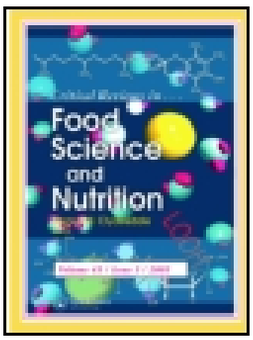

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REVIEW

The effects of *Anethum graveolens* (dill) supplementation on lipid profile and glycemic control: a systematic review and meta-analysis of randomized controlled trials

Seyed Mohammad Mousavi[a], Ana Beatriz Pizarro[b], Camellia Akhgarjand[c], Amir Bagheri[a], Emma Persad[d], Elmira Karimi[a], Alexei Wong[e], and Ahmad Jayedi[f]

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ABSTRACT

There is an increased interest in the potential health benefits of nutraceutical therapies, such as *Anethum graveolens* (dill). Therefore, this systematic review and meta-analysis aimed to evaluate the effects of *Anethum graveolens* supplementation on lipid profiles and glycemic indices in adults. A systematic search was performed for literature published through November 2020 via PubMed/Medline, Scopus, ISI Web of Science, and Embase to find randomized controlled trials (RCTs) evaluating the effects of oral supplementation with *A. graveolens* on lipid profile and measures of glycemic control in adults. The random-effects model was applied to establish the weighted mean difference (WMD) and associated 95% confidence intervals (CI). Seven RCTs with a total number of 330 subjects were included in the final analysis. Pooled results indicated that *A. graveolens* supplementation significantly decreased low-density lipoprotein cholesterol (LDL) concentration (WMD: −15.64 mg/dL; 95% CI: −24.55 to −6.73; $P = 0.001$), serum insulin (WMD: −2.28 μU/ml; 95% CI: −3.62 to −0.93; $P = 0.001$), and HOMA-IR (WMD: −1.06; 95% CI: −1.91 to −0.20; $P = 0.01$). However, there was no significant effect on serum total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL), and fasting blood glucose (FBS). Subgroup analysis suggested that using *A. graveolens* in higher doses and long-term duration had beneficial effects on lipid profiles. Dose-response analysis also showed a significant reduction in FBS at doses of 1500 mg/d. The present meta-analysis indicated that *Anethum graveolens* could exert favorable effects on insulin resistance and serum LDL. Further research is necessary to confirm our findings.

KEYWORDS

Anethum graveolens; herbal medicine; hyperlipidemia; insulin resistance; lipid profile; meta-analysis

Introduction

Cardiovascular disease (CVD) is a multifactorial condition that is the leading cause of death per year worldwide (Nichols et al. 2014; Estruch et al. 2013). Among the most important risk factors of CVD is dyslipidemia (Wood 2001), defined as having elevated total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C) and triglycerides (TG), as well as a decreased high-density lipoprotein cholesterol (HDL-C) (Miller 2003; DAHLöF 2010). Along with CVD, diabetes mellitus (DM) is currently one of the most challenging disorders for health care professionals (Zheng, Ley, and Hu 2018). Globally, about one in 11 adults have DM, and approximately 90% of them have type 2 diabetes (T2D) (Zheng, Ley, and Hu 2018). This metabolic disease is characterized by insulin resistance, dyslipidemia, and hyperglycemia (Patrone, Eriksson, and Lindholm 2014). Cardiovascular complications are the leading cause of morbidity and mortality in patients with T2D (Zheng, Ley, and Hu 2018). Although a wide range of lipid- and glucose-lowering drugs have been recognized (Shattat 2014; Freeland and Farber 2015), they are associated with a multitude of side effects, such as gastrointestinal disorders, myopathy, rhabdomyolysis, peripheral neuropathy, and hepatic and renal failure (Muscari, Puddu, and Puddu 2002; Freeland and Farber 2015). Therefore, many patients and clinicians are eager to use natural products and nutraceutical therapies to prevent or treat dyslipidemia and T2D (Yeh et al. 2002; Mousavi et al. 2019).

Anethum graveolens L., known commonly as dill, is an annual plant of the Apiaceae family frequently used as a spice (Saleh-E-In et al. 2010; Yazdanparast and Bahramikia 2008; Husain et al). This plant usually grows in Europe, the Mediterranean region, central and southern Asia, and Iran (Yazdanparast and Bahramikia 2008). *A. graveolens* leaves are a potential source of nutrients, including vitamin C, carotenoids, beta-carotene, chlorophylls, and polyphenols (Lisiewska, Kmiecik, and Korus 2006). This plant is also

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known as a powerful antioxidant source that has antimicrobial and antispasmodic properties (Singh et al. 2006). Moreover, recent preclinical studies have suggested its anticancer, anti-gastric irritation, hypoglycemic, and anti-inflammatory effects (Oshaghi et al. 2016). However, the impact of *A. graveolens* supplementation on lipid profile and glycemic indices have been inconclusive. Some studies showed the favorable effects of *A. graveolens* on these parameters (Haidari et al. 2020; Mobasseri et al. 2014), while the others failed to support such findings (Kojuri, Vosoughi, and Akrami 2007; Mansouri et al. 2012). Despite the inconsistent results on the improvement of dyslipidemia and diabetic parameters following *A. graveolens* supplementation, we are aware of no earlier study summarized findings on these issues. Thus, the aim of this systematic review and dose-response meta-analysis of randomized controlled trials (RCTs) is to evaluate the effects of *A. graveolens* supplementation on lipid profile and glycemic indices in adults.

Methods

The Preferred Reporting Items of Systematic Reviews and Meta-Analysis (PRISMA) Guideline was followed to report the results of this meta-analysis (Shamseer et al. 2015). This study's protocol has been priori registered in the center for Open Science Framework (OSF) database (https://www.osf.io, ID: 10.17605/OSF.IO/GV3NH).

Search strategy

We comprehensively searched four medical databases, including PubMed/Medline, Scopus, Web of Science, and Embase, to obtain relevant randomized controlled trials (RCTs) up to November 10, 2020. The MESH and non-MESH terms used in this stage included: ("Anethum graveolens" OR " OR "Dill Plant" OR "Dill Plants" OR "Dill" OR "Dills" OR "Dill Weed" OR "Dill Weeds") AND ("Random Allocation" OR "Single-Blind Method" OR "Double-Blind Method" OR "Cross-Over Studies" OR "Clinical Trials as Topic" OR RCT OR "Intervention Studies" OR intervention OR "controlled trial" OR randomized OR randomized OR random OR randomly OR placebo OR assignment OR trial). No limitation regarding language or date of publication was applied. We additionally hand-searched reference lists of all related studies, review articles, key journals to ensure no eligible articles had been overlooked.

Eligibility criteria

Two investigators (SMM, AB) independently searched the mentioned online databases to retrieve potentially related articles. Any disagreement regarding study selection was resolved through discussion with a chief reviewer (AJ), and a consensus was reached. We considered randomized controlled trials (RCTs) as eligible if they were performed on adult samples (aged $>$ 18 years old), and assessed the effect of oral *Anethum graveolens* (dill) supplementation in comparison to placebo (control intervention) on at least one of our outcomes of interest; including TG, TC, LDL, HDL, fasting blood glucose (FBS), insulin, and HOMA-IR.

We excluded studies performed in children, pregnant or lactating women, and those with no clear or insufficient presentation of changes in the outcome measures. Furthermore, investigations assessing the effect of *A. graveolens* supplementations in combination with other components were also excluded. When more than one published paper existed for the same data, the one with the most complete information was selected for inclusion.

Data extraction

Two independent investigators (SMM and AB) excluded irrelevant articles through title and abstract screening. Thereafter, full texts of the remaining articles were reviewed, and eligible studies were considered. Any discrepancy was resolved by the chief investigator (AJ). Full texts of the included studies were eventually examined to obtain the following information: (1) the numbers of subjects in the intervention and control groups, (2) the baseline subjects' characteristics including gender, mean age, and health status, (3) the study's location, first author name and year of publication, (4) intervention duration and dosages of *A. graveolens* supplements, (5) mean and standard deviation (SD) of the mentioned outcomes values in the study baseline and after the supplementation (or the outcomes measures changes during the intervention). When these outcomes were reported in different units, we converted them to the most commonly used unit.

Risk of bias assessment

Two investigators assessed the quality rating of each included paper (SMM and ABP) through the use of the Cochrane quality assessment tool for RCTs (Higgins et al. 2011), according to the following items: (a) random sequence generation, (b) allocation concealment, (c) blinding of participants and personnel (d) blinding of study outcome examination, (e) selective reporting, (f) completeness of study outcome information, and (g) other possible sources of biases. There was one of the three possible answers for each item: yes, no, and unclear, which were representative of high, low, or unclear quality, respectively.

