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The Effect of *Anethum Graveolens L.* (Dill) on Lipid Profile in Adults with Cardiovascular Risk Factors: A Systematic Review and Meta-Analysis of Controlled Clinical Trials

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ABSTRACT

Background: Several randomized clinical trials (RCTs) has assessed the effect of *Anethum graveolens L.* (AG) or dill supplementation on lipid profile in adults with cardiovascular risk factors with different results. Therefore, we decided to conduct a systematic review and meta-analysis regarding the available randomized controlled trials to assess AG supplementation's efficacy on lipid profile in adults with cardiovascular risk factors.

Methods: PubMed, Embase, Cochrane's database, Ovid, Web of Science, ProQuest, Scopus, and Google Scholar were searched to find relevant articles investigating the effect of AG on the lipid profile of adults with risk factors for cardiovascular disease up to December 2020. Six trials with seven treatment armsmet the inclusion criteria. A random-effects model was used in the meta-analysis. To test heterogeneity, I^2 statistics and Cochrane Q test were applied.

Results: The results reported a significant improving effect of AG on TG [WMD = -29.20, 95% confidence interval (CI): -34.73,-23.68 mg/dL, $p < 0.001$], TC (WMD = -16.46, 95%CI: -21.54,-11.39 mg/dL, $p < 0.001$), LDL-C (WMD = -13.90, 95%CI: -16.08, -11.72 mg/dL, $p < 0.001$), and HDL-C (WMD = 4.01, 95%CI: 3.48, 4.54 mg/dL, $p < 0.001$).

Conclusion: This meta-analysis of randomized controlled clinical trials revealed that consuming AG extract for more than six weeks might improve lipid profile in adults with cardiovascular risk factors.

Keywords: Dill, Lipid profile, Cardiovascular disease, Systematic review, Meta-analysis

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Introduction

Dyslipidemia, a well-founded modifiable cardiovascular risk factor, is characterized by reduced levels of high-density lipoprotein cholesterol (HDL-C) and increased levels of triglycerides, total cholesterol (TC), and low-density lipoprotein cholesterol (LDL-C). Several factors, including genetics, lifestyle, and dietary factors, are shown to affect lipid profile *[1]*. Diet therapy and pharmacological interventions are approaches for controlling dyslipidemia *[2, 3]*. However, taking

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lipid-lowering medications has some limitations due to their adverse effects and attenuated efficacy after prolonged use*[4-7]*. Considering these limitations, a great interest has been expressed in nutraceuticals as a complement for drug treatments. According to the literature, nutraceuticals and dietary supplementations can improve lipid profile by several mechanisms such as lipid absorption and metabolism *[8-10]*. It is proposed that *Anethum graveolens L.* (AG) can improve lipid profile by several mechanisms, including 1) binding to bile acids and reducing cholesterol absorption, 2) inhibiting acetyl-CoA carboxylase and HMG-CoA reductase, which consequently reduces fatty acid and cholesterol synthesis and leads to cholesterol clearance and up-regulation of LDL-C receptors *[11]*.

Anethum graveolens L. known as dill, is one of the most common herbs used as spice in foods *[12, 13]*. It is cultivated in different regions of the world, including southeastern Iran *[13]*. The leaves of AG contain 24 types of minerals, proteins, and fibers *[14]*. Pharmacological effects of AG include: antibacterial *[15, 16]*, antimicrobial *[17-19]*, anti-inflammatory *[20]*, anti-oxidative, anti-hyperglycemia *[19, 21-23]*, anti-hyperlipidemia, and anti-hypercholesterolemia *[21, 24, 25]*. Several studies showed that the intake of AG could improve serum levels of TC, LDL-C, TG, and HDL-C. However, other trials failed to observe an improvement in lipid parameters measured in blood after AG intake *[26-30]*.

Because of the the mentioned controversies between the available documents, we carried out a systematic review and meta-analysis on the available randomized controlled trials (RCTs). The aim was to assess AG supplementation's efficacy on lipid profile in adults with cardiovascular risk factors.

Materials and Methods

This systematic review and meta-analysis was registered in the international prospective register of systematic reviews (PROSPERO) website (https://www. crd.york.ac.uk/prospero/) with the registration number of CRD42020115000. The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guideline was used to conduct the systematic review process.

Search strategy

PubMed, Embase, Cochrane's database, Ovid, Web of Science, ProQuest, Scopus, and Google Scholar were searched to find related articles investigating AG's impact on the lipid profile of adults with cardiovascular disease risk factors up to December 2020. Moreover, we investigated the reference lists of the included studies manually to find other relevant studies. The search was not limited based on language, but the search limitation was applied to find human clinical trials.

