots depicting the effect of Ginger supplement on TG.

7.79 mg/dL, P=0.000) (Figure 4) respectively. Random effects model indicated that ginger supplementation increased HDL level; however, it was not statistically significant (MD = 0.12 mg/dL; 95% CI, -1.01 to 1.24 mg/dL, P=0.839) (Figure 5). No statistical heterogeneity was seen in any of the lipid parameter analyses. LDL-C, total cholesterol, triglycerides and HDL-C had I^2 values were 20.9%, 0.0%, 0.0% and 0.0% respectively.

Publication Bias

No publication bias was observed when funnel plots were examined. Moreover, the results of Egger's tests did not indicate any publication bias for the considered markers (LDL Egger's tests: P=0.653)

As far as we know this study is the first meta-analysis investigating the impacts of ginger supplementation on lipid profile. Meta-analysis of eight RCTs suggested that ginger supplementation did not significantly change serum level of LDL, HDL, TC and TG. In a sensitivity analysis after excluding the study by Azimi *et al.* due to its outlier results, a statistically significant decrease was found in LDL, TC and TG level when ginger supplementation was used. Moreover, we found out that ginger supplementation could increase plasma

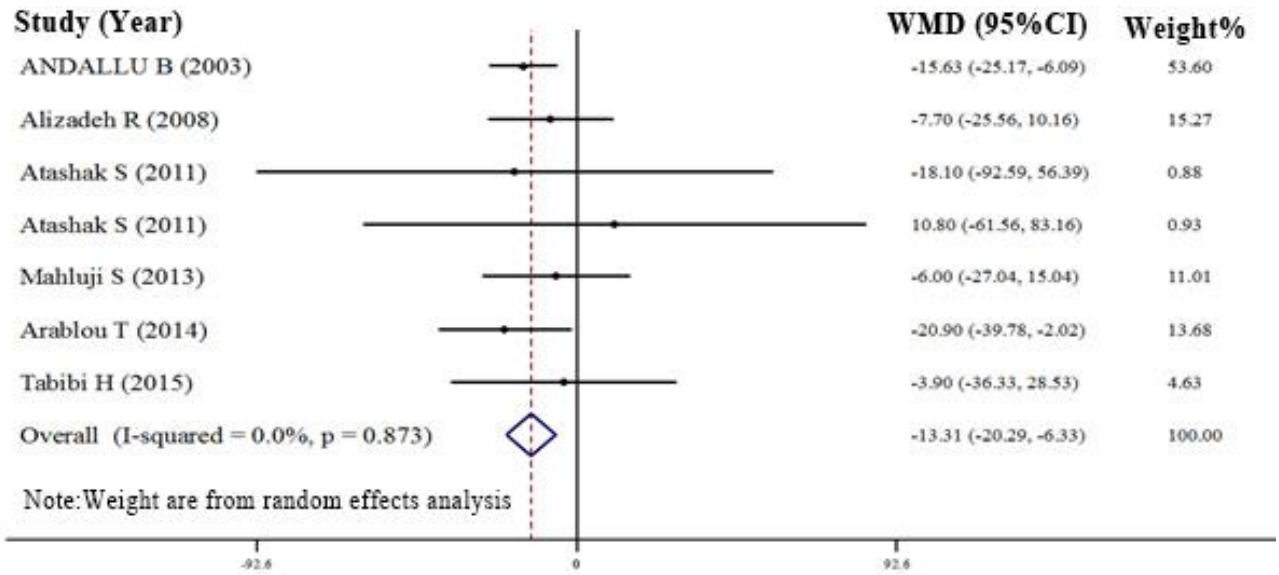

Figure 5. Forest plots depicting the effect of Ginger supplement on TC.

HDL, though not significantly. Furthermore, no significant heterogeneity among RCT's was found for LDL, HDL, TC and TG.

There are certain biological mechanisms proposed for the effects of ginger supplementation on lipid profile. The hypotriglyceridemic effect of ginger could be explained by increasing the activity of lipoprotein lipase enzyme which leads to the hydrolysis of circulatory TG and its subsequent decreasing serum TG (10). Ginger also reduces the ChREBP gene expression in the liver. Reduction of ChREBP expression decreases fatty acid synthase, and glucogenic as well as lipogenic proteins. It also reduces fat accumulation in the liver which results in reduced levels of serum TG (25). Overall, the hypocholesterolemic effect of ginger might be due to the inhibition of cellular cholesterol biosynthesis (26), increased hepatic cholesterol 7a-hydroxylase enzyme activity (27), increased activity of LDL receptor as the result of reduced cellular cholesterol biosynthesis (28), reduced lipid peroxidase (29), increased pancreatic lipase and amylase (30), increased conversion of cholesterol to bile acids (27), increased intestinal peristalism (31), and inhibited lipid hydrolyze in intestinal tract (32).

In general, the results of this study showed that ginger supplementation could remarkably exert beneficial effects on certain lipid markers. As it was confirmed in the present research, another review by Ali *et al.* indicated that distinct forms of ginger extracts might differently affect lipid levels, body weight, hyperglycemia and hyperinsulinemia (33). Beside these human trials in our meta-analysis, some animal studies also indicated the effects of ginger supplementation on lipid profile. In agreement with our findings, 200 mg/kg of ethanolic extract of ginger for 10 weeks resulted in the reduction of TG level in rabbits compared to gemfibrozil (1). This effect was also observed in mice (34) and rats (35). High dosage of ginger, 500 mg/kg, either orally or intra-peritoneal reduced the level of TC in rats (30). Several other investigations have also reported this beneficial effect (36-41). Fuhrman *et al*., reported that the consumption of 250 mg/kg of ginger extract could reduce serum LDL among apolipoprotein E deficient mice (26). Moreover, results of 2 other animal studies indicated that ginger consumption could increase serum HDL level (37, 38).