Quantitative data synthesis and statistical analysis

The mean difference and SD of outcome values were used for effect size calculation. When the SD of the mean change during study intervention was not reported, it was calculated by the following formula: S.D change = square root $[(SD_{baseline})^2 + (SD_{final})^2 - (2 \times R \times SD_{baseline} \times SD_{final})]$ (Borenstein et al. 2011). For estimating SD when the standard error of the mean (S.E.M) was reported, the following formula was applied: $S.D = S.E.M \times \sqrt{n}$ (n is the number of subjects in each group). Finally, the overall effect size magnitude was described by two parameters: weighted mean difference (WMD) and 95% CI in a random effect model.

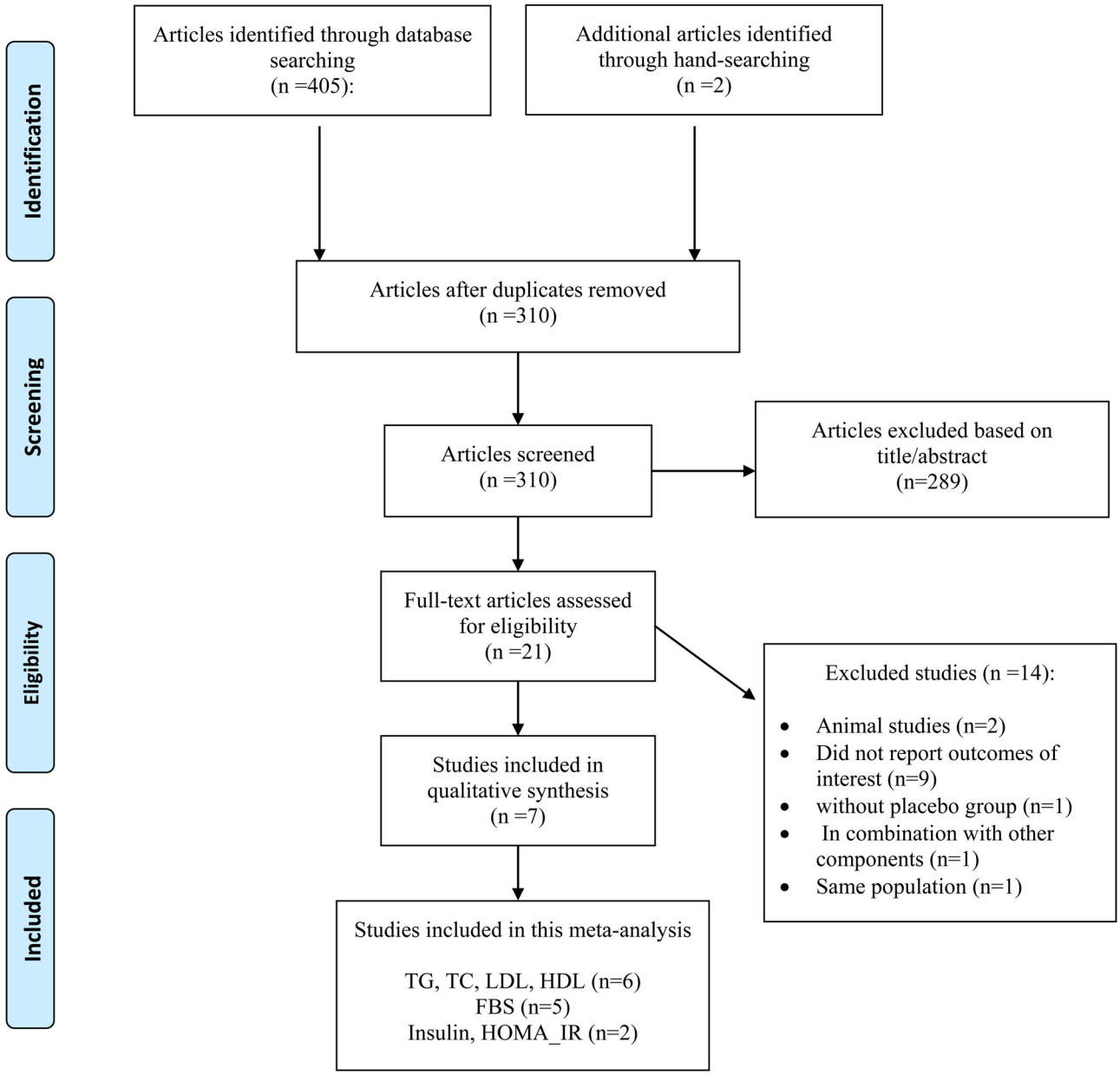

Figure 1. Flow diagram of the study selection process.

The pooled estimates were computed using the random-effects model with the method developed by derSimonian and Laird (Dersimonian and Laird 1986). I-square (I^2) test was applied to identify and describe heterogeneity among the results of included articles, with a significance level of $p < 0.10$. To find the potential sources of any heterogeneity, subgroup analyses based on mean age (<50 years/≥50 years), health status (diabetic/hyperlipidemic) as well as intervention dosage (<1000 mg/d/>1000 mg/d) and duration (<8 weeks/≥8 weeks) were conducted. The sensitivity analysis for examining the influence of each individual study on the overall effect size was carried out through the leave-on-out method (i.e. removing a study at a time and repeating the analysis) (Sahebkar 2014). Moreover, the non-linear impacts of *A. graveolens* supplements dosages and duration on outcomes values were identified through fractional polynomial modeling (Fan and Gijbels 1996). Due to the low number of included studies ($n < 10$), we did not evaluate publication bias (Higgins 2008). In this paper, all mathematical analyses were carried out by Stata software (Version 14.0, Stata Corp, College Station, TX) in which P-values less than 0.05 were assumed significant.

Results

Study selection

A total of 407 articles were found in the primary searches through databases and reference lists. Of these, 97 duplicates were removed, and 310 records remained. The detailed process of the literature search is shown in Figure 1. After reviewing articles based on titles and abstracts, 21 papers were considered for an additional examination of full-texts. Of these 14 studies were excluded because of the following reasons: did not provide sufficient information about outcomes of interest (nine studies), performed in animals (two

Table 1. Characteristics of the included studies.

First author (year)	Year	country	Study design	Gender	Mean age (year)	Duration of study (weeks)	Study population	Sample size (intervention/ placebo)	Dosage (mg/d)	Outcome
Kojuri et al.	2007	IRAN	R/SB/PL	F/M	55.5	6	Hyperlipidemia patients	50/50	1300	TG, TC, LDL, HDL
Mansouri et al.	2012	IRAN	R/DB/PL	F/M	38.2	12	Metabolic syndrome	10/10	600	TG, TC, LDL, HDL, FBS
Sahib et al.	2012	IRAQ	R/PL	F/M	44-6	4	Hyperlipidemia patients	15/15	1000	TG, TC, LDL, HDL
Rashidlamir et al.	2012	IRAN	R/DB/PL	F	51.2	4	Diabetic women	10/10	900	TG, TC, LDL, HDL, FBS
Mobasseri et al.	2014	IRAN	R/DB/PL	F/M	53.1	8	Diabetic patients	26/26	3300	TG, TC, LDL, HDL, FBS, insulin, HOMA-IR
Sargolzaei et al.	2017	IRAN	R/PL	F/M	46.3	6	Type 2 diabetes	30/30	1500	FBS
Haidari et al.	2020	IRAN	R/DB/PL	F/M	50.6	8	Type 2 diabetes	24/24	3000	TG, TC, LDL, HDL, FBS, insulin, HOMA-IR

Abbreviations: R; randomized, DB; double-blind, SB; single blind, PL; placebo, F; female, M; male, TG: triglyceride, TC: total cholesterol; LDL: low-density lipoprotein; HDL: high-density lipoprotein; FBS: fasting blood sugar

studies), did not have a control group (one study), used other components in combination with *A. graveolens* (one study), or had the same dataset (one study). Finally, seven RCTs were included in the final quantitative analysis (Haidari et al. 2020; Rashidlamir et al. 2012; Sahib, Mohammad, and Al-Gareeb 2012; Sargolzaei et al. 2017; Mobasseri et al. 2014; Mansouri et al. 2012; Kojuri, Vosoughi, and Akrami 2007).