Three authors conducted the search to find relevant clinical trials evaluating the relationship between AG and lipid profile based on medical subject headings (MeSH terms) as follows: [Anethum Graveolens OR Dill] AND [lipid profile OR Lipid metabolism disorders OR Low-density lipoprotein OR High-density lipoprotein OR Cholesterol OR Triglycerides OR LDL OR HDL OR TC OR TG OR Cardiomyopathies OR Coronary heart disease OR CHD OR Heart failure OR Myocardial Ischemia OR Hyperlipidaemia OR Hypercholesterolemia OR Dyslipidaemia OR hypertriglyceridemia OR Hypercholesterolemia OR Hypertriglyceridemia OR Obesity OR Obese subject OR Obesity OR Metabolic syndrome OR MetS OR Metabolic syndrome X OR Type 2 diabetes OR hypothyroidism OR non-alcoholic steatohepatitis OR NASH OR Non-alcoholic fatty liver disease OR NAFLD OR Polycystic ovarian syndrome OR PCOS] AND [Randomized clinical trial OR Clinical trial OR Clinical study OR Double-blind randomized clinical trial].

Inclusion and exclusion criteria

After removing the duplicates by using EndNote software, the selected trials' titles and abstracts were

reviewed to assess their systematic review eligibility. The irrelevant articles were removed, and full texts of the eligible trials were reviewed.

Eligibility criteria were defined based on the following inclusion criteria:

1.Study design: randomized clinical trials

2.Participants: adults with cardiovascular risk factors

3.Comparison: intervention group supplemented with powder or extract of AG versus the control group

4.Outcomes: serum level of at least one of the lipid parameters including TC, TG, LDL-C, and HDL-C

Exclusion criteria were animal trials and studies with the participation of children and adolescents.

Data extraction

Data extraction was performed based on the 'authors' name, publication date, trial design and location, 'participants' mean age, body mass index (BMI), AG dose, supplement type (leaf powder or extract), follow-up duration, sample size, and measurements. Extracted data were recorded on a Microsoft Excel sheet for further use.

Quality assessment

The Cochrane risk of bias tool was applied by three reviewers to evaluate the quality of eligible trials methodologically*[31]*. Quality assessment was applied based on several items, including random sequence generation, allocation concealment, blinding of participants and personnel, incomplete outcome data, and other sources of bias. "Yes," "no," and "unclear" were defined as the low, high, and unknown risk of bias according to the Cochrane guideline. NutriGrade scoring system was applied to assess and score the overall quality of meta-analysis using the following domains: precision; study quality, risk of bias, limitations; directness; heterogeneity; publication bias, study design, and funding bias *[32, 33]*.

Data analysis

We used Stata SE software (version 12) to conduct the meta-analysis. The Cochrane guideline was applied to calculate the standard deviations (SDs) of the mean changes using the following formula:

$$\sqrt{\begin{array}{c}(\text{SD pre}-\text{treatment})^2+(\text{SD post}-\text{treatment})^2\\ -\ (2R\ \times\ \text{SD pre}-\text{treatment}\ \times\ \text{SD post}-\text{treatment})\end{array}}$$

Correlation coefficients (R) of the trials were calculated. If R was not mentioned in a study, R = 0.5 was assumed. The effect size was defined as weighted mean difference (WMD) with a 95% confidence interval (CI). A random-effects model was used to conduct the meta-analysis. I-squared statistic and Cochran Q test were used to assess the heterogeneity. Heterogeneity significance level was considered at I^2 value > 50% or $p \leq 0.05$ for Cochran Q test . The effect of each trial on the overall effect size was evaluated using sensitivity analysis. The subgroup analysis was used to detect the heterogeneity sources. Publication bias was checked using funnel plots and statistical asymmetry tests (Egger's test and Begg's test).

Results

A total of 121 articles were identified after database research, of which the full-text of eight studies was reviewed for eligibility assessment. Six studies met the inclusion criteria and were included in the meta-analysis *[11, 26-30]*, and two studies were excluded because anti-hyperlipidemic drugs were only taken by the control groups *[34, 35]*. **Figure 1**. shows a flowchart of the study process.