The side effects of ginger consumption are uncommon. However, mild gastro-intestinal symptoms, including heartburn, diarrhea, and mouth irritation have been reported (42). Only one trial (43) included in the meta-analysis reported one case of heartburn in the intervention group while other six trials did not report any adverse effect in either treatment or placebo groups.

The current meta-analysis faced some limitations. First, partially few RCTs with the modest number of

Table 1: Characteristics of Studies Investigating the Effect of Ginger on serume lipides (TC, TG, LDL, HDL).

Study's first outher	Year	Country	Study design	Participant	Group	Gender (M/F)	BMI (SD)	AGE (SD)	Dose (mg)	Sampel size	Duration (week)	Jadad score
Andallu B	2003	india	NR	hypercholesterolemic patients	I	8/0	NR/NR	40-60	3000	8	4.28	**0**
					C	8/0	NR/NR	40-60	0	8		
Alizadeh-navaei R	2008	Iran	RCT, Double blind	hypercholesterolemic patients	I	16/29	31 (4.4)	53.8 (11.8)	3000	45	6.42	**2**
					C	18/22	34.5 (7.7)	53.5 (11)	3000	40		
Atashk S	2011	Iran	RCT, Double blind	obese men	I	8/0	31.2 (0.6)	23.6 (3.3)	1000	8	10	**3**
					C	8/0	32.2 (2.3)	25.3 (2.2)	1000	8		
Atashk S	2011	Iran	RCT, Double blind	obese men	I	8/0	32.5 (2.3)	23.6 (4.4)	1000	8	10	**3**
					C	8/0	32.8 (2.3)	23.7 (3.8)	1000	8		
Mahluji S	2013	Iran	RCT, Double blind	patients with type 2 diabetes mellitus	I	14/12	29.2 (4.0)	49.2 (5.1)	2000	26	8	**5**
					C	16/12	29.8 (5.0)	53.1 (7.9)	2000	28		
Arablou T	2014	Iran	RCT, Double blind	patients with type 2 diabetes mellitus	I	8/25	26.9 (3.6)	52.6 (8.4)	1600	33	12	**4**
					C	7/23	26.8 (3.4)	52 (9.0)	1600	30		
Azimi P	2014	Iran	RCT, Single blind	patients with type 2 diabetes mellitus	I	15/26	29.05 (0.2)	55.21 (1.1)	3000	41	8	**1**
					C	15/24	28.40 (0.2)	53.64 (1.3)	0	39		
Tabibi H	2015	Iran	RCT, Double blind	peritoneal dialysis (PD) patients	I	11/7	27 (1.0)	56 (2.5)	1000	18	10	**4**
					C	10/8	27 (1.0)	58 (3.0)	1000	18		

NR, not reported

participants were available for the meta-analysis. Second, participants were heterogeneous in terms of conditions and diseases. Third, the Jadad score of two studies was < 2 and finally, most of the papers did not provide any explanation for the methods of blinding and randomization.

Conclusion

Due to its outlier results, the results of the present meta-analysis indicated that ginger supplementation could significantly decrease the serum LDL, TC, TG levels and increase serum HDL level. Nevertheless, it was not statistically significant. Therefore, ginger supplementation could be efficient in the preliminary prevention of hypercholesterolemia and might reduce risk factors for CVD. Further human clinical trials are required to confirm these findings.

Acknowledgment

ZF, KD and SS-b contributed to the accomplishment of designing the research, data gathering and data analysis. ZF wrote the paper and SS-b revised the draft. All authors read the final manuscript and agreed over all aspects of the work.

Conflict of Interest

The authors declare that they have no conflict of interest.

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identifies the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provides a structured summary including the background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describes the rationale for the review in the context of what is already known.	3
Objectives	4	Provides an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
METHODS			
Protocol and registration	5	Indicates if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provides registration information including registration number.	4
Eligibility criteria	6	Specifies study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describes all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Presents full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4
Study selection	9	States the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4
Data collection process	10	Describes the method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5
Data items	11	Lists and defines all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5

Risk of bias in individual studies	12	Describes methods used for the assessing risk of the bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5
Summary measures	13	States the principal summary measures (e.g., risk ratio, difference in means).	5
Synthesis of results	14	Describes the methods of handling the data and combining the results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specifies any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	6
Additional analyses	16	Describes methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	6
RESULTS			
Study selection	17	Gives numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	6
Study characteristics	18	For each study, presents the characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provides the citations.	7
Risk of bias within studies	19	Presents data on the risk of the bias of each study and, if available, any outcome level assessment (see item 12).	
Results of individual studies	20	For all outcomes considered (benefits or harms), presents for each study: (a) a simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	7-8
Synthesis of results	21	Presents the results of each meta-analysis done, including confidence intervals and measures of consistency.	7-8
Risk of bias across studies	22	Presents the results of any assessment of risk of bias across studies (see Item 15).	8
Additional analysis	23	Gives the results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	-
DISCUSSION			
Summary of evidence	24	Summarizes the main findings including the strength of evidence for each main outcome; considers their relevance to key groups (e.g., healthcare providers, users, and policy makers).	8-9
Limitations	25	Discusses limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	10
Conclusions	26	Provides a general interpretation of the results in the context of other evidence, and implications for future research.	10

FUNDING			
Funding	27	Describes the sources of funding for the systematic review and other supports (e.g., supply of data); role of funders for the systematic review.	-

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