Study characteristics

The general characteristics of seven qualified trials included in the current meta-analysis are summarized in Table 1. These studies were published between 2007 and 2020 and were performed in Iran (Haidari et al. 2020; Rashidlamir et al. 2012; Sargolzaei et al. 2017; Kojuri, Vosoughi, and Akrami 2007; Mansouri et al. 2012; Mobasseri et al. 2014) and Iraq (Sahib, Mohammad, and Al-Gareeb 2012). The sample size ranged from 20 to 100 subjects with a total number of 330 patients. Participants' mean age ranged from 38 to 55 years. Six studies were performed on both genders, and one trial only included women (Rashidlamir et al. 2012). The intervention duration varied from 4 to 12 weeks, and the dosage of *A. graveolens* supplementation ranged from 600 to 3300 mg/d. In regards to the characteristics of the participants in the included trials, three studies were conducted among patients with metabolic syndrome or hyperlipidemia (Sahib, Mohammad, and Al-Gareeb 2012; Kojuri, Vosoughi, and Akrami 2007; Mansouri et al. 2012), and all other studies were among diabetic patients (Rashidlamir et al. 2012; Sargolzaei et al. 2017; Mobasseri et al. 2014; Haidari et al. 2020). Regarding the outcomes, six trials investigated the effect of *A. graveolens* on lipid profile (Rashidlamir et al. 2012; Sahib, Mohammad, and Al-Gareeb 2012; Kojuri, Vosoughi, and Akrami 2007; Mansouri et al. 2012; Mobasseri et al. 2014; Haidari et al. 2020), five on serum FBS (Rashidlamir et al. 2012; Sargolzaei et al. 2017; Haidari et al. 2020; Mansouri et al. 2012; Mobasseri et al. 2014), and two on insulin and HOMA-IR (Mobasseri et al. 2014; Haidari et al. 2020).

Risk of bias assessment

The risk of bias was assessed for primary outcomes in the seven included studies using seven domains. Figure 2 shows the summary and graph, respectively. Cochrane Risk of Bias tool contains seven entries related to selection bias, performance bias, detection bias, attrition bias, reporting bias, and other biases. None of the studies met the criteria for low risk of bias across all domains. For the general heading of randomization to dill administration or placebo, sequence generation was reported by 72% of the trials and rated low, whilst 85% of the studies were considered at an unclear risk of bias due to not explicitly explaining allocation concealment. Three studies (Kojuri, Vosoughi, and Akrami 2007; Mansouri et al. 2012) were rated at a low risk of bias for blinding of outcome assessment by the administration, caregivers and researchers, whilst four studies did not report blinding of outcome assessors, increasing detection bias. Under the domain for incomplete outcome data, only 42% of the studies were considered at a low risk of bias as they reported and followed an existing protocol and reported the chosen outcomes. For selective reporting, four studies were low risk, two were high risk and one remained unclear. For other biases, all the studies had low risk as they did not state any important concerns not covered by other domains in the tool.

Effect of A. graveolens on serum TG levels

A total of six trials including 270 participants (intervention = 135 and control = 135) investigated the effect of *A. graveolens* supplementation on serum TG levels (Kojuri, Vosoughi, and Akrami 2007; Mansouri et al. 2012; Rashidlamir et al. 2012; Sahib, Mohammad, and Al-Gareeb 2012; Mobasseri et al. 2014; Haidari et al. 2020). The pooled results from the random-effects model showed that *A. graveolens* had no significant effect on serum TG concentrations compared to the placebo (WMD: −17.91 mg/dl; 95% CI: −46.88 to 11.06; $P = 0.22$), with a significant degree of heterogeneity ($I^2 = 76.6\%$, $P = 0.001$) (Figure 3A). Based on subgroup analysis, trial duration was the potential source of heterogeneity ($I^2 = 0.0\%$, $P = 0.46$); for which TG levels were significantly decreased in trials with a long-term intervention (≥8 weeks) (WMD: −33.8 mg/dl; 95% CI: −58.24, −9.37; $P = 0.007$). In addition, participant's mean age was another potential source of heterogeneity ($I^2 = 8.2\%$, $P = 0.29$); *A. graveolens* significantly reduced serum TG levels in participants who had <50 years compared with those

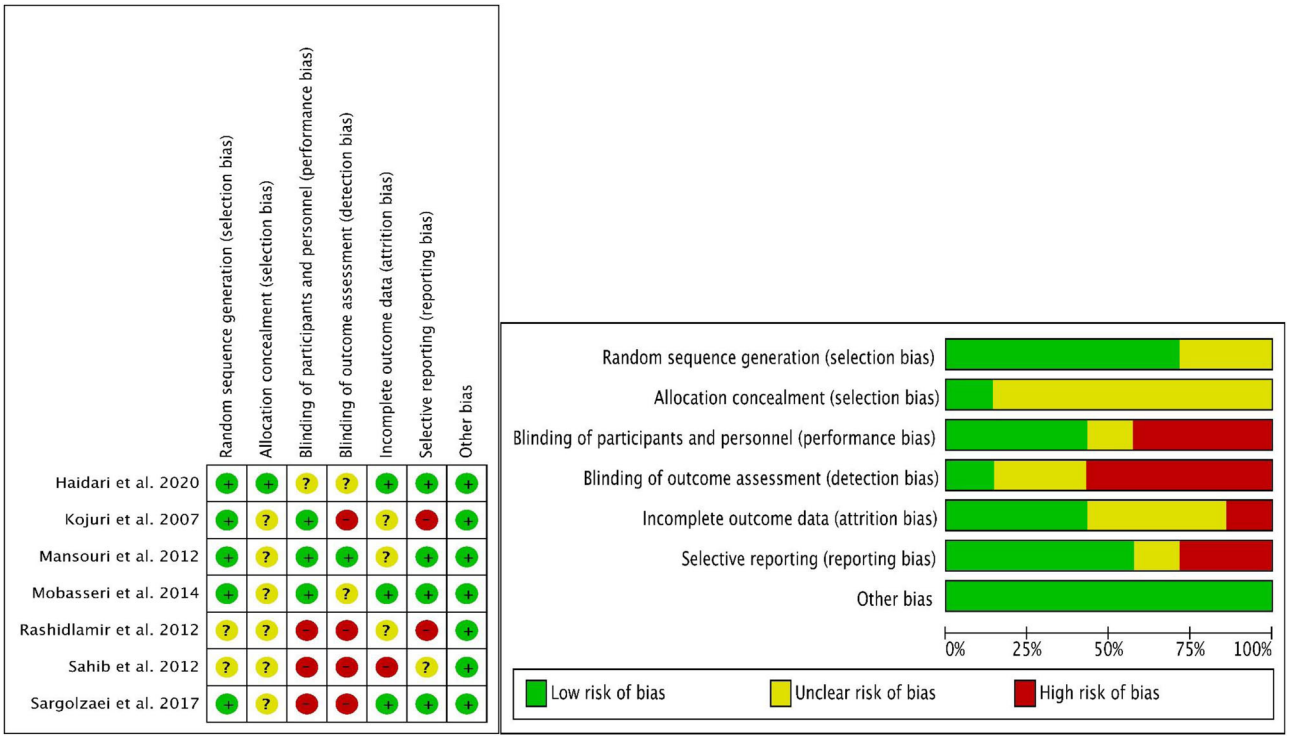

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

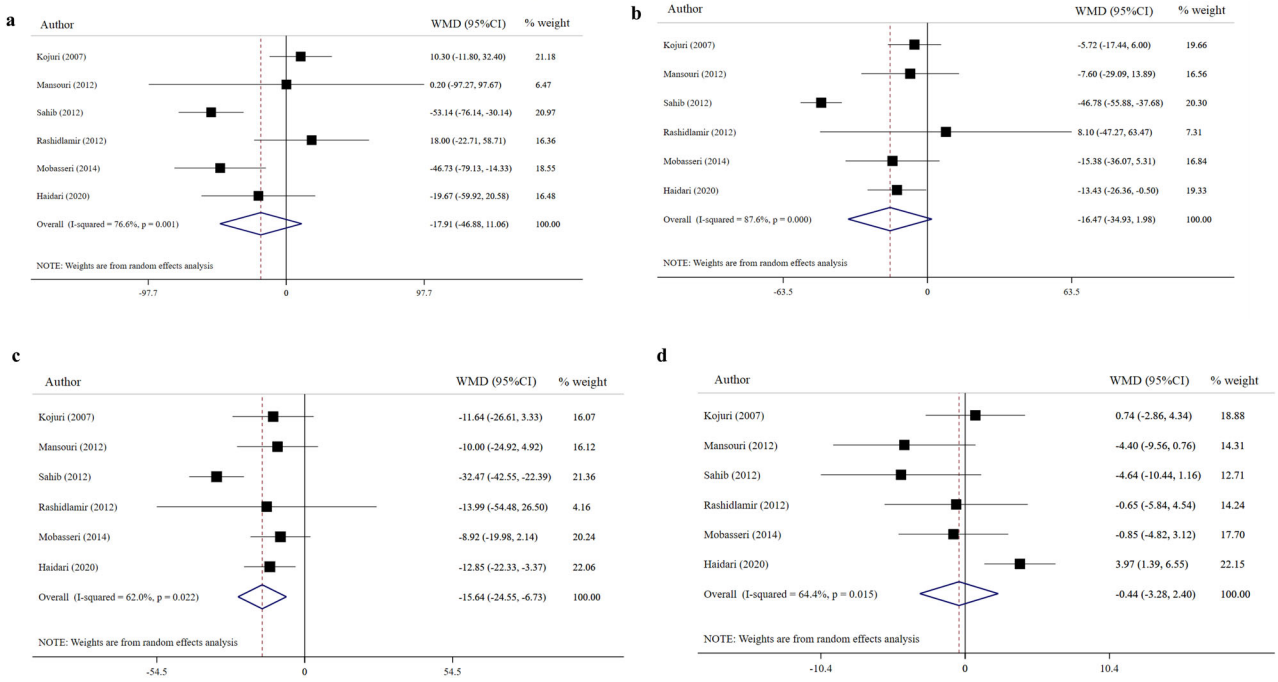

Figure 3. Forest plot depicting the weighted mean difference and 95% confidence intervals for the effect of *A. graveolens* supplementation on serum (a) TG, (b) TC, (c) LDL, and (d) HDL.