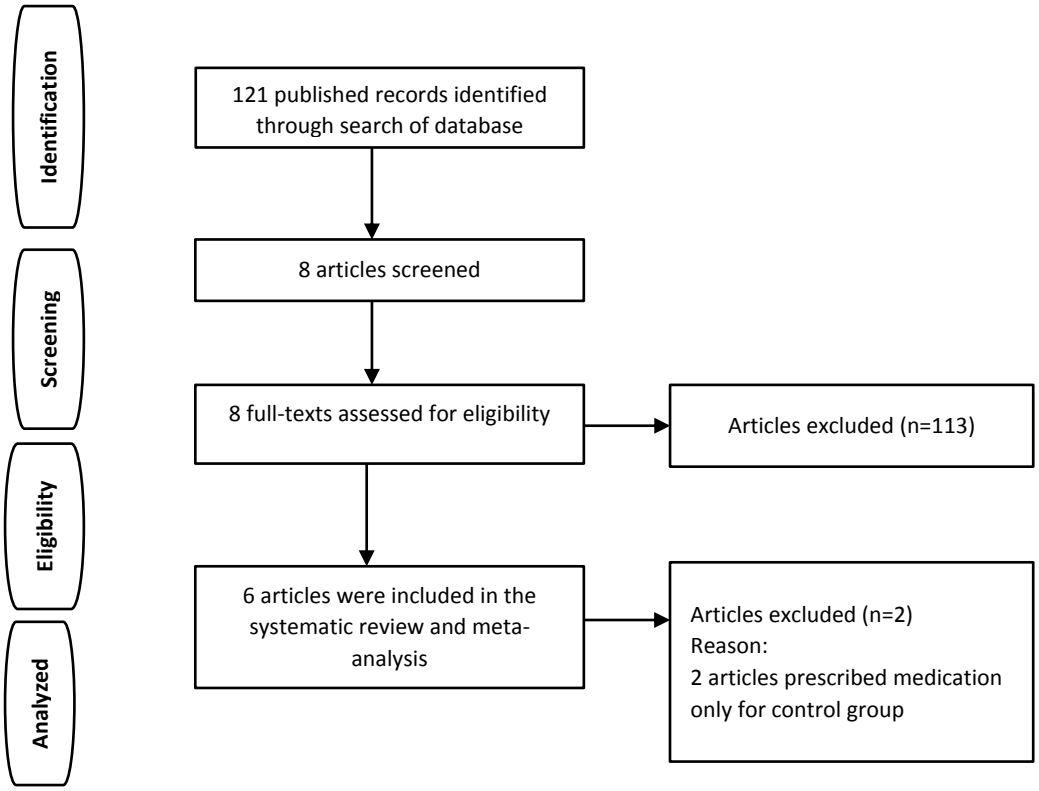

Figure 1. The Study Process of the Systematic Review and Meta-Analysis

Studies characteristics

In this meta-analysis, six eligible trials were included with seven treatment arms and a total of 291 participants (n = 146 in the control group and n = 145 in the melatonin group). All trials were conducted in Iran. Studies with the largest and lowest sample sizes had 100 *[30]* and 20 *[26]* participants, respectively. Supplementation was done using AG extracts and AG powder in two *[27, 28]* and four studies *[11, 26, 29, 30]*, respectively. Treatments included a wide range of AG supplementation; from 2 mg/kg/day to 600 mg/day AG extract and from 3.3 gr/day to 900 mg/kg/day AG powder. The supplementation duration ranged between four weeks *[30]* and eight weeks*[11, 27-30]*. Participants were affected by type two diabetes mellitus *[11, 26, 29]*, hyperlipidemia *[30]*, obesity *[28]*, and metabolic syndrome *[27]*. The study characteristics are represented in **Table 1**.

Quality assessment and quality of meta-evidence

Quality assessment of eligible studies was done based on Cochrane Collaboration's tool *[31]* (**Table 2**). Based on the findings, two studies had a good quality*[11, 29]*, two trials had n acceptable quality *[27, 28]*, and two research had poor quality *[26, 30]*. This meta-analysis's total quality score was calculated as 7 using the NutriGrade scoring system, which shows a moderate quality of meta-evidence. However, further research may affect overall estimates found in the present study.

Meta-analysis

The effect of dill on serum triglycerides

A significant decrease after AG supplementation was observed after pooling the seven intervention arms comparing with the control group [WMD = -29.20, 95% confidence interval (CI): -34.73,-23.68 mg/dL, $p < 0.001$; Cochran's Q test, $p < 0.001$, I^2 =

92.9%) (**Figure 2**). Subgroup analysis was performed to find the possible sources of heterogeneity. Subgroup analysis based on quality of trials revealed a reduced heterogeneity in trials with a good quality (WMD = -37.30, 95%CI: -62.69,-11.92 mg/dL, p = 0.004; Cochran's Q test, p = 0.32, I^2 = 0.0%) (**Table3**). However, subgroup analysis based on supplement type and supplementation duration revealed no information with regard to the heterogeneity source. However, significant results were observed after supplementation with AG extract (WMD = -42.66, 95%CI: -49.24,-36.08 mg/dL, p < 0.001; Cochran's Q test, p = 0.002, I^2 = 84.40%) and more than 6 weeks of supplementation (WMD = -42.32, 95%CI: -48.69,-35.96 mg/dL, p < 0.001; Cochran's Q test,p = 0.007, I^2 = 71.3%) compared with the control group. According to the leave-one-out sensitivity analysis, removing a trial by Ostadrahimi *et al. [28]* showed a significant impact as the overall effect became non-significant (WMD= -3.15, 95% CI: -11.64, 5.34).

The effect of dill on serum total cholesterol

Based on the findings, the supplementation had a significant effect on serum TC and the heterogeneity was high (WMD = -16.46, 95%CI: -21.54,-11.39 mg/dL, p < 0.001; Cochran's Q test, p < 0.001, I^2 = 90.5%) (**Figure 3)**. Subgroup analysis based on quality and duration showed that the source of heterogeneity was reduced in studies with poor quality (WMD = 6.45, 95%CI: -3.28,16.1 mg/dL, p = 0.19; Cochran's Q test, p = 0.82, I^2 = 0.0%), good quality (WMD = -14.42, 95%CI:-24.06,-4.79 mg/dL, p = 0.003; Cochran's Q test, p = 0.84, I^2 = 0.0%), and supplementation duration ≤ 6 weeks (WMD = 6.45, 95%CI: -3.28, 16.19 mg/dL, p = 0.19; Cochran's Q test, p = 0.82, I^2 = 0.0%). Although heterogeneity was not reduced based on the type of supplement, significant reduction was found in the pooled effect size of trials with AG extract supplementation (WMD = -31.57, 95%CI:-39.13,-24.00 mg/dL, p < 0.001; Cochran's Q test, p < 0.001, I^2 = 90.5%). Sensitivity analysis showed that removing the study by Ostadrahimi *et al. [28]*had a significant effect and turned the overall estimate to non-significant (WMD= -1.71, 95% CI: -7.62, 4.18).