who had ≥50 years (WMD: −48.36 mg/dl; 95% CI: −78.21, −18.51; $P < 0.001$) (Table 2). Also, sensitivity analyses showed that the step-by-step omission of each trial at a time did not remarkably change the overall effect size.

Effect of A. graveolens on serum TC levels

Six trials, including a total of 270 participants, reported TC as an outcome measure (Kojuri, Vosoughi, and Akrami 2007; Mansouri et al. 2012; Rashidlamir et al. 2012; Sahib, Mohammad, and Al-Gareeb 2012; Mobasseri et al. 2014; Haidari et al. 2020). Combining effects sizes from the random-effects model showed no significant changes in serum TC levels following *A. graveolens* intake (WMD: −16.47 mg/dl; 95% CI: −34.93 to 1.93; $P = 0.08$), with a significant between-study heterogeneity ($I^2 = 87.6\%$, $P < 0.001$) (Figure 3B). The sensitivity analysis suggested that the overall effect size was heavily influenced by the study by Sahib et al

Table 2. Results of subgroup-analysis for the effects of *A. graveolens* on lipid profile and glycemic indices. (all analyses were conducted using random-effects model).

Study group	Number of trials	Meta-analysis		Heterogeneity		
		WMD (95% CI), mg/dl	P-effect	I^2 (%)	P-within group	P-between group
TG						
Anethum dosage (mg/d)						0.06
<1000	3	−16.14 (−72.56, 40.27)	0.57	78.7	0.009	
>1000	3	−17.14 (−53.85, 19.57)	0.36	76.2	0.01	
Study duration (week)						0.20
<8	3	−9.61 (−56.91, 37.67)	0.69	89.0	<0.001	
≥8	3	−33.80 (−58.24, −9.37)	0.007	0.0	0.46	
Mean age						0.001
<50 years	2	−48.36 (−78.21, −18.51)	<0.001	8.2	0.29	
≥50 years	4	−9.23 (−39.16, 20.69)	0.54	69.8	0.02	
Health status						0.91
hyperlipidemic	3	−17.51 (−55.61, 13.87)	0.52	87.0	<0.001	
diabetic	3	−17.66 (−55.17, 19.83)	0.35	66.4	0.05	
TC						
Anethum dosage (mg/d)						<0.001
<1000	3	−20.87 (−48.01, −31.45)	0.24	85.5	0.001	
>1000	3	−10.12 (−18.12, −2.11)	0.01	0.0	0.59	
Study duration (week)						0.003
<8	3	−19.32 (−54.82, 16.17)	0.28	93.6	<0.001	
≥8	3	−12.66 (−22.42, −2.89)	0.01	0.0	0.86	
Mean age						<0.001
<50 years	2	−28.44 (−66.76, 9.86)	0.14	90.8	0.001	
≥50 years	4	−9.74 (−17.67, −1.82)	0.01	0.0	0.69	
Health status						0.01
hyperlipidemic	3	−20.66 (−51.43, 10.10)	0.20	94.1	0.0	
diabetic	3	−13.14 (−23.90, −2.38)	0.01	0.0	0.73	
LDL						
Anethum dosage (mg/d)						0.01
<1000	3	−20.94 (−38.97, −2.91)	0.02	68.1	0.04	
>1000	3	−11.27 (−17.75, −4.78)	0.001	0.0	0.86	
Study duration (week)						0.006
<8	3	−21.84 (−38.57, −5.11)	0.01	63.2	0.06	
≥8	3	−10.96 (−17.44, −4.47)	0.001	0.0	0.86	
Mean age						0.009
<50 years	2	−21.93 (−43.91, 0.04)	0.05	83.3	0.01	
≥50 years	4	−11.33 (−17.74, −4.93)	0.001	0.0	0.96	
Health status						0.03
hyperlipidemic	3	−18.86 (−34.57, −3.16)	0.02	76.4	0.01	
diabetic	3	−11.27 (−18.35, −4.18)	0.002	0.0	0.86	
HDL						
Anethum dosage (mg/d)						0.005
<1000	3	−3.13 (−6.22, −0.04)	0.04	0.0	0.50	
>1000	3	1.59 (−1.36, 4.54)	0.29	57.3	0.09	
Study duration (week)						0.18
<8	3	−0.86 (−3.80, 2.07)	0.56	16.1	0.30	
≥8	3	−0.04 (−4.94, 4.85)	0.98	79.8	0.007	
Mean age						0.004
<50 years	2	−4.50 (−8.36, −0.65)	0.02	0.0	0.95	
≥50 years	4	1.26 (−1.25, 3.78)	0.32	46.6	0.13	
Health status						0.02
hyperlipidemic	3	−2.25 (−6.05, 1.54)	0.24	47.4	0.15	
diabetic	3	1.24 (−2.30, 4.79)	0.49	61.7	0.07	
FBS						
Anethum dosage (mg/d)						<0.001
<1000	2	5.83 (−9.34, 21.02)	0.45	67.0	0.08	
>1000	3	−28.02 (−66.00, 9.96)	0.15	85.8	0.001	
Study duration (week)						0.16
<8	2	−23.07 (−95.96, 49.81)	0.53	97.8	<0.001	
≥8	3	−3.48 (−13.55, 6.60)	0.50	0.0	0.80	
Mean age						<0.001
<50 years	2	−30.69 (−88.38, 26.99)	0.29	96.8	<0.001	
≥50 years	3	2.68 (−14.71, 20.08)	0.76	43.2	0.17	
Health status						0.13
hyperlipidemic	1	−1.60 (−13.16, 9.96)	0.78	–	–	
diabetic	4	−16.53 (−56.32, 23.25)	0.41	93.5	<0.001	

Abbreviations: TG: triglyceride, TC: total cholesterol; LDL: low-density lipoprotein; HDL: high-density lipoprotein; FBS: fasting blood sugar; WMD; weighted mean difference.

(Sahib, Mohammad, and Al-Gareeb 2012). When this study was excluded, there was a significant association between *Anethum* intake and TC concentration (WMD: −9.49 mg/dl; 95% CI: −16.92 to −2.05). Between-study heterogeneity was removed after subgroup analysis by intervention dosage (I^2=0.0%, $P = 0.59$) and duration (I^2=0.0%, $P = 0.86$),

participant's mean age (I^2=0.0%, P = 0.69) and health status (I^2=0.0%, P = 0.73). In addition, these analyses indicated that *Anethum* supplementation can reduce serum TC levels in trials that used high doses of *Anethum* (WMD: −10.12 mg/dl; 95% CI: −18.12 to −2.11; P = 0.01,), lasted more than 8 weeks (WMD: −12.66 mg/dl; 95% CI: −22.42 to −2.89; P = 0.01), were performed on subjects ≥50 years (WMD: −9.74 mg/dl; 95% CI: −17.67 to −1.82; P = 0.01) and in diabetic patients (WMD: −13.14 mg/dl; 95% CI: −23.9 to −2.38; P = 0.01).

Effect of A. graveolens on serum LDL levels

The impact of *Anethum* supplementation on serum levels of LDL was detected in six trials with a total of 270 patients (Kojuri, Vosoughi, and Akrami 2007; Mansouri et al. 2012; Rashidlamir et al. 2012; Sahib, Mohammad, and Al-Gareeb 2012; Mobasseri et al. 2014; Haidari et al. 2020). Polling effect sizes by the random-effects model showed a significant reduction in serum LDL following *Anethum* intake (WMD: −15.64 mg/dl; 95% CI: −24.55 to −6.73; P = 0.001), compared with the placebo group. There was moderate heterogeneity among the studies (I^2= 62.0%, P = 0.02) (Figure 3C). Potential heterogeneity sources were assessed by subgroup analysis; there was no heterogeneity in trials using high doses supplementation, those that lasted ≥8 weeks, and those that administered *Anethum* in diabetic patients with less than 50 years. Moreover, the pooled results remained unchanged throughout the subgroup analyses.