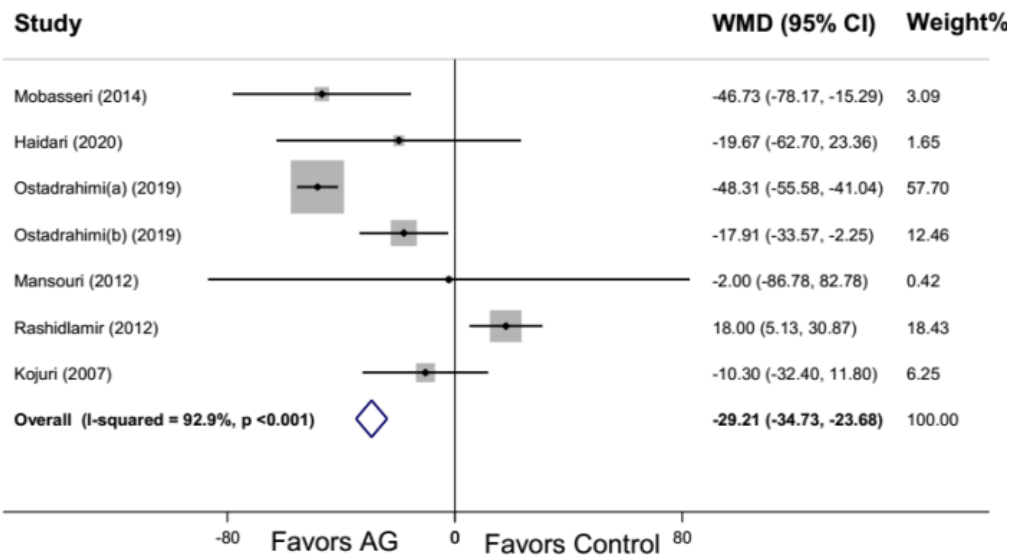

Figure 2. Forest Plot of Trials Experimenting the Effect of AG on TG

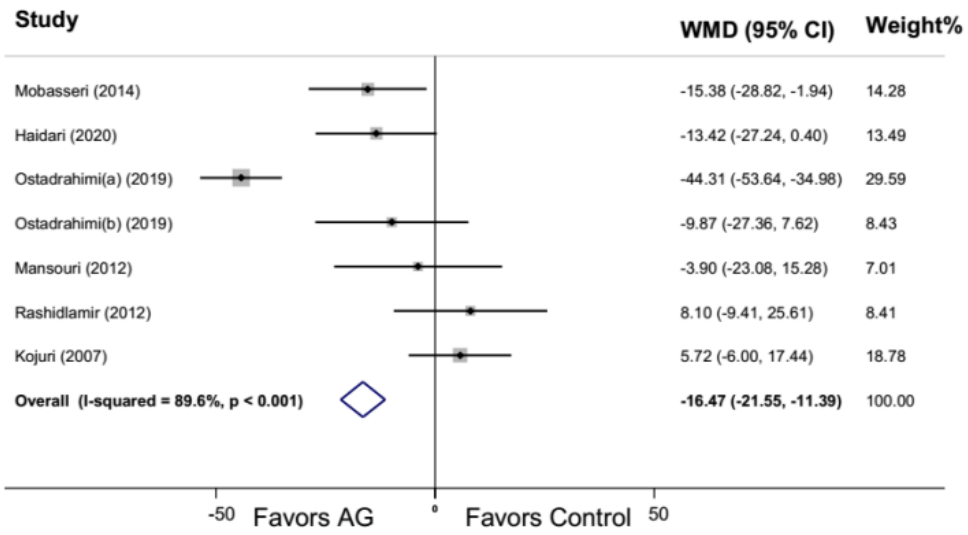

Figure 3. Forest Plot of Trials Experimenting the Effect of AG on TC

The effect of dill on serum low-density lipoprotein cholesterol

Meta-analysis of seven intervention arms showed a significant effect of oral AG on LDL-C (WMD = -13.90, 95%CI: -16.08, -11.72 mg/dL, p < 0.001; Cochran's Q test, p = 0.01, I^2 = 63.8%) (**Figure 4**). In accordance with the subgroup analysis based on quality, reduced heterogeneity was observed in trials with good quality (WMD = -10.45, 95%CI: -16.79, - 4.11 mg/dL, p = 0.001; Cochran's Q test, p = 0.55, I^2 = 0.0%). Trials with AG extract supplementation had a lower heterogeneity in their results (WMD = -15.04, 95%CI: -17.43,-12.65 mg/dL, p <0.001; Cochran's Q test, p = 0.22, I^2 = 33.7%). A reduced heterogeneity had was also found in trials with > 6 weeks of duration (WMD = -14.47, 95%CI: -16.71, -12.23 mg/dL, p < 0.001; Cochran's Q test, p = 0.27, I^2 = 22.1%). Sensitivity analysis displayed no significant effect on the pooled effect size after omitting the studies by Ostadrahimi *et al. [28]* (WMD= -13.53, 95% CI: -15.85,-11.20) and Kojuri *et al.* (WMD=-14.46, 95% CI:-16.66,-12.25).

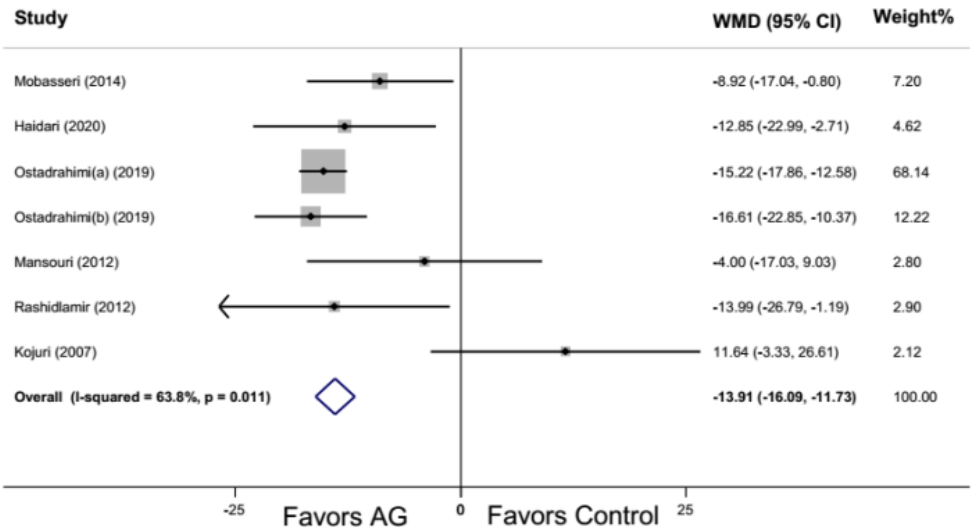

Figure 4. Forest Plot of Trials Experimenting the Effect of AG on LDL-C

The effect of dill on serum high-density lipoprotein cholesterol

The meta-analysis showed a significant increase in HDL-C with high heterogeneity between studies (WMD = 4.01, 95%CI: 3.48, 4.54 mg/dL, p < 0.001; Cochran's Q test, p < 0.001, I^2 = 94.2%) (**Figure 5**). Although heterogeneity was reduced in trials with poor quality (WMD = -0.66, 95%CI: -2.05, 0.73 mg/dL, p = 0.93; Cochran's Q test, p = 0.97, I^2 = 0.0%), only studies with fair quality had a significant effect on serum HDL-C levels (WMD = 5.34, 95%CI: 4.72, 5.95 mg/dL, p < 0.001; Cochran's Q test, p < 0.001, I^2 = 91%). The significant effect of AG was also observed just in trials with extract supplementation (WMD = 5.34, 95%CI: 4.72, 5.95, p < 0.001; Cochran's Q test, p < 0.001, I^2 = 91%). Heterogeneity was reduced in study duration of ≤ 6 weeks (WMD = -0.66, 95%CI:-2.05,0.73 mg/dL, p = 0.35; Cochran's Q test, p = 0.97, I^2 = 0.0%). Moreover, a significant increase was observed in HDL-C in studies with duration of > 6 weeks (WMD = 4.81, 95%CI:4.23,5.39 mg/dL, p < 0.001; Cochran's Q test, p < 0.001, I^2 = 92.5%). Sensitivity analysis revealed no significant effect of removing the studies one by one from the analysis.