Effect of A. graveolens on serum HDL levels

Pooled results from six studies using the random-effects model indicated that *A. graveolens* as an intervention had no significant effect on serum HDL alteration (WMD: −0.44 mg/dl; 95% CI: −3.28 to 2.39; P = 0.76). There was also moderate between-study heterogeneity (I^2= 64.4%, P = 0.01) (Figure 3D). The potential sources of heterogeneity were explained by *Anethum* dosage, duration of intervention, participant's health status, and mean age. Surprisingly, subgroup analyses indicated that *Anethum* can decrease serum levels of HDL when administered in low doses (WMD: −3.13 mg/dl; 95% CI: −6.22 to −0.04; P = 0.04) and in subjects under 50 years (WMD: −4.50 mg/dl; 95% CI: −8.36 to −0.65; P = 0.02). In addition, sensitivity analysis results showed that no single study greatly influenced the overall effect.

Effect of A. graveolens on glycemic indices

The effect of *A. graveolens* supplementation on serum FBS levels was evaluated in five trials, including 200 subjects (Mansouri et al. 2012; Rashidlamir et al. 2012; Mobasseri et al. 2014; Sargolzaei et al. 2017; Haidari et al. 2020). Pooled results indicated that *Anethum* intake did not affect serum FBS (WMD: −13.34 mg/dl; 95% CI: −40.56 to 13.87; P = 0.33), compared to the placebo group. There was a high level of heterogeneity between-studies (I^2= 91.8%, P < 0.001) (Figure 4A). When performing subgroup analysis based on study duration (I^2= 0.0%, P = 0.80) and participant's mean age (I^2= 43.2%, P = 0.17), the heterogeneity disappeared. In these analyses, we failed to find a significant effect of *Anethum* on serum FBS. Besides, in the sensitivity analysis, the pooled effect size was robust.

Two trials also reported the effect of *A. graveolens* on serum insulin and HOMA-IR (Mobasseri et al. 2014; Haidari et al. 2020). Pooling effects sizes based on the random-effects model showed *A. graveolens* significantly reduced serum levels of insulin (WMD: −2.28 μU/ml; 95% CI: −3.62 to −0.93; P = 0.001) (Figure 4B), and HOMA-IR (WMD: −1.06; 95% CI: −1.91 to −0.20; P = 0.01) (Figure 4C).

Dose-response analysis

The non-linear estimation indicated a significant association between the duration of *A. graveolens* intake and serum TG ($P_{\text{non-linearity}}$ = 0.01) (Figure 5A). Also, we explored a significant relationship between *Anethum* dosage and serum FBS levels ($P_{\text{non-linearity}}$ <0.001); the trend of FBS levels reduction continued until 1500 mg/day of *Anethum* dose, and then this effect was reversed. However, no significant associations were found for other outcomes (Figure 5B).

Quality of evidence assessment

The quality of evidence for each factor was evaluated using the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) (Balshem et al. 2011). Our assessment showed "low" quality for FBS and "very low" for TG, TC, LDL, HDL, insulin, HOMA-IR. Detailed results are provided in Table 3.

Discussion

The present systematic review and meta-analysis of RCTs is the first study that critically evaluated the effects of supplementation with *A. graveolens* on lipid profile and indices of insulin resistance and glycemic control in adults. The present study's findings suggested that A. graveolens supplementation may improve serum LDL levels and markers of insulin resistance, including serum insulin concentration and HOMA-IR. There were also some suggestions of favorable effects on TG and TC concentrations in the subgroup analyses. *A. graveolens* supplementation had no significant effects on HDL and FBS that persisted across all subgroups.

Natural and herbal products are being increasingly used with lipid- and blood glucose-lowering drugs as a complementary approach in patients with dyslipidemia and T2D (Yeh et al. 2002; Mousavi, Karimi, et al. 2020). Lipid- and blood glucose-lowering drugs have some side effects, limiting their utilization for CVD and T2D management (Freeland and Farber 2015; Muscari, Puddu, and Puddu 2002). Studies have shown that supplementation with some natural and herbal products such as cinnamon (Asbaghi et al. 2020; Mousavi, Rahmani, et al. 2020), saffron (Asbaghi

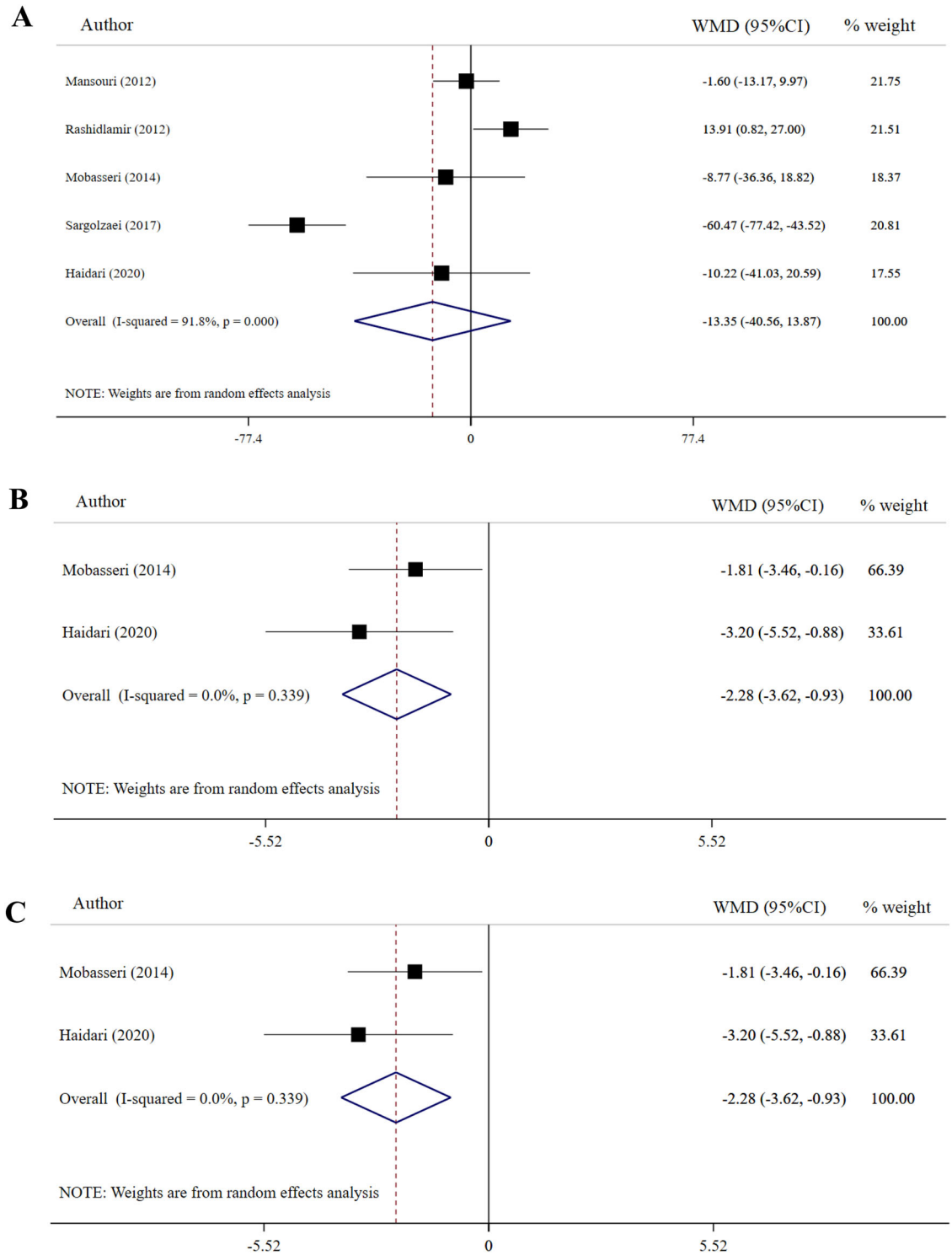

Figure 4. Forest plot depicting the weighted mean difference and 95% confidence intervals for the effect of A. graveolens supplementation on serum (a) FBS, (b) insulin, (c) HOMA-IR.

et al. 2020), cumin (Jafarnejad et al. 2018), and curcumin (Mousavi, Milajerdi, et al. 2020) may be beneficial in the management of CVD risk factors. *Anethum graveolens* L. is an annual herb of the Apiaceae family that is frequently used as a spice, especially in India and Iran (Jana and Shekhawat 2010). It has some antioxidant, anti-inflammatory, and hypoglycemic properties that may explain its favorable effects against insulin resistance and dyslipidemia (Jana and Shekhawat 2010; Oshaghi et al. 2016). *Anethum graveolens* L. seeds, leaves, and roots have some antioxidant phytochemicals such as tannins and some flavonoid subclasses including quercetin and isorhamnetin that could counteract with free radicals (Mahran et al. 1992; Möhle et al. 1985) and thereby can repair β cell function and improve insulin secretion (Madani, Ahmady Mahmoodabady, and Vahdati 2005; Pi et al.).