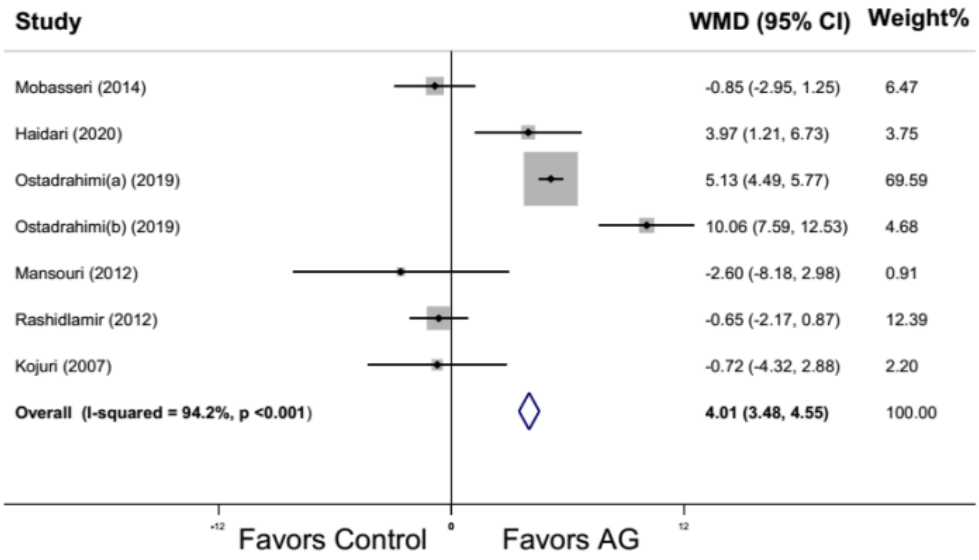

Figure 5. Forest Plot of Trials Experimenting the Effect of AG on HDL-C

Publication bias

No asymmetry was observed in funnel plots for meta-analysis of TG, TC, LDL-C, and HDL-C (**Figures 6-9**). Furthermore, no significant publication bias was found for TG, TC, LDL-C, and HDL-C by 'Egger's regression analysis in the trials assessing AG's effect on lipid profile (p for bias 0.42, 0.15, 0.08, and 0.32, respectively).

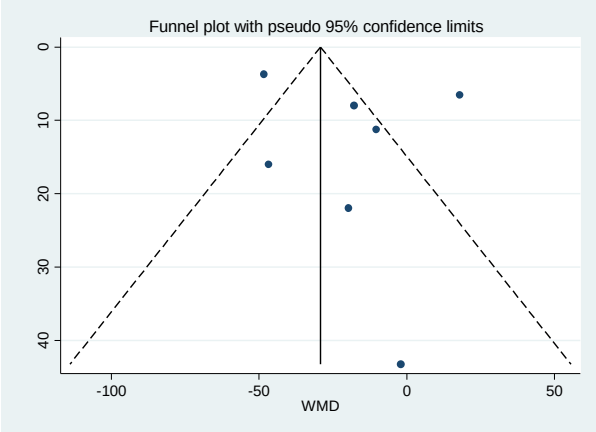

Figure 6. Funnel Plot of Trials Experimenting the Effect of AG on TG

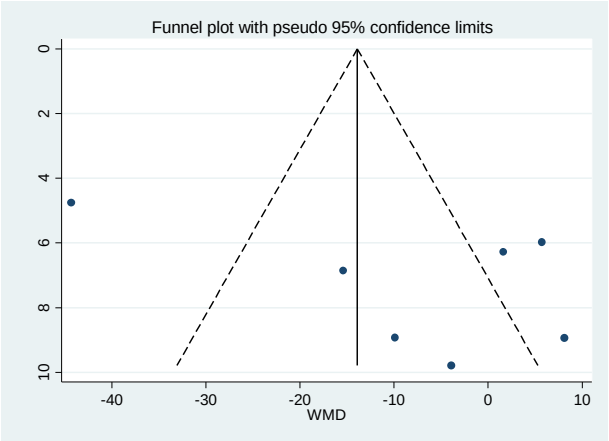

Figure 7. Funnel Plot of Trials Experimenting the Effect of AG on TC

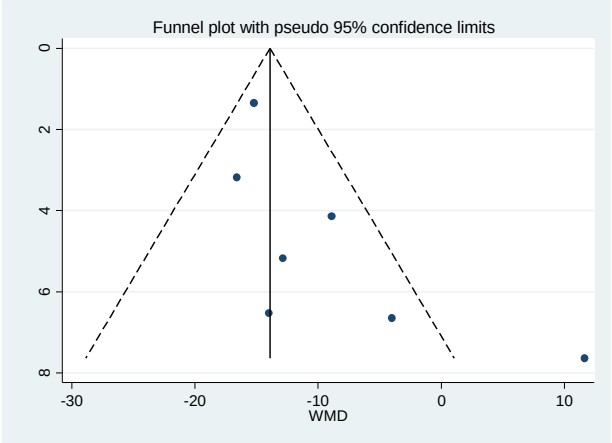

Figure 8. Funnel Plot of Trials Experimenting the Effect of AG on LDL-C

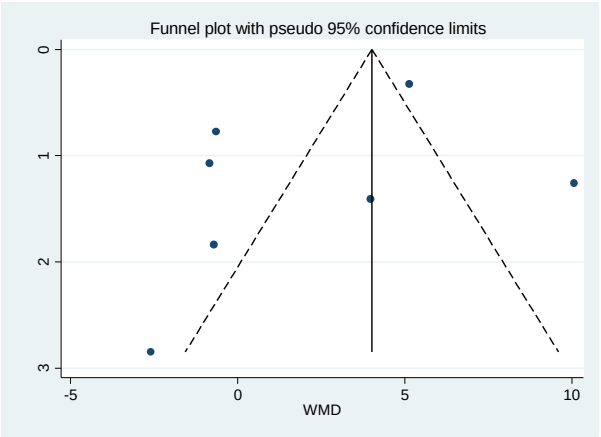

Figure 9. Funnel Plot of trials Experimenting the Effect of AG on HDL-C

Table1. Characteristics of studies included in the meta-analysis.