Some subclasses of terpenoids, a large, diverse class of natural organic chemicals with antioxidant properties

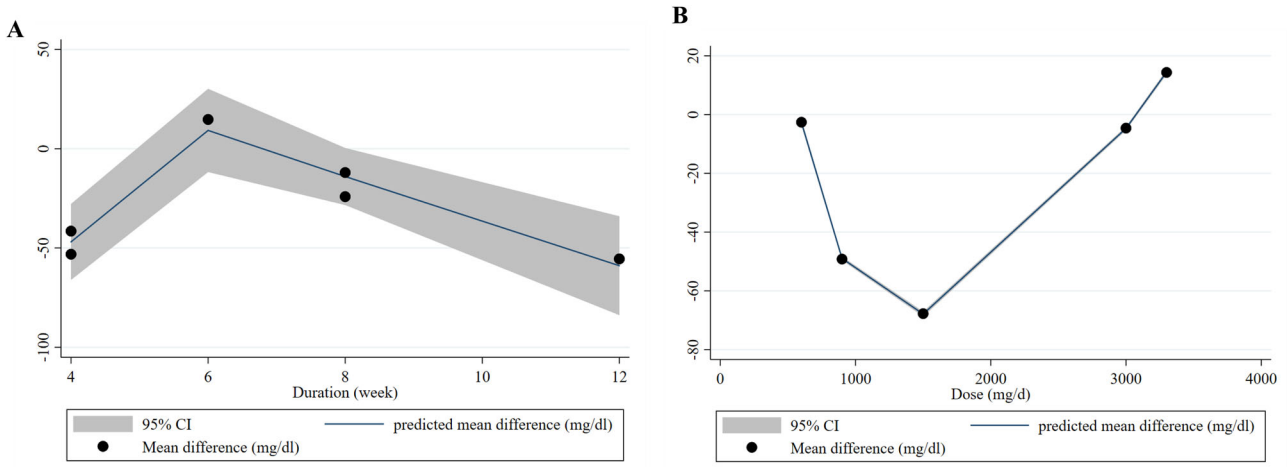

Figure 5. Non-linear dose-response association between duration of supplementation and TG (A), and dosage and FBS (B). The 95% CI is revealed in the shaded regions.

Table 3. Quality of evidence using GRADE assessment.

Outcome	No. of studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Quality	No of participants		Effect Pooled effect size WMD (95%CI)
								Intervention	Control	
TG, mg/dl	6	Serious	Serious	Not serious	Serious	Undetected	⊕ooo Very low	135	135	−17.91 (−46.88, 11.06)
TC, mg/dl	6	Serious	Serious	Not serious	Serious	Undetected	⊕ooo Very low	135	135	−16.47 (−34.93, 1.93)
LDL, mg/dl	6	Serious	Serious	Not serious	Serious	Undetected	⊕ooo Very low	135	135	−15.64 (−24.55, −6.73)
HDL, mg/dl	6	Serious	Serious	Not serious	Not serious	Undetected	⊕ooo Very low	135	135	−0.44 (−3.28, 2.39)
FBS, mg/dl	5	Not serious	Serious	Not serious	Serious	Undetected	⊕⊕oo Low	100	100	−13.34 (−40.56, 13.87)
Insulin, μU/ml	2	Not serious	Not serious	Serious	Very serious	Undetected	⊕ooo Very low	50	50	−2.28 (−3.62, −0.93)
HOMA-IR	2	Not serious	Not serious	Serious	Very serious	Undetected	⊕ooo Very low	50	50	−1.06 (−1.91, −0.20)

Abbreviations: TG: triglyceride, TC: total cholesterol; LDL: low-density lipoprotein; HDL: high-density lipoprotein; FBS: fasting blood sugar; WMD; weighted mean difference

(Grassmann 2005), have also been isolated from *A. graveolens* L. seeds, leaves, and roots (Jana and Shekhawat 2010). Studies have also extracted two anti-inflammatory components, carvone (Golshani et al. 2004) and limonene (do Amaral et al. 2007), from *A. graveolens* seeds (Valadi et al. 2010). Carvone and limonene are the two antioxidant phytochemicals that can increase glutathione transferase activity, an essential part of the antioxidant defense system (Zheng, Kenney, and Lam 1992). Therefore, these components might help combat oxidative stress (Rains and Jain 2011) and low-grade systemic inflammation (Shah et al. 2008). The two underlying pathophysiological mechanisms playing an important role in the development and progression of insulin resistance. Supplementation with *A. graveolens* also led to a substantial decrease in LDL concentration in adults robust across all subgroups. The binding of *A. graveolens* to bile acids could counteract these compounds' enterohepatic cycle, leading to a decrease in cholesterol absorption and an increase in faecalis bile acids excretion (Senanayake et al. 2004). *A. graveolens* can also suppress the activity of acetyl-CoA carboxylase and HMG-COA reductase enzymes (Lemhadri et al. 2006) and as a result, can inhibit the synthesis of cholesterol and fatty acids (Bopanna et al. 1997). Moreover, the high content of quercetin in *A. graveolens* can decrease hepatic production of ApoB-100 and thereby can reduce circulating levels of TG and LDL (Pal et al. 2003). In addition, quercetin stimulates cholesterol clearance by increasing LDL receptors (Haghighi, Kharazizadeh, and Atar 2007) and can inhibit the oxidation of LDL-C particles in the blood (Bok et al. 2002). Considering the importance of LDL on the development and progression of CVD, medical guidelines emphasize lowering LDL concentrations as a crucial strategy to decrease cardiovascular risk (Goodman et al. 1988). Studies have shown that every 1-mmol/L (38.7 mg/dL) reduction in LDL concentration by lipid-lowering interventions (i.e., statins, bile acid sequestrants, ileal bypass, diet, and ezetimibe) can reduce the risk of major vascular events by 23–25% (Silverman et al. 2016). Our findings indicated a 15 mg/dL reduction in serum LDL concentration following administration of *A. graveolen*. Therefore, supplementation with *A. graveolen* can be considered a safe and relatively effective strategy, that might be used in parallel with other common interventions for the management of dyslipidemia. However,

the interpretation of the results is limited by the low number of trials included in our review and thus, more research is needed to fully investigate the lipid- and glucose-lowering effects of *A. graveolen*.

Our review also indicated that supplementation with *A. graveolen* had no significant effects on TG and TC concentrations in the main analyses. However, the subgroup analyses suggested strong lipid-lowering effects in the subgroup with a long-term intervention (≥8 weeks) and in subjects who had <50 years for TG, and in trials that administered high doses of *Anethum* (>1000 mg/d), trials that lasted over 8 weeks and in subjects ≥50 years for TC. Only a few trials were included in the subgroups, and therefore, more research is needed to confirm the findings observed in the subgroups.

The present meta-analysis has several strengths. This is the first study to systematically gather existing evidence regarding supplementation effects with *A. graveolen* on health outcomes. We conducted several subgroup analyses to find the effects across different subgroups and to detect the potential source of heterogeneity. In addition, we completed the dose-response analysis to find an optimal dosage and duration for *A. graveolen* intervention. The main limitation is the low number of trials included in the analyses, which lowers the study's power. In addition, all trials were conducted in the Middle-East (six trials in Iran and one trial in Iraq). This highlights the need for more extensive research in other geographical regions and ethnic cohorts to expand the generalizability of the results. Taking into account that a high LDL concentration is a major cardiovascular risk factor, it is important to point out that subjects included in our current meta-analytic work did not specifically have CVD, although they had other disorders, such as diabetes and hyperlipidemia. Therefore, further research in individuals with cardiovascular conditions is needed before our reported LDL-lowering effect by *A. graveolen* supplementation can be considered an effective strategy for CVD prevention and management.

Conclusions

The present meta-analysis of trials indicated that supplementation with *A. graveolen* can lower serum LDL concentrations and improve adults' insulin resistance. Some suggestions of favorable effects on TG and TC concentrations were also found in the subgroups. *A. graveolen* supplementations had no significant impact on blood glucose levels. Further high-quality studies in different ethnic groups and cohorts with CVD are needed to establish the plant's clinical efficacy.

Disclosure statement

All authors declared any personal or financial conflicts of interest.

Authors' contributions

SMM and AJ designed the study. AB, CA, APB conducted the literature search and performed data extraction and quality assessment. SMM and EK performed the statistical analysis. AW and EP revised the statistical analysis and final version of the manuscript. All authors read and approved the final protocol manuscript.

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References

Asbaghi, O., M. Sadeghian, O. Sadeghi, S. Rigi, S. C. Tan, A. Shokri, and S. M. Mousavi. 2021. Effects of saffron (Crocus sativus L.) supplementation on inflammatory biomarkers: A systematic review and meta-analysis. *Phytotherapy Research* 35 (1):20–32. doi:10.1002/ptr.6748.

Balshem, H.,. M. Helfand, H. J. Schunemann, A. D. Oxman, R. Kunz, J. Brozek, G. E. Vist, Y. Falck-Ytter, J. Meerpohl, S. Norris, et al. 2011. GRADE guidelines: 3. Rating the quality of evidence. *Journal of Clinical Epidemiology* 64 (4):401–6. doi: 10.1016/j.jclinepi.2010.07.015.

Bok, S.-H., S.-Y. Park, Y. B. Park, M.-K. Lee, S.-M. Jeon, T.-S. Jeong, and M.-S. Choi. 2002. Quercetin dihydrate and gallate supplements lower plasma and hepatic lipids and change activities of hepatic antioxidant enzymes in high cholesterol-fed rats. *International Journal for Vitamin and Nutrition Research. Internationale Zeitschrift Fur Vitamin- Und Ernahrungsforschung. Journal International de Vitaminologie et de Nutrition* 72 (3):161–9. doi: 10.1024/0300-9831.72.3.161.

Bopanna, K., J. Kannan, G. Sushma, R. Balaraman, and S. Rathod. 1997. Antidiabetic and antihyperlipaemic effects of neem seed kernel powder on alloxan diabetic rabbits. *Indian Journal of Pharmacology* 29:162.

Borenstein, M., L. V. Hedges, J. P. Higgins, and H. R. Rothstein. 2011. *Introduction to meta-analysis*. USA: John Wiley & Sons.

DAHLöF, B. 2010. Cardiovascular disease risk factors: Epidemiology and risk assessment. *The American Journal of Cardiology* 105 (1 Suppl):3A–9A. doi: 10.1016/j.amjcard.2009.10.007.

Dersimonian, R., and N. Laird. 1986. Meta-analysis in clinical trials. *Controlled Clinical Trials* 7 (3):177–88. doi: 10.1016/0197-2456(86)90046-2.

do Amaral, J. F., M. I. G. Silva, M. R. d A. Neto, P. F. T. Neto, B. A. Moura, C. T. V. de Melo, F. L. O. de Araújo, D. P. de Sousa, P. F. de Vasconcelos, S. M. M. de Vasconcelos, et al. 2007. Antinociceptive effect of the monoterpene R-(+)-limonene in mice. *Biological & Pharmaceutical Bulletin* 30 (7):1217–20. doi: 10.1248/bpb.30.1217.

Estruch, R., E. Ros, J. Salas-Salvadó, M.-I. Covas, D. Corella, F. Arós, E. Gómez-Gracia, V. Ruiz-Gutiérrez, M. Fiol, J. Lapetra, et al. 2013. Primary prevention of cardiovascular disease with a Mediterranean diet. *New England Journal of Medicine* 368 (14):1279–90., doi: 10.1056/NEJMoa1200303.

Fan, J., and I. Gijbels. 1996. *Local polynomial modelling and its applications: monographs on statistics and applied probability 66*. USA: CRC Press.

Freeland, B., and M. S. Farber. 2015. Type 2 diabetes drugs: A review. *Home Healthcare Now* 33 (6):304–10. doi: 10.1097/NHH.0000000000000243.

Golshani, S.,. F. Karamkhani, H. R. Monsef-Esfehani, and M. Abdollahi. 2004. Antinociceptive effects of the essential oil of *Dracocephalum kotschyi* in the mouse writhing test. *J Pharm Pharm Sci* 7:76–9.

Goodman, D. S., S. B. Hulley, L. T. Clark, C. Davis, V. Fuster, J. C. Larosa, A. Oberman, E. J. Schaefer, D. Steinberg, and W. V. Brown. 1988. Report of the National Cholesterol Education Program Expert

Panel on detection, evaluation, and treatment of high blood cholesterol in adults. *Archives of Internal Medicine* 148 (1):36–69. doi: 10.1001/archinte.1988.00380010040006.

Grassmann, J. 2005. Terpenoids as plant antioxidants. *Vitamins and Hormones* 72:505–35. doi: 10.1016/S0083-6729(05)72015-X.

Haghighi, B., M. Kharazizadeh, and M. Atar. 2007. Possible involvement of hepatic phosphatidate phosphohydrolase in the mechanisms of actions of certain antilipemic drugs in rats.

Haidari, F., M. Zakerkish, F. Borazjani, K. A. Angali, and G. A. Foroushani. 2020. The effects of *Anethum graveolens* (dill) powder supplementation on clinical and metabolic status in patients with type 2 diabetes. *Trials* 21 (1):483.

Higgins, J. P. 2008. Cochrane handbook for systematic reviews of interventions version 5.0. 1. The Cochrane Collaboration. http://www.cochrane-handbook. org.

Higgins, J. P., D. G. Altman, P. C. GøTZSCHE, P. Juni, D. Moher, A. D. Oxman, J. Savović, K. F. Schulz, L. Weeks, and J. A. Sterne. 2011. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *Bmj* 343 (oct18 2):d5928–d5928. doi: 10.1136/bmj.d5928.

Jafarnejad, S., C. Tsang, M. Taghizadeh, Z. Asemi, and S. A. Keshavarz. 2018. A meta-analysis of cumin (*Cuminum cyminim* L.) consumption on metabolic and anthropometric indices in overweight and type 2 diabetics. *Journal of Functional Foods* 44:313–21. doi: 10.1016/j.jff.2018.03.026.

Jana, S., and G. Shekhawat. 2010. Anethum graveolens: An Indian traditional medicinal herb and spice. *Pharmacognosy Reviews* 4 (8):179–84. doi: 10.4103/0973-7847.70915.

Kojuri, J., A. R. Vosoughi, and M. Akrami. 2007. Effects of *Anethum graveolens* and garlic on lipid profile in hyperlipidemic patients. *Lipids in Health and Disease* 6 (1):5. doi: 10.1186/1476-511X-6-5.

Lemhadri, A., L. Hajji, J.-B. Michel, and M. Eddouks. 2006. Cholesterol and triglycerides lowering activities of caraway fruits in normal and streptozotocin diabetic rats. *Journal of Ethnopharmacology* 106 (3):321–326. doi: 10.1016/j.jep.2006.01.033.

Lisiewska, Z., W. Kmiecik, and A. Korus. 2006. Content of vitamin C, carotenoids, chlorophylls and polyphenols in green parts of dill (*Anethum graveolens* L.) depending on plant height. *Journal of Food Composition and Analysis* 19 (2-3):134–140. doi: 10.1016/j.jfca.2005.04.009.

Madani, H., N. Ahmady Mahmoodabady, and A. Vahdati. 2005. Effects of hydroalchoholic extract of *Anethum graveolens* (Dill) on plasma glucose an lipid levels in diabetes induced rats. *Iranian Journal of Diabetes and Metabolism* 5:109–116.

Mahran, G., H. Kadry, C. Thabet, M. EL-Olemy, M. Al-Azizi, P. Schiff, L. Wong, and N. Liv. 1992. GC/MS analysis of volatile oil of fruits of *Anethum graveolens*. *International Journal of Pharmacognosy* 30 (2):139–144. doi: 10.3109/13880209209053978.

Mansouri, M., N. Nayebi, A. Keshtkar, S. Hasani-Ranjbar, E. Taheri, and B. Larijani. 2012. The effect of 12 weeks *Anethum graveolens* (dill) on metabolic markers in patients with metabolic syndrome; a randomized double blind controlled trial. *Daru: Journal of Faculty of Pharmacy, Tehran University of Medical Sciences* 20 (1):47 doi: 10.1186/2008-2231-20-47.

Miller, M. 2003. Niacin as a component of combination therapy for dyslipidemia. *Mayo Clinic Proceedings* 78 (6):735–742. Elsevier, doi: 10.4065/78.6.735.

Mobasseri, M., A. Ostadrahimi, M. A. Jafarabadi, and S. Mahluji. 2014. *Anethum graveolens* supplementation improves insulin sensitivity and lipid abnormality in type 2 diabetic patients. *Pharmaceutical Sciences* 20:40–45.