Study characteristics	Location	Gender and health condition	No. of participants (AG/control)	Trial duration	Intervention	Control	BMI (AG/control)
Kojuri et al. (2007)	Iran	37 males and 83 females with hyperlipidemia	50/50	6 weeks	Leaf powder (650 mg twice daily)	Placebo	NR
Rashidlamir et al. (2012)	Iran	Females with type 2 diabetes mellitus	10/10	4 weeks	Leaf powder (900 mg/kg)+ aerobic training	aerobic training	NR
Mansouri et al. (2012)	Iran	13 males and 11 females with metabolic syndrome	12/12	8 weeks	Extract (600 mg/day)	Placebo	36.60±8.10 / 37.80 ±7.40
Mobasseri et al. (2014)	Iran	Males with type 2 diabetes mellitus	26/26	8 weeks	Leaf powder (3.3 gr/day)	Placebo	28.20±3.93/30.63±5.19
Ostadrahimi et al.[a] (2019)	Iran	Males with obesity & Hyperlipidemia	13/15	8 weeks	Extract (2 mg/kg/day three times a day)	control	32.32± 2.22/34.18±1.92
Ostadrahimi et al.[b] (2019)	Iran	Males with obesity & Hyperlipidemia	13/12	8 weeks	Extract (2 mg/kg/day three times a day) + aerobic training	aerobic training	33.15± 2.58/ 33.15±2.88
Haidari et al. (2020)	Iran	12 females and 30 males with type 2 diabetes mellitus	21/21	8 weeks	Leaf powder (3 gr/day)	Placebo	29.42± 3.24/27.29 ± 8.42

Values are as mean ± SD.
Abbreviations: AG: Anethum Graveolens; BMI: body mass index.

Table2. Quality assessment of studies included in the meta-analysis.

study	Random sequence generation	Allocation concealment	Participants & personnel Blinding	Incomplete outcome data	Selective reporting	Free of other bias	(total quality)
Mobasseri et al. (2014)	L[α]	L	L	L	L	L	G
Haidari et al. (2020)	L	L	L	L	L	L	G
Ostadrahimi et al. (2019) [a]	L	U	L	U[γ]	L	L	F
Ostadrahimi et al. (2019) [b]	L	U	L	U	L	L	F
Mansouri et al. (2012)	L	U	L	L	L	U	F
Rashidlamir et al. (2012)	L	U	U	U	L	L	P
Kojuri et al. (2007)	L	U	H[β]	L	L	U	P

Abbreviations: [α]Low risk of bias, [β]High risk of bias, [γ]Un clear risk of bias; G: good quality, F: fair quality, P: poor quality.

Table 3. Overall effect as well as Subgroup and Heterogeneity analysis of trials investigating the effect of oral AG on lipid profile.

study	Quantitative data synthesis						
	No. of Trials	WMD [§]	95% CI	*Z* value	*P* value [ϕ]	I^2	P
Serum Trigluceride levels (overall effect)*	7	-29.20	-34.73,-23.68	10.36	< 0.001	92.9%	< 0.001
Quality	3	-42.66	-49.24,-36.08	12.71	< 0.001	84.4%	0.002
Fair	2	-37.30	62.69,-11.92	2.88	0.004	0.0%	0.32
Good	2	10.83	-0.29,21.95	1.91	0.05	78.7%	0.03
Poor							
Type of supplement	4	3.08	-7.10,13.26	0.59	0.55	82.6%	0.001
Powder	3	-42.66	-49.24,-36.08	12.71	< 0.001	84.4%	0.002
Extract							
Supplementation duration	5	-42.32	-48.69,-35.96	13.03	< 0.001	71.3%	0.007
> 6 weeks	2	10.83	-0.29, 21.95	1.91	0.05	78.7%	0.03
≤ 6 weeks							
Serum total cholesterol (overall effect)	7	-16.46	-21.54,-11.39	6.36	< 0.001	90.5%	< 0.001
Quality	3	-31.57	-39.13,-24.00	8.18	< 0.001	90.5%	< 0.001
Fair	2	-14.42	24.06,-4.79	2.94	0.003	0.0%	0.84
Good	2	6.45	-3.28,16.19	1.30	0.19	0.0%	0.82