MöHLE, B., W. Heller, and E. Wellmann. 1985. UV-induced biosynthesis of quercetin 3-O-β-D-glucuronide in dill cell cultures. *Phytochemistry* 24 (3):465–467. doi: 10.1016/S0031-9422(00)80748-7.

Mousavi, S. M., E. Karimi, M. Hajishafiee, A. Milajerdi, M. R. Amini, and A. Esmaillzadeh. 2020. Anti-hypertensive effects of cinnamon supplementation in adults: A systematic review and dose-response meta-analysis of randomized controlled trials. *Critical Reviews in Food Science and Nutrition* 60 (18):3144–3154. doi: 10.1080/10408398.2019.1678012.

Mousavi, S. M., A. Milajerdi, H. K. Varkaneh, M. M. Gorjipour, and A. Esmaillzadeh. 2020. The effects of curcumin supplementation on body weight, body mass index and waist circumference: A systematic review and dose-response meta-analysis of randomized controlled trials. *Critical Reviews in Food Science and Nutrition* 60 (1):171–180. doi: 10.1080/10408398.2018.1517724.

Mousavi, S. M., J. Rahmani, H. Kord-Varkaneh, A. Sheikhi, B. Larijani, and A. Esmaillzadeh. 2020. Cinnamon supplementation positively affects obesity: A systematic review and dose-response meta-analysis of randomized controlled trials. *Clinical Nutrition* 39 (1):123–133. doi: 10.1016/j.clnu.2019.02.017.

Mousavi, S. M., S. Shab-Bidar, H. Kord-Varkaneh, M. Khorshidi, and K. Djafarian. 2019. Effect of alpha-lipoic acid supplementation on lipid profile: A systematic review and meta-analysis of controlled clinical trials. *Nutrition (Burbank, Los Angeles County, Calif.)* 59:121–130. doi: 10.1016/j.nut.2018.08.004.

Muscari, A., G. M. Puddu, and P. Puddu. 2002. Lipid-lowering drugs: Are adverse effects predictable and reversible? *Cardiology* 97 (3):115–121. doi: 10.1159/000063326.

Nichols, M., N. Townsend, P. Scarborough, and M. Rayner. 2014. Cardiovascular disease in Europe 2014: Epidemiological update. *European Heart Journal* 35 (42):2950–2959. doi: 10.1093/eurheartj/ehu299.

Oshaghi, E. A., I. Khodadadi, H. Tavilani, and M. T. Goodarzi. 2016. Effect of dill tablet (*Anethum graveolens* L) on antioxidant status and biochemical factors on carbon tetrachloride-induced liver damage on rat. *International Journal of Applied and Basic Medical Research* 6:111.

Pal, S., N. Ho, C. Santos, P. Dubois, J. Mamo, K. Croft, and E. Allister. 2003. Red wine polyphenolics increase LDL receptor expression and activity and suppress the secretion of ApoB100 from human HepG2 cells. *The Journal of Nutrition* 133 (3):700–706. doi: 10.1093/jn/133.3.700.

Patrone, C., O. Eriksson, and D. Lindholm. 2014. Diabetes drugs and neurological disorders: New views and therapeutic possibilities. *The Lancet. Diabetes & Endocrinology* 2 (3):256–262. doi: 10.1016/S2213-8587(13)70125-6.

Pi, J., Q. Zhang, and M. Andersen. 2014. Reactive oxygen species and antioxidants in pancreatic β-cell function-Yin and Yang.

Rains, J. L., and S. K. Jain. 2011. Oxidative stress, insulin signaling, and diabetes. *Free Radical Biology & Medicine* 50 (5):567–75. doi:10.1016/j.freeradbiomed.2010.12.006. PMC: 21163346

Rashidlamir, A.,. S. Gholamian, A. H. Javaheri, and M. Dastani. 2012. The effect of 4-weeks aerobic training according with the usage of *Anethum graveolens* on blood sugar and lipoproteins profile of diabetic women. *Annals of Biological Research* 3:4313–4319.

Sahebkar, A. 2014. Are curcuminoids effective C-reactive protein-lowering agents in clinical practice? Evidence from a meta-analysis. *Phytotherapy Research: PTR* 28 (5):633–642. doi: 10.1002/ptr.5045.

Sahib, A. S., I. Mohammad, and A. Al-Gareeb. 2012. Effects of *Anethum graveolens* leave powder on lipid profile in hyperlipidemic patients. *Spatula DD - Peer Reviewed Journal on Complementary Medicine and Drug Discovery* 2 (3):153–158. doi: 10.5455/spatula.20120907123553.

Saleh-E-In, M. M., A. Sultana, M. Husain, and S. K. Roy. 2010. Chemical constituents of essential oil from *Anethum sowa* L. herb (leaf and stem) growing in Bangladesh. *Bangladesh Journal of Scientific and Industrial Research* 45 (2):173–176. doi: 10.3329/bjsir.v45i2.5721.

Sargolzaei, M. S., A. Mansouri, H. Shahdadi, N. Masinaei Nezhad, and M. Poodineh Moghadam. 2017. The effect of dill tablet on the level of fasting blood sugar in patients with type II diabetes. *Journal of Diabetes Nursing* 5:86–94.

Senanayake, G. V., M. Maruyama, M. Sakono, N. Fukuda, T. Morishita, C. Yukizaki, M. Kawano, and H. Ohta. 2004. The effects of bitter melon (*Momordica charantia*) extracts on serum and liver lipid parameters in hamsters fed cholesterol-free and cholesterol-enriched diets. *Journal of Nutritional Science and Vitaminology* 50 (4):253–257. doi: 10.3177/jnsv.50.253.

Shah, A., N. Mehta, and M. P. Reilly. 2008 Nov-Dec. Adipose inflammation, insulin resistance, and cardiovascular disease. *JPEN. Journal of Parenteral and Enteral Nutrition* 32 (6):638–44. doi:10.1177/0148607108325251. PMC: 18974244

Shamseer, L., D. Moher, M. Clarke, D. Ghersi, A. Liberati, M. Petticrew, P. Shekelle, and L. A. Stewart. 2015. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: Elaboration and explanation. *BMJ* 349 (jan02 1): g7647–g7647. doi: 10.1136/bmj.g7647.

Shattat, G. F. 2014. A review article on hyperlipidemia: Types, treatments and new drug targets. *Biomedical and Pharmacology Journal* 7 (2):399–409. doi: 10.13005/bpj/504.

Silverman, M. G., B. A. Ference, K. Im, S. D. Wiviott, R. P. Giugliano, S. M. Grundy, E. Braunwald, and M. S. Sabatine. 2016. Association between lowering LDL-C and cardiovascular risk reduction among different therapeutic interventions: A systematic review and meta-analysis. *Jama* 316 (12):1289–1297. doi: 10.1001/jama.2016.13985.

Singh, G., S. Maurya, M. P. Lampasona, and C. Catalan. 2006. Chemical constituents, antimicrobial investigations, and antioxidative potentials of *Anethum graveolens* L. essential oil and acetone extract: Part 52. *Journal of Food Science* 70 (4):M208–M215. doi: 10.1111/j.1365-2621.2005.tb07190.x.

Valadi, A., S. Nasri, N. Abbasi, and G. Amin. 2010. Antinociceptive and anti-inflammatory effects of hydroalchoholic extract of *Anethum graveolens* L. seed. *Journal of Medicinal Plants* 9:124–130.

Wood, D. 2001. Established and emerging cardiovascular risk factors. *American Heart Journal* 141 (2):S49–S57. doi: 10.1067/mhj.2001.109951.

Yazdanparast, R., and S. Bahramikia. 2008. Evaluation of the effect of *Anethum graveolens* L. crude extracts on serum lipids and lipoproteins profiles in hypercholesterolaemic rats. *DARU Journal of Pharmaceutical Sciences* 16:88–94.

Yeh, G. Y., D. M. Eisenberg, R. B. Davis, and R. S. Phillips. 2002. Use of complementary and alternative medicine among persons with diabetes mellitus: Results of a national survey. *American Journal of Public Health* 92 (10):1648–1652. doi: 10.2105/ajph.92.10.1648.

Zheng, G.-Q., P. M. Kenney, and L. K. Lam. 1992. Anethofuran, carvone, and limonene: Potential cancer chemopreventive agents from dill weed oil and caraway oil. *Planta Medica* 58 (4):338–341. doi: 10.1055/s-2006-961480.

Zheng, Y., S. H. Ley, and F. B. Hu. 2018. Global aetiology and epidemiology of type 2 diabetes mellitus and its complications. *Nature Reviews. Endocrinology* 14 (2):88–98. doi: 10.1038/nrendo.2017.151.