study	Quantitative data synthesis						
	No. of Trials	WMD [§]	95% CI	*Z* value	*P* value [ϕ]	I^2	P
Poor							
Type of supplement	4	-4.09	-10.94, 2.75	1.17	0.24	66.7%	0.02
Powder	3	-31.57	-39.13,-24.00	8.18	< 0.001	90.5%	< 0.001
Extract							
Supplementation duration	5	-25.03	-30.98, -19.08	8.24	< 0.001	86%	< 0.001
> 6 weeks	2	6.45	-3.28, 16.19	1.30	0.19	0.0%	0.82
≤ 6 weeks							
Serum low-density lipoprotein cholesterol (overall effect)	7	-13.90	-16.08, -11.72	12.50	< 0.001	63.8%	0.01
Quality	3	-15.04	-17.43, -12.65	12.34	< 0.001	33.7%	0.22
Fair	2	-10.45	-16.79, - 4.11	3.23	0.001	0.0%	0.55
Good	2	-3.16	-12.89, 6.56	0.64	0.52	84.6%	0.01
Poor							
Type of supplement	4	-8.28	-13.59, -2.97	1.62	0.03	64.2%	0.03
Powder	3	-15.05	-17.44, - 12.66	5.18	< 0.001	33.7%	0.22
Extract							
Supplementation duration	5	-14.47	-16.71, -12.23	12.68	< 0.001	22.1%	0.27
> 6 weeks	2	-3.16	-12.89, 6.567	0.64	0.52	84.6%	0.01
≤ 6 weeks							
Serum high-density lipoprotein cholesterol (overall effect)		4.01	3.48, 4.54	14.74	< 0.001	94.2%	< 0.001
Quality	3	5.34	4.72, 5.95	17.01	< 0.001	91.0%	< 0.001
Fair	2	0.92	-0.75, 2.59	1.08	0.28	86.6%	0.006
Good	2	-0.66	-2.05, 0.73	0.93	0.35	0.0%	0.97
Poor							
Type of supplement	4	-0.009	-1.08, 1.06	0.02	0.98	68.3%	0.02
Powder	3	5.34	4.72, 5.95	17.01	< 0.001	91.0%	< 0.001
Extract							
Supplementation duration	5	4.81	4.23, 5.39	16.33	< 0.001	92.5%	< 0.001
> 6 weeks	2	-0.66	-2.05, 0.73	0.93	0.35	0.0%	0.97
≤ 6 weeks							

[*] Random effects model. [ϕ] P value <0.05 was considered significant. [§] Weight mean difference.

Discussion

To the best of our knowledge, this is the first systematic review and meta-analysis assessing the effect of AG supplementation on lipid profile in adults with cardiovascular risk factors. A significant reduction was observed in TG, TC, and LDL-C levels, but a significant increase was found in serum HDL-C. Subgroup analysis revealed AG's significant effect on lipid profile in studies with high quality, supplementation with AG extracts, and supplementation duration of higher than six weeks.

Sensitivity analysis revealed the significant effect of the study conducted by Ostadrahimi on the pooled effect size of TG and TC, which may be due to its fair design and more detailed inclusion criteria. Furthermore, assessment of the publication bias confirmed the effect of oral AG on the lipid profile. Additionally, eligible studies reported no significant side effects during AG supplementation.

In addition, AG has an anti-hyperlipidemic effect through several possible mechanisms: 1) decreasing intestinal cholesterol absorption that leads to binding with bile acids, increasing fecal excretion, and producing bile acids; 2) reducing acetyl CoA carboxylase or 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase, which is a key enzyme in cholesterol metabolism; 3) increasing liver LDL-C receptors, reducing fatty acid synthesis, and inducing lipoprotein homeostasis; 4) anti-inflammatory effects of some components of AG such as flavonoids, terpenoids, alkaloids, tannins, and polyphenols on the formation of AGEs as sources of oxidative stress and inflammation; 5) improving insulin resistance and lipid profile by activating peroxisome proliferation-activated receptor-α (PPAR-α), 6) and gene expression of enzymes, which are involved in fatty acid oxidation *[23]*.

Subgroup analysis showed no significant result on TC, TG, and HDL-C in studies with poor quality, which could be due to bias in the study design with regard to the participants' blinding and allocation concealment *[26, 30]*. Moreover, sub-group analysis based on the supplementation type (extract or powder) showed significantly affected lipid profile in participants supplemented with AG extract, which may be due to other factors such as type of metabolic disorder. According to the subgroup analysis in terms of the study duration, supplementation duration of ≤ 6 weeks had no significant effect on lipid profile *[26, 30]*. It should be noted that the supplement type was leaf powder of AG in these studies, and they were designed with poor quality. Hence, further research is needed to make a more comprehensive conclusion.

The present study included randomized controlled clinical trials investigating the effect of AG supplementation on lipid profile in adults with cardiovascular risk factors for the first time. Furthermore, subgroup analysis was performed based on the study quality, supplement type, and supplementation duration. However, there were some limitations. First, the number of eligible studies in this study was low. However, most trials had good and fair quality. Second, the included trials were heterogeneous, which was explained by subgroup analysis. Third, the subgroup analysis was impossible based on the supplementation dose. Therefore, it was not possible to determine the effective dose of AG powder or extract. Forth, all trials were conducted in Iran; so, further research is suggested among other populations and races.

The findings revealed that consuming AG extract for more than six weeks might improve adults' lipid profile with cardiovascular risk factors. However, more RCTs are suggested with a larger sample size and stronger control of confounding variables such as weight and BMI to better understand the AG's effect on lipid profile.

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Nothing to declare

Authors' contributions

M.A and A.M designed the study and searched the database. Z.S performed the data extraction; A.M

and A.M conducted the data analysis; M.A and Z.S prepared the manuscript; SAH, A.M, and R.H revised the manuscript. All the authors approved the manuscript.

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Conflict of interest

This study was not funded by the public and commercial agencies. The authors declare that they have no conflict of interest.

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